

Atrial-Selective Sodium Channel Block Strategy to Suppress Atrial Fibrillation: Ranolazine versus Propafenone

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ABSTRACT

Ranolazine has been shown to produce atrial-selective depression of sodium channel-dependent parameters and suppress atrial fibrillation (AF) in a variety of experimental models. The present study contrasts the effects of ranolazine and those of a clinically used anti-AF class IC agent, propafenone. Electrophysiological and anti-AF effects of propafenone and ranolazine were compared at clinically relevant concentrations (i.e., 0.3–1.5 and 1–10 μM , respectively) in canine isolated coronary-perfused atrial and ventricular preparations. Transmembrane action potential and pseudo-ECG were recorded. Both ranolazine and propafenone produced atrial-selective prolongation of action potential duration. Propafenone depressed sodium channel-mediated parameters [maximum rate of rise of the action potential upstroke (V_{max}), conduction time, and diastolic threshold of excitation] and induced postrepolarization refrac-

toriness to a greater degree than ranolazine, and these effects, unlike those induced by ranolazine, were not or only mildly atrial-selective at normal rates (cycle length 500 ms). At fast pacing rates, however, the effects of propafenone on V_{max} and conduction time became atrial-selective, because of the elimination of diastolic interval in atria, but not in ventricles. Propafenone (1.5 μM) and ranolazine (10.0 μM) were effective in preventing the initiation of persistent acetylcholine-mediated AF (6/7 and 9/11 atria, respectively), its termination (8/10 and 8/12 atria, respectively), and subsequent reinduction (8/8 and 7/8 atria, respectively). Thus, propafenone and ranolazine both suppress AF, but ranolazine, unlike propafenone, does it with minimal effects on ventricular myocardium, suggesting a reduced potential for promoting ventricular arrhythmias.

Introduction

A limitation of the use of the currently available anti-atrial fibrillation (AF) agents is the risk of induction of ventricular arrhythmias. This has prompted the development of atrial-specific antiarrhythmic agents. We have shown that ranolazine, an antianginal agent possessing antiarrhythmic properties (Antzelevitch et al., 2004), selectively affects sodium channel-dependent parameters in canine atria versus ventricles and effectively suppresses AF in vitro (Burashnikov et al., 2007). Similar atrial selectivity of ranolazine as well as its anti-AF efficacy have been demonstrated in the porcine heart in vivo (Kumar et al., 2009; Carvas et al., 2010). Consistent with these experimental observations, clinical studies have shown anti-AF efficacy of ranolazine (Scirica et al.,

2007; Murdock et al., 2008, 2009, 2010). Propafenone, a potent sodium channel blocker, is used for termination as well as prevention of AF in the clinic (Alboni et al., 2004; Fuster et al., 2011). The aim of the present study was to compare the electrophysiological effects of ranolazine and propafenone in isolated canine coronary-perfused atrial and ventricular preparations and their anti-AF efficacy in an experimental model of AF.

Materials and Methods

This investigation conformed to the *Guide for Care and Use of Laboratory Animals* published by the National Institutes of Health (Institute of Laboratory Animal Resources, 1996) and was approved by the animal care and use committee of the Masonic Medical Research Laboratory. Experiments were performed by using isolated arterially perfused canine right atrial preparations and left ventricular arterially perfused wedge preparations ($\approx 2 \times 1 \times 1$ cm). Detailed methods for the isolation and perfusion of these preparations have been described previously (Antzelevitch et al., 2004; Burashnikov et al., 2004). In brief, the preparations were dissected from hearts removed from anesthetized (sodium pentobarbital) adult

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ABBREVIATIONS: AF, atrial fibrillation; ACh, acetylcholine; AP, action potential; APD, AP duration; CL, cycle length; DTE, diastolic threshold of excitation; ERP, effective refractory period; PM, pectinate muscle; PRR, postrepolarization refractoriness; V_{max} , maximum rate of rise of the AP upstroke; AZD1305, *tert*-butyl (2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)carbamate; E-4031, *N*-[4-[1-[2-(6-methylpyridin-2-yl)ethyl]piperidine-4-carbonyl]phenyl]; GE-68, 1-[3-(phenylethyl)-2-benzofuryl]-2-(propylamino)-ethanol hydrochloride.

