Intracellular Na$^+$ Concentration Is Elevated in Heart Failure But Na/K Pump Function Is Unchanged

Sanda Despa, PhD; Mohammed A. Islam, PhD; Christopher R. Weber, PhD; Steven M. Pogwizd, MD; Donald M. Bers, PhD

Background—Intracellular sodium concentration ([Na$^+$]) modulates cardiac contractile and electrical activity through Na/Ca exchange (NCX). Upregulation of NCX in heart failure (HF) may magnify the functional impact of altered [Na$^+$].

Methods and Results—We measured [Na$^+$]$_i$ by using sodium binding benzofuran isophthalate in control and HF rabbit ventricular myocytes (HF induced by aortic insufficiency and constriction). Resting [Na$^+$]$_i$ was 9.7±0.7 versus 6.6±0.5 mmol/L in HF versus control. In both cases, [Na$^+$]$_i$ increased by ~2 mmol/L when myocytes were stimulated (0.5 to 3 Hz). To identify the mechanisms responsible for [Na$^+$]$_i$ elevation in HF, we measured the [Na$^+$]$_i$ dependence of Na/K pump–mediated Na$^+$ extrusion. There was no difference in $V_{\text{max}}$ (8.3±0.7 versus 8.0±0.8 mmol/L/min) or $K_m$ (9.2±1.0 versus 9.9±0.8 mmol/L in HF and control, respectively). Therefore, at measured [Na$^+$]$_i$ levels, the Na/K pump rate is actually higher in HF. However, resting Na$^+$ influx was twice as high in HF versus control (2.3±0.3 versus 1.1±0.2 mmol/L/min), primarily the result of a tetrodotoxin-sensitive pathway.

Conclusions—Myocyte [Na$^+$]$_i$ is elevated in HF as a result of higher diastolic Na$^+$ influx (with unaltered Na/K-ATPase characteristics). In HF, the combined increased [Na$^+$]$_i$, decreased Ca$^{2+}$ transient, and prolonged action potential all profoundly affect cellular Ca$^{2+}$ regulation, promoting greater Ca$^{2+}$ influx through NCX during action potentials. Notably, the elevated [Na$^+$]$_i$ may be critical in limiting the contractile dysfunction observed in HF. (Circulation. 2002;105:2543-2548.)

Key Words: sodium ■ heart failure ■ calcium

Cardiac contractile dysfunction in heart failure (HF) is due largely to altered Ca$^{2+}$ transport. Specifically, HF cardiac myocytes exhibit depressed and prolonged Ca$^{2+}$ transients.$^1$ These changes can be explained by reductions in sarcoplasmic reticulum (SR) Ca$^{2+}$-ATPase$^2$ and increased Na/Ca exchange (NCX)$^5$–$^6$ function.

Intracellular sodium concentration ([Na$^+$]$_i$) affects excitation-contraction coupling by modulating pH and [Ca$^{2+}$], through Na/H exchange and NCX, respectively.$^6$ The upregulated NCX in HF may increase the functional impact of altered [Na$^+$]$_i$. Recent reports$^7$–$^{10}$ indicate that [Na$^+$]$_i$ is increased in hypertrophy; however, HF data are limited. Preliminary data in human HF suggest some increase in [Na$^+$]$_i$, but a slight decrease in [Na$^+$]$_i$ was found in pacing-induced HF rabbits.$^{12}$

Higher [Na$^+$]$_i$ could be explained by lower Na/K pump activity, consistent with reports of decreased Na/K pump expression and isoform shifts in some HF models.$^{13}$–$^{17}$ However, functional studies in HF ventricular myocytes are sparse and contradictory.$^{8,15}$ Enhanced Na$^+$ influx could also raise [Na$^+$]$_i$, and this explains the higher [Na$^+$]$_i$ in rat versus rabbit ventricular myocytes.$^{18}$

