Combined Na^+/Ca^{2+} Exchanger and L-Type Calcium Channel Block as a Potential Strategy to Suppress Arrhythmias and Maintain Ventricular Function

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Background—L-type calcium channel (LTCC) and Na^+/Ca^{2+} exchanger (NCX) have been implicated in repolarization-dependent arrhythmias, but also modulate calcium and contractility. Although LTCC inhibition is negative inotropic, NCX inhibition has the opposite effect. Combined block may, therefore, offer an advantage for hemodynamics and antiarrhythmic efficiency, particularly in diseased hearts. In a model of proarrhythmia, the dog with chronic atrioventricular block, we investigated whether combined inhibition of NCX and LTCC with SEA-0400 is effective against dofetilide-induced torsade de pointes arrhythmias (TdP), while maintaining calcium homeostasis and hemodynamics.

Methods and Results—Left ventricular pressure (LVP) and ECG were monitored during infusion of SEA-0400 and verapamil in anesthetized dogs. Different doses were tested against dofetilide-induced TdP in chronic atrioventricular block dogs. In ventricular myocytes, effects of SEA-0400 were tested on action potentials, calcium transients, and early afterdepolarizations. In cardiomyocytes, SEA-0400 (1 μmol/L) blocked 66±3% of outward NCX, 50±2% of inward NCX, and 33±9% of LTCC current. SEA-0400 had no effect on systolic calcium, but slowed relaxation, despite action potential shortening, and increased diastolic calcium. SEA-0400 stabilized dofetilide-induced lability of repolarization and suppressed early afterdepolarizations. In vivo, SEA-0400 (0.4 and 0.8 mg/kg) had no effect on left ventricular pressure and suppressed dofetilide-induced TdPs dose dependently. Verapamil (0.3 mg/kg) also inhibited TdP, but caused a 15±8% drop of left ventricular pressure. A lower dose of verapamil without effects on left ventricular pressure (0.06 mg/kg) was not antiarrhythmic.

Conclusions—In chronic atrioventricular block dogs, SEA-0400 treatment is effective against TdP. Unlike specific inhibition of LTCC, combined NCX and LTCC inhibition has no negative effects on cardiac hemodynamics. (***Circ Arrhythm Electrophysiol*. 2013;6:371-379.**)

Key Words: antiarrhythmic drug ■ calcium channel ■ heart failure ■ long QT syndrome ■ Na^+/Ca^{2+} exchange ■ Torsade de Pointes

The 2006 guidelines for treatment of life-threatening ventricular arrhythmias advocate device therapy for high-risk patients over drug therapy as primary strategy. Unsuccessful antiarrhythmic drug trials, together with positive implantable cardioverter-defibrillator trials, are at the basis of this approach. Despite successful device therapy, an unmet need for efficient drug therapy exists, for cost reasons as well as shock reduction and improved quality of life. Novel targets offer opportunities to revisit drug therapy.

Clinical Perspective on p 379

Remodeling in failure or compensated hypertrophy is often accompanied by action potential (AP) prolongation[1] and susceptibility for repolarization-dependent arrhythmias. Calcium

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channel antagonists, like the L-type calcium channel (LTCC) blocker verapamil, and magnesium sulfate[2] can effectively treat torsade de pointes arrhythmias (TdP) in experimental and clinical settings,[2–4] but are negative inotropic[5,6] and, therefore, contraindicated in heart failure patients.

In this study, we explore whether combined LTCC and Na^+/Ca^{2+} exchanger (NCX) block by SEA-0400 is a potential antiarrhythmic strategy against early afterdepolarizations (EADs) and TdPs, which overcomes the negative inotropic effects of selective LTCC block by limiting Ca^{2+} efflux via NCX. Also, the NCX current has been implicated in EAD formation,[7,8] and thus inhibition of NCX may add to the antiarrhythmic effect. Importantly, in the normal heart, SEA-0400 has no negative effects on $[Ca^{2+}]_i$,[9,10] or even positive effects.[9–11] The net effect of SEA-0400 in disease could be different because of disturbed Ca^{2+} and Na^+ balances.[12]

The antiarrhythmic potential of SEA-0400 is not completely established. In long QT syndrome models, data are contradictory, with positive[7,13,14] and negative results.[15,16] Recently, SEA-0400 was reported to be antiarrhythmic in failing rabbit hearts.[17]

The present study is the first to explore the combination of antiarrhythmic efficacy with the presumed neutral hemodynamic effects of SEA-0400, in a model with high TdP susceptibility, the dog with chronic atrioventricular block (CAVB) and ventricular hypertrophy.[18] Common calcium channel antagonists, despite antiarrhythmic potential, have limited usefulness because of negative inotropic effects. SEA-0400 might be able to maintain hemodynamics and thus open calcium channel block to wider clinical application. Its effects are compared with the classical calcium channel antagonist verapamil, which is very effective in abolishing TdP.[3]

Materials and Methods

In Vivo Experiments

In 15 dogs 37 interventions were performed: 28 interventions for hemodynamics or arrhythmia testing, 9 interventions for atrioventricular block creation without hemodynamic or arrhythmia study.

In a first series of tests (n=16), hemodynamic effects were determined by measuring left ventricular pressure (LVP) during infusion of verapamil or SEA-0400.

In the second series of tests (n=12), arrhythmias were induced using dofetilide, after which verapamil or SEA-0400 was infused as an antiarrhythmic.

For additional details, see online-only Data Supplement.