mongrel dogs (20–25 kg). Unfolded right atria with a rim of the right ventricle was cannulated and perfused through the ostium of the right coronary artery, and the left ventricular wedge was perfused through a branch of the left coronary artery. Unperfused tissue was removed with a razor blade or scissors. The cut ventricular and atrial branches were ligated by using silk thread. After these procedures (performed in cold cardioplegic solution, 4–8°C), the preparations were transferred to a temperature-controlled bath and arterially perfused with Tyrode's solution by use of a roller pump. The composition of the Tyrode's solution was 129 mM NaCl, 4 mM KCl, 0.9 mM NaH₂PO₄, 20 mM NaHCO₃, 1.8 mM CaCl₂, 0.5 mM MgSO₄ 0.5, and 5.5 mM D-glucose, buffered with 95% O₂ and 5% CO₂ (37 ± 0.5°C; pH 7.35).

Transmembrane action potential (AP) recordings (sampling rate 41 kHz) were obtained by using standard or floating glass microelectrodes (2.7 M KCl; 10–25 MΩ DC resistance). A pseudo-ECG was recorded by using two electrodes consisting of Ag/AgCl half cells placed in the Tyrode's solution, 1.0 to 1.2 cm from opposite ends of the atrial or ventricular coronary-perfused preparations. Conduction time was 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 and 90% of P-wave or QRS amplitude. Diastolic threshold of excitation (DTE) was determined by increasing stimulus intensity in 0.01-mA steps. Maximum amplitude of stimulation used for the study was 10 times of the DTE determined in the beginning of each experiment. Effective refractory period (ERP) was measured by delivering premature stimuli after every 10th regular beat at a pacing cycle length (CL) of 500 and 300 ms (with 10-ms resolution; stimulation with a 2× DTE amplitude, determined at each CL). Postrepolarization refractoriness (PRR) was considered to be present when ERP exceeded APD₉₀ in the ventricle and APD₇₅ in atria. Under control conditions, ventricular ERP coincided with APD₉₀, whereas atrial ERP generally coincided with APD₇₅.

Maximum Rate of Rise of the AP Upstroke. Stable AP recordings and maximum rate of rise of the AP upstroke (V_{\max}) measurements are difficult to obtain in vigorously contracting perfused preparations. In coronary-perfused atria and ventricles, the effects of propafenone and ranolazine on V_{\max} were determined by comparing the largest V_{\max} recorded at any given condition. Because of a substantial interpreparation variability, V_{\max} values were normalized for each experiment and then averaged.

Experimental Protocols. The equilibration period for the preparations was 30 to 60 min. The concentrations of ranolazine (1.0, 5.0, and 10.0 μM) and propafenone (0.3 and 1.5 μM) were increased in a stepwise manner, with at least 20 min for ranolazine and 40 min for propafenone at each concentration before starting the collection of the data. This difference reflects the various exposure durations that are required to achieve a steady state in electrophysiological actions of the agents (Delgado et al., 1985; Antzelevitch et al., 2004). The concentrations of the drugs used were within the therapeutic relevant ranges of ranolazine and propafenone achieved when the drugs are prescribed at their recommended doses (Grant, 1996; Antzelevitch et al., 2011). To compare the antiarrhythmic potential of propafenone and ranolazine, we used an acetylcholine (ACh; 0.5–1.0 μM)-dependent AF model in coronary-perfused right atria, where persistent AF is inducible in 100% of preparations (by a single premature beat or rapid pacing) (Burashnikov and Antzelevitch, 2003; Burashnikov et al., 2007). We determined the effect of propafenone and ranolazine to prevent (series 1) the induction of AF as well as, in different preparations, the effect of these drugs to terminate (series 2) persistent AF. In the first series, ACh was added to the perfusate ≥40 min after the start of 1.5 μM propafenone and ≥20 min after the start of 10 μM ranolazine, followed by attempts to induce arrhythmias using programmed electrical stimulation. In the second series, the effect of propafenone or ranolazine to terminate persistent AF was tested by adding these drugs to the coronary perfusate solution after 5 to 8 min of persistent AF. After AF termi-

nation, reinduction of the arrhythmia was attempted by using programmed electrical stimulation.

