An increase of late sodium current induces delayed afterdepolarizations and sustained triggered activity in atrial myocytes

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Song Y, Shryock JC, Belardinelli L. An increase of late sodium current induces delayed afterdepolarizations and sustained triggered activity in atrial myocytes. Am J Physiol Heart Circ Physiol 294: H2031–H2039, 2008.—This study determined the role of a slowly inactivating component of sodium current (I_{Na,M}), late I_{Na,M} to induce delayed afterdepolarizations (DADs) and triggered activity. We hypothesized that an increase of late I_{Na,M} may induce not only early afterdepolarizations (EADs), but also intracellular calcium overload and DADs. Guinea pig atrial myocytes were studied using the whole cell patch-clamp technique. Anemone toxin II (ATX-II) (5–10 nmol/l) was used to enhance late I_{Na,M}. Ranolazine (10 μmol/l) and TTX (2 μmol/l) were applied to block ATX-II-induced late I_{Na,M}. ATX-II prolonged action potential duration and induced EADs. In the continuous presence of ATX-II, following the appearance of EADs, both DADs and sustained triggered activity occurred. Triggered activity was abolished and DADs were reduced by either ranolazine or TTX. Consistent with induction of DADs, ATX-II induced the transient inward current (I_{TI}). The amplitude of I_{TI} was significantly reduced by ranolazine. ATX-II induced only EADs, but no DADs, in the presence of the sodium-calcium exchange inhibitor KB-R7943 or the sarcoplasmic reticulum calcium release channel inhibitor ryanodine, or when the calcium chelator EGTA or BAPTA was included in the pipette solution. In conclusion, an increase of late I_{Na,M}, in addition to inducing EADs, can cause cellular calcium overload and induce DADs and sustained triggered activity in atrial myocytes. The data reveal that an increase of late I_{Na,M} is a novel mechanism for initiation of atrial arrhythmic activity.

CARDIAC AFTERDEPOLARIZATIONS are transient membrane depolarizations that may occur either before [early afterdepolarizations (EADs)] or after [delayed afterdepolarizations (DADs)] completion of action potential repolarization. When their amplitude is sufficiently large, and their timing appropriate, EADs and DADs may activate additional depolarizing current and cause rapid, repetitive action potentials, i.e., triggered activity. Experimental evidence strongly suggests that afterdepolarizations and triggered activity are one of the major cardiac arrhythmogenic mechanisms (12, 30, 46, 47).

The mechanisms of inducing DADs and EADs apparently differ. It is generally agreed that DADs are the consequence of intracellular Ca^{2+} overload (21). Excessive Ca^{2+} loading results in oscillatory Ca^{2+} releases from the sarcoplasmic reticulum (SR) during diastole, which, in turn, activate a transient inward current (I_{TI}) (20, 23). I_{TI} is the underlying ionic current responsible for DADs (23). In contrast, induction of EADs requires a prolongation of the action potential duration (APD) with reactivation of Na^{+} or Ca^{2+} channels (9, 19). An increased magnitude of inward Na^{+}-Ca^{2+} exchange current (I_{NCX}) facilitates EAD formation (43), but EADs may occur without significant cellular Ca^{2+} loading (5, 19, 29, 38). Thus inhibition of Ca^{2+} release from the SR by ryanodine or intracellular Ca^{2+} buffering by BAPTA both diminish intracellular Ca^{2+} transients and suppress DADs, but not EADs (29).

The slowly inactivating component of sodium current (I_{Na,M}), late I_{Na,M}, is a depolarizing current that increases the duration of the ventricular action potential (4, 17, 22) and thereby facilitates induction of EADs in ventricular myocytes (11, 36). Late I_{Na} can be enhanced by anemone toxin II (ATX-II) (18) and is sensitive to inhibition by tetrodotoxin (TTX) (10, 27) and the anti-ischemic/antianginal drug ranolazine (1, 36). Due to its persistence throughout the plateau of the action potential, an increase of late I_{Na} results in a substantial Na^{+} loading of cells (26, 28, 32, 35). This, in turn, may lead to cellular Ca^{2+} overload (13) when intracellular Na^{+} is exchanged for extracellular Ca^{2+} via the sodium-calcium exchanger (NCX) (32). In addition, the late I_{Na}-induced prolongation of APD can increase Ca^{2+} entry by facilitation of reactivation of Ca^{2+} channels that have inactivated earlier during the long action potential plateau (34). In support of this hypothesis, blocking I_{Na} has been shown to reduce sodium-dependent calcium loading (16, 35).