Cellular Experiments

Experiments were performed at 37°C in myocytes, enzymatically isolated from the LV midmyocardial layer of CAVB hearts.[19]

Action potentials (APs) and membrane currents were recorded in the whole-cell patch clamp mode, with simultaneous recording of Ca^{2+} signals in epifluorescence mode.[20] See online-only Data Supplement for protocols and solutions.

SEA-0400 Plasma Concentrations

Blood samples were collected through a venous catheter every 5 minutes during experiment. Heparin-treated samples were centrifuged at 1300 rcf and stored at −80°C for further analysis. Concentrations of SEA-0400 were determined by high-performance liquid chromatography.

Statistics

For cellular data, paired *t* test or 1-way ANOVA for repeated measurements (Bonferroni post test) was performed as appropriate. For the in vivo data, 1-way repeated measures ANOVA was combined with a post hoc Holm–Sidak analysis. In vivo data are presented as mean±SD, N values are number of dogs. For cellular data mean±SE are shown, n values are numbers of cells.

Results

Quantification of NCX and LTCC Block by SEA-0400

We quantified the effect of 1 μmol/L SEA-0400 on NCX-mediated currents (I_{NCX}) and inward Ca^{2+} current mediated through LTCC (I_{CaL}) in CAVB myocytes.

I_{NCX} was measured as the Ni^{2+} sensitive current during voltage ramps, at constant $[Na^+]_i$ (10 mmol/L) and $[Ca^{2+}]_i$ (≈100 nmol/L free Ca^{2+}; Figure 1A). SEA-0400 inhibited 66±3% of outward and 50±2% of inward I_{NCX} (n=5; Figure 1B).

I_{CaL} was measured during a depolarizing step to +10 mV (low sarcoplasmic reticulum [SR] Ca^{2+} load, 0.1 Hz repletion rate; Figure 1C). I_{CaL} block by SEA-0400 was 33±9% (n=6; Figure 1D), comparable with values reported in a previous study in which we characterized SEA-0400 effects over a wider voltage range.[12] Note the reduced inward tail current on repolarization (Figure 1E-a), despite higher $[Ca^{2+}]_i$ levels (Figure 1E-b, c), which reflects forward NCX block (n=4; Figure 1E-d). Despite partial LTCC block, peak and amplitude of the Ca^{2+} transient were increased.

SEA-0400 Effects on AP and $[Ca^{2+}]_i$

The effect of SEA-0400 on $[Ca^{2+}]_i$ and APs is illustrated in Figure 2A. Red traces were recorded when wash-in of SEA-0400 had reached steady state. SEA-0400 had no effects on peak $[Ca^{2+}]_i$, but increased diastolic $[Ca^{2+}]_i$, slowed relaxation, and shortened action potential duration (APD) (Figure 2). We also recorded Ca^{2+} transients and APs during wash-out (blue traces). We have previously observed that LTCC block by SEA-0400 was rapidly reversible on wash-out, whereas NCX block was not.[12] The removal of LTCC inhibition had pronounced effects on the Ca^{2+} transients during wash-out. There was a 2-fold increase of peak $[Ca^{2+}]_i$, further impairment of relaxation, and a larger increase of diastolic $[Ca^{2+}]_i$. APs relengthened (n=5; Figure 2B).

These data illustrate that partial NCX block causes a net gain of Ca^{2+}, which is counterbalanced by reduced I_{CaL} during combined block. The changes in AP may contribute to these changes in Ca^{2+} balance.

Effects of SEA-0400 on EADs and APD

Figure 3A shows a typical experiment testing effects of SEA-0400 against dofetilide-induced EADs in a CAVB cell, and Figure 3B shows beat-to-beat changes in APD and short-term variability (STV, red line) of repolarization, a marker of proarrhythmia. Typically, dofetilide prolonged AP and increased STV. SEA-0400 was applied after the first EAD appeared. In all cells (n=11), SEA-0400 suppressed EADs and restored STV (Figure 3C). In Figure 3D, we plotted individual data of STV in function of APD. This revealed a positive relation between STV and AP prolongation in the presence of dofetilide; SEA-0400 caused a downward shift of this curve. In a subset of cells (n=5), we monitored changes in $[Ca^{2+}]_i$ during wash-in of dofetilide and SEA-0400 (Figure 3E). Dofetilide alone increased peak and amplitude

