Increased Na⁺-Ca²⁺ Exchanger in the Failing Heart

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Heart failure (HF) is a significant problem, affecting more than 2 million people in the United States alone. When severe, it is associated with a 50% 2-year mortality rate attributable to either contractile dysfunction or sudden death from ventricular tachycardia and ventricular fibrillation. The underlying molecular mechanisms have not yet been defined, but there is considerable evidence from studies in experimental models of HF and in the failing human heart that alterations in intracellular Ca²⁺ handling could play a role in both the contractile abnormalities and arrhythmogenicity.²,³

Specifically, HF cardiac myocytes exhibit Ca²⁺ transients with decreased amplitude and prolonged Ca²⁺ decline.⁴,⁵ These changes have been associated with altered expression and function of several Ca²⁺ regulatory proteins. There has been considerable interest in alterations of sarcoplasmic reticulum (SR) function, particularly the SR Ca²⁺-ATPase (SERCA) and its inhibition by phospholamban. Reduced SERCA mRNA has been noted in animal models of HF⁶,⁷ and in the failing human heart.⁸,⁹ but alterations in SERCA protein levels and SR Ca²⁺ uptake have been inconsistent and more controversial.¹⁰,¹¹ The same is true for changes in phospholamban.⁹–¹²

More recently, additional attention has been focused on the Na⁺-Ca²⁺ exchanger (NCX). NCX is a transsarcolemmal protein that plays an important role in controlling levels of [Ca²⁺].¹³ NCX can operate in both a forward mode (Ca²⁺ out, Na⁺ in) and a reverse mode (Na⁺ out, Ca²⁺ in), and most evidence to date¹⁴ has suggested that it does so with a stoichiometry of 3:1 (ie, it exchanges 3 Na⁺ ions for every 1 Ca²⁺ ion). As a result, NCX is electrogenic, producing an inward current (I_{NCX}) when Ca²⁺ is extruded from the cell. This current is believed to underlie the development of an arrhythmogenic transient inward current that produces delayed afterdepolarizations (DADs) and triggered activity.¹⁵ NCX activity is regulated by levels of intracellular Ca²⁺ and Na⁺,¹⁶,¹⁷ although the magnitude and physiological significance of this regulation remains to be defined. NCX has been found to be upregulated (on both an mRNA level and a protein level) in the failing human heart¹⁸,¹⁹ and in some experimental models of HF.²⁰ However, there is limited data on NCX function in HF. Litwin and Bridge²¹ demonstrated increased I_{NCX} in the infarcted rabbit heart. We recently showed a parallel 2-fold increase in NCX mRNA, protein, rate of [Ca²⁺], decline, and I_{NCX} (both inward and outward) in an arrhythmogenic rabbit model of heart failure (combined aortic insufficiency and aortic constriction).²⁰

NCX expression and function have been extensively studied in the pacing-induced HF model in dogs and rabbits. Although this model lacks myocardial hypertrophy and the heart failure is reversible with termination of pacing,⁵,²² it exhibits severe left ventricular systolic dysfunction, impaired relaxation, increased LV filling pressures, and alterations in ionic currents similar to those of human heart failure.⁵,²³ Myocardium from dogs with pacing-induced HF exhibits significant downregulation of SERCA (mRNA and protein), and isolated HF myocytes exhibit Ca²⁺ transients with decreased amplitude and prolonged Ca²⁺ declines (consistent with the decreased SERCA expression).²⁴ However, the results of studies of NCX function have been conflicting. O’Rourke et al²⁵ studied dogs with pacing-induced HF and reported a 2-fold increase in NCX protein compared with controls. NCX function (assessed by the rate of Ca²⁺ decline with SERCA inhibited by cyclopiazonic acid) was increased, but not significantly. Rose et al²⁶ studied rabbits with pacing-induced HF and found a 44% increase in NCX protein versus control but no change in I_{NCX} density. In contrast, using a similar model, Yao et al²⁷ found decreased NCX mRNA levels associated with a significant reduction in I_{NCX}. Thus, it remains unclear whether and how NCX function is altered in the pacing-induced HF model.

