Rate-Dependent Effects of Vernakalant in the Isolated Non-Remodeled Canine Left Atria Are Primarily Due to Block of the Sodium Channel

Comparison With Ranolazine and dl-Sotalol

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Background—Several clinical trials have shown that vernakalant is effective in terminating recent onset atrial fibrillation (AF). The electrophysiological actions of vernakalant are not fully understood.

Methods and Results—Here we report the results of a blinded study comparing the in vitro canine atrial electrophysiological effects of vernakalant, ranolazine, and dl-sotalol. Action potential durations (APD_{50,75,90}), effective refractory period (ERP), post repolarization refractoriness (PRR), maximum rate of rise of the action potential (AP) upstroke (V_{max}), diastolic threshold of excitation (DTE), conduction time (CT), and the shortest S_1-S_1 permitting 1:1 activation (S_1-S_1) were measured using standard stimulation and microelectrode recording techniques in isolated normal, non-remodeled canine arterially perfused left atrial preparations. Vernakalant caused variable but slight prolongation of APD_{90} (P=not significant), but significant prolongation of APD_{50} at 30 μmol/L and rapid rates. In contrast, ranolazine and dl-sotalol produced consistent concentration- and reverse rate-dependent prolongation of APD_{90}. Vernakalant and ranolazine caused rate-dependent, whereas dl-sotalol caused reverse rate-dependent, prolongation of ERP. Significant rate-dependent PRR developed with vernakalant and ranolazine, but not with dl-sotalol. Other sodium channel-mediated parameters (ie, V_{max}, CT, DTE, and S_1-S_1) also were depressed significantly by vernakalant and ranolazine, but not by dl-sotalol. Only vernakalant elevated AP plateau voltage, consistent with blockade of ultrarapid delayed rectified potassium current and transient outward potassium current.

Conclusions—In isolated canine left atria, the effects of vernakalant and ranolazine were characterized by use-dependent inhibition of sodium channel-mediated parameters, and those of dl-sotalol by reverse rate-dependent prolongation of APD_{90} and ERP. This suggests that during the rapid activation rates of AF, the I_{Na} blocking action of the mixed ion channel blocker vernakalant takes prominence. This mechanism may explain vernakalant’s anti-AF efficacy. (Circ Arrhythm Electrophysiol. 2012;5:400-408.)

Key Words: pharmacology ■ electrophysiology ■ sodium channel block ■ atrial fibrillation

There is a need for effective and safe agents for rhythm control of patients with atrial fibrillation (AF). Prolongation of the effective refractory period (ERP) of atrial myocardium commonly is associated with antiarrhythmic outcomes. The drug-induced electrophysiological changes required for prolongation of the ERP include increased action potential duration (APD_{70-90}) and the development of the post repolarization refractoriness (PRR), where refractoriness extends beyond APD. The former commonly is due to block of potassium channels and the latter is due to inhibition of sodium channel. These electrophysiological changes are not necessarily confined to the atria, but also can interfere with ventricular repolarization and impulse conduction and thus may induce ventricular arrhythmias. Therefore, an ideal drug for the treatment of AF should selectively affect the electrophysiological properties of the atria only, leaving the ventricles unaffected.

Clinical Perspective on p 408

Vernakalant, a novel antiarrhythmic agent, has shown efficacy in terminating recent onset AF.1-4 Vernakalant inhibits a number of potassium channel currents, that is, the ultrarapid delayed rectified potassium current (I_{KUR}), the transient outward potassium current (I_{TO}), the rapidly activating delayed rectified potassium current (I_{KRA}), and the acetylcholine-regulated inward rectifying potassium current (I_{KAC})...
In addition, vernakalant inhibits cardiac sodium channels in a voltage- and frequency-dependent manner.\(^5\) Although vernakalant inhibits \(I_{Kt}\), effects on ventricular repolarization are limited due to concomitant blockade of late \(I_{Na}\).\(^6\) In humans, dogs, and pigs, vernakalant has been shown to preferentially increase the atrial versus ventricular ERP.\(^7\)–\(^9\) The chief aim of the present study was to compare the electrophysiological effects of vernakalant with those caused by ranolazine, which inhibits peak \(I_{Na}\), late \(I_{Na}\), and \(I_{Kr}\), and dl-sotalol, which primarily blocks \(I_{Kr}\), in normal non-remodeled coronary perfused canine left atria.

