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QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

Late Na^+ Current Inhibition by Ranolazine Reduces Torsades de Pointes in the Chronic Atrioventricular Block Dog Model

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Objectives This study investigated whether ranolazine reduces dofetilide-induced torsades de pointes (TdP) in a model of long QT syndrome with down-regulated K^+ currents due to hypertrophic remodeling in the dog with chronic atrioventricular block (cAVB).

Background Ranolazine inhibits the late Na^+ current (I_{NaL}) and is effective against arrhythmias in long QT3 syndromes despite its blocking properties of the rapid component of delayed rectifying potassium current.

Methods Ranolazine was administered to cAVB dogs before or after TdP induction with dofetilide and electrophysiological parameters were determined including beat-to-beat variability of repolarization (BVR). In single ventricular myocytes, effects of ranolazine were studied on I_{NaL}, action potential duration, and dofetilide-induced BVR and early afterdepolarizations.

Results After dofetilide, ranolazine reduced the number of TdP episodes from 10 ± 3 to 3 ± 1 ($p < 0.05$) and partially reversed the increase of BVR with no abbreviation of the dofetilide-induced QT prolongation. Likewise, pre-treatment with ranolazine, or using lidocaine as a specific Na^+ channel blocker, attenuated TdP, but failed to prevent dofetilide-induced increases in QT, BVR, and ectopic activity. In cAVB myocytes, ranolazine suppressed dofetilide-induced early afterdepolarizations in 25% of cells at 5 μmol/l, in 75% at 10 μmol/l, and in 100% at 15 μmol/l. At 5 μmol/l, ranolazine blocked 26 ± 3% of tetrodotoxin-sensitive I_{NaL}, and 49 ± 3% at 15 μmol/l. Despite a 54% reduction of I_{NaL} amplitude in cAVB compared with control cells, I_{NaL} inhibition by 5 μmol/l tetrodotoxin equally shortened relative action potential duration and completely abolished dofetilide-induced early afterdepolarizations.

Conclusions Despite down-regulation of I_{NaL} in remodeled cAVB hearts, ranolazine is antiarrhythmic against drug-induced TdP. The antiarrhythmic effects are reflected in concomitant changes of BVR. (J Am Coll Cardiol 2010;55:801–9) © 2010 by the American College of Cardiology Foundation

The voltage-dependent sodium channels produce a fast inward current upon depolarization that marks the initial upstroke of the cardiac action potential. Following activation, most channels rapidly inactivate, but some sustained activity remains: the late sodium current (I_{NaL}) (1). I_{NaL} is up-regulated in heart failure (2,3), and inhibition of I_{NaL} abolished early afterdepolarizations (EADs) in failing myocytes (4). A link between enhanced I_{NaL} and proarrhythmia has been revealed by our understanding of the long QT3 syndrome: gain-of-function of Na^+ channels induces torsades de pointes (TdP) (5). These findings have renewed our interest in Na^+ channel blockers as potential antiarrhythmic strategy. Ranolazine is an antianginal agent that has been explored recently for its antiarrhythmic action. Its block against I_{NaL} is more sensitive than for peak Na^+ current (6) and may be of importance in heart failure where conduction is already compromised (7). Ranolazine also blocks the rapid component of the delayed rectifying potassium current (I_{Kr}) (8,9) and prolongs QT in patients (10), but it is not proarrhythmic (8,9,11) and shortens QT and suppresses arrhythmias in long QT3 syndrome (12–14).

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Abbreviations and Acronyms

APD = action potential duration

BVR = beat-to-beat variability of repolarization

cAVB = chronic atrioventricular block

EAD = early afterdepolarization

EB = ectopic beat

I_{Kr} = rapid component of the delayed rectifying potassium current

I_{Ks} = slow component of the delayed rectifying potassium current

I_{NaL} = sustained component of the sodium current referred to as late sodium current

LQTS = long QT syndrome

MAPD = monophasic action potential duration

QTc = corrected QT interval

STV = short-term beat-to-beat variability of LV (M)APD to quantify BVR

TdP = torsades de pointes

TTX = tetrodotoxin

Likewise, ranolazine stabilized repolarization in failing myocytes with prolonged repolarization and up-regulated I_{NaL} (15). Interestingly, ranolazine has been proven antiarrhythmic in long QT syndromes (LQTS) caused by mechanisms other than abnormal Na^+ channel activity (16,17). Ranolazine also lowered incidence of arrhythmias in patients who survived an acute coronary syndrome (18), and first reports in patients with atrial fibrillation are promising (19).

The dog with chronic atrioventricular block (cAVB) model is well-characterized. Its high susceptibility to TdP relates to abnormal repolarization: down-regulation of K^+ currents and up-regulation of Na/Ca exchange current (20). In this study, the effect of ranolazine on suppression and prevention of TdP induced by the I_{Kr} blocker dofetilide was tested and compared with lidocaine, an I_{Na} blocker with less selectivity than ranolazine for I_{NaL} over peak I_{Na} (21), but with no or much weaker inhibitory effects on I_{Kr} (22). Arrhythmogenic outcome was linked to electrophysiological parameters, including beat-to-beat variability of repolarization (BVR) because of its high predictive value of TdP risk (23).