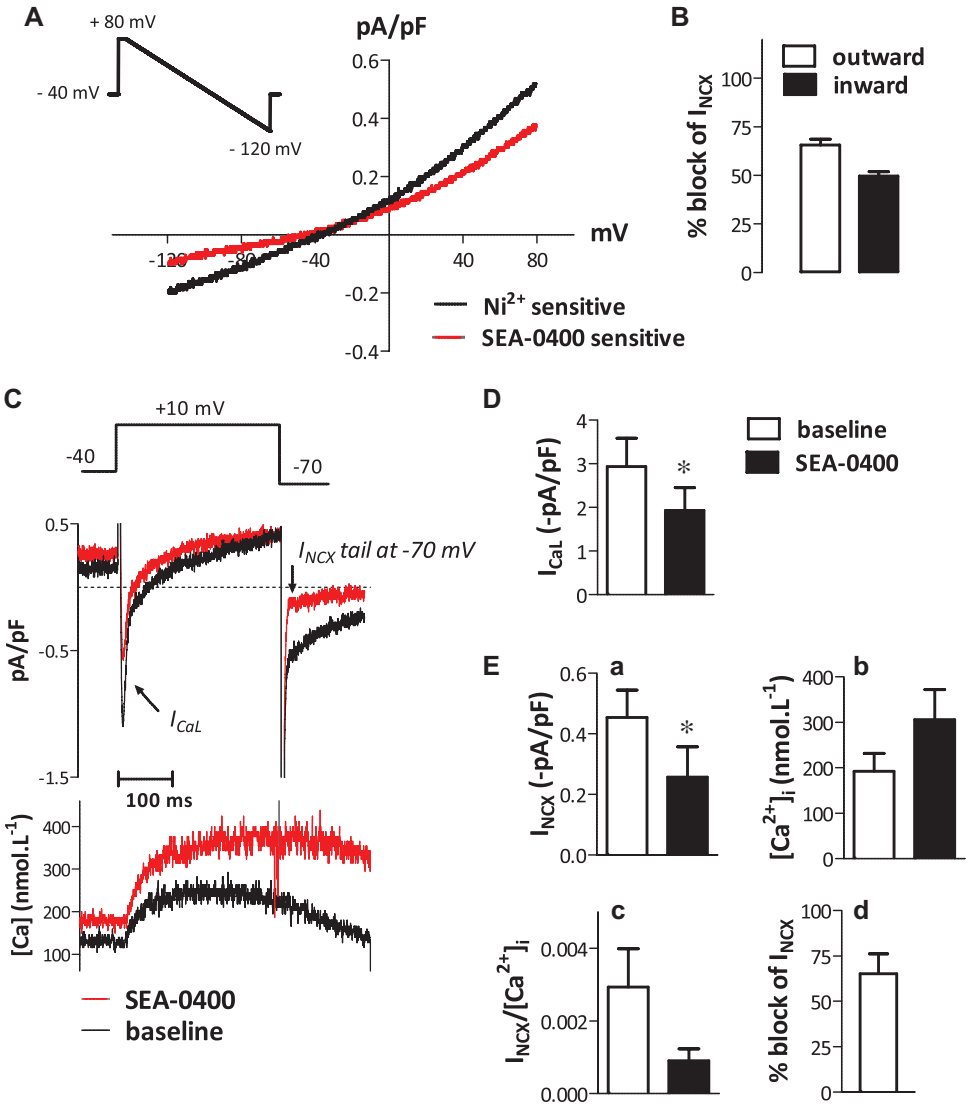

Figure 1. Block of Na^+/Ca^{2+} exchanger (NCX) and I_{CaL} by SEA-0400. **A**, NCX currents sensitive to 5 mmol/L Ni^{2+} (total I_{NCX}, black) and 1 µmol/L SEA-0400 (red) during repolarizing ramps (step from –40 to +80 mV, descending ramp to –120 mV in 2 s; averaged current traces of 5 cells). **B**, Fraction of total I_{NCX} blocked by 1 µmol/L SEA-0400. Outward and inward I_{NCX} were calculated at 60 mV on either side of the reversal potential. **C**, Example of I_{CaL} and Ca^{2+} transients recorded during a depolarizing step to +10 mV before and after 1 µmol/L SEA-0400. I_{Na} was inactivated by a prepulse to –40 mV, and currents were recorded in K^+ and EGTA-free solutions. **D**, I_{CaL} amplitude under baseline and with SEA-0400 (n=6). **E**, Pooled data of NCX tail current density (**a**) and $[Ca^{2+}]_i$ (**b**) on repolarization to –70 mV; (**c**) I_{NCX} normalized to $[Ca]^{2+}$; (**d**) percentage of NCX tail current block at –70 mV (n=4, *P<0.05, paired t test).

of the Ca^{2+} transient. SEA-0400 caused a further increase of diastolic, but not peak $[Ca^{2+}]_i$; the amplitude was comparable with baseline.

SEA-0400 Preserves LVP, While Verapamil Is Negative Inotropic

Before antiarrhythmic testing, we examined baseline effects of SEA-0400 in anesthetized sinus rhythm and CAVB dogs. CAVB dogs have lower heart rates, prolonged QT, and higher LVP. SEA-0400 was administered in cumulative doses >5-minute infusion period, to a final dose of 0.4 or 0.8 mg/kg. This resulted in peak plasma concentrations of 5±1 and 11±2 µmol/L at 5 minutes after the start of infusion, and 1.5±0.3 and 4.2±0.5 µmol/L at 10 minutes (n=3–7). Neither SEA-0400 dose had an effect on heart rate, QT time, STV-QT nor diastolic and maximal LVP (Table).

In Figure 4, the relative change of LVP during infusion of SEA-0400 was compared with verapamil. At a cumulative dose of 0.3 mg/kg, verapamil caused a 15% drop in systolic LVP, with no effects on HR, QT, or baseline STV (Table). On the basis of this dose–pressure response (Figure 4), 2 dosages of verapamil were chosen for antiarrhythmic testing: a hemodynamically neutral (0.06 mg/kg) and a negative inotropic dose (0.3 mg/kg). Absolute changes in LVP can be found in the Table for both SR and CAVB dogs; CAVB dogs are known to have a higher baseline LVP.