Focal ectopic activity arising from triggered activity is considered as one of the major mechanisms underlying atrial tachyarrhythmias (30, 46). The above evidence suggests that Ca^{2+}-dependent triggered activity may be caused by agents and pathological conditions that enhance late I_{Na}. Therefore, in this study, we examined the hypothesis that calcium overload due to an increase of late I_{Na} may activate I_{TI} and induce DADs in atrial myocytes.

MATERIALS AND METHODS

Cell isolation. Experiments were performed on guinea pig isolated atrial myocytes. Hartley guinea pigs were ordered from Charles River Laboratories (Wilmington, MA), and myocytes were isolated as previously described (36). Briefly, hearts of adult guinea pigs of either sex were isolated and perfused via the aorta with warm (35°C) and oxygenated solutions as follows: 1) Tyrode solution containing (in mmol/l) 135 NaCl, 4.6 KCl, 1.8 CaCl2, 1.1 MgSO4, 10 glucose, and 10 HEPES, pH 7.4, for 5 min; 2) Ca^{2+}-free solution containing (in mmol/l) 100 NaCl, 30 KCl, 2 MgSO4, 10 glucose, 10 HEPES, 15 taurine, and 5 pyruvate, pH 7.4, for 5 min; and 3) Ca^{2+}-free solution containing collagenase (120 U/ml) and albumin (2 mg/ml) for 20 min.

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At the end of the perfusion, the atria were minced and gently shaken for 10 min in solution 3 to free single cells for study. Animal use was approved by the University of Florida Institutional Animal Care and Use Committee, and conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85–23, revised 1996).

**Electrophysiological recording.** Transmembrane voltages and currents were measured with an Axopatch-200 amplifier, a Digidata-1322A digitizer, and pCLAMP-9 software (Axon Instruments, Union City, CA). The whole cell patch-clamp technique was used in electrophysiological recording. All experiments were performed at 36°C. Action potentials were elicited by 3-ms depolarizing pulses. The APD was measured from the beginning of depolarization to the time when 30% (APD30) and 90% (APD90) of repolarization were completed. The amplitude of EADs was measured from the take-off potential to the peak of the largest EAD during an action potential. The values obtained from five consecutive action potentials were then averaged. The amplitude of DAD was determined from the resting membrane potential to the peak of the largest (usually the first) DAD following an action potential. To measure $I_{Ti}$, a 200-ms depolarizing pulse from $-80$ to $+20$ mV was applied. $I_{Ti}$ was induced after the membrane potential repolarized to the holding potential of $-80$ mV. The amplitude of $I_{Ti}$ was measured from the holding current at $-80$ mV to the peak inward current. Late $I_{Na}$ was activated by 300-ms voltage-clamp pulses from $-90$ to $-40$ mV. The magnitude of late $I_{Na}$ was calculated as integrated current during the last 50 ms of depolarizing pulse.

During measurements of action potential and $I_{Ti}$, myocytes were incubated in the above-mentioned Tyrode solution. The recording pipettes were filled with a solution containing (in mmol/l) 120 potassium-aspartate, 20 KCl, 1 MgSO₄, 4 Na₂ATP, 0.1 Na₃GTP, and 10 HEPES, pH 7.3. When measuring late $I_{Na}$, K⁺ in both Tyrode and pipette solutions was replaced with Cs⁺ to minimize contamination with potassium currents, and nitrendipine (10 μmol/l) was added to the bath solution to block calcium channels. All electrical stimuli were applied at a frequency of 0.16 Hz. This relatively slow stimulation frequency was chosen to avoid overdrive-induced Ca²⁺ overload.

**Chemicals.** Ranolazine was obtained from CV Therapeutics (Palo Alto, CA), KB-R7943 was from Tocris (Ellisville, MO), and TTX, ATX-II, and ryanodine were from Sigma (St. Louis, MO). Ryanodine was dissolved in dimethyl sulfoxide to form a 10 mmol/l stock solution, which was then diluted to 1 μmol/l in bath solution. All other chemicals were directly dissolved in water. Ranolazine and TTX were
applied at a low concentration to selectively block late $I_{\text{Na}}$, whereas ATX-II was used to enhance the current.