Drugs. Ranolazine (Gilead Sciences, Palo Alto, CA), propafenone (Sigma, St. Louis, MO), and acetylcholine (Sigma) all were dissolved in distilled water, and each was prepared fresh as a stock of 1 to 10 mM before each experiment.

Statistics. Statistical analysis was performed by using paired or unpaired *t* tests and one-way repeated-measures or multiple comparison analysis of variance followed by Bonferroni's test, as appropriate. All data are expressed as mean ± S.D.

Results

Propafenone versus Ranolazine: APD₉₀, ERP, PRR, DTE, V_{\max} , and Conduction Time. Both propafenone and ranolazine produced atrial, but not ventricular, prolongation of APD₉₀ (Fig. 1). Propafenone rate-dependently lengthened ERP much more than APD_{75–90} in both atria and ventricles, thereby inducing a significant PRR in both chambers (Fig. 2). Ranolazine induced rate-dependent atrial-selective prolongation of ERP and the development of PRR only in atria (Fig. 2).

DTE was significantly increased by propafenone in both atria and ventricles at 500 and 300 CLs (Fig. 3). In contrast, ranolazine increased DTE selectively in atria, with a much greater increase at 300 versus 500 ms CL (Fig. 3). Propafenone potently depressed V_{\max} and increased conduction time similarly in atria and ventricles at a CL of 500 ms, but altered those parameters to a greater extent in atria versus ventricles at a CL of 300 ms (Figs. 4 and 5). Ranolazine produced atrial-selective reduction in V_{\max} and increase in conduction time, which was more pronounced at faster pacing rates (Figs. 4 and 5). Ranolazine produced a weaker depression of V_{\max} and conduction velocity compared with propafenone. Figure 4A reveals the mechanisms contributing to the atrial selectivity of propafenone and ranolazine to reduce V_{\max} at rapid pacing rates. Because of the slow repolarization phase of the atrial action potential and the effect of both propafenone and ranolazine to further slow phase 3, acceleration of rate leads to elimination of the diastolic interval in atria but not in the ventricles. Because much of the recovery from sodium channel block occurs during the diastolic interval, greater accumulation of block occurs in atria versus ventricles at rapid rates of activation.

Propafenone versus Ranolazine: Anti-AF Action. ACh (0.5 μM) alone significantly abbreviated atrial APD₉₀ [from 198 ± 17 to 45 ± 9 ms; *p* < 0.001; *n* = 10 for each; pectinate muscle (PM), CL = 500 ms] and ERP (from 149 ± 12 to 51 ± 7 ms; *p* < 0.001; *n* = 10 for each; PM, CL = 500 ms), permitting the induction of persistent AF in 100% of atria (10/10 atria). Addition of ACh (0.5 μM) to atrial preparations pretreated with propafenone (1.5 μM) and ranolazine (10 μM) abbreviated APD and ERP to an extent that was less than that observed in the absence of propafenone and ranolazine (Table 1). Under these conditions, both agents were very effective in preventing the induction of persistent ACh-mediated AF, with propafenone being slightly more effective compared with ranolazine (Table 1). In a different set of atrial preparations, we tested the effect of the two drugs to terminate persistent ACh-mediated AF. The addition of propafenone (1.5 μM) or ranolazine (10.0 μM) to the perfusion solution on the fifth to eighth minute of persistent AF terminated the arrhythmia in 8/10 and 8/12 atria, respectively (Fig. 6; Table 1). Average time for AF termination

