Published in final edited form as:

Heart Rhythm. 2008 October ; 5(10): 1453–1454. doi:10.1016/j.hrthm.2008.08.016.

Antiarrhythmic Benefits of Targeting the Na⁺/Ca²⁺ Exchanger Editorial Comment

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Long QT syndrome (LQTS) is the abnormal prolongation of the QT interval on the ECG. Individuals with LQTS have increased risk to syncope, polymorphic ventricular tachycardia and sudden cardiac death (SCD) (for reviews, see Priori et al¹; Moss and Kass²). LQTS may be acquired (drug-induced) resulting from action potential-prolonging antiarrhythmic drugs³⁻⁵ or may be inherited as a genetic channelopathy in which a number of ion channels function improperly to cause a delay in cardiac repolarization¹. Currently, the prevalence of LQTS is approximately 1:5,000 individuals, and this may be an underestimate⁶.

Presently, ten forms of the inherited LQTS have been identified and are associated with mutations in the genes encoding ion channels or their associated proteins. Thus, mutations have been identified in genes encoding the alpha subunits of voltage-gated K⁺, Na⁺ and Ca²⁺ channels (LQT1-3, LQT7&8), in genes encoding auxiliary subunits of K⁺, and Na⁺ channels (LQT5&6, LQT10), or in the gene encoding the cytoskeletal membrane adaptor protein, ankyrin-B (LQT4) and the scaffolding protein, caveolin-3 (LQT9). At the cellular level, prolongation of repolarization results from reduction of outward repolarizing (potassium) currents (loss-of-function mutations) or from a persistent or late influx of depolarizing (sodium or calcium) ions (gain-of-function mutations) during an action potential. LQTS is associated with SCD, caused by torsade de pointes (TdP) that are triggered by early afterdepolarizations (EADs).

Other than ion channels, ion exchangers can also be electrogenic, generating currents that can modulate an action potential. The Na⁺/Ca²⁺ exchanger (NCX) has a stoichiometry of 3Na⁺ 1Ca²⁺ and generates an inward, depolarizing current in the forward mode as calcium is extruded from the cell⁷⁻⁹. The activity of the NCX therefore is thought to play a role in maintaining the action potential plateau^{7, 9, 10}. Given that the NCX functions in a bidirectional manner, its activity depends on parameters such as the transmembrane concentration gradients of Na⁺ and Ca²⁺, as well as the membrane potential. NCX activity has profound consequences on contractility and on arrhythmogenesis. In the latter case, it has been suggested that the effect is due to the generation of delayed after depolarizations (DADs) and EADs¹⁰⁻¹⁴. Nevertheless, the precise mechanisms underlying the arrhythmogenesis are yet to be elucidated. Thus, experimental investigations that specifically target the NCX are warranted.

The Study of Milberg et al.

In the present issue of *HeartRhythm*, Milberg et al¹⁵ investigated the antiarrhythmic potential of an NCX inhibitor (SEA0400) in an experimental model of LQT2 and LQT3, as well as in

a computer model of the rabbit ventricular myocyte¹⁶. Specifically, Milberg et al tested the hypothesis that the NCX inhibitor will reduce the incidence of EADs and thus TdPs. In the study, sotalol (100 μ M), an inhibitor of the rapidly activating delayed rectifier potassium current (I_{Kr}) and veratridine (0.5 μ M) an inhibitor of sodium channel inactivation, were used to prolong monophasic action potential (MAP) duration, thereby “mimicking”, respectively, the acquired forms of LQT2 and LQT3. The authors reported that MAPs in bradycardic hearts resulted in increased dispersion of repolarization and that sotalol and veratridine induced TdPs in the hearts tested, respectively by 56% and 63%. Importantly, they reported that SEA0400 suppressed EADs in 15 of 16 hearts (sotalol) and in 7 of 13 hearts (veratridine). Also, the investigators demonstrated that the NCX inhibitor shortened MAP durations significantly. Finally, the accelerated repolarization and the reduced incidence of EADs following NCX inhibition were both demonstrable in the computer model of the ventricular myocyte. The authors concluded that NCX inhibition, by suppressing EADs, reversing the prolongation of the action potential and diminishing the dispersion of repolarization, was effective in preventing TdPs in their LQT2 and LQT3 models.

