Atrium-Selective Sodium Channel Block as a Strategy for Suppression of Atrial Fibrillation

Differences in Sodium Channel Inactivation Between Atria and Ventricles and the Role of Ranolazine

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Background—The development of selective atrial antiarrhythmic agents is a current strategy for suppression of atrial fibrillation (AF).

Methods and Results—Whole-cell patch clamp techniques were used to evaluate inactivation of peak sodium channel current ($I_{\text{Na}}$) in myocytes isolated from canine atria and ventricles. The electrophysiological effects of therapeutic concentrations of ranolazine (1 to 10 μmol/L) and lidocaine (2.1 to 21 μmol/L) were evaluated in canine isolated coronary-perfused atrial and ventricular preparations. Half-inactivation voltage of $I_{\text{Na}}$ was $\approx$ 15 mV more negative in atrial versus ventricular cells under control conditions; this difference increased after exposure to ranolazine. Ranolazine produced a marked use-dependent depression of sodium channel parameters, including the maximum rate of rise of the action potential upstroke, conduction velocity, and diastolic threshold of excitation, and induced postrepolarization refractoriness in atria but not in ventricles. Lidocaine also preferentially suppressed these parameters in atria versus ventricles, but to a much lesser extent than ranolazine. Ranolazine produced a prolongation of action potential duration (APD$_{90}$) in atria, no effect on APD$_{90}$ in ventricular myocardium, and an abbreviation of APD$_{90}$ in Purkinje fibers. Lidocaine abbreviated both atrial and ventricular APD$_{90}$. Ranolazine was more effective than lidocaine in terminating persistent AF and in preventing the induction of AF.

Conclusions—Our study demonstrates important differences in the inactivation characteristics of atrial versus ventricular sodium channels and a striking atrial selectivity for the action of ranolazine to produce use-dependent block of sodium channels, leading to suppression of AF. Our results point to atrium-selective sodium channel block as a novel strategy for the management of AF. (Circulation. 2007;116:1449-1457.)

Key Words: action potentials | antiarrhythmia agents | atrial fibrillation | electrophysiology | pharmacology

Antiarrhythmic drug therapy remains the principal approach for suppressing atrial fibrillation (AF), atrial flutter (AFl), and their recurrence. Among the current strategies for suppressing AF/AFl is the development of antiarrhythmic agents that preferentially affect atrial rather than ventricular electrical parameters. Inhibition of the ultrarapid delayed rectified potassium current ($I_{\text{Kur}}$), present in atria but not ventricles, is an example of an atrium-selective approach. $I_{\text{Kur}}$ block selectively prolongs atrial repolarization and can suppress AF. The present study examines the hypothesis that sodium channel characteristics differ between atrial and ventricular cells and that atrium-selective sodium channel block is another effective strategy for the management of AF. Our study identifies ranolazine and, to a much lesser extent, lidocaine as agents that apparently can exploit the differences in sodium channel inactivation between atrial and ventricular cells. Ranolazine, an antianginal agent, has previously been shown in experimental models to possess antiarrhythmic properties in the ventricle related to inhibition of late sodium channel current (late $I_{\text{Na}}$). Results presented herein show that ranolazine exerts a potent atrium-selective use-dependent inhibition of the maximum rate of rise of the action potential upstroke ($V_{\text{max}}$) and other electrophysiological parameters dependent on the sodium channels underlying early $I_{\text{Na}}$, making it effective in suppression of AF in 2 experimental models.