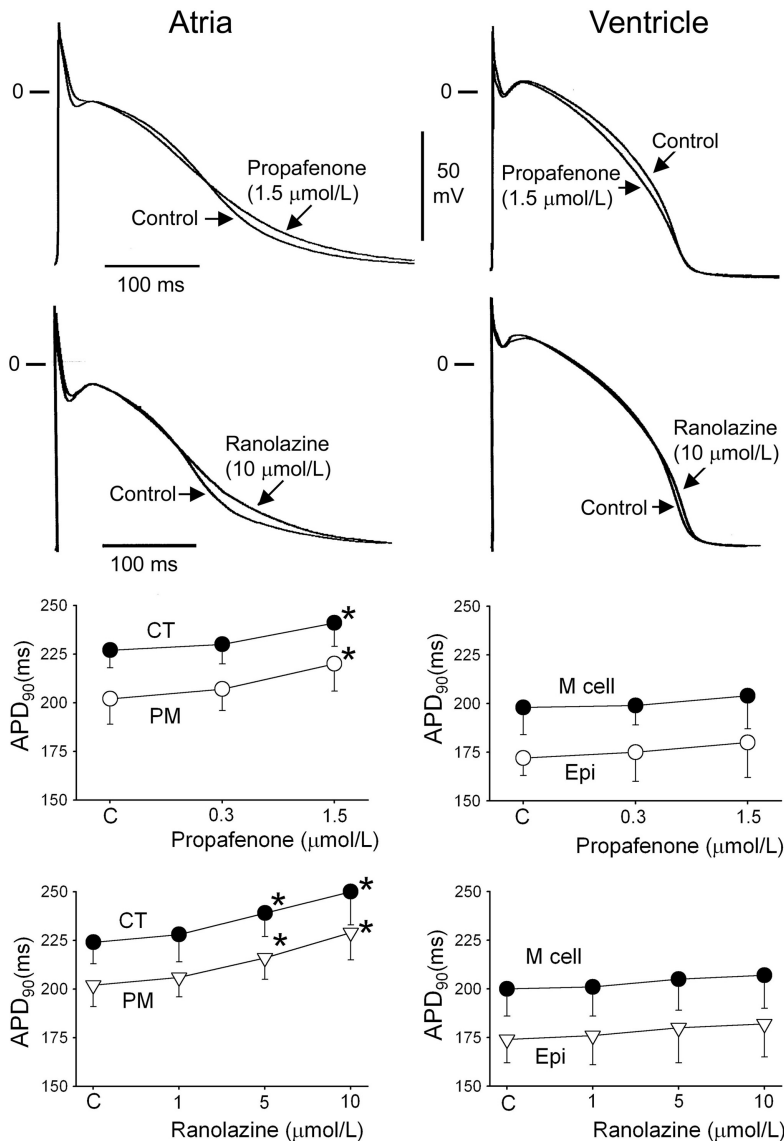


Fig. 1. Effects of propafenone and ranolazine on transmembrane APs from various atrial (left) and ventricular (right) regions. Shown are representative examples of APs and summary data of the effect of propafenone and ranolazine on APD₉₀ in atrial and ventricular preparations stimulated at a cycle length of 500 ms. CT, crista terminalis; M cell, subendocardial region; Epi, epicardium. *, $p < 0.05$ versus control. $n = 6-18$.

was 7 ± 5 min for propafenone and 14 ± 7 min for ranolazine. Both propafenone and ranolazine effectively prevented the reinduction of persistent AF (Table 1). Brief episodes of nonsustained AF or atrial flutter (<1-min duration) could still be induced in 3/8 and 5/8 atria in the presence of propafenone and ranolazine, respectively. These anti-AF actions of propafenone and ranolazine were associated with rate-dependent depression of excitability, making it impossible for the atria to beat at rapid rates such as those during AF (Fig. 6).

Discussion

The main result of the current experimental study is that although both ranolazine and propafenone effectively terminate ACh-mediated AF and prevent the induction of the arrhythmia, ranolazine, in contrast to propafenone, does it without producing significant electrophysiological effects in the ventricles.

Atrial-Selective Sodium Channel Block and AF Suppression. The risk of induction of ventricular proarrhythmia and/or organ toxicity is a major limitation of currently clinically

available anti-AF agents (Fuster et al., 2011). The availability of atrial-specific or atrial-selective agents could obviate this problem. Block of I_{Kur} has long been considered to be a promising atrial-selective approach for the management of AF. However, studies indicate that “pure” I_{Kur} block is unlikely to be effective in suppressing AF (Burashnikov and Antzelevitch, 2008b,c, 2010; Pandit et al., 2011; Ravens and Wettwer, 2011).