SEA-0400 Suppresses TdP, While Preserving LVP

Dofetilide induced TdP in 6 of 9 dogs (67%; Figure 5A). TdPs were suppressed by verapamil and SEA-0400 (Figure 5B and 5C). Dofetilide caused QT prolongation and increased STV-QT. Subsequent administration of a low dose of

Table. Electrophysiological and Left Ventricular Pressure Changes After SEA-0400 and Verapamil Infusion

	Sinus Rhythm		Chronic AVB		Chronic AVB	
SEA-0400						
Dose	0 mg	0.4 mg	0 mg	0.4 mg	0 mg	0.8 mg
HR	95±25	92±27	43±6	42±6	28±15	36±11
QT	264±28	267±31	424±105	411±85	406±48	434±35
QT-STV	1±1	1±1	11±5	11±5	8±7	6±6
LVP_{sys}	96±21	96±20	90±13	90±14	82±28	85±18
LVP_{diast}	3±1	3±1	7±8	5±8	13±12	13±12
N	3	3	3	3	4	4
Verapamil						
Dose	0 mg	0.3 mg	0 mg	0.3 mg		
HR	101±9	100±15	42±7	43±5		
QT	302±15	304±18	551±59	558±41		
QT-STV	0.5±0.2	0.5±0.2	11±6	9±5		
LVP_{sys}	70±7	54±4*	97±4	89±2*		
LVP_{diast}	4±3	4±2	9±1	7±2		
N	3	3	3	3		

Parameters were determined after 5-min infusion of SEA-0400 to a final dose of 0.4 mg/kg (sinus rhythm and CAVB dogs) and 0.8 mg/kg (CAVB dogs only), and verapamil (0.3 mg/kg). AVB indicates atrioventricular block; HR, heart rate (beats per minute); LVP_{diast} and LVP_{sys}, diastolic and systolic left ventricular pressure (mm Hg); N, no. of animals; and QT-STV, QT and short-term variability of QT interval (ms). *$P<0.05$ vs baseline (0 mg/kg).

verapamil did not suppress TdPs (11±6 episodes per 5 minutes versus 12±7), whereas the higher dose was completely effective (0 TdPs). This was associated with reduced STV-QT, without shortening QT time (Figure 5A, lower graph). These parameters could not be determined at the low dose of verapamil because arrhythmias interfered with measurements.

SEA-0400 was antiarrhythmic (Figure 5C) with a dose-dependent effect: 0.4 mg/kg partially suppressed (from 7±4 to 3±4 episodes per 5 minutes), and 0.8 mg/kg completely abolished TdPs. The partial antiarrhythmic effect of 0.4 mg/kg SEA-0400 did not prevent occurrence of extra beats, which excluded reliable STV-QT measurements. At 0.8 mg/kg, SEA-0400 tended to reduce STV-QT and had no effect on dofetilide-induced QT prolongation.

Discussion

Our data show that SEA-0400, a NCX blocker with additional LTCC inhibition, is an effective antiarrhythmic against dofetilide-induced EADs and TdPs. It has an advantage over primary block of LTCC with verapamil, another efficient antiarrhythmic, because of the lack of negative inotropy at equal antiarrhythmia efficacy.

Clinical Need for New Drugs in Heart Failure

With aging of the population and improved postinfarction survival, the number of patients treated for arrhythmias is increasing. Especially in the group with heart failure, there is a growth in number of implantable cardioverter-defibrillator implants. In recent years, new antiarrhythmic drugs have been tested to relieve the burden of implantable cardioverter-defibrillator shock: adjunct therapy. Until now, these trials with azimilide[21] and celivarone[22] have been insufficiently successful for a broad clinical implication. In part this can be attributed to the limitations in dosage of the applied drugs because of adverse effects, based either on proarrhythmia or on negative inotropism. Therefore, there is an unmet need to develop new drugs that are devoid of adverse actions and can be applied in these patient populations.

CAVB Dog Model

Induction of chronic, complete atrioventricular block results in ventricular remodeling and encompasses molecular and cellular changes at the electric, contractile (enhanced Ca^{2+} transient), and structural level.[18] In the CAVB dog, the beneficial adaptations that lead to compensated biventricular hypertrophy are counteracted by TdP susceptibility in vivo (eg, incidence with dofetilide, 75%) and EADs in vitro.[3,19] The model is, therefore, suited to address the question how an antiarrhythmic action of SEA-0400 can be combined with maintained LV contractile performance.

Comparison With Other Antiarrhythmics in the CAVB Dog

Over the years, numerous antiarrhythmics have been tested in this model. Considering possible confounding influences as drug dosage and duration of administration, 3 categories of action can be identified:

1. Ca^{2+} antagonists, verapamil and flunarizine, are very effective agents that prevent and suppress TdP and EADs.
2. Ranolazine and lidocaine suppress about 60% of the drug-induced TdP. Late sodium current inhibition is effective, although the current density was reduced in CAVB dogs as compared with SR.[19] We have also found that subsarcolemmal $[Na^+]$ is increased in this model related to altered Na/K pump function.[23] This is also of importance in identifying the effects of SEA-0400, as higher sodium concentrations promote NCX reverse