In this issue of Circulation Research, Hobai and O’Rourke²⁸ report on NCX function in the canine-pacing HF model and expand on their previous work.³ They assessed NCX function by numerous approaches and under various conditions. When [Ca²⁺], was buffered to 200 nmol/L, I_{NCX} (measured as Ni-sensitive current) was similar in both HF and control myocytes. But when they allowed [Ca²⁺]₀ to rise freely (by buffering with only 50 μmol/L indo-1 in the pipette), they found that the decline of normalized caffeine transients (reflecting Ca²⁺ efflux primarily by NCX) was 2.2-fold faster in HF. When NCX function was assessed with SR Ca²⁺ uptake inhibited by thapsigargin (again with minimal Ca²⁺ buffering), depolarizing pulses increased reverse-mode NCX activity (increased [Ca²⁺]₀) and outward I_{NCX} (consistent with the 2-fold increased NCX protein levels).²⁸ Repolarizing pulses increased inward I_{NCX} and rate of [Ca²⁺]₀ decline, but I_{NCX} was not different when normalized to [Ca²⁺]₀. Thus, Ca²⁺ transport and outward I_{NCX} seem to be upregulated, but not inward I_{NCX}. This presents an interesting paradox: how do more NCX molecules enhance Ca²⁺ efflux without increasing inward I_{NCX}? This also raises several questions.

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First, how does one resolve this paradox? There are two possible explanations. One could argue that unknown currents complicate the interpretation. However, Hobai and O’Rourke did a thorough job of excluding additional Ca\(^{2+}\)-activated currents other than I\(_{\text{NCX}}\). Alternatively, as Hobai and O’Rourke propose, altered NCX stoichiometry in HF myocytes could account for these findings. This suggestion is intriguing, especially in light of recent data from Egger and Niggli demonstrating that the stoichiometry and electrogenticity of the exchanger could change under varying ionic conditions, such as decreased extracellular pH. On the other hand, this would not explain why outward I\(_{\text{NCX}}\) was increased in proportion to the rise in [Ca\(^{2+}\)], that it produced. Hobai and O’Rourke also proposed differences in allosteric regulation of NCX\(^{16,28}\) to explain the effect of heavy buffering on I\(_{\text{NCX}}\). This raises the specter of more complex regulatory changes in NCX in pacing-induced HF. Additional studies are needed to substantiate this, and until then, these mechanisms remain only speculative.

Second, can these findings be generalized to other HF models and to the failing human heart? Our recent findings of parallel upregulation of NCX mRNA, protein, Ca\(^{2+}\) extrusion, and inward and outward I\(_{\text{NCX}}\) in our rabbit heart model\(^{20}\) suggest that the findings of Hobai and O’Rourke\(^{26}\) may not be applicable generally to all HF models. The enhanced inward I\(_{\text{NCX}}\) in our HF model could underlie activation of the transient inward current and development of DADs. In this model, DADs seem to be the predominant arrhythmia mechanism\(^{29}\) responsible for the high incidence of spontaneous ventricular tachycardia, which initiates by a nonreentrant mechanism.\(^{20}\) How all these findings extend to human HF\(^{31}\) needs to be determined.

Third, would enhanced NCX function in the absence of enhanced inward I\(_{\text{NCX}}\) still play a significant role in both contractile alterations and arrhythmias in pacing-induced HF? This is likely for contractile dysfunction, because enhanced Ca\(^{2+}\) efflux could decrease SR Ca\(^{2+}\) load.\(^{32}\) As for arrhythmias, the lack of enhanced inward I\(_{\text{NCX}}\) may limit DAD-initiated arrhythmias. But if action potentials are long, induction of early afterdepolarizations may be facilitated. Thus, it may be expected that fewer DADs would occur in pacing-induced HF such that early afterdepolarizations would be the dominant arrhythmogenic event. Nuss et al\(^{33}\) have shown this to be the case.

Fourth, how does one resolve the differences in NCX expression and function among the multiple studies of pacing-induced HF\(^{25-23,34}\) compared with other HF models?\(^{20,21,34}\) It is likely that differences in HF induction protocols (including pacing rate and duration), HF severity, and species may contribute. Along this line, in human HF, Hasenfus et al\(^{15}\) found differential alterations of cardiac NCX and SERCA expression, depending on the extent of diastolic dysfunction. Hearts with preserved diastolic function had higher NCX protein levels (and less depression of SERCA protein), whereas hearts with diastolic dysfunction had less NCX upregulation (but more decreased SERCA protein levels). Thus, alterations in NCX expression and function can be variable, even in the failing human heart, and are likely attributable to factors such as severity of systolic and diastolic dysfunction, etiology, time course, neurohumoral changes, and hemodynamic load. Thus, it is likely that there is a continuum of altered expression of Ca\(^{2+}\) regulatory proteins: one that may evolve over time with the development and progression of heart failure.

Overall, the study by Hobai and O’Rourke\(^{26}\) provides interesting new data on the complex relationship between enhanced NCX expression and function in the failing heart. Additional studies will be needed to determine whether and how the regulation of NCX is altered in HF and whether altered stoichiometry could be a potential target for antiarrhythmic approaches in the failing heart.

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**References**


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