We provided evidence in support of the hypothesis that atrial-selective sodium channel block may effectively suppress AF without inducing ventricular arrhythmias (Burashnikov et al., 2007). This concept stemmed from the finding that certain biophysical properties (e.g., steady-state inactivation) of the sodium channels and action potential morphology in atria differ from those in the ventricles (Burashnikov et al., 2007). Both ranolazine and amiodarone were shown to “take advantage” of these distinctions, producing significant depression of sodium channel-dependent parameters in canine atrial, but not in ventricular, preparations, thus leading to effective suppression of AF at concentrations causing minimal to no effect on ventricular electrophysiology (Burash-

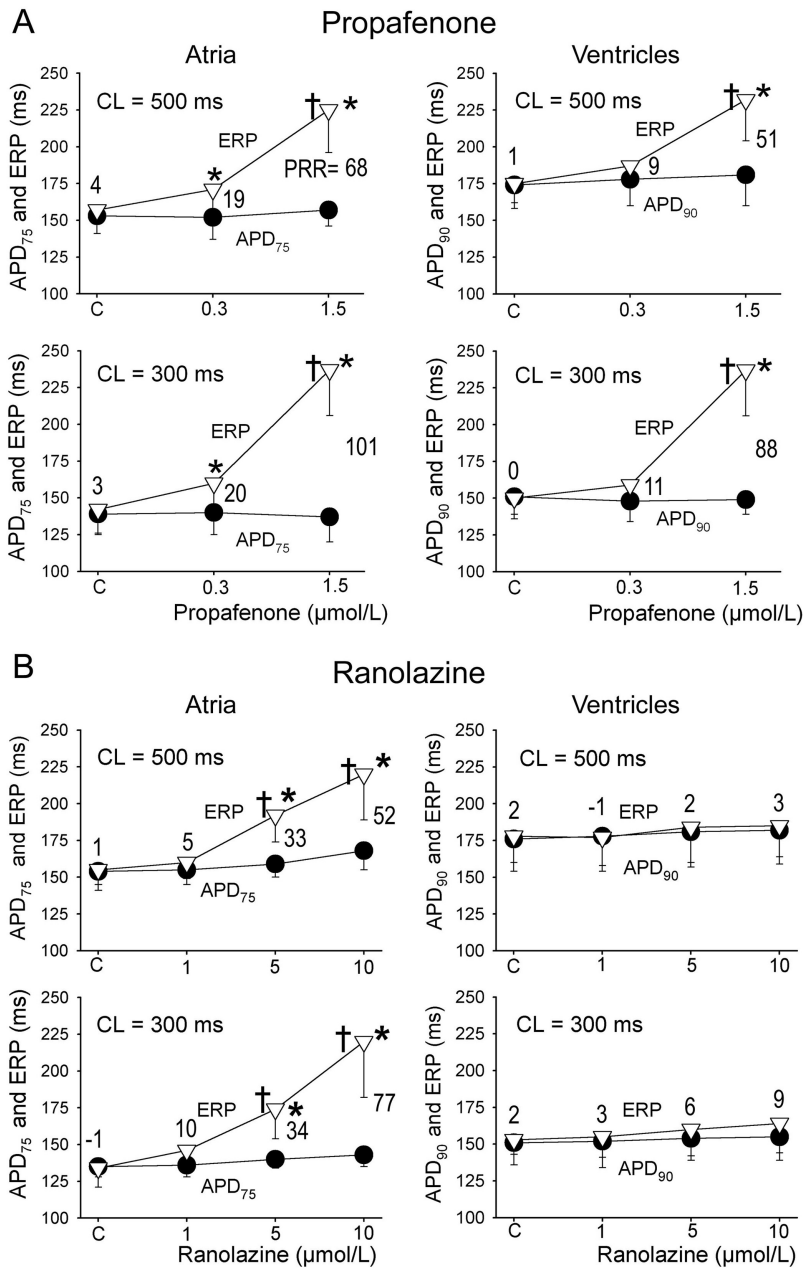


Fig. 2. Effects of propafenone (A) and ranolazine (B) on ERP, APD, and PRR in atrial and ventricular preparations. PRR was measured as the difference between ERP and APD₇₅ in atria and between ERP and APD₉₀ in ventricles (ERP is coincident with APD₇₅ in atria and APD₉₀ in ventricles). Note: whereas APD₉₀ was prolonged by the agents, APD₇₅ was not (see Fig. 1). Ventricular data were obtained from epicardium, and atrial data were from pectinate muscle. *, $p < 0.05$ versus control. †, $p < 0.05$ versus APD₇₅ values in atria and APD₉₀ in ventricles. $n = 6-18$.