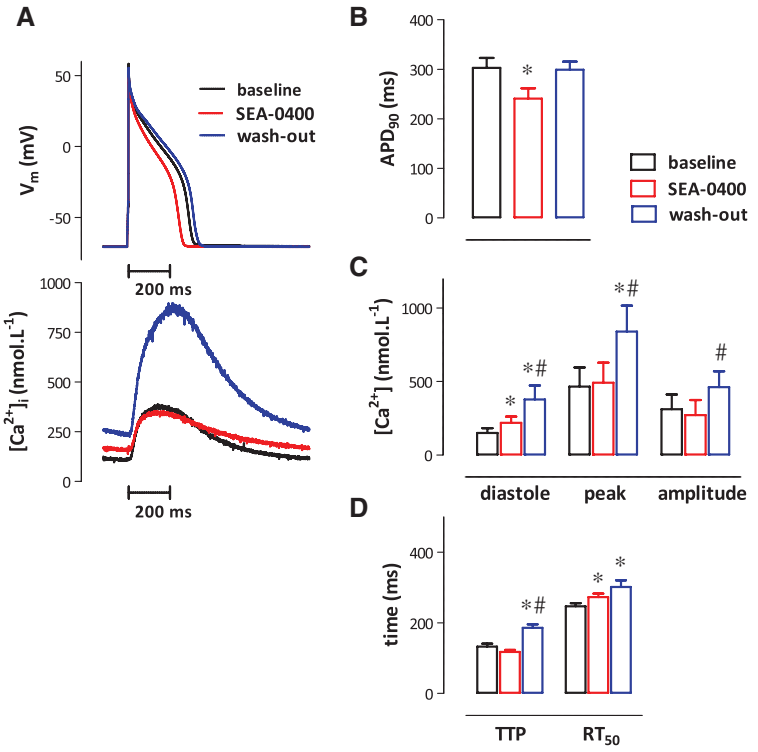

Figure 2. Effects of SEA-0400 on action potential (AP) and Ca^{2+} transients. **A**, Example of APs (**top**) and Ca^{2+} transients (**bottom**), under baseline (black), 1 μmol/L SEA-0400 (red) and during wash-out (blue), in a chronic atrioventricular block cell at 1 Hz. **B**, Pooled data of APD_{90}. **C**, Diastolic and peak $[Ca^{2+}]_i$, and Ca transient amplitude (peak-baseline). **D**, Kinetics of Ca^{2+} transient. TTP indicates time-to-peak; RT_{50}, time to half maximal relaxation. *P<0.05 vs baseline, # vs SEA-0400 (ANOVA for repeated measurements, n=5 cells).

mode and enhance SEA-0400 NCX block. In the CAVB dog, forward and reverse NCX are increased.[24]

3. Drugs, such as K201 and AVE0118, were not effective at all in controlling these arrhythmias.

The superior antiarrhythmic action of Ca^{2+} antagonists is, however, accompanied by reduced LV (−26%) and systolic blood pressure (−27%) with flunarizine (2 mg/kg),[25] whereas 0.3 mg/kg verapamil (this study) lowered LVP by 15%. In contrast, the SEA-0400 dosage could be increased to 0.8 mg/kg to have 100% efficacy without compromising LV function.

Mechanisms of Antiarrhythmic Activity of SEA-0400

The antiarrhythmic effect of SEA-0400 was linked to reduced beat-to-beat variability (STV_{QT} or STV_{APD}), whereas it did not shorten QT time or APD. The link between variability and TdPs has been well established.[3] Similarly, verapamil also did not shorten the QT interval, but decreased STV_{QT} and $STV_{LV\ MAPD}$,[3] suggesting that LTCC block is involved in reducing STV and net inward current during the AP plateau. This may directly reduce the likelihood of EADs, related to reactivation of LTCC.

Furthermore, in the absence of dofetilide, the inhibition by SEA-0400 is responsible for some AP shortening (Figure 2). In the presence of dofetilide, this shortening is no longer apparent, yet STV is reduced. The lack of shortening may be because of the predominant effect of dofetilide, but the shift in balance of currents during the AP plateau, favoring repolarization because of reduced inward current, is presumably still present and thus reduces variability.

Reduced NCX current by itself could also contribute to the observed effects. The role of NCX in EADs is less equivocal than in delayed afterdepolarizations (DADs), but several lines of evidence support its contribution.[26] The reduced variability can also be partly ascribed to Ca^{2+}-dependent activation of NCX during the AP plateau, as intracellular $[Ca^{2+}]_i$ buffering reduces STV after I_K block.[13]

SEA-0400 may exert its effects via forward and reverse mode block of NCX as it blocks both modes equally in dog myocytes. This is not unique to the dog, but has previously also been shown in pig and mouse[12] and in guinea pig.[27]

In summary, both NCX and the LTCC inhibition contribute to the antiarrhythmic effect of SEA-0400. This mechanism of action complements reported effects of SEA-0400 on DADs through NCX block in isoproterenol-induced arrhythmias.[28] Preliminary data suggest that in the CAVB dog, SEA-0400 is also effective on afterdepolarizations related to spontaneous Ca^{2+} release.

Mechanism of Preserved LV Function: Calcium Balance

In pig and mouse myocytes, SEA-0400 induced a Ca^{2+} transient[12] increase, whereas others have demonstrated variable effects in dog and rabbit.[7,17] The data underscored that SEA-0400 effects will depend on the prevailing Ca^{2+} fluxes and balance between LTCC, Ca^{2+} influx and removal by NCX, and SR Ca^{2+} release and reuptake. This is supported by the observation that in 2 mouse models of disease (hypertrophy and heart failure), the net effect on Ca^{2+} handling was different from that in healthy hearts.[12] In the hypertrophic remodeling consequent to CAVB, SEA-0400 during 1 Hz pacing did not increase the $[Ca^{2+}]_i$ transient amplitude, although diastolic Ca^{2+} increased slightly.