Potential Clinical Implications

The study of Milberg et al¹⁵ clearly presents some interesting findings; however the interpretations should be handled with caution. For example, in the familial forms of the LQTS (compared to the acquired forms) compensatory changes in other ionic currents may contribute to the electrophysiological properties under investigation. Given the role the NCX plays in cardiac myocyte calcium handling and in arrhythmias, it is reasonable to expect that approaches that inhibit exchanger activity could have potential antiarrhythmic benefits, especially in myocardial ischemia/reperfusion and in heart failure^{8, 17}. Specific targeting of the NCX activity (the forward as well as the reverse modes) is key. Currently available inhibitors are hindered by their lack of specificity, given that effects on other ion channels and carrier mechanisms have been documented¹⁷. Whereas the study of Milberg and associates provides some interesting observations on the role of NCX in arrhythmogenesis, a number of key questions remain, some of which could have been answered by more rigorous electrophysiological and electrocardiographic measurements. For example, the experiments could have been complemented with the use of other (more specific) inhibitors of the NCX. Cellular electrophysiology would have very properly complemented the computer simulations and could provide some mechanistic insight. Finally, *sensu stricto*, TdP is electrocardiographic by definitions, and as a key word in this study, a good number of such recordings would have complemented the histograms presented as figures.

References

- (1). Priori SG, Barhanin J, Hauer RN, et al. Genetic and molecular basis of cardiac arrhythmias; impact on clinical management. Study group on molecular basis of arrhythmias of the working group on arrhythmias of the european society of cardiology. Eur Heart J Feb;1999 20(3):174–95. [PubMed: 10082151]
- (2). Moss AJ, Kass RS. Long QT syndrome: from channels to cardiac arrhythmias. J Clin Invest Aug; 2005 115(8):2018–24. [PubMed: 16075042]
- (3). Tomaselli GF, Marban E. Electrophysiological remodeling in hypertrophy and heart failure. Cardiovascular Research 1999;42(2):270–283. [PubMed: 10533566]1999/5
- (4). Antzelevitch C. Cardiac repolarization. The long and short of it. Europace Sep;2005 7(Suppl 2):3–9. [PubMed: 16102498]
- (5). Bednar MM, Harrigan EP, Anziano RJ, et al. The QT interval. Prog Cardiovasc Dis Mar-Apr;2001 43(5 Suppl 1):1–45. [PubMed: 11269621]
- (6). Goldenberg I, Moss AJ. Long QT syndrome. J Am Coll Cardiol Jun 17;2008 51(24):2291–300. [PubMed: 18549912]

- (7). Janvier NC, Harrison SM, Boyett MR. The role of inward Na^{+} – Ca^{2+} exchange current in the ferret ventricular action potential. *J Physiol* Feb 1;1997 498(Pt 3):611–25. [PubMed: 9051574]
- (8). Spencer CI, Sham JS. Effects of $\text{Na}^{+}/\text{Ca}^{2+}$ exchange induced by SR Ca^{2+} release on action potentials and afterdepolarizations in guinea pig ventricular myocytes. *Am J Physiol Heart Circ Physiol* Dec; 2003 285(6):H2552–62. [PubMed: 12933341]
- (9). Bers DM. Calcium fluxes involved in control of cardiac myocyte contraction. *Circ Res* Aug 18;2000 87(4):275–81. [PubMed: 10948060]
- (10). Benardeau A, Hatem SN, Rucker-Martin C, et al. Contribution of $\text{Na}^{+}/\text{Ca}^{2+}$ exchange to action potential of human atrial myocytes. *Am J Physiol* Sep;1996 271(3 Pt 2):H1151–61. [PubMed: 8853354]
- (11). Kass RS, Tsien RW, Weingart R. Ionic basis of transient inward current induced by strophanthidin in cardiac Purkinje fibres. *J Physiol* Aug;1978 281:209–26. [PubMed: 702372]
- (12). Berlin JR, Cannell MB, Lederer WJ. Cellular origins of the transient inward current in cardiac myocytes. Role of fluctuations and waves of elevated intracellular calcium. *Circ Res* Jul;1989 65(1):115–26. [PubMed: 2736729]
- (13). Luo CH, Rudy Y. A dynamic model of the cardiac ventricular action potential. II. Afterdepolarizations, triggered activity, and potentiation. *Circ Res* Jun;1994 74(6):1097–113. [PubMed: 7514510]
- (14). Volders PG, Vos MA, Szabo B, et al. Progress in the understanding of cardiac early afterdepolarizations and torsades de pointes: time to revise current concepts. *Cardiovasc Res* Jun; 2000 46(3):376–92. [PubMed: 10912449]
- (15). Milberg P, Eckardt L, Pott C, et al. Inhibition of the $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger suppresses Torsade de Pointes in an intact heart model of LQT2 and LQT3. *Heart Rhythm*. In Press
- (16). Shannon TR, Wang F, Puglisi J, et al. A mathematical treatment of integrated Ca dynamics within the ventricular myocyte. *Biophys J* Nov;2004 87(5):3351–71. [PubMed: 15347581]
- (17). Akabas MH. $\text{Na}^{+}/\text{Ca}^{2+}$ exchange inhibitors: potential drugs to mitigate the severity of ischemic injury. *Mol Pharmacol* Jul;2004 66(1):8–10. [PubMed: 15213290]