nikov et al., 2007, 2008; Sicouri et al., 2009; Antzelevitch et al., 2011). The atrial selectivity of ranolazine as well as its anti-AF efficacy have been demonstrated in both in vitro and in vivo animal studies (Burashnikov et al., 2007; Kumar et al., 2009; Carvas et al., 2010; Szél et al., 2011) Atrial-selective depression of sodium channel-mediated parameters in the canine heart has also been reported with exposure to chronic amiodarone and acute *tert*-butyl (2-[7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]ethyl)carbamate (AZD1305) (Burashnikov et al., 2008, 2010). In a large clinical study in patients with non-ST segment elevation acute coronary syndrome (Scirica et al., 2007) treatment with ranolazine was associated with the reduced incidence of supraventricular arrhythmias and a 30% reduction in new onset AF. A number of relatively small clinical studies have shown a potent anti-AF efficacy of ranolazine for the termination of paroxysmal AF (Mur-

dock et al., 2008, 2009, 2010). In an exploratory (not placebo-randomized control) clinical study, ranolazine was found to be more effective than amiodarone in preventing postoperative AF (AF incidence was 17.5 versus 26.5%) (Miles et al., 2011). Ranolazine can inhibit early I_{Na} , late I_{Na} , I_{Kr} , and late I_{Ca} (Antzelevitch et al., 2004; Burashnikov et al., 2007). Inhibition of early I_{Na} by ranolazine is atrial-selective and markedly rate-dependent, which is consistent with the differential effect (atria versus ventricle) of ranolazine on V_{max} (Fig. 4) and P-wave and QRS duration (Fig. 5) (Zygmunt et al., 2011). At therapeutically relevant concentrations (1–10 μ M) ranolazine possesses antiarrhythmic properties in the ventricles, primarily because of its potent effect to inhibit late I_{Na} (Antzelevitch et al., 2004, 2011; Wu et al., 2004), whereas in the atria, this is principally because of its effect to inhibit early I_{Na} (Burashnikov et al., 2007). Unlike the block of peak I_{Na} ,

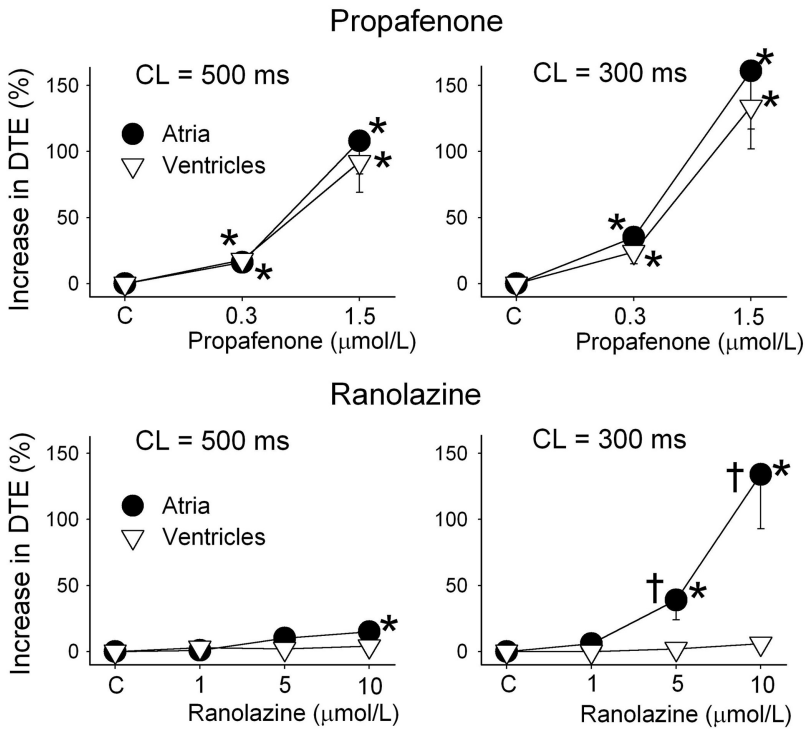


Fig. 3. Ranolazine (bottom), but not propafenone (top), causes an atrial-selective, rate-dependent increase in DTE. The increase in DTE caused by propafenone is greater than that of ranolazine. DTE measurements obtained from crista terminalis and pectinate muscle are combined under atria, and those from ventricular epicardium and endocardium are combined under ventricles. *, $p < 0.05$ versus control. †, $p < 0.05$ versus values in ventricles. $n = 6-10$.