**Methods**

Class A beagle dogs (10 females and 11 males) weighing 20 to 35 kg were anticoagulated with heparin and anesthetized with pentobarbital (30–35 mg/kg IV). The chest was opened via a left thoracotomy, and the heart was excised, placed in a cardioplegic solution consisting of cold (4°C) or room temperature Tyrode solution containing 8.5 [K\(^+\)] and buffered with 95% O\(_2\) and 5% CO\(_2\) (37.0±0.5°C). The initial temperature of the coronary perfusate was 30°C and warmed to 37°C over a period of 5 to 6 minutes. The temperature was maintained at 37°C (Cole Parmer Instrument Co.). The perfusate was circulated around the bottom of the bath through a metal hypo tube (Small Parts Inc.) before flowing to the preparation so that the temperature of the perfusate matched that of the bath. The perfusate was delivered to the artery by a roller pump. An air trap was used to avoid bubbles in the perfusion line. Perfused atrial preparations were allowed to equilibrate in the tissue bath until electrically stable, usually 30 minutes, while pacing at cycle lengths (CL) of 500 to 800 ms. Basic stimulation was applied using a pair of thin silver electrodes insulated except at their tips.

Transmembrane action potentials (AP; sampling rate 41 kHz) were recorded using floating glass microelectrodes (2.7 mol/L KCl, 10–25 mol/L DC resistance) connected to a high input impedance amplification system (World Precision Instruments). The signals were displayed on oscilloscopes, amplified, digitized, and analyzed (Cambridge Electronic Design) and stored on computer hard drive or CD. Electronic differentiation of the action potential to obtain \(V_{\text{max}}\) was accomplished using operational amplifiers or by digitally using a sampling rate of 41 kHz.\(^1\)\(^,\)\(^2\) A pseudo-ECG was recorded using 2 electrodes consisting of Ag/AgCl half cells placed in the Tyrode solution 1.0 to 1.2 cm from the opposite ends of the preparation, thus measuring the electric field of the preparation as a whole. The diastolic threshold of excitation (DTE) was determined by increasing stimulus intensity in 0.01 mA steps starting from 0.1 mA, until a steady 1:1 activation was achieved. The ERP was measured by delivering premature stimuli after every 10th regular beat (with 5–10 ms resolution; stimulation with a 2 x DTE amplitude). PRR was defined as the difference between ERP and action potential duration at 75% repolarization (APD\(_{75}\); ERP corresponds to APD\(_{70–75}\) in the atria).\(^1\)\(^,\)\(^2\) Maximum rate of rise of the AP upstroke \(V_{\text{max}}\): stable AP recordings and \(V_{\text{max}}\) measurements are difficult to obtain in vigorously contracting perfused preparations. A large variability in \(V_{\text{max}}\) measurements is normally encountered under any given condition, primarily due to variability in the amplitude of phase 0 of the AP, which strongly determines \(V_{\text{max}}\) values. The effects of the test drugs on \(V_{\text{max}}\) were determined by comparing the largest \(V_{\text{max}}\) recorded under any given condition at a CL of 500 ms. Changes in \(V_{\text{max}}\) values on acceleration from a CL of 400 to 500 ms were recorded using floating glass microelectrodes (2.7 mol/L KCl, 10–25 mol/L DC resistance) connected to a high input impedance amplification system (World Precision Instruments). The signals were displayed on oscilloscopes, amplified, digitized, and analyzed (Cambridge Electronic Design) and stored on computer hard drive or CD. Electronic differentiation of the action potential to obtain \(V_{\text{max}}\) was accomplished using operational amplifiers or by digitally using a sampling rate of 41 kHz.\(^1\)\(^,\)\(^2\) A pseudo-ECG was recorded using 2 electrodes consisting of Ag/AgCl half cells placed in the Tyrode solution 1.0 to 1.2 cm from the opposite ends of the preparation, thus measuring the electric field of the preparation as a whole. The diastolic threshold of excitation (DTE) was determined by increasing stimulus intensity in 0.01 mA steps starting from 0.1 mA, until a steady 1:1 activation was achieved. The ERP was measured by delivering premature stimuli after every 10th regular beat (with 5–10 ms resolution; stimulation with a 2 x DTE amplitude). PRR was defined as the difference between ERP and action potential duration at 75% repolarization (APD\(_{75}\); ERP corresponds to APD\(_{70–75}\) in the atria).\(^1\)\(^,\)\(^2\) Maximum rate of rise of the AP upstroke \(V_{\text{max}}\): stable AP recordings and \(V_{\text{max}}\) measurements are difficult to obtain in vigorously contracting perfused preparations. A large variability in \(V_{\text{max}}\) measurements is normally encountered under any given condition, primarily due to variability in the amplitude of phase 0 of the AP, which strongly determines \(V_{\text{max}}\) values. The effects of the test drugs on \(V_{\text{max}}\) were determined by comparing the largest \(V_{\text{max}}\) recorded under any given condition at a CL of 500 ms. Changes in \(V_{\text{max}}\) values on acceleration from a CL of 400 to 500 ms were determined as well. Due to a substantial interpreparation variability, \(V_{\text{max}}\) values were normalized to a CL of 500 ms for each experiment and then averaged. Conduction time (CT): changes in conduction