Methods

Animal handling was in accordance with the European Directive for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (86/609/EU). The experiments were approved by the Utrecht University Committee for Experiments on Animals.

In vivo studies. Thirty-two experiments were performed in 14 adult mongrel dogs with cAVB (24 ± 3 kg, Marshall, North Rose, New York). We used radiofrequency ablation to create AVB (24). Experiments were performed 4 weeks after AVB when electrical remodeling is completed (24). Details concerning anesthesia, animal care, data collection, and analysis have been described previously (25). Parameters were measured before the first extrasystolic beat or 10 min after dofetilide, ranolazine at 15 min, and lidocaine at 5 min after the start of infusion.

To induce TdP, cAVB dogs received a dose of 0.025 mg/kg dofetilide over 5 min or until TdP occurred within this period (Fig. 1A). Noninducible dogs (n = 3) were excluded from further study. Ranolazine was given to 5 animals (Fig. 1A); a second group of 6 dogs received lidocaine (B. Braun Melsungen AG, Melsungen, Germany) at a dose of 3 mg/kg in 2 min. Six TdP-inducible cAVB dogs were used for serial testing (3 experiments) to determine the effect of ranolazine and lidocaine to prevent TdP induction (Fig. 2A).

Cellular experiments. For cell isolation, we refer to previous publication (26). Age-matched dogs with normal sinus rhythm served as control subjects. Action potentials were recorded at 0.5 Hz (Axopatch 200B, MDS Analytic Technologies, Sunnyvale, California) under whole-cell current-clamp using the perforated patch technique. Patch pipettes (resistance of 1 to 3 MΩ) were filled with internal solution (in mmol/l): 130 KCl, 10 HEPES, 5 MgATP, 0.5 $MgCl_2$, 10 NaCl, 1 $CaCl_2$, 0.00026 amphotericin B, pH 7.20 using KOH. External solution contained (in mmol/l): 137 NaCl, 5.4 KCl, 0.5 $MgCl_2$, 1.8 $CaCl_2$, 11.8 HEPES, and 10 glucose, pH 7.40 with NaOH. Signals were low-pass filtered at 2 kHz and sampled at 4 kHz using a Digidata 1200 analog-to-digital converter and PClamp 9 software (MDS Analytic Technologies).

Whole-cell Na^+ currents were measured in ruptured patch configuration. In the solutions, K^+ was replaced by Cs^+ to block K^+ currents and nifedipine (20 μmol/l) was added to block Ca^{2+} currents. The persistent component of the Na^+ current, I_{NaL}, was measured as the tetrodotoxin (TTX)-sensitive current elicited by 500-ms depolarizing pulses from −130 to −40 mV. Interval between pulses was 30 s. The current amplitude was calculated by subtracting a current trace, recorded in the presence of 5-μmol/l TTX from a trace under baseline, and was measured at the end of pulse. Membrane currents were sampled at 10 kHz and normalized to cell capacity (pA/pF). All experiments were done at 37°C.

Plasma concentrations. Blood samples were collected from a venous catheter every 5 min during experiment. Heparin-treated samples were centrifuged at 4,000 rpm at 4°C and stored at −80°C for further analysis. Concentrations of ranolazine were determined using high-performance liquid chromatography at CV Therapeutics, Palo Alto, California.

Statistics. Data are expressed as mean ± SEM. For comparisons between groups, unpaired Student *t* test was used. For dependent measurements, analysis of variance for repeated measurements was used with Bonferroni post-hoc testing. Number of ectopic beats and TdP episodes were compared using nonparametric Wilcoxon signed-ranks test or Friedman analysis of variance with Student-Newman-Keuls post-hoc testing for multiple comparisons. Statistical analysis was performed in SigmaStat version 3.10 (Systat Software, Inc., Chicago, Illinois). Values of $p < 0.05$ were considered significant.