Our first aim was to determine whether [Na$^+$]$_i$ is altered in a nonischemic rabbit HF model that we have extensively characterized.$^{4,19}$ HF induced by aortic insufficiency and constriction resulted in 90% of animals having nonsustained ventricular tachycardias (10% incidence of sudden death). NCX expression is 2-fold increased, and contractions, Ca$^{2+}$ transients, and SR Ca$^{2+}$ load are reduced.$^4,19$ We measured [Na$^+$]$_i$ in ventricular myocytes at 37°C, using the fluorescent indicator sodium binding benzofuran isophthalate (SBFI) and validated calibration methods.$^{18}$ We found that [Na$^+$]$_i$ is higher in HF versus control myocytes at rest and during stimulation. A second aim was to determine why [Na$^+$]$_i$ is higher in HF (altered extrusion or influx). Using Na$^+$ loading/recovery protocols$^{18}$ to measure Na$^+$ extrusion by the Na/K pump, we found that the maximal Na$^+$ transport rate ($V_{\text{max}}$) and [Na$^+$]$_i$, for half-maximal stimulation ($K_m$) are comparable in control and HF myocytes. On the other hand, resting Na$^+$ influx (measured as the initial rate of [Na$^+$]$_i$ rise on abrupt Na/K pump inhibition) was significantly higher in HF than control. Therefore, higher [Na$^+$]$_i$ is due to elevated diastolic Na$^+$ influx rather than altered Na/K pump characteristics in this HF model. We also show how the elevated [Na$^+$]$_i$ in HF has major functional consequences for calcium flux during the action potential (AP).

Methods

Rabbit HF Model and Myocyte Isolation

HF was induced in rabbits by aortic insufficiency, followed 2 to 4 weeks later by aortic constriction as described.$^{19}$ Rabbits were...
studied ~5 months later, when the left ventricular end-systolic dimension exceeded 1.20 cm (University of Illinois Animal Studies Committee–approved protocols). Myocytes were isolated as described,4,19 with back-flow across the incompetent aortic valve in HF rabbits blocked by an inflated balloon-tipped catheter. Data were obtained from 14 control and 11 HF rabbits.

**[Na+] Measurements**

Myocytes were plated on laminin-coated coverslips and incubated with 10 μmol/L SBFI-AM and Pluronic F-127 (0.05% wt/vol) for 90 minutes at room temperature. After washout, SBFI-AM was allowed to deesterify for 20 minutes. The normal Tyrode’s solution contained (in mmol/L): 140 NaCl, 4 KCl, 1 MgCl₂, 2 CaCl₂, 10 HEPES, and 10 glucose (pH 7.4). Fluorescence excitation at 340 and 380 nm (F₃40 and F₃80, alternating at 100 Hz) was by a 75-W xenon lamp, and emission was recorded at 535±20 nm. F₃40/F₃80 was calculated after background subtraction and converted to [Na⁺] by calibration at the end of each experiment (using divalent-free solutions with 0, 10, or 20 mmol/L extracellular [Na⁺]; [Na⁺]) in the presence of 10 μmol/L gramicidin and 100 μmol/L strophanthidin.10 Measurements were at 35 to 37°C.