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Methods

See the online-only Data Supplement (available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.704890/DC1) for detailed information about the methods used.
Experiments were performed using isolated arterially perfused canine right atrial (RA) preparations and left ventricular arterially perfused wedge preparations (≈2×1×1 cm), as well as superfused left ventricular epicardial and M-cell tissue slice (≈1×0.5×0.1 cm) and left and right ventricular Purkinje fibers. Transmembrane action potential (AP) recordings were obtained from standard or floating glass microelectrodes. A pseudo-ECG was recorded with 2 electrodes consisting of Ag/AgCl half-cells placed in the Tyrode’s solution, bathing the preparation 1.0 to 1.2 cm from the 2 opposite sides of the atrial or ventricular coronary-perfused preparations. Conduction velocity (CV) was measured in atria on the endocardial cristal terminals with 2 unipolar electrodes placed 1 cm apart. To directly compare atria and ventricles, changes in CV also were approximated by measuring the duration of the P-wave complex in atria and the QRS complex in ventricles on the ECG at a level representing 10% of P-wave or QRS amplitude. Diastolic threshold of excitation (DTE) was determined by increasing stimulus intensity in 0.01-mA steps. Effective refractory period (ERP) was measured by delivering premature stimuli after every 10th regular beat at pacing cycle lengths (CLs) of 500 and 300 ms (with 10-ms resolution; stimulation with a 2× DTE amplitude determined at each CL). Postpolarization refactoriness (PPR) was recognized when ERP exceeded AP duration measured at 90% repolarization (APD90) in the ventricle and APD3 in atria. Ventricular ERP coincided with APD90, whereas atrial ERP generally coincided with APD70.

**Voltage Clamp of Atrial and Ventricular Myocytes**

Whole-cell peak sodium currents were recorded at 37°C in low-sodium external solution from myocytes isolated from the right atrium and left ventricle of adult mongrel dogs, as previously described. The current–voltage relation was determined in external solution containing 1 mmol/L CaCl2 over a voltage range of −65 to −15 mV from a holding potential of −140 mV. Steady-state inactivation was measured with a standard dual-pulse protocol. Cells were held at −90 mV before evoking a 1-second conditioning pulse immediately followed by a 20-ms pulse to −30 mV to measure sodium current. Conditioning pulses ranged from −120 to −50 mV increased in 10-mV steps. Current was normalized to the peak current recorded after a conditioning step to −120 mV. The normalized current was plotted as a function of conditioning step voltage and fit to a standard Boltzmann equation.

**Drugs**

Ranolazine (CV Therapeutics, Palo Alto, Calif), lidocaine, acetylcholine (ACh), and isoproterenol (Sigma, St Louis, Mo) all were dissolved in distilled water and prepared fresh as a stock of 1 to 10 mmol/L before each experiment.

**Statistical Analysis**

Statistical analysis was performed through the use of a paired or unpaired Student t test and 1-way repeated-measures or multiple-comparison ANOVA followed by Bonferroni’s test, as appropriate. All data are expressed as mean±SD. Statistical significance was assumed at P<0.05.

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Sodium Channel Inactivation Characteristics in Isolated Atrial Versus Ventricular Myocytes**

The I-V relationship recorded from atrial and ventricular myocytes demonstrate both voltage control of the preparation and a greater density of sodium channels in atrial versus ventricular cells (−89.59±41.05 versus −50.20±3.34 pA/pF, respectively; P<0.001; n=6 to 8; Figure 1A). Current density peaked at −25 mV in atrial and at −35 mV in ventricular cells. The half-inactivation voltage (V1/2) in atrial myocytes was 16.2 mV more negative than that recorded in ventricular myocytes (−88.80±0.19 versus −72.64±0.14 mV; Figure 1B), indicating that a greater percentage of atrial versus ventricular sodium channels would be inactivated at a given resting or takeoff potential.

Because ranolazine has recently been identified as an inactivated-state blocker with little effect on peak IS in ventricular myocardium at therapeutic concentrations, we hypothesized that this agent may exert a differential effect on sodium channels in canine atria versus ventricles, in light of the results illustrated in Figure 1B and the well-known fact that resting membrane potential (RMP) in atrial cells is less negative than in ventricular cells (Figure 2).

We first examined the effect of ranolazine on sodium channel inactivation using another set of atrial and ventricular myocytes. Ranolazine (15 μmol/L) caused an apparent shift in both atrial and ventricular inactivation curves, increasing the mean difference in V1/2 between atrial and ventricular cells from 13.82 to 16.57 mV (Figure 1C).