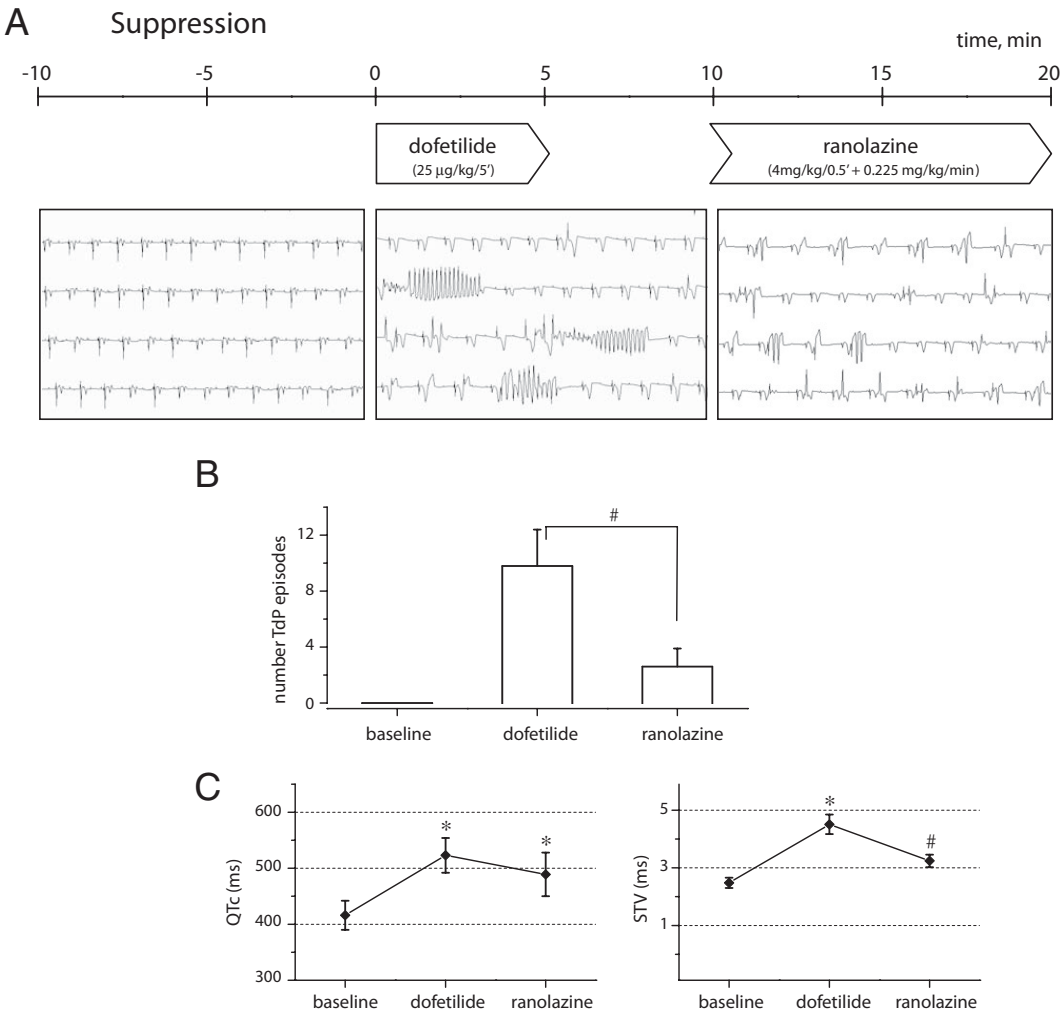

Figure 1 **Suppression of Dofetilide-Induced TdP in cAVB Dogs by Ranolazine**

(A) Representative electrocardiogram trace (lead II) under baseline **(left)**, after dofetilide **(middle)**, and during ranolazine **(right)** showing torsades de pointes (TdP) episodes **(middle)** and suppressive effects of ranolazine **(right)**. **(B)** Number of TdP episodes counted over a 10-min period, $n_{dogs} = 5$. **(C)** Averaged data for corrected QT interval (QTc) **(left)** and short-term beat-to-beat variable (STV) **(right)**, $n_{dogs} = 5$. The QT intervals were corrected for heart rate using the Van de Water method (Van de Water A, Verheyen J, Xhonneux R, Reneman RS. An improved method to correct the QT interval of the electrocardiogram for changes in heart rate. J Pharmacol Meth 1989;22:207–17). $p < 0.05$ *versus baseline, #versus dofetilide. cAVB = chronic atrioventricular block.

Results

Ranolazine reduces proarrhythmic activity in cAVB dogs. Figure 1A shows a representative example of the ventricular rhythm at baseline (left), after dofetilide (middle), and with ranolazine (right). Dofetilide prolonged corrected QT interval (QTc), increased short-term beat-to-beat variability (STV), and induced TdP (Figs. 1B and 1C). Ranolazine significantly reduced the number of TdP episodes (Fig. 1B). This was associated with a reduction of STV, while QTc remained prolonged (Fig. 1C). Proarrhythmic activity was not completely suppressed by ranolazine, as evidenced by the presence of multiple ectopic beats (EBs) and TdP episodes (Figs. 1A and 1B) remaining in 4 of 5 dogs. Plasma levels of ranolazine reached 15.7 ± 0.6 μmol/l at 10 min ($n_{dogs} = 3$), which is comparable to values reported in a previous study with larger sample size (11).

In prevention experiments (Fig. 2A), ranolazine plasma levels reached a plateau at 5-min infusion and remained constant throughout the experiment; concentration was 20 ± 3 μmol/l at 15 min (Fig. 2B). Ranolazine alone did not produce significant changes in QTc or STV (Fig. 2C). Despite pre-administration of ranolazine, dofetilide prolonged QTc and tended to increase STV, but the latter increase was no longer significant (Fig. 2C, Table 1). Ranolazine reduced the number of dofetilide-induced TdP episodes (Fig. 2D). Albeit less frequently and of shorter duration, TdP was still seen in 4 of 6 dogs (Fig. 2D). The TdP duration was shortened from 11 ± 2 s to 5 ± 2 s ($p <$