**Na⁺ Efflux Through the Na/K Pump**

Na/K pump flux was determined as the rate of pump-mediated [Na⁺] decline,18 Myocytes were Na⁺-loaded by inhibiting the Na/K pump in a K⁺-free solution containing (in mmol/L): 145 NaCl, 2 EGTA, 10 HEPES, and 10 glucose (pH 7.4). [Na⁺] decline was measured on pump reactivation in solution containing (mmol/L): 140 TEA-Cl, 4 KCl, 2 EGTA, 10 HEPES, and 10 glucose (pH 7.4). Since cell volume did not change with this protocol (n=4), [Na⁺] decline reflects Na⁺ efflux. The rate of [Na⁺] decline (−d[Na⁺]/dt) was plotted versus [Na⁺], and fitted with Jₑ±=[V-max/(1+[Ca²⁺]/[Na⁺])]²⁶⁵. In some experiments, this protocol was repeated with the use of whole-cell voltage clamp or current clamp; 5 to 10 MΩ pipettes were filled with (in mmol/L): 30 KCl, 110 K-aspartate, 5 NaCl, 10 HEPES, 5 MgATP, 0.72 MgCl₂ (1 free [Mg²⁺]), 3 BAPTA, 1.15 CaCl₂ (100 μmol/L free [Ca²⁺]), and 0.2 SBFI, pH 7.2. In some experiments, further isolation of the Na/K pump current (Iₚ) used isosmotic replacement of (mmol/L) 20 internal KCl with TEA-Cl, and 7 external NaCl or TEA-Cl with 5 NiCl₂ and 2 BaCl₂, with Eₑᵢ=-₃₀ mV to inactivate sodium channels.

**Resting Na⁺ Influx**

Resting Na⁺ influx was taken as the initial rate of [Na⁺] rise, after abrupt Na/K pump inhibition with strophanthidin (200 μmol/L), with physiological [Na⁺], and [Ca²⁺]. Some measurements were made with tetrodotoxin, HOE 642 (provided by Dr J. Punter, Aventis Pharma, Frankfurt, Germany), and/or Ni²⁺ present.

**Statistical Analysis**

Data are expressed as mean±SEM, and the Student’s unpaired t test was used.

**Results**

**[Na⁺] at Rest and During Stimulation**

[Na⁺], was measured in control and HF myocytes at rest and during stimulation at 0.5 to 3 Hz. Figure 1, A and B, shows a control cell in which [Na⁺] was measured in normal Tyrode’s solution, first at rest and then stimulated at 3 Hz for 10 minutes, reaching a new steady state in 3 to 5 minutes. When stimulation was stopped, [Na⁺] returned to baseline (Figure 1A, inset shows SBFI calibration).18 Resting [Na⁺], was significantly higher in HF (9.7±0.7 mmol/L, n=20) versus control (6.6±0.5 mmol/L, n=24; Figure 1D and the Table). On stimulation, [Na⁺], rose by similar amounts in control and HF at all frequencies (Figure 1C). Thus, [Na⁺], remained significantly higher in HF during stimulation. Because there was little difference in [Na⁺], between 0.5 to 3 Hz, we pooled all the stimulation data for Figure 1D and the Table. Average [Na⁺], in contracting myocytes was 11.3±0.9 mmol/L (n=15) in HF and 8.0±1.1 mmol/L (n=12) in control.

**Na/K Pump–Mediated Na⁺ Efflux**

Higher [Na⁺], in HF versus control might be explained by a reduced ability of the Na/K pump to extrude Na⁺. To test this, we determined [Na⁺], dependence of Na⁺ efflux through the Na/K pump. Myocytes were Na⁺-loaded by incubating in K⁺-free solution to block the Na/K pump (Figure 2A). Extracellular Na⁺ was then removed, and we measured the time course of [Na⁺], decline with the Na/K pump active (4 mmol/L K⁺). Additionally, [Na⁺], decline was measured with 100 μmol/L strophanthidin to isolate passive sodium efflux. To determine Na/K pump–mediated flux, [Na⁺], decline in the presence and in the absence of strophanthidin was numerically differentiated, and d[Na⁺]/dt was plotted as a function of [Na⁺], (Figure 2B). The maximal pump-independent Na⁺ efflux rate (passive) was higher in HF (5.2±0.2 mmol/L/min, n=5, versus 3.2±0.1 mmol/L, n=6, in control, P<0.001). Na/K pump–mediated Na⁺ efflux (total minus passive) is plotted versus [Na⁺], (Figure 2C). Data were fit with a Hill expression to derive...
$V_{\text{max}}$, $K_m$, and $n_{\text{Hill}}$ (Table). These data show that Na/K pump characteristics are similar in control and HF, so elevated $[\text{Na}^+]_i$ in HF is not due to a lower Na/K pump rate. Moreover, Figure 2C shows that at resting $[\text{Na}^+]_i$ (6.6 and 9.7 mmol/L for control and HF), Na$^+$ efflux mediated by the Na/K pump is 2 times higher in HF versus control (Table). Since Na$^+$ influx and efflux must be equal and opposite at steady state, this suggests that resting Na$^+$ influx is also higher in HF; this could cause the higher $[\text{Na}^+]_i$ in HF myocytes.