Using the different kinetics of SEA-0400 for LTCC and NCX, we could demonstrate that the effect of SEA-0400 is the

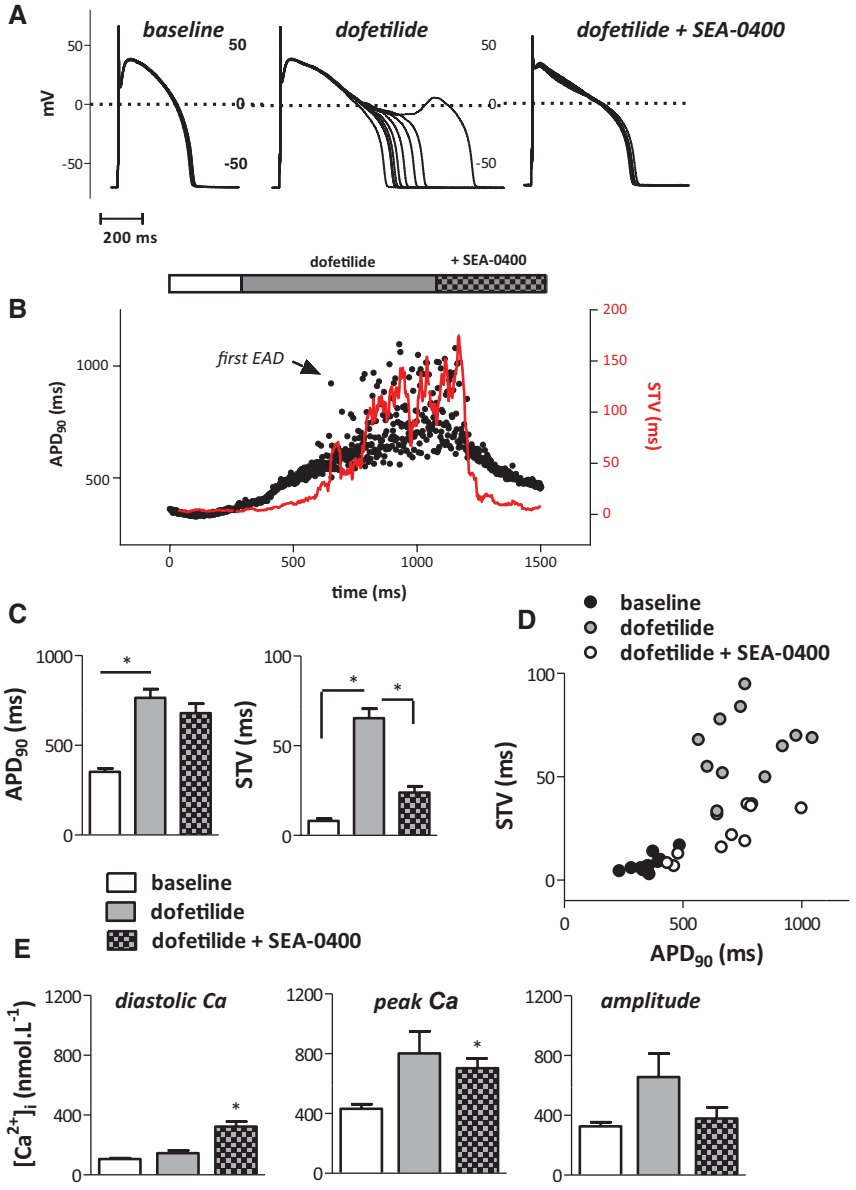

Figure 3. Antiarrhythmic effects of SEA0400 against early afterdepolarizations (EADs). **A**, Recordings of action potentials (APs) at 0.5 Hz in a chronic atrioventricular block cell showing dofetilide-induced EADs and suppression by SEA-0400 (1 μmol/L). **B**, Time-dependent changes in APD_{90} (symbols), short-term variability (STV; red line) and EADs during wash-in of dofetilide and SEA-0400. **C**, Pooled data of APD_{90} (**left**) and STV (**right**) of 11 cells. For dofetilide, APD and STV values are an average of 30 successive beats before the first EAD (*P<0.05). **D**, Individual data of STV in function of APD_{90}. **E**, Parameters of Ca^{2+} transients during the different treatments; averaged data of 5 cells (*P<0.05 vs baseline; ANOVA for repeated measurements).

net result of reduced Ca^{2+} release because of LTCC inhibition and gain of Ca^{2+} through inhibition of NCX. Shortening of the AP with the LTCC inhibition also contributes to maintaining Ca^{2+} balance, as a net gain can be observed under voltage clamp (data not shown).

LTCC inhibition is partially inherent to the properties of SEA-0400 (Figure 1C). However, LTCC inhibition is further enhanced by reduced removal of Ca^{2+} consequent on NCX inhibition. This property may be favorable in protecting against Ca^{2+} overload at higher heart rates.

The cellular data are in line with the preservation of LVP in vivo. However, SEA-0400 did increase diastolic $[Ca^{2+}]_i$ after dofetilide treatment. Data from another study have linked this to diastolic dysfunction.[29] In the present study, we did not observe an increase in diastolic pressure. This may be explained by the fact that diastolic function is only partially dependent on relaxation of the myocyte Ca^{2+} transient.[30] Also, vasodilatation leads to lower diastolic pressures, which may be part of SEA-0400 action (see patent: 7183322 Remedy for hypertension). However, we could not directly assess the effect of vasodilatation on cardiac function, as we only measured pressure, not output. So far, the effects of SEA-0400 on cardiac output are unknown.

Under control conditions the effects of SEA-0400 on diastolic pressure (Table) was negligible, as previously reported,[11] neither did we see effects on relaxation, quantified as –LV d*P*/d*t* (data not shown).

Caveats and Safety Limitations for Use of SEA-0400

NCX and LTCC are also modulators of Ca^{2+} balance in cells other than cardiomyocytes, like smooth muscle cells.