We next contrasted the electrophysiological effects of ranolazine with those of another inactivated-state sodium channel blocker, lidocaine, in ventricular and atrial coronary-perfused preparations. Clinically relevant concen-
trations of ranolazine (1 to 10 μmol/L) and lidocaine (2.1 to 21.0 μmol/L) were used.

**Atrial and Ventricular APDs and Their Modulation by Ranolazine and Lidocaine**

Ranolazine (1, 5, and 10 μmol/L) prolonged atrial APD$_{90}$ more so than APD$_{95}$, but produced no change in APD$_{50}$ (Figure 2 and Figures I and II in the Data Supplement). Ranolazine abbreviated APD in Purkinje fibers and caused little change in APD in ventricular wedges (Figure 2 and Figures I and II in the Data Supplement). Atrial APs, unlike those recorded from ventricular preparations, displayed a much slower late phase 3 (as previously reported), resulting in a much more gradual approach to the RMP in atrial than in ventricular APs. These differences in late repolarization were further accentuated after exposure to ranolazine (Figure 2). Lidocaine (2.1, 10.5, and 21.0 μmol/L) abbreviated APD$_{90}$, APD$_{95}$, and APD$_{90}$ in ventricles. In atria, lidocaine abbreviated APD$_{90}$ and APD$_{95}$ but did not change APD$_{90}$ (Figure 2 and Figures I and II in the Data Supplement). Another distinguishing feature was a more positive RMP in atrial than in ventricular muscle and Purkinje fiber preparations (−83±2, −86±3, and −91±1 mV, respectively; *P*<0.05 between all; n=7 to 11; Figure 2). Ranolazine and lidocaine did not change RMP in any of the preparations tested.

**Effects of Ranolazine and Lidocaine on ERP, DTE, $V_{max}$, and CV**

Under control conditions, atrial ERP corresponded to APD$_{75}$, whereas ventricular ERP corresponded to APD$_{90}$ (Figure 3), contributing to a shorter ERP in atria versus ventricles. Ranolazine prolonged atrial ERP much more than APD$_{75}$ in a rate-dependent manner, leading to the appearance of PRR in atria (Figure 3 and Figure III in the Data Supplement). In contrast, ranolazine produced little change in ventricular ERP; these changes were not rate dependent, and ERP remained equal to APD$_{90}$ (Figure 3 and Figure IV in the Data Supplement). Lidocaine prolonged atrial and to a lesser extent ventricular ERP in a rate-dependent manner.
ventricular ERP, leading to the appearance of a rate-dependent PRR in both the atria and the ventricles, but preferentially in the former (Figure 3 and Figure IV in the Data Supplement).

Atrial PRR developed cumulatively at faster rates. Ranolazine (10 μmol/L) and lidocaine (21 μmol/L) significantly prolonged the briefest S1–S1 permitting 1:1 atrial activation (see the Table). Ranolazine (10 μmol/L) and lidocaine (21 μmol/L) caused loss of 1:1 activation at a CL of 300 in 66% and 43% atrial, respectively, but in none of the ventricular preparations (Figure V in the Data Supplement).

Ranolazine caused a much greater rate-dependent reduction in the maximum rate of rise of the AP upstroke (Vmax), CV slowing, and increase in DTE (Figures 4 and 5 and Figures VI and VII in the Data Supplement) in atrial than ventricular preparations. Lidocaine also preferentially suppressed these parameters in atria versus ventricles, but to a much lesser extent than ranolazine (Figures 4 and 5 and Figures VI and VII in the Data Supplement).