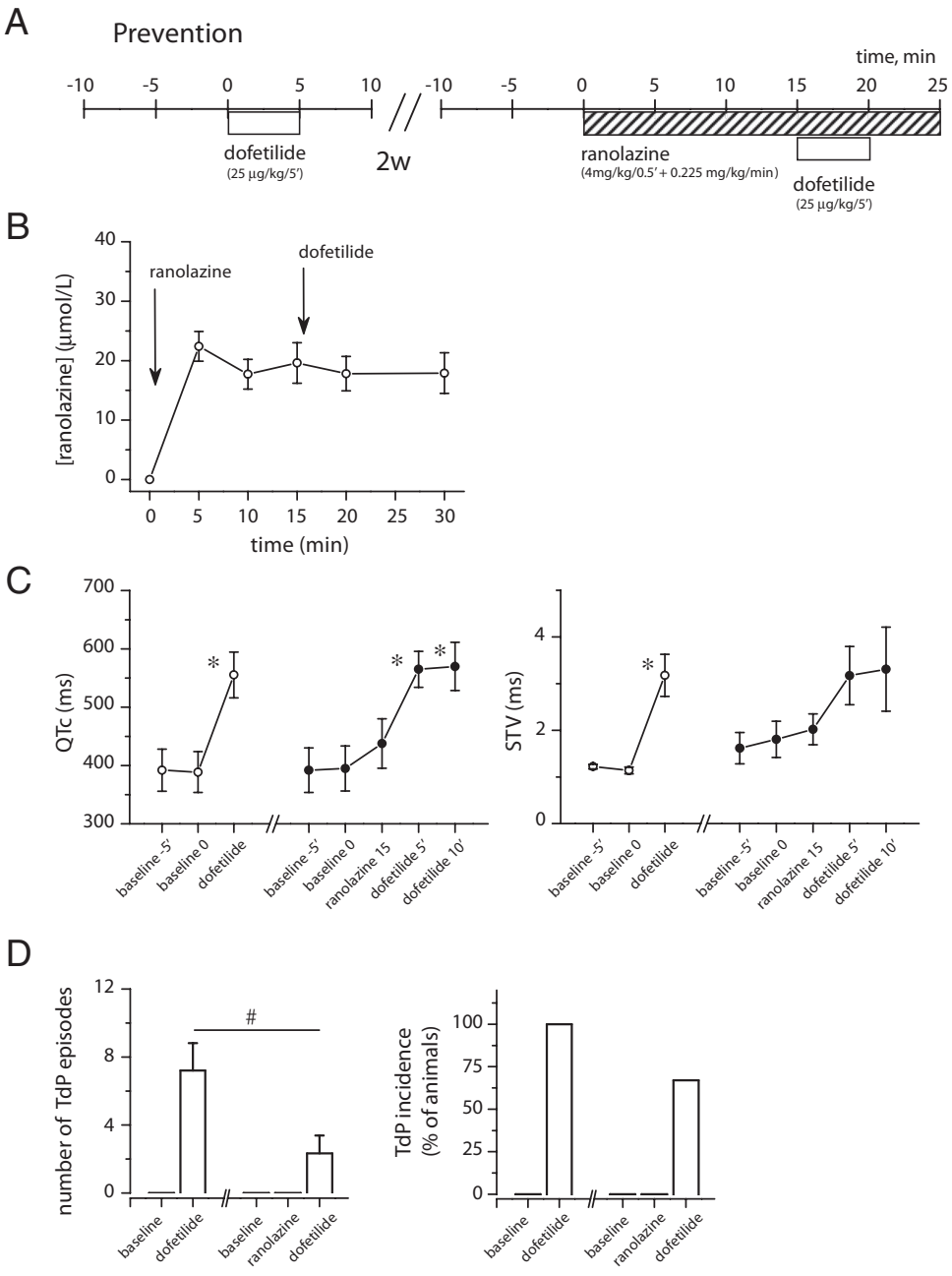

Figure 2 **Prevention of TdP After Ranolazine Pre-Treatment**

(A) Flow chart. In the prevention experiment, the same dose of dofetilide was given as in control. Time between experiments was 2 weeks. **(B)** Plasma concentration of ranolazine. **Arrows** indicate start of 15-min ranolazine and 5-min dofetilide infusion. **(C)** Dofetilide-induced changes in QTc interval **(left)** and STV **(right)**, before and after ranolazine (**open circle** vs. **solid circles**). *$p < 0.05$ versus baseline. **(D)** Number of TdP episodes (**left**, #$p < 0.05$ dofetilide vs. dofetilide after ranolazine) and incidence **(right)** after ranolazine pre-treatment, $n_{dogs} = 6$. Abbreviations as in Figure 1.

0.05). Single and multiple EBs occurred in the majority of animals (5 of 6).

TdP suppression and prevention by lidocaine. Suppression of dofetilide-induced TdP by lidocaine was studied in 6 animals using a similar protocol as described in Figure 1A for ranolazine. Results were comparable: lidocaine reduced the number of TdP episodes to 1.5 ± 2, and TdP remained in 2 of 6 dogs. There was no shortening of the dofetilide-induced QTc prolongation (478 ± 17 ms to 514 ± 27 ms), but the antiarrhythmic effect was associated with a reduction of STV (3.7 ± 1.2 ms with dofetilide vs. 2.3 ± 0.4 ms with lidocaine, $p < 0.05$).