Another potential side effect of LTCC blocking drugs is interference with atrioventricular conduction. In CAVB this is difficult to determine, but in 3 dogs that received SEA-0400 before atrioventricular block in sinus rhythm, heart rate (Table) and atrioventricular conduction (P-R interval

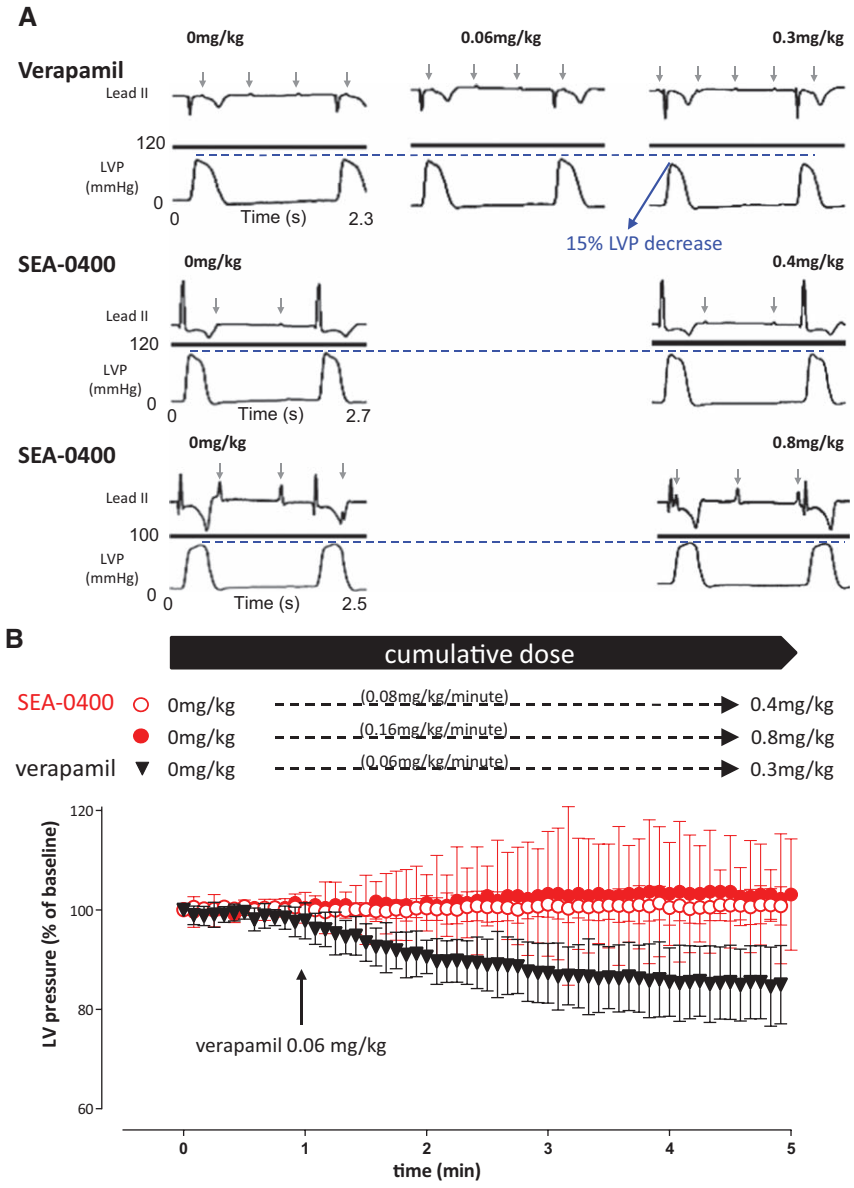

Figure 4. Relative pressure changes during verapamil or SEA-0400 infusion. **A**, Examples of left ventricular pressure (LVP) curves during verapamil of SEA-0400 treatment. Lead II was inserted for reference. P-waves are denoted with grey arrows. Note that, as these are chronic atrioventricular block dogs, P-waves and QRS complexes do not correlate. The blue dashed lines indicate the maximum pressure of the curves at baseline. **B**, Relative changes of systolic LVP during cumulative infusion of (▼) verapamil, 0.3 mg/kg per 5 min (N=6); (○) SEA-0400, 0.4 mg/kg per 5 min (N=6); (●) SEA-0400 0.8 mg/kg per 5 min (●; N=4). Arrow depicts the highest cumulative dose of verapamil without effect on pressure (hemodynamic neutral dose, 0.06 mg/kg).

went from 110±6 to 108±12) were not affected. Other authors[31] have reported atrioventricular block and cardiac stand still after SEA-0400 infusion, but at a 3.75× higher dose, indicating a dose-dependent safety limit.

The promising results of the present study should not be directly transposed to arrhythmias in other disease models. The CAVB dog is a model for compensated hypertrophy, not heart failure. Others' results with SEA-0400 were mixed: positive in an isolated rabbit heart model of TdP induced with veratridine or sotalol,[14] but not with dofetilide.[16] In models of coronary occlusion, arrhythmias were reduced in rat,[32] but not in dog.[31] In the guinea pig treated with aconitine, SEA-0400 was not effective.[15] None of these were studies of chronic disease. Given the delicate balance of Ca^{2+} and the different adaptations in, for example, ischemic cardiomyopathy or pressure overload, this will need further study.

Another complicating factor could be the change of the calcium flux with different heart rates (eg, with adrenergic stimulation). The CAVB dog has an unnatural low beating frequency (Table) and one must be careful in extrapolating these results to situations with higher heart rates.

Also, the dose of SEA-0400 has to be taken into account. In our experiments, we went up to 0.8 mg/kg to achieve efficacy against TdP without adverse hemodynamic effects. Whether the dose can be further increased is not known and of interest for further studies.

Lastly, it should be taken into account that administration of SEA-0400 did increase diastolic calcium levels. Long-term application could potentially lead to the activation of calcium-dependent signaling proteins like calcineurin, which might lead to detrimental cardiac remodeling.