![Figure 1. Effects of vernakalant, ranolazine, and dl-sotalol on action potential duration measured at 90% and 50% repolarization (APD\(_{90}\) and APD\(_{50}\)) in coronary perfused left atria.](http://circp.ahajournals.org/issue)
velocity were assessed by measuring the duration of the ECG activation (P) wave (at 50% of total amplitude of P wave).

Experimental protocols (n=6, 5, and 6 atrial preparations for vernakalant, ranolazine, and dl-sotalol, respectively) in which the following parameters were measured: APD$_{50}$, APD$_{75}$, APD$_{90}$, ERP, PRR, $V_{max}$, DTE, CT, and the shortest S$_1$-S$_2$ showing 1:1 conduction. Most of these parameters were recorded and measured at a basic CL of 1000, 500, and 300 ms. The drugs tested were assigned randomly and blinded to all involved with the conduct of the experimental study, with the blinded test agent code broken only after completion of all studies and data analysis. Left atrial AP measurements were obtained from the epicardial surface of the appendage. The effect of each drug on the electrophysiology of the left atria was evaluated at 3 distinct concentrations (3, 10, and 30 μmol/L). The tissues were exposed to each concentration of the drug for a period of 20 to 30 minutes.

Time control experiments (n=4) were performed to assess the stability of the preparation over a period of 2 hours after the end of the equilibration period. The time control studies were designed to match the duration of the experimental protocols.

Statistics

Statistical analysis was performed using unpaired t test, as well as 1 way repeated measures or multiple comparison ANOVA followed by Bonferroni test, as appropriate. An unpaired t test was used to compare 2 sets of independent parameters (APD$_{50}$ versus ERP). The null hypothesis of an unpaired t test was tested. One way repeated measures ANOVA was used to compare the changes in the same parameters (APD, ERP, etc) induced by 3 progressively increasing concentrations of each drug, as well as respective time controls. One way ANOVA was used was to test the hypothesis of no differences between the several treatment groups. A multiple comparison procedure (Bonferroni test) was used to isolate the control group that differed from the others. All data were expressed as mean±SD. P<0.05 was considered significant.