Membrane potential ($E_m$) was not controlled in Figure 2. Although Na/K pump activity is nearly voltage-insensitive in Na$^+$-free solution, non--pump-mediated Na$^+$ efflux could vary with $E_m$, complicating our analysis. To test this, we repeated Na$^+$ efflux experiments under voltage clamp and current clamp conditions. Figure 3A shows a typical experiment (n=4) in which a myocyte was first clamped at constant $E_m$ ($-80$ mV), whereas $[\text{Na}^+]_i$ declined was measured in the presence and absence of strophanthidin. We then switched to current clamp and repeated the protocol. The cell depolarized to $-25.7$ mV during Na$^+$ loading in K$^+$-free solution (Figure 3A, lower trace). However, with 4 mmol/L K$^+$ during Na$^+$ efflux measurements, $E_m$ repolarized to $-85.3$ and $-86.5$ mV (with and without strophanthidin, respectively). This is consistent with a very small Na/K pump contribution to resting $E_m$ in ventricular myocytes. Figure 3B shows that the rate of $[\text{Na}^+]_i$ decline is similar under voltage clamp and current clamp, both with and without strophanthidin. C. Simultaneous $I_p$ and Na$^+$ efflux measurements showing that $I_p$ and $d[\text{Na}^+]_i/dt$ have comparable $[\text{Na}^+]_i$ dependence.

**Resting Na$^+$ Influx**

To test the hypothesis that resting Na$^+$ influx is higher in HF, we measured resting Na$^+$ influx as the initial rate of $[\text{Na}^+]_i$ increase during Na$^+$ loading in K$^+$-free solution (Figure 3A, lower trace).
Higher Na\(^+\) influx is very important for NCX function and consequently on Ca\(^{2+}\) transients and contractility. Figure 5 shows simulations of how NCX current (I\(_{NCX}\)) and net Ca\(^{2+}\) entry vary during HF. A, Typical control (Ctl) and HF AP at 1 Hz (control AP is from Pogwizd et al\(^{19}\); HF AP was simulated by extending plateau phase by 42 ms).\(^{11}\) B, [Ca\(^{2+}\)]\(_{in}\) in control and HF calculated as described\(^{24}\) from typical control and HF Ca\(^{2+}\) transients. Actual Ca\(^{2+}\) transient from control was used\(^{19}\); for HF, the peak was reduced by 30%.\(^{4}\) C, I\(_{NCX}\) calculated in HF and control by means of the I\(_{NCX}\) equation described by Weber et al.\(^{24}\) Em from Figure 5A, [Ca\(^{2+}\)]\(_{in}\) from Figure 5B, [Na\(^+\)]\(_{i}\) = 8.0 or 11.3 mmol/L, and Vmax\(_{NCX}\) = 6 (control) and 11 A/F (HF). All other parameters were as used in Weber et al.\(^{24}\) D, Cumulative I\(_{NCX}\) Ca flux based on I\(_{NCX}\) integral and cytosolic volume of 27 pL (Ctl) and 55 pL (HF).