Statistics. Data are expressed as means ± SE. Values of $n$ indicate the number of cells studied. Percentage of inhibition by TTX or adenosine of the effects of ATX-II was calculated using the formula 

$$\left( \frac{\text{ATX-II} - \text{TTX or adenosine}}{\text{ATX-II} - \text{control}} \right) \times 100,$$

where ATX-II, TTX or adenosine, and control indicate measurements obtained in the presence of ATX-II alone, ATX-II plus TTX or adenosine, and in the absence of drugs, respectively. The paired Student’s $t$-test was used for statistical analysis of paired data, and the one-way repeated-measures ANOVA followed by Student-Newman-Keuls test was applied for multiple comparisons. A $P$ value $<0.05$ was considered statistically significant.

RESULTS

Effects of ATX-II, ranolazine, and TTX on action potential and afterdepolarization. ATX-II (10 nmol/l) prolonged the APD and induced EADs (Fig. 1B) in all cells tested ($n=31$).

Following the appearance of EADs, first DADs (Fig. 1C) and then sustained triggered activity (Fig. 1, D and E) were observed when calcium chelators were not included in the pipette solution ($n=19$). When the rapid triggered activity occurred, the amplitude of EADs was greatly reduced (Fig. 1E), probably due to a rate-dependent shortening of the APD.

To determine whether ATX-II-induced sustained triggered activity could be attenuated by inhibition of late $I_{\text{Na}}$, ranolazine (10 μmol/l, $n=6$) or TTX (2 μmol/l, $n=4$) was added to the bath solution when the rapid triggered activity occurred. Figure 2 shows records obtained from an experiment, in which ranolazine and TTX were applied successively in the presence of ATX-II. As shown in the figure, the sustained triggered activity was completely abolished by either ranolazine (Fig. 2D) or TTX (Fig. 2G). In this example, ATX-II-induced DADs were also suppressed by ranolazine (Fig. 2D) or TTX (Fig. 2G). In some experiments DADs could be detected in the presence of...
ranolazine after termination of sustained triggered activity (not shown). However, the amplitude of DADs was significantly smaller in the presence of ATX-II plus ranolazine, compared with that in the presence of ATX-II alone. On average, the amplitude of DADs was reduced by ranolazine by 92% from 8.1 ± 1.0 to 0.9 ± 0.8 mV (n = 6, P < 0.05). In the presence of TTX, there were no detectable DADs. EADs were reproducibly induced and increased after washing out ranolazine (Fig. 2E) or TTX (Fig. 2H) in the presence of ATX-II, indicating that EADs were also inhibited by ranolazine and TTX.

In the absence of ATX-II, ranolazine alone (10 μmol/l) shortened the APD30 from 40 ± 4 to 34 ± 3 ms (P < 0.05), but had no significant effect on the APD90 (ranolazine 95 ± 4 ms vs. control 92 ± 4 ms; P > 0.05). TTX (2 μmol/l) caused a slight but statistically insignificant shortening of APD. The values of APD30 were 38 ± 4 and 35 ± 3 ms, and values of APD90 were 87 ± 7 and 82 ± 8 ms, respectively, in the absence and presence of TTX alone (n = 3, P > 0.05).

Ranolazine and TTX reduce ATX-II-stimulated late INa. Late INa was activated by 300-ms-long depolarizing pulses. A small, sustained, inward current could be observed at the end of pulse,
and this current was identified as late $I_{\text{Na}}$. ATX-II (5 nmol/l) increased late $I_{\text{Na}}$ from $-0.774 \pm 0.172$ to $-3.396 \pm 0.459$ nC (integrated over 50 ms; $n = 12$; $P < 0.05$). Myocytes exposed to ATX-II were then treated with either ranolazine (10 $\mu$mol/l) or TTX (2 $\mu$mol/l) in the continuous presence of ATX-II. In ranolazine experiments ($n = 7$), late $I_{\text{Na}}$ was increased by ATX-II from $-0.996 \pm 0.253$ to $-3.539 \pm 0.666$ nC and was decreased by ranolazine to $2.336 \pm 0.474$ nC ($P < 0.05$), a $48 \pm 5\%$ inhibition of ATX-II-induced late $I_{\text{Na}}$ (Fig. 3). Similarly, in TTX experiments ($n = 6$), late $I_{\text{Na}}$ was enhanced by ATX-II from $-0.685 \pm 0.071$ to $-3.098 \pm 0.409$ nC and was reduced to $-1.586 \pm 0.224$ nC after addition of 2 $\mu$M TTX ($P < 0.05$) (Fig. 3), equivalent to an inhibition of $63 \pm 3\%$ of ATX-II-induced late $I_{\text{Na}}$.