Results

Generally, ranolazine and dl-sotalol produced a concentration- and reverse rate-dependent prolongation of APD$_{90}$ (Figure 1). Vernakalant caused a variable effect on APD$_{90}$ (with abbreviation, prolongation, or no change being recorded), on average giving rise to no significant change in APD$_{90}$ (Figure 1), although examination of individual experiments (CL=1000 ms) indicates that most vernakalant treated preparations tended to display modest increases in APD$_{90}$ (Figure 2). APD$_{50}$ was consistently prolonged by dl-sotalol at 10 and 30 μmol/L at a CL of 1000 ms (Figure 1). Vernakalant (30 μmol/L) statistically significantly prolonged APD$_{50}$ at a CL of 300 ms. Ranolazine tended to abbreviate APD$_{50}$, reaching statistical significance at a CL of 500 ms at 30 μmol/L (Figure 1).

The effective refractory period was increased by all test agents in a concentration-dependent manner, but there were important rate-dependent differences between the 3 compounds (Figure 3). At the slowest pacing rate tested (CL=1000 ms), all 3 compounds caused similar ERP prolono-
At faster pacing rates (CL = 500 and 300 ms), the efficacy of dl-sotalol to prolong ERP was reduced and those of vernakalant and ranolazine were increased (Figure 3). In atria, the voltage level of ERP corresponds to the level of APD_{75} to 75. Prolongation of APD_{75} by ranolazine and vernakalant contributed modestly to ERP prolongation induced by these agents at the longest cycle length (1000 ms), and this contribution decreased or disappeared at CLs of 500 and 300 ms (Figure 4). Rate-dependent lengthening of ERP by vernakalant and ranolazine was largely due to the development of PRR (Figure 4), a parameter known to arise as sodium channel activity diminishes. At a concentration of 30 μmol/L, dl-sotalol also induced some PRR at a CL of 500 ms, but to a much lesser extent than vernakalant and ranolazine.

The AP plateau voltage was elevated by vernakalant, but not by ranolazine and dl-sotalol (Figures 1 and 5). The instability of AP recordings due to vigorous contraction of the preparations made it difficult to precisely measure AP amplitude. To quantify changes in AP amplitude, we normalized the amplitude of phase 2 to that of phase 0 (in cases in which the peak of phase 2 was difficult to determine, the plateau amplitude 25 ms after the start of AP was selected).

V_{max} was reduced consistently by vernakalant and ranolazine at a CL of 500 ms (Figure 6). Alterations in V_{max} were not detected with dl-sotalol at a CL of 500 ms. Ranolazine...
produced the greatest reduction of $V_{\text{max}}$ in response to a decrease of CL from 500 to 300 ms, followed by vernakalant (Figure 6, lower right panel). There was a slight decrease of $V_{\text{max}}$ at a CL of 300 ms in the presence of dl-sotalol (Figure 6). This can be explained, at least in part, by a depolarization of the take-off potential at a CL of 300 ms due to prolongation of APD (Figure 1).

Diastolic threshold of excitation was statistically significantly increased following exposure to 30 μmol/L vernakalant or ranolazine (Figure 7, upper panels). The extent of DTE increase was much greater at a CL of 300 versus 500 ms with both agents. DTE was not affected by dl-sotalol at any concentration or frequency. The duration of the P wave was significantly increased by vernakalant and ranolazine at 30 μmol/L at all pacing rates tested (Figure 7, lower panels). The degree of conduction slowing by these test agents was clearly rate-dependent. No significant changes in P wave duration were seen with dl-sotalol.

The shortest $S_1$-$S_1$ interval permitting 1:1 activation was increased significantly by vernakalant and ranolazine to a similar degree (Figure 8). Dl-sotalol also prolonged the shortest $S_1$-$S_1$ interval permitting 1:1 activation, but to a much lesser extent than vernakalant or ranolazine.