The results of the prevention experiments with lidocaine are summarized in Table 1. Lidocaine shortened the QTc interval,

Table 1 Serial Electrophysiological and Proarrhythmic Properties of Dofetilide Before and After Ranolazine-Lidocaine

	Baseline 1	Dofetilide 1	Baseline 2	Ranolazine	Dofetilide 2	Baseline 3	Lidocaine	Dofetilide 3
R-R interval, ms	1,226 ± 148	1,254 ± 155	1,574 ± 102	1,676 ± 74	1,904 ± 141	1,499 ± 133	1,481 ± 129	1,481 ± 129
QT interval, ms	412 ± 29	577 ± 36*	442 ± 46	497 ± 45	644 ± 33†‡	425 ± 41	360 ± 25†	627 ± 41†‡
QTc, ms	392 ± 36	555 ± 39*	392 ± 38	438 ± 43	565 ± 31†‡	382 ± 34	318 ± 20†	586 ± 38†‡
LV MAPD, ms	334 ± 27	525 ± 34*	362 ± 49	410 ± 49	573 ± 56†‡	323 ± 41	281 ± 25	522 ± 51†‡
RV MAPD, ms	274 ± 21	361 ± 23*	330 ± 24	384 ± 24	503 ± 41†‡	270 ± 17	247 ± 14	352 ± 25†‡
ΔMAPD, ms	54 ± 4.3	147 ± 27*	53 ± 14	47 ± 15	73 ± 26	53 ± 29	36 ± 11	169 ± 44†‡
LV STV, ms	1.2 ± 0.1	3.1 ± 0.6*	1.6 ± 0.3	2.0 ± 0.3	3.3 ± 0.9	1.4 ± 0.3	1.2 ± 0.2	3.1 ± 0.4†‡
Single EBs	6 ± 3	62 ± 18*	1 ± 0.4	1 ± 1	84 ± 38	1 ± 0.3	0	27 ± 14
Multiple EBs	0	21 ± 8*	0	0	6 ± 3	0	0	2 ± 1§
nr TdPs	0	7 ± 2*	0	0	2 ± 1§	0	0	1 ± 1§
TdP incidence	0	6/6	0	0	4/6	0	0	3/6

There were no significant differences within the baseline data. *$p < 0.05$ versus baseline 1; †versus baseline 2 to 3; ‡versus ranolazine-lidocaine; §versus dofetilide 1.
EB = ectopic beat; LV = left ventricular; ΔMAPD = interventricular dispersion of repolarization duration; nr TdP = number of torsades de pointes/10 min; QTC = corrected QT interval; STV = short-term beat-to-beat variability of LV (M)APD to quantify BVR; TdP = torsades de pointes.

but failed to attenuate dofetilide-induced QT interval prolongation, increases in monophasic action potential duration (MAPD), interventricular dispersion, and STV. As with ranolazine, dofetilide-induced TdP episodes occurred less frequently in the presence of lidocaine, but were still observed in 3 of 6 cAVB dogs; multiple EBs were seen in 4 of 6 dogs.

Figure 3 summarizes individual data on STV according to arrhythmogenic outcome, defined as the occurrence of EBs or TdP. Effective prevention of arrhythmias either with lidocaine or ranolazine ($n_{exp} = 3$) was associated with no change in STV, whereas an increase in STV preceded proarrhythmia ($n_{exp} = 7$).

Late Na^+ current is reduced in cAVB. The late component of the Na^+ current was measured as the current sensitive to 5-μmol/l TTX (Fig. 4A, left). The amplitude of the inward current was significantly reduced in cAVB: −0.08 ± 0.01 vs. −0.173 ± 0.03 pA/pF in control cells ($p < 0.05$) (Fig. 4A, right). Despite its smaller amplitude, the TTX-sensitive current equally contributed to APD in cAVB: 5-μmol/l TTX shortened APD_{90} by 29 ± 3% in cAVB (n = 9) and by 28 ± 4% in control cells (n = 8, p = NS) (Fig. 4B).

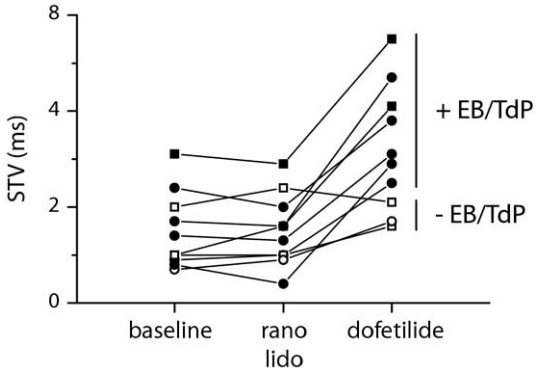

Figure 3 Relation Between STV and Ectopic Activity/TdP (EB/TdP)

Individual changes of STV depicted under baseline, ranolazine **(squares)** or lidocaine **(circles)**, and after dofetilide. Data are grouped according to ectopic beats (EBs) and/or TdP (+EB/TdP, **closed symbols**, $n_{exp} = 7$; −EB/TdP, **open symbols**, $n_{exp} = 3$). Abbreviations as in Figure 1.