We evaluated the rate of onset and recovery from use-dependent sodium channel block by measuring Vmax changes during acceleration and deceleration of pacing rate in the

**Ranolazine (10 μmol/L) Versus Lidocaine (21 μmol/L) to Suppress Atrial Excitability and ACh-Mediated AF in the Isolated Canine Coronary Perfused Right Atria**

<table>
<thead>
<tr>
<th></th>
<th>APD90 (ms)</th>
<th>ERP (ms)</th>
<th>Shortest S1–S1 (ms)</th>
<th>Persistent AF, %</th>
<th>Termination of Persistent AF, %</th>
<th>Prevention of AF Recurrence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>204±11</td>
<td>158±17</td>
<td>129±8</td>
<td>0</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>RAN</td>
<td>228±14*</td>
<td>218±37*</td>
<td>295±32*</td>
<td>0</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>LID</td>
<td>193±8*</td>
<td>208±15*</td>
<td>276±39*</td>
<td>0</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>ACh (0.5 μmol/L)</td>
<td>43±10</td>
<td>58±8</td>
<td>73±8</td>
<td>100 (10/10)</td>
<td>0 (0/10)</td>
<td>…</td>
</tr>
<tr>
<td>ACh + RAN</td>
<td>68±18†</td>
<td>115±22†</td>
<td>181±57†</td>
<td>20 (2/10)</td>
<td>66 (4/6)</td>
<td>75 (3/4)</td>
</tr>
<tr>
<td>ACh + LID</td>
<td>57±14†</td>
<td>87±19†</td>
<td>128±42†</td>
<td>43 (3/7)</td>
<td>33 (2/6)</td>
<td>50 (1/2)</td>
</tr>
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RAN indicates ranolazine; LID, lidocaine; and Shortest S1–S1, the shortest CL permitting 1:1 activation at a DTE × 2 determined at a CL of 500 ms. Experiments to prevent AF and to terminate AF were performed in different atria. APD and ERP data presented in the table were obtained from the pectinate muscle region of coronary-perfused atria at a CL of 500 ms (n=6 to 18).

*P<0.05 vs control; †P<0.05 vs ACh alone; ‡P<0.05 vs ACh + LID.
Antiarrhythmic Effects of Ranolazine and Lidocaine

Premature electrical stimulation (a single premature stimulus) and rapid pacing (CL up to 80 ms for 3 to 10 seconds) did not induce arrhythmias under baseline conditions or in the presence of ranolazine (1 to 50 μmol/L) or lidocaine (2.1 to 21 μmol/L) in atrial (n = 6 to 15) or ventricular (n = 6 to 7) coronary-perfused preparations. Spontaneous arrhythmias were not observed under these conditions.

ACh (0.5 μmol/L) significantly abbreviated APD90 and ERP (see the Table). Both ranolazine and lidocaine blunted the effect of ACh to abbreviate APD, with ranolazine being slightly more effective than lidocaine (Table). In the presence of ACh alone, induction of persistent AF was observed in 100% of RA preparations (10 of 10).10 Ranolazine was more effective than lidocaine in preventing the initiation of ACh-mediated AF, terminating persistent AF, and preventing its reinduction (Table and Figure 7). In the presence of ACh, the effect of ranolazine to reduce excitability was better preserved than that of lidocaine (Table). Acceleration of pacing rate from a CL of 500 to 200 ms in the presence of ACh plus ranolazine (10 μmol/L) and ACh plus lidocaine (21 μmol/L) reduced Vmax by 23 ± 8% and 16 ± 10%, respectively (P < 0.06 versus by 2 ± 3% with ACh alone; P < 0.001 for each; n = 8 to 9; Figure 7B). Vmax reduction occurred despite the maintenance of relatively long diastolic intervals (Figure 7B).

The antifibrillatory effects of ranolazine were further evaluated in another model of AF.11 In 5 RAs subjected to ischemia (30 to 40 minutes) and subsequent reperfusion (40 to 60 minutes), the addition of isoproterenol (0.2 μmol/L) permitted reproducible induction of nonsustained AF/AFl (<1 minute). Note that β-adrenergic stimulation does not promote AF/AFl significantly in “healthy” atria.11 Ranolazine at a concentration of 5 μmol/L prevented the induction of arrhythmia in 3 of 5 RA preparations (Figure 7C). Arrhythmia induction was prevented by 10 μmol/L in 1 resistant RA preparation and by 20 μmol/L ranolazine in the other. Ranolazine caused a pronounced PRR in the ischemia/reperfusion-damaged RA preparations, which prevented closely coupled extrasystoles or rapid pacing (Figure 7C).