on abrupt Na/K pump inhibition (Figure 4A). As expected, Na\(^+\) influx was twice as high in HF (2.26 \pm 0.31 mmol/L/min, n=9) versus control (1.13 \pm 0.15 mmol/L/min, n=10) (Figure 4B). Next we investigated various Na\(^+\) entry pathways. First, we measured Na\(^+\) influx with Na\(^+\)/K channels blocked (30 \mu mol/L tetrodotoxin, TTX). Figure 4B shows that TTX abolishes the HF versus control difference and that TTX-sensitive Na\(^+\) entry is significantly higher in resting HF versus control cells. This higher TTX-sensitive Na\(^+\) entry accounts for \approx 85% of the difference in the total Na\(^+\) entry. In another series of experiments, we measured Na\(^+\) influx in the presence of TTX (30 \mu mol/L), HOE 642 (2 \mu mol/L, to block the Na/H exchange), and Ni\(^{2+}\) (5 mmol/L, to block NCX). The presence of all these blockers did not completely abolish Na\(^+\) influx, suggesting that other mechanisms may contribute to Na\(^+\) entry (eg, TTX-insensitive background Na\(^+\) leak channel or Na/K/2Cl cotransport). Subtracting the influx measured in the presence of all three blockers from that in the presence of TTX gives the Ni\(^{2+}\)- and HOE 642-sensitive pathways, which are not significantly altered in HF (Figure 4B).

**Discussion**

We studied Na\(^+\) regulation in myocytes from a rabbit model of HF. Using SBFI, we determined [Na\(^+\)]\(_{i}\), the [Na\(^+\)]\(_{i}\) dependence of Na\(^+\) transport by the Na/K pump, and the rate of Na\(^+\) influx. We found that (1) [Na\(^+\)]\(_{i}\), is higher in HF versus control, both at rest and during stimulation, (2) [Na\(^+\)]\(_{i}\), dependence of the Na/K pump is unchanged in HF, (3) resting Na\(^+\) influx and efflux are greater in HF, and (4) increased Na\(^+\) influx in HF is largely TTX-sensitive.

**[Na\(^+\)]\(_{i}\) is higher in HF Myocytes: Physiological Consequences**

[Na\(^+\)]\(_{i}\), is \approx 3 mmol/L higher in resting as well as contracting HF myocytes. Higher [Na\(^+\)]\(_{i}\), has been reported in cardiac hypertrophy,\(^2\)–\(^10\) but the only published [Na\(^+\)]\(_{i}\), measurements in HF\(^{12}\) showed a slight decrease (by 0.8 mmol/L) in rabbits with pacing-induced HF. However, this HF model differs significantly from the model used here because the density of the NCX current was significantly reduced, whereas in our model\(^4\)–\(^19\) and in human HF,\(^3\) NCX expression is increased.

Higher [Na\(^+\)]\(_{i}\), in HF has very important implications for NCX function and consequently on Ca\(^{2+}\) transients and contractility. Figure 5 shows simulations of how NCX current (I\(_{NCX}\)) and net Ca\(^{2+}\) transport by NCX (f\(_{NCX}\)) may be expected to vary during a steady-state AP in HF and control, with the use of values of [Na\(^+\)]\(_{i}\), measured here (8.0 and 11.3 mmol/L in control and HF myocytes, respectively). I\(_{NCX}\) was calculated by means of the equation described by Weber et al.\(^{24}\) and we accounted for enhanced NCX expression, AP prolongation by 42 ms (Figure 5A), and reduced [Ca\(^{2+}\)]\(_{i}\) transients, as previously recorded in HF.
and control rabbit myocytes. Because NCX actually senses the submembrane \([Ca^{2+}]_{i}\), \((\langle Ca^{2+}\rangle_{im})\), which can differ from the bulk \([Ca^{2+}]\), we approximated \([Ca^{2+}]_{im}\) by using the procedure described by Weber et al.\(^{24}\) (Figure 5B). We assumed that submembrane \([Na^{+}]\), \((\langle Na^{+}\rangle_{im})\) is equal to bulk \([Na^{+}]\). However, this may not be the case, because \([Na^{+}]_{im}\) may be elevated transiently as the result of \(Na^{+}\) influx through \(Na^{+}\) channels or NCX, favoring more outward \(I_{\text{NCX}}\).