Figure 4C shows the duration of successive APs and STV during the time course of a typical experiment where dofetilide was used to induce EADs, which were typically preceded by AP prolongation and an increase of STV. Addition of 5-μmol/l TTX fully suppressed EADs, and reversed the dofetilide-induced increase of APD and STV to baseline values.

Suppression of afterdepolarizations by ranolazine is concentration-dependent. In cAVB dogs, total ranolazine concentrations were between 7 and 30 μmol/l. Assuming that 65% of ranolazine is bound to plasma proteins, the calculated free drug concentration lies between 5 and 15 μmol/l. These concentrations were used for cellular experiments. The proportion of TTX-sensitive current blocked by ranolazine in cAVB was 26 ± 3% at 5 μmol/l (n = 6), and 49 ± 3% at 15 μmol/l (n = 8).

Figure 5A shows typical recordings of action potentials and dofetilide-induced EADs in a cAVB cell, with, in the lower panel, changes in APD and STV. Early afterdepolarizations were suppressed by 15 μmol/l ($n_{cells} = 9$), although ranolazine did not shorten APD following dofetilide ($p = 0.27$), or significantly reduced STV ($p = 0.13$) (Fig. 5B). However, values were no longer different from baseline. In the particular example of Figure 5A, EADs were not suppressed by ranolazine when applied at 5 μmol/l. The concentration-dependent suppression of EADs by ranolazine is summarized in Figure 5C: in 25% of cAVB cells at 5 μmol/l (n = 4), versus 75% at 10 μmol/l (n = 4) and in 100% at 15 μmol/l (n = 9).

Discussion

In the cAVB dog model, ranolazine significantly suppressed and prevented dofetilide-induced TdP arrhythmias. However, BVR was only slightly reduced, in line with the observation that proarrhythmic activity was not completely

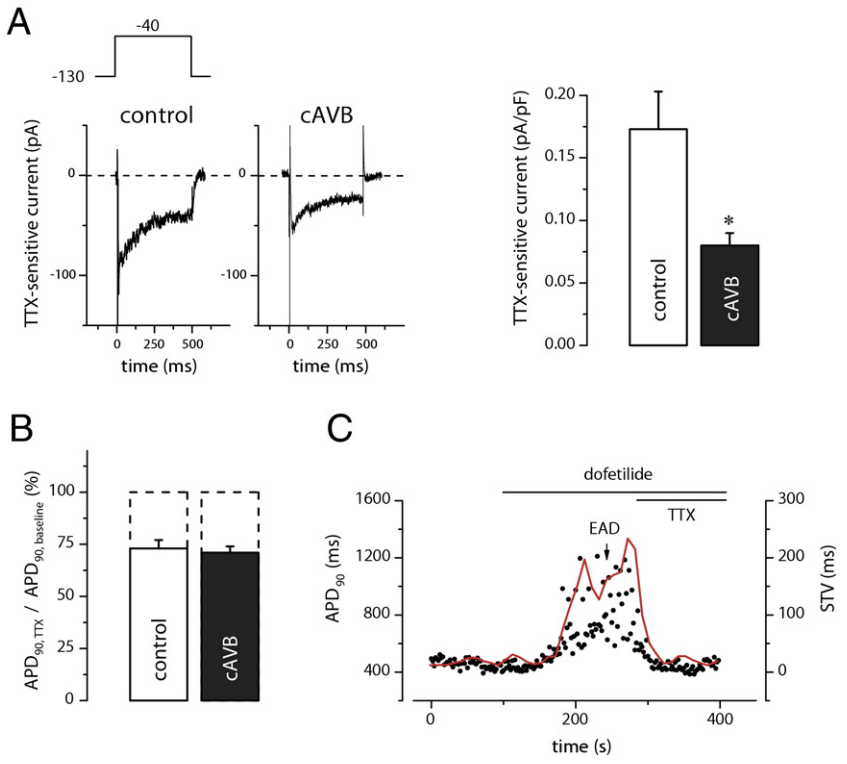

Figure 4 **Late Na^+ Current Is Reduced in cAVB**

(A) Tetrodotoxin (TTX)-sensitive currents in control versus cAVB cells **(left)**. Averaged data of current densities (pA/pF) in 6 control cells (n_{dogs} = 3) and 12 cAVB cells (n_{dogs} = 4, $p < 0.05$) **(right)**. **(B)** Relative action potential duration (APD_{90}) in the presence of 5 μmol/l TTX in cAVB (n = 9) versus control cells (n = 8, NS). **(C)** Time course of APD_{90} **(circles)** and STV values **(red line)** is depicted under baseline, dofetilide (1 μmol/l), and TTX (5 μmol/l) in a cAVB cell. Addition of TTX started after the appearance of early afterdepolarizations (EADs) (indicated by **arrow**). Abbreviations as in Figure 1.

abolished. Lidocaine, a specific Na^+ blocker, had similar effects. An interesting finding of the present study was that inhibition of I_{NaL} by TTX fully suppressed dofetilide-induced EADs in single cells, despite the fact that I_{NaL} was down-regulated in cAVB. Ranolazine abolished EADs but only at higher concentrations. Thus the incomplete antiarrhythmic activity of ranolazine in cAVB dogs is not due to I_{Kr} block, but more likely to reduced I_{NaL} and concentration-dependent effects.