Ranolazine attenuates ATX-II-induced $I_{\text{T}}$. The $I_{\text{T}}$ is generated under conditions of intracellular $Ca^{2+}$ overload and is the underlying ionic mechanism for DADs (20, 23). In the absence of drugs, $I_{\text{T}}$ was not observed in the present study. Consistent with its effect to induce DADs, ATX-II (10 nmol/l) induced $I_{\text{T}}$ in atrial myocytes (Fig. 4B). The amplitude of $I_{\text{T}}$ was reversibly reduced by ranolazine (10 $\mu$mol/l; Fig. 4C) in the presence of 10 nmol/l ATX-II by $87 \pm 6\%$, from $59 \pm 12$ to $12 \pm 7$ pA ($n = 10$, $P < 0.05$).

Interventions known to reduce $Ca^{2+}$ overload or spontaneous $Ca^{2+}$ release abolished ATX-II-induced DADs, but not EADs. ATX-II is reported to cause a Na+-dependent positive inotropic effect (17) that progresses to $Ca^{2+}$ overload (13) and triggered activity (18). Cellular $Ca^{2+}$ overload is known to give rise to spontaneous releases of $Ca^{2+}$ from the SR, $I_{\text{T}}$, and DADs (20, 23). To establish the association of $Ca^{2+}$ overload with the occurrence of $I_{\text{T}}$, DADs, and triggered activity induced by ATX-II, experiments were carried out using the NCX inhibitor KB-R7943, the SR calcium release inhibitor ryanodine, and the calcium chelators EGTA and

![Fig. 5. KB-R7943 (KBR) prevented ATX-II-induced DADs. All action potential records were obtained from a single cell. Each panel consists of 5 consecutive and superimposed records. A: absence of drug. B: in the presence of 10 nmol/l ATX-II for 7 min, both EADs (thin arrow) and DADs (thick arrow) were induced. C: after washout of ATX-II for 4 min, EADs and DADs were not observed. D: in the presence of both 0.1 $\mu$mol/l KBR and 10 nmol/l ATX-II for 7 min, EADs but not DADs were observed. E: after washout of KBR in the continued presence of ATX-II for 3 min, both EADs and DADs were again observed.](http://ajpheart.physiology.org/)

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**LATE $I_{\text{Na}}$ AS A MECHANISM FOR $I_{\text{T}}$ AND DADs**

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BAPTA to reduce or prevent Ca\textsuperscript{2+} overload and spontaneous Ca\textsuperscript{2+} releases.

In the series of experiments using KB-R7943 (n = 5; Fig. 5), ATX-II (10 nmol/l) alone induced both EADs and DADs (amplitude = 13 ± 3 mV). When KB-R7943 (0.1 μmol/l) was present, ATX-II-induced only EADs, but no DADs. The ATX-II-induced EADs appeared not to be affected by KB-R7943.

The amplitudes of EADs in the absence and presence of KB-R7943 were 17 ± 1 and 18 ± 1 mV, respectively (P > 0.05). Similarly, in ryanodine experiments (n = 5; Fig. 6), ATX-II (10 nmol/l)-induced DADs (amplitude = 10 ± 1 mV) were completely abolished by ryanodine (1 μmol/l), but the EADs were not significantly altered. The amplitudes of EADs in the absence and presence of ryanodine were 16 ± 3 and 16 ± 2 mV, respectively (P > 0.05). When EGTA (1 mmol/l, n = 6; Fig. 7A) or BAPTA (1 mmol/l, n = 6; Fig. 7B) was added to the pipette solution to buffer changes in the intracellular calcium concentration, only EADs, but no DADs, were induced by ATX-II (10 nmol/l). The amplitudes of ATX-II-induced EADs in the presence of EGTA and BAPTA were 18 ± 2 and 15 ± 1 mV, respectively, which were comparable to those observed in the presence of ATX-II alone.

