Sodium-Calcium Exchange
The Phantom Menace
Joshua I. Goldhaber

Researchers have been aware of the existence of a membrane transporter in cardiac myocytes that exchanged calcium for sodium for more than 30 years. In that period of time, even as the molecular details of the sodium-calcium exchanger (NaCaX) were being worked out, its physiological role had still not been clearly defined. Early reports focused on the role of the exchanger as an important source of Ca\(^{2+}\) influx and as a regulator of contractile force, an important issue given that the most commonly used inotropic agent at the time was digitalis. By the mid-1980s, when it had become clear that Ca\(^{2+}\) entry via L-type Ca\(^{2+}\) channels was the major trigger for contractile Ca\(^{2+}\) release from the sarcoplasmic reticulum (SR), it became widely accepted that the chief role of the exchanger was to remove Ca\(^{2+}\) from the cytosol during diastole. Interest in the exchanger as an important Ca\(^{2+}\) entry mechanism resurfaced early in this decade when LeBlanc and Hume demonstrated sodium-current–dependent Ca\(^{2+}\) influx via the exchanger, capable of triggering contraction; however, this idea has remained controversial. Now, as we approach the new millennium and study excitation-contraction (E-C) coupling at the subcellular level, the importance of the exchanger as a modulator of Ca\(^{2+}\) release and E-C coupling gain is becoming clearer.

The pathophysiological roles of the exchanger have been much less controversial. In the ischemic/reperfused heart, a rise in intracellular sodium frustrates the ability of the exchanger to remove Ca\(^{2+}\). Stimulation of the exchanger by oxygen free radicals may further accelerate the rise in cell Ca\(^{2+}\) under sodium-loaded conditions. The resulting Ca\(^{2+}\) overload is not only detrimental to contractile function, metabolism, and cellular integrity, but it is also thought to be an important cause of spontaneous Ca\(^{2+}\) release from the SR. This in turn triggers the transient inward current (I\(_{\text{T-I}}\)), of which NaCaX is a major component. This inward current underlies delayed afterdepolarizations (DADs), the source of deadly triggered ventricular arrhythmias. Ca\(^{2+}\) overload via NaCaX and subsequent activation of I\(_{\text{T-I}}\) during spontaneous Ca\(^{2+}\) release from the SR is also a well-known complication of overzealous digitalis treatment. This relatively rare complication is characterized by a chaotic focal arrhythmia.

With regard to heart failure, a fairly common finding among several different animal models, as well as in human tissue, is an increase in NaCaX mRNA and protein. In heart failure, an upregulated exchanger has generally been regarded in a positive light, for it has been assumed that the exchanger acts as a compensatory Ca\(^{2+}\) entry mechanism, taking up the slack in an otherwise dysfunctional E-C coupling system. The exchanger is also credited with helping to preserve diastolic function in failing hearts.

In this issue of Circulation Research, Pogwizd et al focus our attention on a negative consequence of upregulated NaCaX in heart failure: arrhythmogenesis. Given the prevalence of sudden death due to arrhythmias in the 4.6 million patients living with heart failure in the United States, any information that helps unravel the pathogenesis of this lethal aspect of congestive heart failure is of supreme importance. The authors have used a multipronged approach in their study. Their elegant model of arrhythmogenic heart failure in the rabbit is created by a combination of volume and pressure overload due to mechanical injury of the aortic valve, followed 2 to 4 weeks later by aortic constriction. The model is relevant to human valvular cardiomyopathy, and its attractiveness as a general model of heart failure is further enhanced by its independence from the genetic abnormalities so common to many other models, such as the spontaneously hypertensive rat. The authors used echocardiography to validate the presence of aortic regurgitation and subsequently to document the extent of left ventricular enlargement and dysfunction. Continuous electrocardiographic monitoring was carried out on all animals to document an impressive burden of ventricular ectopy, which is one of the unique features of this model. Ten percent of the animals died suddenly over the 2-year course of the study, similar to the annual incidence of sudden death in human dilated cardiomyopathy.

Cardiac NaCaX mRNA and protein levels were on average elevated in the heart failure group, and the highest levels of NaCaX mRNA were found in the hearts with the worst left ventricular function. However, half of the hearts had exchanger mRNA levels that were no different from control. Functionally, patch-clamp experiments demonstrated a 2-fold increase in NaCaX current, whereas Ca\(^{2+}\) current (I\(_{\text{Ca}}\)) was unchanged. Increased NaCaX was also confirmed by a functional assay: an increase in the rate of relaxation and rate of decline of the [Ca\(^{2+}\)] transient during continuous application of caffeine to disable SR Ca\(^{2+}\) uptake. A surprising result was that there was no difference in the half time of relaxation after an electrically stimulated twitch, despite the finding that...
NaCaX was increased 2-fold. This is typical of other heart failure models, where SERCA2 levels are generally decreased, accounting for a reduction in SR Ca\(^{2+}\) uptake.\(^{16}\) However, SERCA2 levels were not significantly lower in the rabbit heart failure model in the Pogwizd et al\(^{19}\) study, although two of the animals with the worst left ventricular function apparently did show a marked decrease in SERCA2. Considering that SERCA2 levels were on average unchanged, one can only speculate that the function of the SR Ca\(^{2+}\) pump was reduced by other mechanisms: either by altered expression of a regulatory protein such as phospholamban\(^{21}\) (or its phosphorylation state) or perhaps a change in the metabolic state of the cell.\(^{22}\) SR Ca\(^{2+}\) content appeared to be decreased, but this is presumably a consequence of successful competition for Ca\(^{2+}\) by NaCaX over the SR Ca\(^{2+}\) pump.