Remodeling of I_{NaL} in hypertrophy vs. heart failure. The cAVB heart develops compensated hypertrophy, and electrical remodeling includes changes in delayed rectifying K^+ currents and Na/Ca exchange (27–29). Additionally, in the present study, we found a decrease of I_{NaL}. This is at odds with heart failure, where I_{NaL} is up-regulated despite smaller peak currents (2) and contributes to prolongation and abnormal repolarization (4). In cAVB, we previously reported lower messenger ribonucleic acid expression levels of cardiac Na^+ channels together with a reduction of peak current (30).

Possible mechanisms underlying antiarrhythmic effects of ranolazine. In vitro, the antiarrhythmic properties of ranolazine were reported at first in LQTS type 3 (13,14) and confirmed in failing myocytes with up-regulated I_{NaL} (15). Hence, the efficacy of ranolazine was ascribed to its I_{NaL}-blocking properties. Interestingly, ranolazine was proven antiarrhythmic against EADs and TdP caused by mechanisms other than abnormal I_{NaL}, including enhanced Ca^{2+} channel activity mimicking the LQTS type 8 (16), and through inhibition of I_{Kr} as a model for the LQTS type 2 (8). Reduced transmural dispersion as well as a decrease of repolarization variability were proposed as antiarrhythmic mechanisms (13,15,16). BVR originates in the plateau phase of the action potential and I_{NaL} may indeed contribute to variability (31). In cAVB, ranolazine attenuated changes in dofetilide-induced BVR, but only to a limited extent.

Ranolazine prevents excessive Ca^{2+} loading of the cell by lowering Na^+ levels through inhibition of I_{NaL} (32). In cAVB, Na^+ levels are high, which enhances Ca^{2+} loading (33). The subsequent increase of sarcoplasmic reticulum Ca^{2+} release may facilitate EADs by promoting inward Na/Ca exchange current allowing Ca^{2+} window currents to develop, and more Ca^{2+} channels may be available for reactivation due to a larger recovery from release-dependent inactivation (28,34). In addition, high Ca^{2+} loads favor spontaneous Ca^{2+} release and delayed afterdepolarizations (27). By reversing the increased Na^+ levels, ranolazine may reduce triggered activity in cAVB.