**DISCUSSION**

The major findings of the study were as follows: 1) an increase of late \(I_{Na}\) by ATX-II was followed by the sequential appearance of EADs, DADs, and sustained triggered activity; 2) the late \(I_{Na}\) enhancer ATX-II induced \(Ca^{2+}\)-dependent \(I_{TI}\); 3) the effects of ATX-II were reduced or abolished by the late \(I_{Na}\) inhibitors ranolazine and TTX; 4) occurrences of DADs and sustained triggered activity in the presence of ATX-II were abolished by \(Ca^{2+}\) chelating agents (BAPTA and EGTA), the NCX blocker (KB-R7943), and the SR \(Ca^{2+}\) release inhibitor (ryanodine), but the induction by ATX-II of EADs was not prevented by these interventions. Although ATX-II is well known to prolong the duration of the ventricular action potential and induce EADs and triggered activity (17, 18, 36), this study is the first to show that \(I_{TI}\) is induced by ATX-II. These data indicate that an increase of late \(I_{Na}\) directly prolongs duration of the action potential and facilitates EADs, and indirectly causes cellular \(Ca^{2+}\) overloading that leads to \(I_{TI}\) and DADs. Because EADs are associated with bradycardia, whereas cellular \(Ca^{2+}\) loading and DADs are facilitated by tachycardia (6), an increase of late \(I_{Na}\) may contribute to arrhythmogenesis, facilitated by either brady- or tachycardias.
In guinea pig ventricular myocytes, an increase of late $I_{Na}$ by ATX-II rarely leads to DADs, unless inward rectifier K$^+$ current ($I_{K1}$) is also reduced by barium (Y. Song, online supplement) (The online version of this article contains supplemental data.) The different responses of atrial and ventricular myocytes to ATX-II are likely to reflect differences in channel function and/or mechanisms of ion homeostasis in the two tissues. In the atrium, the magnitude of $I_{K1}$ is less than in the ventricle (15, 45). In addition, the density of Na$^+$ channels is greater (24) and the activity of Na$^+$-K$^+$-ATPase is lower (44) in atrial than in ventricular myocardium, and a strong NCX activity exists in the atrium (3, 25). Each of these factors may predispose the atrial myocyte to the development of Ca$^{2+}$ overload-induced $I_{TI}$ and DADs. However, late $I_{Na}$-induced $I_{TI}$ and DADs have also been observed in mouse ventricular myocytes expressing the ΔKPQ mutant Na$^+$ channel (14). Regardless, the effect of augmented late $I_{Na}$ to cause DAD-related sustained triggered activity appears to be tissue (i.e., atria vs. ventricle), species, and condition dependent (e.g., $I_{K1}$ may be reduced in heart failure and myocardial infarction, but enhanced in atrial fibrillation) (31).

ATX-II-induced EADs were not suppressed by the SR Ca$^{2+}$ release inhibitors ryanodine and thapsigargin (5, 37) (Fig. 6), the Ca$^{2+}$ chelators EGTA and BAPTA (Fig. 7), or the NCX inhibitor KB-R7943 (Fig. 5). Because an increase of intracellular Na$^+$ concentration should increase outward $I_{NCX}$ at plateau potentials, ATX-II-induced EADs are unlikely to depend on inward $I_{NCX}$ following Ca$^{2+}$ release from the SR. Rather, they are inhibited by TTX and ranolazine (5, 36, 37) and thus depend on Na$^+$ influx during the action potential plateau.

The development of DADs and sustained triggered activity occurred after the appearance of EADs (Fig. 1), consistent with a gradual accumulation of intracellular Ca$^{2+}$, secondary to an increase of late $I_{Na}$. In contrast to EADs, DADs were abolished by KB-R7943 (Fig. 5), ryanodine (Fig. 6), or intracellular application of EGTA or BAPTA (Fig. 7). $I_{TI}$, DADs, and sustained triggered activity were also abolished by the late $I_{Na}$ inhibitors ranolazine and TTX (Figs. 2–4). This finding is similar to the observation that $I_{TI}$ of myocytes expressing the LQT3 mutant Na$^+$ channel ΔKPQ was EGTA, TTX, and flecainide sensitive (14). The results of both studies indicate that an increase of late $I_{Na}$ can lead to $I_{TI}$, DADs, and sustained triggered activity via a mechanism that likely involves cellular Ca$^{2+}$ overload. This interpretation is supported by previous studies showing that an increased intracellular Na$^+$ concentration is followed by signs of Ca$^{2+}$ overload (16, 17, 35, 40, 42, 48). The effect of 0.1 μmol/l KB-R7943 to inhibit DADs in the presence of ATX-II was consistent with the hypothesis that ATX-II-induced Ca$^{2+}$ overload is due to an increased Ca$^{2+}$ entry via the NCX in response to a rise of intracellular Na$^+$, although a direct inhibition by KB-R7943 of DADs cannot be excluded at present.