**Discussion**

The results of this blinded study indicate that in healthy non-remodeled isolated canine left atria, the electrophysiological effects of vernakalant and ranolazine are characterized largely by frequency-dependent depression of sodium channel-mediated parameters and those of dl-sotalol by reverse rate-dependent prolongation of APD$_{90}$, and thereby ERP. Vernakalant and ranolazine are shown to induce rate-dependent depression of $V_{\text{max}}$ pointing to use-dependent reduction of peak I$_{\text{Na}}$, leading to an increase in DTE, CT, and the briefest CL permitting 1:1 activation and development of PRR. Vernakalant, but not ranolazine or dl-sotalol, also produces an elevation of the atrial action potential plateau voltage, consistent with its effect to inhibit early repolarizing currents (ie, I$_{\text{Kur}}$, I$_{\text{to}}$).

**Electrophysiological Effects of Vernakalant, Ranolazine, and dl-Sotalol in Left Atria**

Vernakalant inhibits I$_{\text{Kur}}$, I$_{\text{Na}}$, peak and late I$_{\text{Na}}$, I$_{\text{Kr}}$, and I$_{\text{K(ACH)}}$. The results of our study suggest that the electrophysiological effects of vernakalant in isolated canine left atria preparations were due largely to block of the channel responsible for peak I$_{\text{Na}}$. Indeed, sodium channel-mediated electrophysiological parameters (such $V_{\text{max}}$, PRR, DTE, CT, and the shortest $S_1$-$S_1$ CL permitting 1:1 activation) were altered by vernakalant in a rate-dependent fashion. ERP was prolonged principally by the development of PRR secondary to inhibition of I$_{\text{Na}}$.

A functional manifestation of block of I$_{\text{Kur}}$ (and likely I$_{\text{to}}$) is a significant elevation of the action potential plateau voltage. Mathematical modeling indicates that “pure” block of I$_{\text{Kur}}$ (80% to 90% of the current) should decrease the magnitude of phase 1 by about 25%.$^{15,16}$ The practical elimination of the atrial AP notch by vernakalant (at 10 and 30 μmol/L; Figure 1) is consistent with an additional significant block of I$_{\text{to}}$. Elevation of the plateau voltage by I$_{\text{Kur}}$ blockers leads to an augmentation of I$_{\text{Kp}}$ and slowly activating delayed rectified potassium current (I$_{\text{Ks}}$), which serves to abbreviate APD$_{70}$ to 90 in normal atrial cells. A number of studies have shown an abbreviation of APD$_{70}$ to 90 with I$_{\text{Kur}}$ blockers in non-remodeled atria.$^{11,16,17}$ Of note, in remodeled atria, which commonly exhibit a triangular AP morphology, I$_{\text{Kur}}$ blockers cause a small prolongation in APD$_{70}$ to 90.$^{10,16}$ Inhibition of late I$_{\text{Na}}$ acts to reduce the height of the AP plateau and abbreviates APD. Vernakalant induced late I$_{\text{Na}}$ block appears to contribute relatively little to modulation of APD in our study. Vernakalant tends to prolong APD$_{75}$ to 90 in atria (Figures 1 and 2). This APD prolonging effect of vernakalant is likely due to the combined inhibition of multiple atrial K$^+$ currents. Vernakalant induced I$_{\text{Ks}}$ block appears to counterbalance the APD$_{90}$ abbreviating effect in I$_{\text{Kur}}$ and late I$_{\text{Na}}$ inhibition.