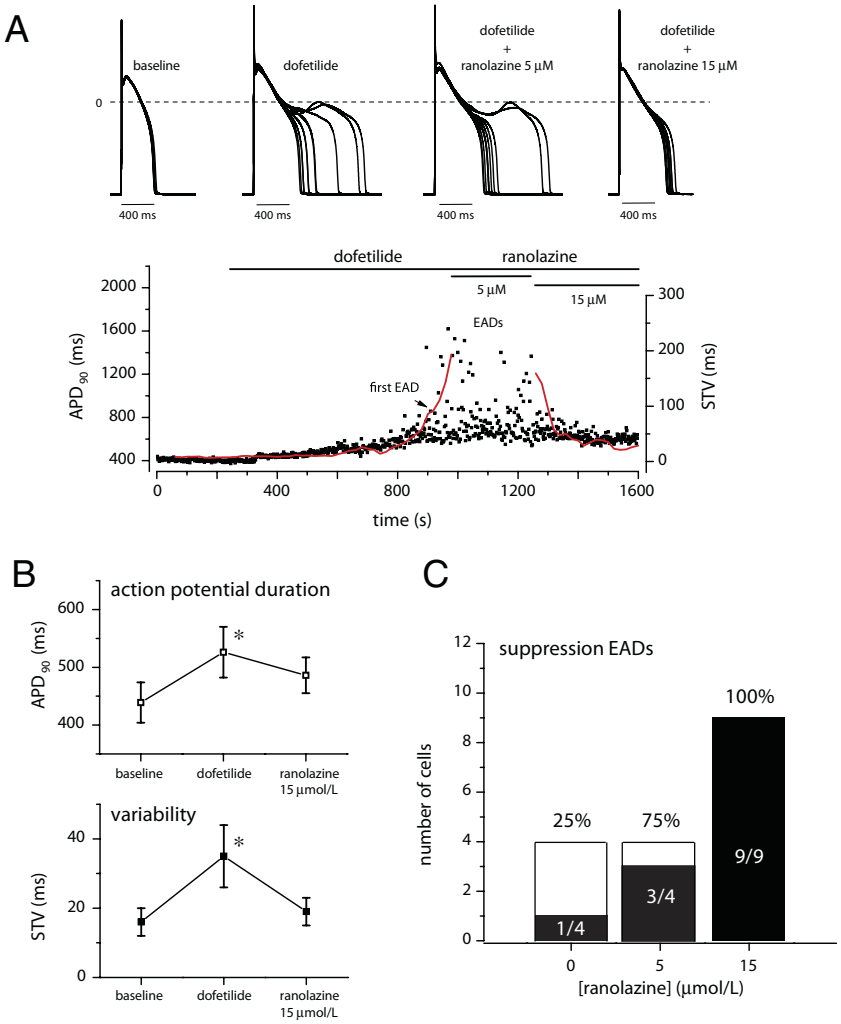

Figure 5 **Ranolazine Suppression is Concentration-Dependent**

(A) Action potentials in a cAVB cell are shown during ranolazine following dofetilide-induced EADs. The **lower panel** shows time-dependent changes in APD_{90} **(circles)**, STV **(red line)**, and EAD occurrence. Early afterdepolarizations continued with 5-μmol/l ranolazine, but disappeared completely with 15 μmol/l. **(B)** APD_{90} **(upper)** and STV **(lower)**. Averaged data from 9 cAVB cells ($n_{dogs} = 5$), *$p < 0.05$ versus baseline. **(C)** Proportion of cAVB cells showing EAD suppression at different concentrations of ranolazine. Abbreviations as in Figures 1 and 4.

Limited antiarrhythmic potential of Na^+ channel blockers in cAVB. Although TdP occurs less, ranolazine did not completely abolish ectopic activity. At the therapeutic range, ranolazine blocks I_{Kr} (8). In the remodeled cAVB heart with reduced repolarization reserve, an additional block of I_{Kr} could confound the antiarrhythmic effects of ranolazine through inhibition of I_{NaL}. Incomplete antiarrhythmic activity, however, was also seen with lidocaine. This agent has no inhibitory effects on I_{Kr} at clinically relevant concentrations and is considered a selective blocker of I_{Na} (22). It is therefore unlikely that the I_{Kr} block contributes to the incomplete antiarrhythmic potential of ranolazine.

The main target for ranolazine, I_{NaL}, is decreased and not increased in the cAVB heart. The block of I_{NaL} by ranolazine is insufficient to balance the down-regulation of repolarizing K^+ currents (I_{Ks} [slow component of the delayed rectifying potassium current], I_{Kr}) and ranolazine therefore cannot completely prevent or suppress proarrhythmia. On the other hand, in conditions with increased I_{NaL} (LQTS type 3, heart failure) the block of I_{NaL} should be sufficient as documented in LQTS type 3 (12,14) and/or heart failure (15).

Interestingly, in single cells, 15-μmol/l ranolazine fully suppressed EADs, whereas lower concentrations of 5 μmol/l could not. This concentration-dependent effect was also observed by others (8). On a background of down-regulated I_{NaL}, the higher degree of Na^+ block might be required to tip the balance toward strengthened repolarization preventing the development of EADs despite blockage of I_{Kr}. In the intact animal, the concentration of available ranolazine is likely less and below the critical level

for complete suppression of EADs. Higher plasma concentrations such as 20 μmol/l would far exceed the therapeutic range (2 to 6 μmol/l) and could experimentally not be achieved in the dog.

BVR. BVR is a reliable parameter to predict drug-induced TdP and is superior to QT interval prolongation. A torsadogenic drug increases BVR, and this is independent of total duration of repolarization; a drug that does not increase BVR is considered safe (20). Fewer studies have addressed the potential of BVR for predicting successful antiarrhythmic treatment, where one expects a decrease and/or prevention of BVR increase if the drug is antiarrhythmic (35). The strong antiarrhythmic activity of the Ca^{2+} channel antagonist flunarizine, evidenced by complete inhibition of arrhythmogenic events, is associated with full reversal of BVR to baseline levels and lack of increase upon an arrhythmogenic challenge (36) and is in support of this premise. This finding is unlike the modest effects of Na^+ blockers on BVR, which correspond to the inability of the blockers to fully prevent or suppress EBs and TdP. Proarrhythmic outcome was related to an increase of BVR in the susceptible animal and confirms the value of BVR as a marker of proarrhythmic risk. BVR was reflected already in ectopic beat formation (Fig. 3). In the noninducible animals, there was no change of BVR.

Clinical implications. The observation that ranolazine did not produce any proarrhythmic effects, rather was antiarrhythmic against dofetilide-induced TdP and EADs, further substantiates that ranolazine is a safe drug despite I_{Kr}-blocking properties. The concentration at which maximal antiarrhythmic effects were seen in the setting of reduced I_{NaL} in the cAVB model (15 μmol/l) was approximately 1.5 to 3 times higher than the clinical therapeutic concentrations. Yet, antiarrhythmic efficacy at therapeutic concentrations has been documented in the MERLIN–TIMI 36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction 36) trial (18).

Conclusions

The antiarrhythmic properties of ranolazine are most obvious under conditions of abnormal and increased I_{NaL}, including LQTS type 3. Albeit with less efficacy, ranolazine and other Na^+ blockers are also antiarrhythmic against EADs and TdP in cAVB dogs with acquired LQTS, despite down-regulation of I_{NaL} due to remodeling. Antiarrhythmic effects were reflected in BVR, in single myocytes as well as in the intact animal.

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Key Words: arrhythmias ■ long QT syndromes ■ sodium channels ■ antiarrhythmic agents.