Neither TTX nor ranolazine, at the concentrations used, is known to significantly reduce peak L-type calcium channel current and $I_{NCX}$ (1). Whereas 2 μmol/l TTX may reduce peak $I_{Na}$, ranolazine inhibits peak $I_{Na}$ only at concentrations severalfold higher than that used in this study (40). On the other hand, both ranolazine and TTX significantly inhibit late $I_{Na}$ at study concentrations (1, 40). Furthermore, DADs induced by either forskolin or ouabain are not reduced by ranolazine (Y. Song, unpublished data). Hence, the findings indicate that both ranolazine and TTX suppress $I_{TI}$ indirectly by reduction of late $I_{Na}$ and, therefore, of late $I_{Na}$-induced Na$^+$ and Ca$^{2+}$ overload.

Implications. The magnitude of late $I_{Na}$ is known to be increased by a wide variety of both inherited and acquired Na$^+$ channelopathies (2, 4, 40, 41). Increases of late $I_{Na}$ are commonly associated with bradyarrhythmia-triggered and pause-induced arrhythmic activity (8). In contrast, Ca$^{2+}$ overload, $I_{TI}$, and DADs are associated with an increase of pacing (heart) rate. The finding that prolonged action potentials, EADs, DADs, and $I_{TI}$ are induced by ATX-II, therefore, potentially implicates altered Na$^+$ channel activity with increased late $I_{Na}$ in the genesis of arrhythmias associated with both brady- and tachycardias. This hypothesis is consistent with the results of a recent clinical trial that the late $I_{Na}$ inhibitor ranolazine significantly reduced incidence of cardiac arrhythmias in patients who had undergone PCI.
with acute coronary syndrome (33). The action of ranolazine to effectively inhibit late $I_{Na}$ and triggered activity of atrial myocytes is also in agreement with a recent report that ranolazine is an atrium-selective Na$^{+}$-channel blocker and suppresses atrial fibrillation in the dog (7).

Limitations. An obvious limitation of the present study is that measurements of intracellular concentrations of Na$^{+}$ and Ca$^{2+}$ and $I_{SCEX}$ were not done, and therefore assumptions of actions of drugs on these parameters need to be tempered by caution. Previous studies using fluorescent Na$^{+}$ and Ca$^{2+}$ indicators showed that ATX-II increased intracellular concentrations of Na$^{+}$ in guinea pig and rat ventricular myocytes (17) and of Ca$^{2+}$ in rat hearts (13). The ATX-II-induced increase of intracellular Ca$^{2+}$ in rat hearts could be prevented by low concentrations (4 and 9 μmol/l) of ranolazine (13). In addition, hydrogen peroxide-induced intracellular Na$^{+}$ and Ca$^{2+}$ overload, which was associated with an enhanced late $I_{Na}$, was attenuated by 10 μmol/l ranolazine (35). The arrhythmogenic effects of enhancing late $I_{Na}$ by other mechanisms should also be investigated. Nonetheless, the principle that an increase of late $I_{Na}$ can induce Ca$^{2+}$ overload and arrhythmias has been validated by reports of the effects of “gain of function” Na$^{+}$ channel mutations to cause cardiac electrical and mechanical dysfunction (4, 14, 39).

In conclusion, the results of this study suggest that enhanced late $I_{Na}$ is a potential mechanism to cause both EADs and Ca$^{2+}$ overloading that results in $I_{IIR}$, DADs, and triggered activity. Inhibitors of late $I_{Na}$ may, therefore, be of therapeutic benefit to reduce the contributions of EADs, $I_{IIR}$, and DADs to arrhythmogenesis.

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DISCLOSURES

J. Shryock and L. Belardelli are employees of CV Therapeutics, Inc.

REFERENCES