In control, outward \(I_{\text{NCX}}\) is only expected for a brief period (Figure 5, C and D). The rise in \([Ca^{2+}]_{im}\) quickly favors inward \(I_{\text{NCX}}\). This would also be true in HF if \([Na^{+}]\), were unaltered (Figure 5C, dotted line). However, the measured \([Na^{+}]\), increase in HF shifts \(I_{\text{NCX}}\) in the outward direction. Outward \(I_{\text{NCX}}\) produces calcium entry for \(\approx 150\) ms, reducing the time for NCX-mediated \(Ca^{2+}\) efflux. Indeed, in human HF, it was suggested that \(Ca^{2+}\) influx through outward \(I_{\text{NCX}}\) may occur during the AP.

Three factors contribute to the increase in \(Ca^{2+}\) influx through NCX in HF: higher \([Na^{+}]\), prolonged AP, and smaller \(Ca^{2+}\) transients. Figure 6 shows the individual effect of each of these factors on the total \(Ca^{2+}\) influx through NCX. That is, the \(I_{\text{NCX}}\) integral is less inward as \([Na^{+}]\) rises, twitch \(\Delta [Ca]\) declines, and AP duration increases. For the changes observed in this HF model (reported here and by Pogwizd et al.\(^{4,19}\)) increased \([Na^{+}]\) has the largest impact on NCX function. Indeed, the greater \(Ca^{2+}\) influx and lower \(Ca^{2+}\) efflux would tend to load the cell (and SR) with \(Ca^{2+}\), making more available for contractile activation. Therefore, by favoring \(Ca^{2+}\) influx through NCX, higher \([Na^{+}]\), may minimize contractile dysfunction in HF. Moreover, we speculate that NCX upregulation is compensatory in allowing NCX to still extrude the greater amount of calcium that enters during the AP.

### [Na\(^{+}\)]\_ Dependence of the Na/K Pump Is Unchanged in HF Myocytes

We found that \(V_{\text{max}}\) and \(K_{m}\) for the Na/K pump are similar in control and HF. This is somewhat surprising, considering that several biochemical studies revealed decreased expression and/or isoform shifts of the Na/K pump in failing or hypertrophied hearts.\(^{13-17}\) However, most of these studies were performed in tissue homogenates and might reflect changes in nonmyocytes. Moreover, such measurements cannot differentiate between the internalized versus the sarcosommal Na/K pumps\(^{26}\) nor between functional and inactive pumps. It is therefore possible that whereas the total pool size of immunoreactive subunits decreases, the density of the Na/K pump in the sarcolemma is relatively unchanged. There are several functional Na/K pump studies in HF myocytes, with somewhat contradictory results. Decreased \(V_{\text{max}}\) and unchanged \([Na^{+}]\) affinity have been reported in rats with HF after myocardial infarction.\(^{15}\) On the contrary, unaltered maximal \(I_{\text{p}}\) and lower \([Na^{+}]\) affinity have been found in myocytes from dogs with chronic atrioventricular block and hypertrophy.\(^{8}\) Reduced \(I_{\text{p}}\) has been reported in a hypertrophic rat model with increased SR \(Ca^{2+}\) content.\(^{10}\)

The \(V_{\text{max}}\) values here at 37°C are approximately twice what we measured at 23°C in rabbit ventricular myocytes.\(^{18}\) The \(K_{m}\) found here compares well with values derived from Na/K pump current measurements in cardiac cells in the presence of intraacellular \(K^{+}\) or \(Cs^{+} .\(^{20,27,28}\) The most important result regarding the Na/K pump is that under physiological conditions (ie, appropriate resting \([Na^{+}]\),) the rate of \(Na^{+}\) extrusion by the pump is higher in HF (Table and Figure 2C). Higher resting Na/K pump current (\(\approx 2\)-fold) has also been reported for dogs with chronic atrioventricular block.\(^{8}\)