Discussion

Our study demonstrates very significant differences in the inactivation characteristics of atrial versus ventricular sodium channels and a striking atrial selectivity for the action of ranolazine to produce use-dependent block of the sodium channels, leading to depression of excitability, development of PRR, and suppression of AF.

Our hypothesis that ranolazine could exploit the atrioventricular differences in sodium channel inactivation was derived in part from our previous demonstration that the action of the drug on sodium channel–dependent parameters (Vmax) in the canine ventricle is negligible at therapeutic concentrations (1 to 10 μmol/L).1,4 and from the recent demonstration that the drug is an inactivated-state blocker.6 In support of the hypothesis that the presence of a greater percentage of atrial sodium channels in the inactivated state would enhance the action of the drug in the atria, we demonstrate a striking atrial selectivity in the actions of ranolazine to induce potent...
use-dependent effects on \( V_{\text{max}} \), DTE, PRR, and CV; these parameters are dependent on the sodium channels underlying early \( I_{\text{Na}} \), ie, peak (transient) \( I_{\text{Na}} \). Associated with these actions of the drug is its effectiveness to suppress and/or prevent the induction of AF in 2 experimental models. These data provide support for the hypothesis that atrium-selective sodium channel block may be an effective strategy for the management of AF.

Lidocaine, another predominantly inactivated-state sodium channel blocker, also produced an atrium-selective depression of sodium channel–dependent parameters (\( V_{\text{max}} \), CV, DTE, and PRR), providing support for the hypothesis that inactivated-state sodium channel blockers are likely to be atrium selective. It is noteworthy that lidocaine was much less atrium selective than ranolazine.

Further evidence in support of the hypothesis derives from the demonstration that propafenone, a predominantly open-state sodium channel blocker, is not atrium selective. In isolated canine ventricular myocytes, ranolazine has been shown to inhibit a number of ion channel currents, including late \( I_{\text{Na}} \) (IC\(_{50}\)=6 \( \mu \)mol/L), rapidly activating potassium-delayed rectifier (\( I_{\text{Kr}} \), IC\(_{50}\)=12 \( \mu \)mol/L), and late L-type calcium (late \( I_{\text{Ca}} \), IC\(_{50}\)=50 \( \mu \)mol/L); 25% to 30% reduction of late \( I_{\text{Ca}} \) is observed at 5 \( \mu \)mol/L ranolazine. Other potassium (\( I_{\text{Ks}} \), \( I_{\text{to}} \), \( I_{\text{K1}} \)), calcium (peak \( I_{\text{Ca}} \)), and Na–Ca exchanger currents are not affected by ranolazine or are affected at much higher concentrations, well beyond the therapeutic range of the drug (1 to 10 \( \mu \)mol/L).

Previous studies also have shown that ranolazine blocks \( I_{\text{Kr}} \) with an IC\(_{50}\) of 294 \( \mu \)mol/L in canine ventricular myocytes (at 0.1 Hz) and suppresses \( V_{\text{max}} \) with an IC\(_{50}\) of >100 \( \mu \)mol/L in Purkinje fibers and M-cell preparations paced at a CL of 500 ms. In sharp contrast, the results of the present study demonstrate prominent use-dependent reduction of \( I_{\text{Na}} \) (estimated from \( V_{\text{max}} \)) in atrial preparations at concentrations within the therapeutic range of ranolazine. Lidocaine is a fairly specific sodium channel blocker. Intrinsic atrioventricular differences in RMP and slope of late repolarization are largely explained by a smaller \( I_{\text{K1}} \) in atrial versus ventricular cells.