The electrophysiological effects of ranolazine and dl-sotalol in the current study are consistent with previously published data and with the ion channel blocking profiles of these agents.$^{13,18}$ Indeed, the electrophysiological effects of ranolazine are readily explained by potent use-dependent block of the sodium channels (both peak and late I$_{\text{Na}}$) and reverse use-dependent block of I$_{\text{Kr}}$.$^{13}$ Ranolazine produced little change in APD$_{50}$ and a slight prolongation of APD$_{90}$, presumably due to a combined effect of the drug to inhibit late I$_{\text{Na}}$ and I$_{\text{Kr}}$ (acting to abbreviate and prolong APD, respectively). Pure I$_{\text{Ks}}$ block produces a prolongation of both APD$_{50}$ and APD$_{90}$ in atria.$^{11}$ The principle effect of dl-sotalol was a reverse use-dependent prolongation of APD and ERP, consistent with its primary effect to inhibit I$_{\text{Kr}}$. At a concentration of 30 μmol/L, dl-sotalol produced mild depression of I$_{\text{Na}}$-mediated parameters ($V_{\text{max}}$, PRR, the shortest $S_1$-$S_1$). It is noteworthy that dl-sotalol previously has been demonstrated to inhibit I$_{\text{Na}}$ in ventricular muscles and Purkinje fibers at high concentrations (>100 μmol/L).$^{19}$ While I$_{\text{Na}}$ block with sotalol at therapeutic concentrations is not functionally detectable in the ventricles, it may be detectable in atria (considering the atrial selectivity of many I$_{\text{Na}}$ blockers$^{20}$). Intra-atrial conduction time in human atria has been reported.

![Figure 5](http://circep.ahajournals.org/)
to be increased by dl-sotalol in a use-dependent fashion, consistent with block of peak INa. The prolongation of APD with dl-sotalol, leading to a reduction in diastolic interval, may have promoted block of INa at rapid activation rates in our study.

**IKur, INa or Multi Ion Channel Block? What Determines Vernakalant Induced Atrial-Selective ERP Prolongation?**

The effective refractory period can be prolonged either by prolongation of APD70 to 90 (commonly due to block of atrial repolarizing potassium currents) or by development of PRR (secondary to block of peak INa). Preferential prolongation of the atrial ERP by vernakalant has been reported in a number of experimental and clinical studies. This atrial-selective effect of vernakalant commonly has been ascribed to the ability of vernakalant to inhibit potassium channels, particularly IKur, INa, and IKr. In addition to inhibiting these potassium currents, however, vernakalant blocks peak INa in a voltage and frequency-dependent manner, which also may cause atrial-selective ERP prolongation. Atrial-selective ERP prolongation due to block of peak INa has been reported for a number of INa blockers (ranolazine, amiodarone, dronedarone, and AZD1305). The effect of vernakalant on atrial APD has not been studied in great detail. However, preliminary data from APs recorded from patients with chronic AF showed that vernakalant prolongs both APD90 and ERP to a similar degree at a CL of 1000 ms (by 6 and 8%, respectively), suggesting a role of K+ channel inhibition in ERP prolongation in electrically remodeled AP. Only 1 pacing CL was tested in that study (ie, 1000 ms). Considering the frequency dependence of INa block with vernakalant at faster pacing rates, which are more relevant in the setting of AF, ERP prolongation with vernakalant is expected to be greater (due to development of PRR, as in the present study; Figures 3 and 4).

The present study is the first to measure the effect of vernakalant on both APD and ERP in isolated canine atria at several physiologically relevant pacing rates. The data obtained demonstrate that ERP prolongation induced by vernakalant in non-remodeled isolated canine atria is primarily