An important feature of the Pogwizd et al\(^{19}\) study is that single cells isolated from the failing hearts exhibited spontaneous contractions, suggestive of DADs, when treated with isoproterenol. Unfortunately, confirmation of a “DADogenic” mechanism by membrane-voltage recordings was not included. Nevertheless, the dependence of spontaneous activity due to DADs on isoproterenol makes sense for two reasons. First, at the cellular level, isoproterenol enhances both Ca\(^{2+}\) entry and SR Ca\(^{2+}\) uptake to promote Ca\(^{2+}\) overload. Second, at the clinical level, heart failure is associated with an increase in circulating catecholamines, and chronic treatment with β agonists is associated with an increase in sudden death. The lack of spontaneous activity in the absence of isoproterenol also serves to underscore the potential pitfalls of experiments in isolated cells, which at best can only simulate the complex in vivo environment within which these clinical syndromes occur.

Myriad models of heart failure exist, and the relevance of each to human heart failure is of paramount importance when considering the significance of experimental results. Pogwizd et al\(^{19}\) have already demonstrated in clinical studies that focal arrhythmias predominate in idiopathic dilated cardiomyopathy,\(^{23}\) compared with ischemic cardiomyopathy where reentrant arrhythmias are more common.\(^{24}\) Furthermore, they have demonstrated in 3D mapping studies that the rabbit volume/pressure overload model of heart failure appears to faithfully recapitulate the focal ventricular arrhythmias observed in humans.\(^{25}\) Why other animal models of heart failure have not exhibited such arrhythmias is uncertain, although perhaps we have simply not looked hard enough.

It is tempting to compare the rabbit heart failure model with a transgenic model of NaCaX overexpression in mice. In the transgenics, postpartum females have a higher incidence of heart failure and death compared with their wild-type littermates (Ken Philipson, personal communication, October 1999). However, unlike the rabbit heart failure model, the transgenic mice exhibit stable\(^{26}\) or even increased\(^{27}\) SR Ca\(^{2+}\) content without any evidence for functional impairment of the SR Ca\(^{2+}\) pump.\(^{28}\) This implies that in the background of an isolated genetic program to increase NaCaX, the SR Ca\(^{2+}\) pump can compensate and effectively compete for Ca\(^{2+}\). Nevertheless, these mice do show a predilection for premature death, and the increase in NaCaX is the obvious commonality to the rabbit heart failure model. Although differences in species may confuse the issue, these observations both implicate the exchanger and reaffirm the complexity of the failing heart compared with the transgenic model. And just as one Ca\(^{2+}\) handling mechanism may compensate for another in a model of heart failure, similar compensatory mechanisms must also operate in transgenic animals. The challenge now is to take advantage of the availability of newer methodologies, such as adenovirus vectors, which enable investigators to acutely overexpress proteins such as NaCaX. This may evade the problem of compensation, which should help to sort out the issue of whether exchanger upregulation is a primary or secondary event in heart failure. Furthermore, this method will enable investigators to test important hypotheses regarding the role of the exchanger in arrhythmogenesis as well as modulation of E-C coupling.\(^{7,8}\)

Finally, how can we place these results in a clinical context? At the present time, there are no satisfying therapies for preventing the onset of lethal ventricular arrhythmias in patients with heart failure. The most effective therapies, eg, implantable cardioverter defibrillators, are clumsy and expensive. Although it is unclear whether the dominant mechanism of sudden death in humans is a “triggered” arrhythmia or “reentry,” it is likely that a premature ventricular contraction, initiated by a DAD, serves as the trigger for a reentrant ventricular tachycardia that degenerates to ventricular fibrillation.\(^{29}\) Whether NaCaX is an appropriate therapeutic target for preventing triggered arrhythmias is uncertain, especially given the Cardiac Arrhythmia Suppression Trial (CAST),\(^{30}\) which targeted arrhythmia initiation with disastrous results. However, a specific blocker of NaCaX was not clinically available or tested in that trial. Effective blockers of NaCaX (other than XIP\(^{31}\)) remain elusive, although isothiourea derivatives show some promise.\(^{32}\) Whether these can be of any clinical benefit remains to be seen.

References

10. Tan M, Neely JR. Role of intracellular Na\(^{+}\) in Ca\(^{2+}\) overload and depressed recovery of ventricular function of reperfused ischemic rat


4. Terracciano CM, Souza AI, Philipson KD, MacLeod KT. Na<sup>+</sup>-Ca<sup>2+</sup> exchange and sarcoplasmic reticular Ca<sup>2+</sup> regulation in ventricular myocytes from transgenic mice overexpressing the Na<sup>+</sup>-Ca<sup>2+</sup> exchanger. *J Physiol (Lond)*. 1998;512:651–667.


**Key Words:** Na<sup>+</sup>-Ca<sup>2+</sup> exchange | arrhythmia | heart failure | Ca<sup>2+</sup> | excitation-contraction coupling
Sodium-Calcium Exchange: The Phantom Menace
Joshua I. Goldhaber

Circ Res. 1999;85:982-984
doi: 10.1161/01.RES.85.11.982

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/85/11/982