**Atrioventricular Differences in Sodium Channel Inactivation**

Our demonstration of 14- to 16-mV more negative half-inactivation voltage in atria versus ventricles in the canine heart (Figure 1) is qualitatively similar to that reported in the guinea pig heart, where the difference is 9.6±0.3 mV. These differences in biophysical properties suggest the possibility of tissue-specific cardiac sodium channel isoforms or differences in the stoichiometry of auxiliary subunits. Fahmi et al. presented evidence in support of this hypothesis showing that SCN3B, a \( \alpha \)-subunit of the sodium channel, is present in the ventricles but not in the atria of sheep hearts.

A larger density of \( I_{\text{Na}} \) in atrial versus ventricular myocytes, similar to that recorded in our study (at the holding potential of -140 mV; Figure 1A), was reported for guinea pig myocytes. The larger maximum current density may offset...
the intrinsically smaller sodium channel availability in atrial versus ventricular cells at physiological RMP (Figure 2).

**Ranolazine as a Selective Atrial Sodium Channel Block Antiarrhythmic**

In atria, unlike ventricle, ranolazine produces a significant reduction in excitability, leading to the development of a prominent rate-dependent PRR. PRR is a well-known feature of sodium channel blockers or conditions (like ischemia) that reduce excitability. Potassium channel blockers (such as $I_{Kr}$ and/or $I_{Ks}$) prolong repolarization and refractoriness to a similar extent (in a reverse rate-dependent fashion) but do not cause PRR.

There are intrinsic factors that predispose sodium channel current to inhibition by ranolazine and lidocaine in atria more effectively than in ventricular muscle or Purkinje fibers. The intrinsic differences are a more depolarized RMP and a less steep repolarization phase in atria, leading to a shorter diastolic interval at rapid rates (Figure 2). Ranolazine is more atrium selective than lidocaine in suppressing sodium channel–dependent parameters. This may be due in part to the fact that ranolazine prolongs atrial but not ventricular APD$_{90}$, whereas lidocaine abbreviates both atrial and ventricular APD$_{90}$. The prolongation of atrial APD$_{90}$ by ranolazine leads to elimination of diastolic intervals and more depolarized takeoff potentials at rapid rates (Figure 4C). The more negative h curve in atria and acceleration-induced depolarization of takeoff potential act in concert to increase the fraction of channels in the inactivated state, making sodium channels less available and more sensitive to block by ranolazine. The result is a greater suppression of $I_{Na}$-dependent parameters such as $V_{max}$, DTE, and CV and the development of use-dependent PRR. The effect of ranolazine to prolong atrial repolarization potentiates but does not appear to be a determining factor in the atrial specificity and antiarrhythmic efficacy of ranolazine. Propafenone ($I_{Na}$ and $I_{Kr}$ blocker), like ranolazine, selectively prolongs atrial APD$_{90}$ but suppresses $I_{Na}$-dependent parameters in both the atrial and the ventricular preparations to a similar extent, as does GE 68, a propafenone analog. Lidocaine abbreviates both atrial and ventricular APD$_{90}$ but still shows an atrial selectivity in

**Figure 6.** Use-dependent binding/unbinding kinetics of ranolazine and lidocaine to the sodium channel in the ventricle approximated from depression and recovery of the maximum rate of rise of the AP upstroke ($V_{max}$). A, B, $V_{max}$ changes after acceleration and deceleration of pacing rate in coronary perfused ventricular wedges. Both development of and recovery of use-dependent block are slower with ranolazine (30 $\mu$mol/L) than with lidocaine (21 $\mu$mol/L). C, D, Superimposed $V_{max}$ deflections obtained during recovery intervals (pacing coupling intervals up to 5000 ms) after the use-dependent $V_{max}$ depression at a CL of 300 ms. To be better able to discern measurable changes in $V_{max}$ in the ventricles, the concentration of ranolazine was increased to 30 $\mu$mol/L for these experiments. Unbinding kinetics of sodium channel blockers are believed to be independent of drug concentration. Under control conditions, there is little to no change in $V_{max}$ within the pacing CL range of 300 to 5000 ms.