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**Figure 6. Effect of vernakalant, ranolazine, and dl-sotalol on a maximum rate of rise of the action potential upstroke (Vmax).** Upper panels: typical examples of use-dependent reduction of Vmax on decrease of cycle length (CL) from 500 to 300 ms with vernakalant, ranolazine, and dl-sotalol. Bottom panels: normalized changes at a CL of 500 ms (left plot) and on abbreviation of CL from 500 to 300 ms (right plot) in the absence and presence of drugs. Right plot: Vmax value at a CL of 500 ms was taken as 100% for each condition. N=3 to 5. *P<0.05 versus respective control.
due to PRR and that this effect is strongly rate-dependent, largely manifesting at 500 and 300, but not at 1000 ms CLs (Figure 4). It appears that vernakalant is an atrial-selective sodium channel blocker and that its atrial-selective ERP prolongation, at least in normal tissue, is due in large part to block of $I_{\text{Na}}$, although indirect effects on $I_{\text{Na}}$ resulting from changes in AP morphology cannot be excluded. Of note, vernakalant has rapid unbinding kinetics from the sodium channel, a key feature of all atrial-selective sodium channel blockers.\(^{25}\) Note that several prominent $I_{\text{Kur}}$ blockers, along with vernakalant, have been shown to inhibit peak $I_{\text{Na}}$ (such as AZD7009, AZD1305, and AVE0118).\(^{5,27,29,30}\) 3-[(dimethylamino)methyl]-6-methoxy-2-methyl-4-phenylisoquinolin-1(2H)-1 (ISQ1) and 2-phenyl-1,1-dipyridin-3-yl-2-pyrrolidin-1-yl-ethanol (TAEA) also slow conduction velocity in atria but not in ventricles in vivo,\(^{31}\) indicating that they block $I_{\text{Na}}$ selectively in atria. These observations suggest that the atrial selectivity of most of these purported $I_{\text{Kur}}$ blockers to prolong ERP may be mediated predominantly by their ability to inhibit $I_{\text{Na}}$.

**Potassium or Sodium Channel Block? Which Is More Important for Vernakalant’s Anti-AF Action?**

Several large clinical trials have demonstrated the effectiveness of vernakalant to terminate recent onset AF.\(^1\)\(^-\)\(^4\) Prolongation of atrial ERP by vernakalant is thought to be 1 of the mechanisms involved in conversion of AF to normal sinus rhythm. Because vernakalant induced ERP prolongation is primarily due to block of $I_{\text{Na}}$ (at least in non-remodeled canine atria), block of peak $I_{\text{Na}}$ would appear to be the principal contributor to the anti-AF actions of vernakalant.

**Effects of the Drugs in Remodeled Atria**

AF commonly is associated with pathophysiologic conditions that lead to electric and structural remodeling of the atria, and the effects of pharmacological agents may be different in this setting. Remodeled atria typically display a short APD with a triangulated AP morphology. Atrial remodeling caused by heart failure and hypertension can be associated with unchanged or even prolonged APD and ERP.\(^{32-34}\) In these pathologies, atrial APD and ERP are likely to abbreviate secondary to AF. In a ventricular tachypacing induced canine heart failure model, the electrophysiological effects of ranolazine in atria are well preserved (Burashnikov et al, unpublished observation). In tissues isolated from patients with chronic AF, clinically relevant concentrations of vernakalant (10 $\mu$mol/L) caused a statistically significant prolongation of APD and ERP without significantly reducing $V_{\text{max}}$ at a frequency of 1 Hz.\(^{10}\) Under the same experimental conditions, vernakalant caused no significant change in APD, ERP, or $V_{\text{max}}$ in atrial tissues isolated from patients in sinus rhythm.\(^{10}\) This suggests that the potassium channel blocking properties of vernakalant might play a larger role in the electrically remodeled atrium than in the non-remodeled one at normal or slow heart rates. This mechanism might contribute to the prevention of AF recurrence post conversion by vernakalant.\(^{35}\) At faster heart rates, it is expected that the parameters...
determined by the use-dependent \( I_{Na} \) blocking effect of vernakalant would become more manifest. Because \( I_{Kr} \) density is reduced following acceleration of pacing rate\(^{36}\) and also is reduced in atrial cells isolated from patients with persistent AF\(^{37,38}\) the \( I_{Kur} \) blocking effects of vernakalant are expected to be diminished at rapid activation rates in remodeled atria. Ultimately, as vernakalant blocks multiple potassium channel currents including \( I_{Kur}, I_{Kr}, I_{Kach} \) as well as blocking \( I_{Na} \), the electrophysiological actions of vernakalant in remodeled atrium will reflect a balance of effects on all target currents present in this condition. Studies in an atrial pacing model of persistent AF in goats support the preserved activity of vernakalant in the electrically remodeled atrium.\(^{39}\) In the human remodeled atria with persistent AF and in atrial tachypacing remodeled goat atria, ERP prolonging ability of dl-sotalol is reduced.\(^{40,41}\) Depending on the underlying causes of atrial remodeling (heart failure, hypertension, ischemia, age, AF, and their various combinations), electrophysiology and pharmacological response of the remodeled atria can differ significantly depending on a number of factors, including action potential duration and morphology, diastolic interval, resting membrane potential, and rate of atrial activation.