### Higher [Na\(^{+}\)]\_ in HF Is Due to Enhanced Na\(^{+}\) Influx

Higher \(Na^{+}\) efflux in HF must be balanced by enhanced \(Na^{+}\) influx to maintain steady-state \([Na^{+}]\), balance. Our results confirm that resting \(Na^{+}\) influx in HF is twice as high as in control (Table and Figure 4B). Most of the excess resting \(Na^{+}\) influx in HF myocytes occurs through a TTX-sensitive pathway. This suggests that a larger number of \(Na^{+}\) channels are open in quiescent HF myocytes versus control (perhaps like a window current). Resting HF cells were not more depolarized (not shown), ruling out one simple explanation. Another explanation might be functional alteration or expression of \(Na^{+}\) channels in HF. There are indications that the density of a slow inactivating, persistent, TTX-sensitive \(Na^{+}\) current is increased in

### Summary of Results

<table>
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<tr>
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<th>Control (n)*</th>
<th>HF (n)*</th>
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<tr>
<td>([Na^{+}]_{i}), mmol/L</td>
<td>6.6±0.5 (24, 14)</td>
<td>9.7±0.7(\dagger) (20, 11)</td>
</tr>
<tr>
<td>([Na^{+}]_{i}), during stimulation,† mmol/L</td>
<td>8.0±1.1 (12, 5)</td>
<td>11.3±0.9(\dagger) (15, 6)</td>
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- \(V_{\text{max}}\), mmol Na/L per min
- \(K_{m}\) (Na), mmol/L
- \(n_{Hill}\)
- Calculated pump efflux at resting \([Na^{+}]_{i}\), mmol/L per min

\(* First number is number of cells and the second is the number of rabbits.
† Pooled data for frequencies between 0.5 and 3 Hz.
Significantly different between control and HF myocytes: \(\dagger P<0.05\), \(\ddagger P<0.01\), \(\| P<0.001\).
HF depends especially on the elevated \([Na^+]_{cyt}\) in net Ca\(^{2+}\) (others were as for only the indicated parameter was modified from control value to 50% of control. C, AP duration simulations, as in Figure 5. A, \([Na^+]_{cyt}\) during HF. For each panel, the integrated Ca\(^{2+}\) elevation of diastolic \([Na^+]_{cyt}\) was varied from control value to 50% of control. C, AP duration.

Figure 6. Simulations show that outward NCX is more favored during HF. For each panel, the integrated Ca\(^{2+}\) flux through NCX (\(\lambda_{NCX}\)) during an AP plus diastole (0.5 second) is based on simulations, as in Figure 5. A, \([Na^+]_{cyt}\) was varied from control value of 8.0 mmol/L to 12 mmol/L. B, Ca\(^{2+}\) transient amplitude was varied from control value to 50% of control. C, AP duration was varied from control to 100-ms prolongation. In each case, only the indicated parameter was modified (others were as for control). Dashed vertical lines represent HF values used in Figure 5. Control \(V_{max,NCX}\) and cytosolic volume were used (6 A/F and 27 PL). Rise in \([Na^+]_{cyt}\) in HF produces the largest reduction in net Ca\(^{2+}\) extrusion through NCX (55%).

failing ventricular myocytes, with this current being partially responsible for AP prolongation in HF.

In summary, \([Na^+]_{cyt}\), is higher in HF as the result of an elevation of diastolic Na\(^+\) influx with unaltered Na/K pump characteristics. Along with decreased Ca\(^{2+}\) transients and longer AP duration, the increased \([Na^+]_{cyt}\), contributes to greater Ca\(^{2+}\) influx through NCX during the AP in HF. This would increase cellular and SR calcium content. This increased Ca\(^{2+}\) influx in HF depends especially on the elevated \([Na^+]_{cyt}\), and may be functionally important in limiting the extent of contractile dysfunction in HF.

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**References**


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