**Figure 7.** Ranolazine suppresses AF and/or prevents its induction in 2 experimental models involving isolated arterially perfused right atria. A, Persistent ACh-mediated AF (0.5 $\mu$mol/L) is suppressed by ranolazine. AF is initially converted to flutter and then to sinus rhythm. B, Ranolazine prevents rapid-pacing induction of AF after pretreatment with ACh (0.5 $\mu$mol/L). ERP is 140 ms at a CL of 500 ms (left). Acceleration of pacing rate from a CL of 500 to 200 ms permits a 1:1 response only during the first 7 beats (right). C, Rapid-pacing–induced nonsustained AF (48-second duration) induced after ischemia/reperfusion and isoproterenol (ISO, 0.2 $\mu$mol/L) (left) and the effect of ranolazine to prevent pacing-induced AF (right). In both models, ranolazine causes prominent use-dependent induction of PRR.
depression of \( I_{Na} \)-dependent parameters. Also of note is the fact that PRR, the principal factor underlying the antiarrhythmic actions of ranolazine, extends well beyond the end of the AP (Figure 7).

Thus, the \( I_{Kr} \)-blocking effect of ranolazine potentiates the action of the drug to produce inactivated-state block of the sodium channel and thus its effectiveness in the management of AF. This effect of ranolazine also further differentiates it from lidocaine and contributes to its greater potency than lidocaine in the management of AF (Table). This greater potency appears to be due to a greater ability of ranolazine versus lidocaine to suppress atrial excitability when APD is abbreviated (Table).

Previous studies involving sodium channel blockers (quinidine, prajmaline, GE 68), including inactivated-state blockers (lidocaine), have failed to demonstrate atrioventricular differences in \( I_{Na} \) inhibition,\(^{1,6,17} \) comparable to those here reported with ranolazine, suggesting that ranolazine may be unique in this respect. Interestingly, AZD7009, which blocks \( I_{Kr} \), \( I_{Na} \), and \( I_{Kur} \), prolongs ERP and reduces DTE and CV preferentially in canine atria versus ventricles in vivo but produces similar \( V_{max} \) reduction in isolated superfused atrial and ventricular tissue preparations.\(^{18,19} \)

AVE-0118 and low concentrations of 4-AP (both preferentially block \( I_{Kur}/I_{Na} \)) produce an important prolongation of refractoriness in atria of dog and goat but negligible ventricular changes; these differences are explained by the presence of \( I_{Na} \) in atria but not in ventricles.\(^{1,2} \) AVE-0118 suppresses AF in electrically remodeled atria of the goat.\(^{2} \) Ranolazine does not alter phase 1 magnitude of the atrial AP (Figure 2), suggesting that ranolazine is unlikely to block \( I_{Kur} \). Low concentrations of 4-AP, known to selectively block \( I_{Kur} \),\(^{1} \) significantly reduce the magnitude of phase 1 in canine atria.\(^{20} \) \( I_{Ko} \) blockers have been reported to preferentially prolong atrial ERP.\(^{21} \)

We evaluated the potential of ranolazine to prevent the induction of AF/AFl and/or its effect to terminate AF in 2 different models. ACh mimics the conditions that predispose to vagally mediated AF and abbreviates atrial repolarization, mimicking the substrate encountered in electrically remodeled atria. This model generates persistent AF reproducibly,\(^{10,22} \) Ischemia/reperfusion, coupled with isoproterenol, mimics the conditions that prevail during acute myocardial infarction or the substrate encountered postinfarctually. This model generates paroxysmal episodes of AF reproducibly.\(^{11} \) Clinically relevant concentrations of ranolazine (5 to 10 \( \mu \text{mol/L} \)) were effective in preventing and/or terminating AF/AFl in these models.

**Study Limitations**

The atrial selectivity of ranolazine in this study was recorded in “healthy” atrial and ventricular preparations. Electric abnormalities associated with changes in RMP and/or APD (ie, ischemia or electrical remodeling) in either atria or ventricles may modulate atrial selectivity. It is noteworthy that the strong sodium channel–blocking effects of ranolazine in the atria were well preserved in pharmacologically (ACh) remodeled and post-ischemia/reperfusion atria. The absence of autonomic factors, hormones, and other blood-related factors in our Tyrode’s solution–perfused preparations may alter responses from those observed in vivo.