**Study Limitations**

The absence of autonomic and hormone influences, which can significantly modulate cardiac electrophysiology and pharmacological response, are among the limitations of our in vitro investigation. In addition, the results of our study were obtained in “healthy” atria, whereas AF normally occurs in electrically and structurally remodeled atria. Atrial remodeling can significantly modulate the pharmacological response.

**Conclusions**

This is the first full-length paper reporting the detailed effect of vernakalant on isolated canine atrial electrophysiology, with the vernakalant induced changes in APD and ERP directly compared. The results of our study indicate that the rate-dependent effect of vernakalant and ranolazine to prolong refractoriness in non-remodeled isolated canine left atria is due largely to use-dependent block of peak \( I_{Na} \). In contrast, sotalol showed reverse rate-dependent effects on ERP, consistent with its \( I_{Kr} \) blocking profile.

**Sources of Funding**

Supported by a grant from Merck & Co., grant HL47678 (CA) from NHLBI, and Masons of New York State and Florida.

**Disclosures**

Dr Antzelevitch received research support from Merck & Co.; Dr Lynch is an employee of Merck & Co.; Dr Pourrier is an employee of Cardome Pharma Corp.; and Dr Gibson is an employee of AAKVSI Pharma Consulting, LLC.

**References**

K⁺ current similar to Kv1.5 cloned channel currents. Circ Res. 1993;73:1061–1076.


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**CLINICAL PERSPECTIVE**

There is a need for effective and safe agents for rhythm control of patients with atrial fibrillation (AF). Vernakalant is a novel antiarrhythmic agent, which inhibits multiple potassium (I\textsc{kur}, I\textsc{K,ACH}, I\textsc{to}, and I\textsc{K}) and sodium channel (I\textsc{Na}) currents. Vernakalant causes atrial-selective prolongation of the effective refractory period (ERP), terminates recent onset AF, and prevents AF recurrence. The present study compares the electrophysiological effects of vernakalant with ranolazine and dl-sotalol in normal, non-remodeled coronary perfused canine left atria. The electrophysiological actions of vernakalant and ranolazine are characterized largely by frequency-dependent alterations of peak I\textsc{Na}-mediated parameters (including ERP prolongation due to post repolarization refractoriness) and those of dl-sotalol by reverse rate-dependent prolongation of action potential duration (APD\textsubscript{90}) and thereby ERP. Our results confirm previous studies that have attributed the antiarrhythmic actions of ranolazine to atrial-selective inhibition of peak I\textsc{Na} and those of dl-sotalol to inhibition of rapidly activating delayed rectifier potassium current (I\textsc{k}). The results of the present study suggest that vernakalant, like ranolazine, by virtue of its rapid kinetics to inhibit peak I\textsc{Na}, produces atrial-selective prolongation of ERP due to post repolarization refractoriness, which may in part underlie its antiarrhythmic efficacy without promoting ventricular proarrhythmia. Atrial-selective inhibition of potassium currents by vernakalant may contribute as well to its efficacy and safety, but this contribution appears to be limited in non-remodeled atrium.
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Circ Arrhythm Electrophysiol. 2012;5:400-408; originally published online February 9, 2012; doi: 10.1161/CIRCEP.111.968305

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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