



<b>Title</b>	<b>Sarco/Endoplasmic Reticulum Ca-ATPase (SERCA) pump is a more effective Calcium-handling mediator than the Sodium-Calcium Exchanger (NCX) in hESC-derived ventricular cardiomyocytes</b>
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**29] Sarco/Endoplasmic Reticulum Ca-ATPase (SERCA) pump is a more effective Calcium-handling mediator than the Sodium-Calcium Exchanger (NCX) in hESC-derived ventricular cardiomyocytes.**

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Ventricular (V) cardiomyocytes (CMs) are non-regenerative. Self-renewable pluripotent human embryonic stem cells (hESCs) can differentiate into CMs for cell-based therapies. We have previously shown that hESC-derived CMs display immature Ca-handling properties, with smaller transient amplitudes and slower upstroke and decay kinetics. These functional immaturities can be attributed to their proteomic differences in crucial Ca-handling proteins such as the complete absence of triadin, junctin, CSQ, phospholamban. Indeed, forced CSQ expression partially matures Ca transient properties. During diastole, SERCA and NCX sequester and extrude Ca ions, respectively, after the transient peak to return cytosolic Ca to the resting level. We have reported that NCX, robustly expressed in hESC-VCMs but much less so in the adult counterparts (>10-fold), is a functional determinant of immature Ca homeostasis. Unlike NCX, however, SERCA is comparably expressed in hESC- and adult-VCMs. Interestingly, we found that shRNA-based suppression of NCX in hESC-VCMs (to a level similar to adult NCX, and therefore a higher SERCA/NCX ratio than control) similarly led to reduced amplitudes and slowed kinetics of both caffeine- and electrically-induced Ca transients (by ~2-3-fold). By contrast, SERCA overexpression (to similarly increase SERCA/NCX) produced an opposite chronotropic effect by augmenting the same parameters (by ~2-fold). Based on these results, we conclude that SERCA pump is a more effective Calcium-handling mediator than the Sodium-Calcium Exchanger (NCX) to target in hESC-derived ventricular cardiomyocytes for inducing positive chronotropic effects. Simultaneous NCX suppression and SERCA overexpression is being investigated to investigate the underlying intricate relationships.