As always, extrapolation of these results to the clinic must be approached with caution. Although \( V_{max} \) provides the best approximation of peak \( I_{Ko} \) in multicellular cardiac preparations, it has long been appreciated that \( V_{max} \) is not a linear function of peak \( I_{Ko} \). However, the magnitude of ranolazine-induced differences in \( V_{max} \) between atrial and ventricular tissues cannot be explained by the nonlinearity of \( V_{max} \) and \( I_{Ko} \). Moreover, 3 other sodium channel–mediated parameters (CV, PRR, and DTE) are shown to be affected by ranolazine in an atrium-specific manner.

**Clinical Implications**

A number of antiarrhythmic agents have been shown to be effective in terminating and/or preventing clinical AF/AFl. Most of these agents have as a primary action the ability to reduce \( I_{Na} \) (such as propafenone or flecainide) or \( I_{Ko} \) (such as dofetilide) to block multiple channels (\( I_{Na} \), \( I_{Ko} \), \( I_{Kur} \), \( I_{Kr} \), \( I_{Na} \) amiodarone). An important limitation of these antiarrhythmic agents is their potential ventricular proarrhythmic actions and/or organ toxicity at therapeutically effective doses.\(^{3,4,23,24} \) Ranolazine is a novel antianginal agent with relatively mild adverse effects and no known proarrhythmic effects.\(^{25} \) Previous studies have suggested its utility in reducing arrhythmogenesis associated with acquired and congenital long-QT syndrome.\(^{5,4} \) The present study indicates that ranolazine effectively suppresses AF/AFl at concentrations that cause little change in the electric parameters of the ventricle. Although the actions of ranolazine in producing potent block of the sodium channel in the atria may be comparable to those of class IC antiarrhythmic agents such as propafenone and flecainide, it is apparently distinctly different from these agents in its atrial selectivity and rate dependence.

**Conclusions**

Our study demonstrates important differences in the inactivation characteristics of atrial versus ventricular sodium channels and a striking atrial selectivity for the action of ranolazine to produce use-dependent block of sodium channels, leading to suppression of AF. Our findings suggest that atrium-selective sodium channel block may be a valuable strategy to combat AF.

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**Disclosures**

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CLINICAL PERSPECTIVE
Effective and safe pharmacological management of atrial fibrillation (AF) is one of the greatest unmet needs in our society today and one that is growing as the prevalence of AF continues to increase with the aging of the baby-boomer generation. Among current pharmacological strategies for suppression of AF are sodium channel blockers, which are contraindicated in patients with coronary artery or structural heart disease because of their potent effect in the ventricles; potassium channel blockers, which predispose to torsade de pointes arrhythmias because of their potent effect to prolong ventricular repolarization; and mixed ion channel blockers such as amiodarone, which are associated with multiorgan toxicity and ventricular arrhythmias. Accordingly, recent drug development for the management of AF has focused on agents that selectively affect the atria but not the ventricles of the heart. Inhibition of the ultrarapid delayed rectifier potassium current, present in atria but not ventricles, is an example of an atrium-selective approach. The present study introduces the concept of atrium-selective sodium channel block as another strategy to manage AF. We demonstrate important differences in the sodium channel inactivation characteristics between atrial and ventricular myocytes and the ability of ranolazine to take advantage of these ion channel distinctions. Ranolazine produces potent use-dependent depression of sodium channel current and related parameters in the atria but not in the ventricle, leading to effective suppression of AF in 2 experimental models. The results of our study suggest that atrium-selective sodium channel block is a potentially novel strategy for the management of clinical AF.
Atrium-Selective Sodium Channel Block as a Strategy for Suppression of Atrial Fibrillation: Differences in Sodium Channel Inactivation Between Atria and Ventricles and the Role of Ranolazine
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