Perspectives

The concept of multiple targets in antiarrhythmic drugs is not new and has been used to improve efficacy or minimize side effects. The advantage of SEA-0400 is that it is a de facto coinhibitor, composed into 1 drug and its targets are known culprits in arrhythmogenesis.

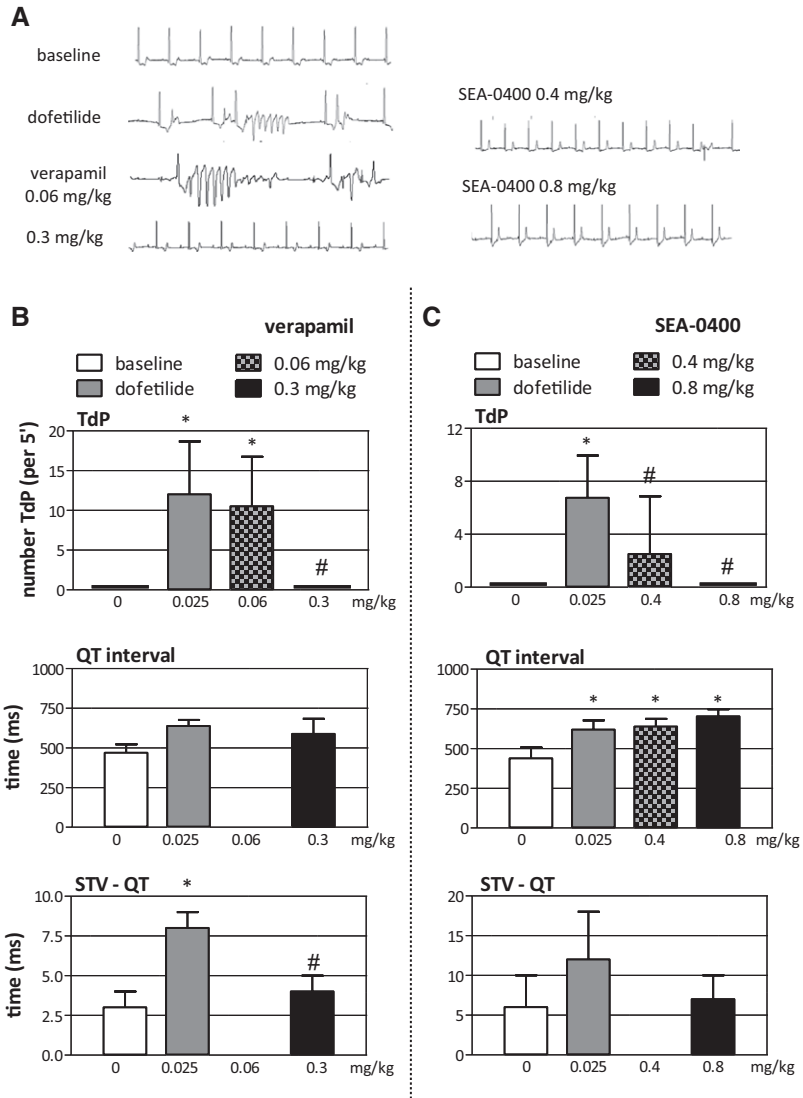

Figure 5. SEA-0400 and verapamil are antiarrhythmic, but verapamil is only effective at a negative inotropic dose. **A**, **Left**, Lead II in a CAVB dog, under baseline, after dofetilide (0.02 mg/kg) showing torsade de pointes (TdP) episodes, and suppression by infusion of 0.3 mg/kg verapamil, but not 0.06 mg/kg. **Right**, TdP suppression by SEA-0400 (0.4 and 0.8 mg/kg). Note the presence of ectopic beats at the lower dose. **B**, Quantification of TdP occurrence, QT interval (middle) and short-term variability of the QT interval (STV-QT), after treatment with verapamil (N=4) and **C**, SEA-0400 (N=8 total, half of the dogs received 0.4 mg/kg, the other half 0.8 mg/kg). **P*<0.05 vs baseline. #*P*<0.05 vs dofetilide. There are no data for QT interval at 0.06 mg/kg verapamil, and for STV-QT at 0.06 mg/kg verapamil and 0.4 mg/kg SEA-0400 as the presence of extra beats or TdP precluded the measurement.

In short, the dual block of NCX and LTCC has promise as a safe and effective strategy against repolarization-dependent arrhythmias, with on top of that the important benefit of preserved hemodynamics.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Despite successful device therapy to treat life-threatening arrhythmias, an unmet need for efficient drug therapy exists. Such drugs should protect against arrhythmias without negative inotropic effects. In the present study, we tested SEA-0400, a drug that inhibits the Na^+/Ca^{2+} exchanger and the L-type Ca^{2+} channel, 2 pathways involved in arrhythmogenesis and in contractility. In the dog with chronic AV block, a model for arrhythmias in the hypertrophied heart, we show that SEA-0400 is effective and superior to L-type Ca^{2+} channel block alone. Moreover, SEA-0400 suppressed evoked torsades de pointes dose dependently without affecting hemodynamics. In isolated cells, SEA-0400 was also effective in suppressing the cellular action potential prolongation and afterdepolarizations. These data indicate that the dual block of NCX and LTCC has promise as a safe and effective strategy against repolarization-dependent arrhythmias, with the important benefit of preserved hemodynamics. Additional studies should evaluate this approach in heart failure where Na^+/Ca^{2+} exchange is upregulated, and maintained hemodynamics are even more important.