Editorial

Effectiveness of Late I_{Na} Versus Peak I_{Na} Block in the Setting of Ventricular Fibrillation

Alexander Burashnikov, PhD; Charles Antzelevitch, PhD

Late sodium channel current (late I_{Na}) has attracted a great deal of attention over the past 2 decades as a target for development of safe and effective antiarrhythmic therapy for disorders associated with QT prolongation and calcium overload, particularly heart failure, ischemia, and long QT syndrome.[1–3] The principal antiarrhythmic mechanisms attributable to late I_{Na} inhibition include (1) suppression of intracellular calcium overload secondary to reduction of intracellular sodium [Na_i], thus diminishing both early and delayed afterdepolarization activity and (2) suppression of reentrant arrhythmias secondary to reduced dispersion of repolarization.[3,4]

See Article by Azam et al

In this issue of *Circulation: Arrhythmia and Electrophysiology*, Azam et al[5] report that ranolazine and GS-458967 (GS-967), agents that inhibit late I_{Na}, abbreviated the duration of ventricular fibrillation (VF) and reduced reinducibility of the arrhythmia in Langendorff-perfused nondiseased rabbit hearts. VF was induced electrically (burst pacing plus 9-V battery) and maintained in the presence of isoproterenol. When VF was first induced, perfusion was stopped for 2 minutes (to simulate global ischemia). Perfusion was then restarted with ranolazine, GS-967, or saline added to the perfusate. VF was terminated at 6 minutes using an external defibrillator, and 4 attempts were subsequently made to electrically reinduce VF. Calcium transients and action potential activity were optically recorded using voltage- and calcium-sanative dyes together with the electromechanical uncoupler, blebbistatin, to suppress contractility and thus prevent motion artifacts.

Ranolazine and GS-967 reduced reinduction of sustained VF to 29% and 46%, respectively, when compared with untreated controls (84.85%). Spontaneous termination of VF after the initial induction of VF was much greater after GS-967 (66.67%, P=0.01) when compared with ranolazine (14.3%) or untreated controls (11.1%).

Ca^{2+} transient duration was reduced in ranolazine-treated but not in GS967-treated hearts compared with controls (P=0.05) as was Ca^{2+} alternans (P=0.03). Action potential duration was not affected by either drug.

The authors conclude that late Na^+ current inhibition during VF reduces the susceptibility to subsequent refibrillation, partially by mitigating dysregulation of intracellular Ca2+, and propose a potential therapeutic use of ranolazine and GS-967 in the setting of cardiac arrest.[5]

There are several mechanistic issues to consider:

1. What is the contribution of late I_{Na} to Na_i loading under the conditions studied?
2. How specific are ranolazine and GS-967 for inhibition of late I_{Na} under the conditions studied?
3. What is the role of late I_{Na} and Na_i in the maintenance of VF?

What Is the Contribution of Late I_{Na} to Na_i Loading Under the Conditions Studied?

In nondiseased cardiac cells, late I_{Na} density is ≤0.1% that of peak I_{Na}.[3,5,6] However, because peak I_{Na} is very brief (1–2 ms), and late I_{Na} spans the length of the action potential (at potentials positive to – 60 mV),[7,8] late I_{Na} contributes considerably more than 0.1% of sodium channel–mediated Na^+ influx. This notwithstanding, under physiologically normal conditions, late I_{Na} is too small to produce a major effect on total Na^+ influx. Peak and late I_{Na} together account for ≈20% to 25%, whereas the Na^+/Ca^{2+} exchanger accounts for ≈60% of total Na influx in stimulated nondiseased mammalian cardiac cells.[8] However, late I_{Na} can be greatly augmented under pathophysiologic conditions, including ischemia,[9] heart failure (secondary to CaMKII-dependent phosphorylation of Nav1.5 channels),[10–12] and with genetic mutations in *SCN5A* responsible for the inherited Long QT Type 3 syndrome.[13] Recent studies have presented evidence pointing to a contribution of neuronal Na channels to late I_{Na} in cardiac myocytes.[14] The contribution of late I_{Na} to Na^+ influx is reported to be reduced at rapid activation rates, because of rate-dependent reduction of late I_{Na} density and abbreviation of action potential duration.[7,15–17]

Acute ischemia augments late I_{Na}, thus contributing to Na_i loading.[3] However, the duration of ischemia in the discussed study[5] is very brief (2 minutes), perhaps too brief to have significant electrophysiological consequences. Even a 10-minute period of acute ischemia followed by reperfusion causes little to no electrophysiological alterations and promotes no or minimal arrhythmogenicity in the rabbit.[18]

The contribution of isoproterenol to Na_i loading is not clear. Isoproterenol produces alterations in ion channel currents, function of pumps and exchangers, and intracellular ion composition. The principal effect is an augmentation of L-type calcium current leading to elevation of Ca_i.[19] In the

From the Lankenau Institute for Medical Research (A.B., C.A.), Lankenau Heart Institute (C.A.), Wynnewood, PA; and Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA (A.B.).

Correspondence to Charles Antzelevitch, PhD, Cardiovascular Research, Lankenau Institute for Medical Research, Lankenau Heart Institute, Wynnewood, PA 19096. E-mail cantzelevitch@gmail.com

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presence of isoproterenol and rapid activation rates (ie, during VF), Ca_i loading likely occurs largely via enhancement of the L-type calcium current. The extent to which Na_i increased and whether Na_i was involved in VF maintenance was not determined in this study.

Thus, in nondiseased rapidly activated ventricles, the contribution of late I_{Na} to Na_i seems to be relatively small and the extent to which an increase in Na_i contributed to the maintenance of VF is unclear.

How Specific Are Ranolazine and GS-967 for Inhibition of Late I_{Na} Under the Conditions Studied

Assuming that late I_{Na} augmentation contributed meaningfully to the induction and maintenance of VF in the discussed investigation, the validity of the conclusions that late Na^+ current inhibition during VF reduced the susceptibility to subsequent refibrillation[5] hinge on whether ranolazine and GS-967 selectively inhibited late I_{Na}. All sodium channel blockers inhibit both peak and late I_{Na}, typically with a higher potency for block of late versus peak I_{Na}.[20] Inhibition of the sodium channel with sodium channel blockers is generally rate dependent, particularly in the case of agents possessing rapid unbinding kinetics, including ranolazine, vernakalant, and lidocaine. Both ranolazine and GS-967 preferentially inhibit late versus peak I_{Na} at slow pacing rates and negative holding potentials (−120 and −140 mV).[21,22] Under these conditions, ranolazine has been shown to be 45 to 78× more potent in blocking late versus peak I_{Na} in isolated ventricular myocytes (the half maximal inhibitory concentration [IC_{50}]=6.5 versus 294 μmol/L and 17 versus 1329 μmol/L).[21,22] At rapid activation rates, however, ranolazine potently inhibits both late and peak I_{Na}. For example, 10 μmol/L ranolazine inhibits ≈50% of peak I_{Na} at rapid pacing rates and −100 mV holding potential in canine ventricular myocytes.[23] The potency of ranolazine to inhibit peak I_{Na} drops from an IC_{50} ≥294 to 10 to 20 μmol/L, when measured at very slow versus rapid activation rates, respectively. The potency of ranolazine to block late I_{Na} is less affected; IC_{50} is 21 μmol/L at a pacing cycle length of 2 s and 6 μmol/L at a cycle length of 0.3 s.[24] There are no published studies investigating the effect of GS-967 to inhibit peak I_{Na} at rapid pacing rates.

Thus, all sodium channel blockers inhibit both peak and late I_{Na}. At slow activation rates, late I_{Na} can be selectively blocked with little to no inhibition of peak I_{Na}. At the rapid activation rates used in the Azam et al[5] study, however, inhibition of peak I_{Na} most likely plays a prominent role.

The difference in efficacy of ranolazine and GS-967 for reinduction of VF after defibrillation may be related to differences between the effects of the 2 drugs to produce rate-dependent inhibition of peak I_{Na} and to differences in ion channel selectivity. In addition to blocking late and peak I_{Na}, ranolazine blocks the rapidly activating delayed rectifier potassium current (I_{Kr}).[24]

What Is the Role of Late I_{Na} and Na_i in the Maintenance of VF?

VF is generally sustained by a reentrant mechanism, at times coupled with Ca_i-mediated triggered activity. VF maintained by reentry is unlikely to be significantly affected by selective late I_{Na} inhibition. VF maintained by Ca_i-mediated triggered activity can be importantly influenced by a reduction in Na_i, which would lead to a reduction in Ca_i. As discussed above, at the rapid rates of VF, inhibition of both peak and late I_{Na} can contribute to a reduction in Na_i.

Because peak I_{Na} contributes more to Na influx, inhibition of peak I_{Na} is expected to cause a greater reduction of Na_i. Peak I_{Na} block also suppresses VF by slowing conduction velocity promoting conduction block.[25] In contrast, selective late I_{Na} inhibition does not affect conduction. Peak I_{Na} inhibition can also suppress ventricular tachycardia/VF by inducing postrepolarization refractoriness, a condition in which the effective refractory period is longer than action potential duration, particularly at rapid activation rates.[26] It is noteworthy that in the discussed investigation, conduction velocity and effective refractory period were not determined.

Conclusions

In nondiseased rabbit ventricles, exposed to a brief period of ischemia and rapid activation rates, the contribution of late I_{Na} to Na_i loading is likely to be small, and a significant inhibition of late I_{Na} by ranolazine and GS-967 is unlikely to occur without considerable inhibition of peak I_{Na}. The latter is expected to be the major contributor to the drugs' anti-VF action. Inhibition of peak I_{Na} can exert its ameliorative effect by (1) reducing Na_i loading, (2) causing conduction block, and (3) prolonging effective refractory period.

Disclosures

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