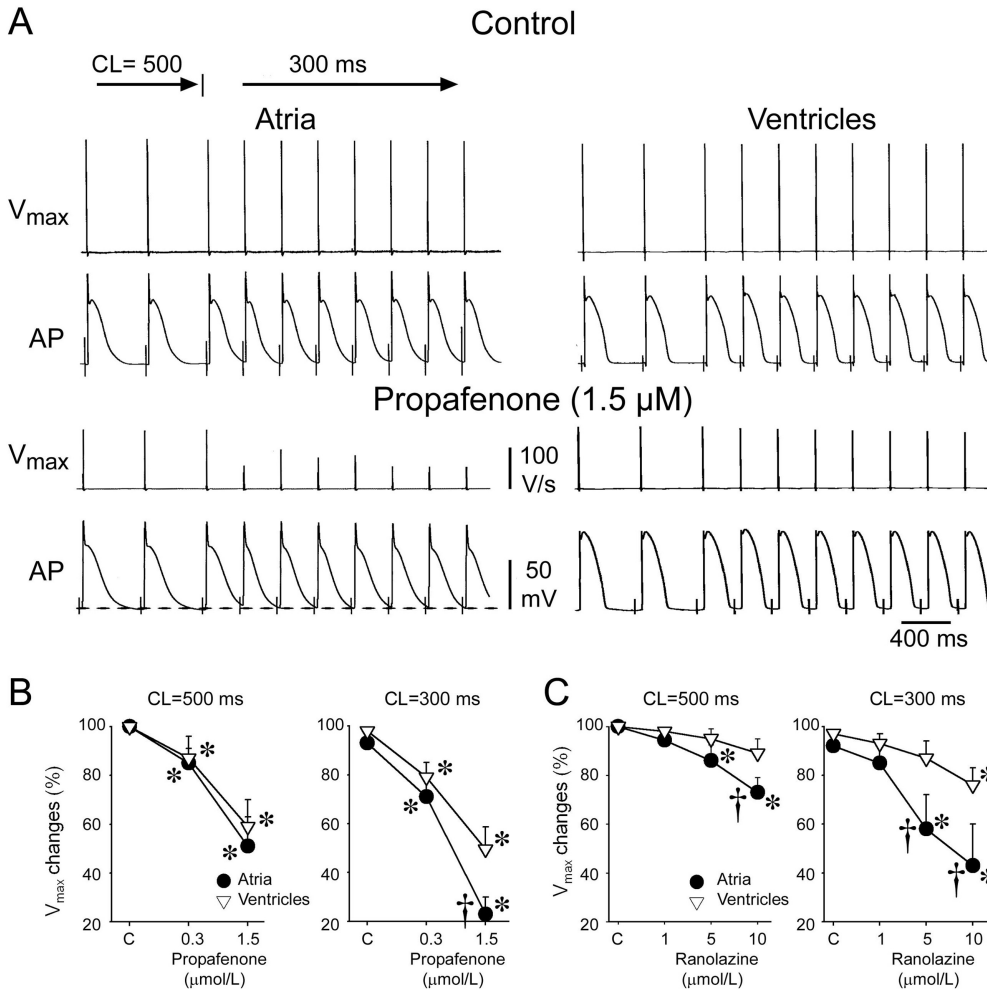


Fig. 4. Rate-dependent effects of propafenone and ranolazine to depress the V_{max} in atrial and ventricular preparations. **A**, representative examples of action potentials and respective V_{max} recorded before and upon acceleration of pacing rate from a CL of 500 to 300 ms in atria and ventricles in the absence (control) and presence of propafenone (the AP tracings were taken from the same atrial and ventricular preparations). **B** and **C**, graphs summarize the changes in V_{max} of atrial and ventricular APs paced at a CL of 500 and 300 ms. Control V_{max} values at a CL of 300 ms were normalized to the respective control V_{max} value obtained at a CL of 500 ms. Atria includes combined PM and conduction time data. Ventricles includes combined epicardium and M cell data recorded from the ventricular wedge. *, $p < 0.05$ versus control. †, $p < 0.05$ versus values in ventricles. $n = 6-10$.

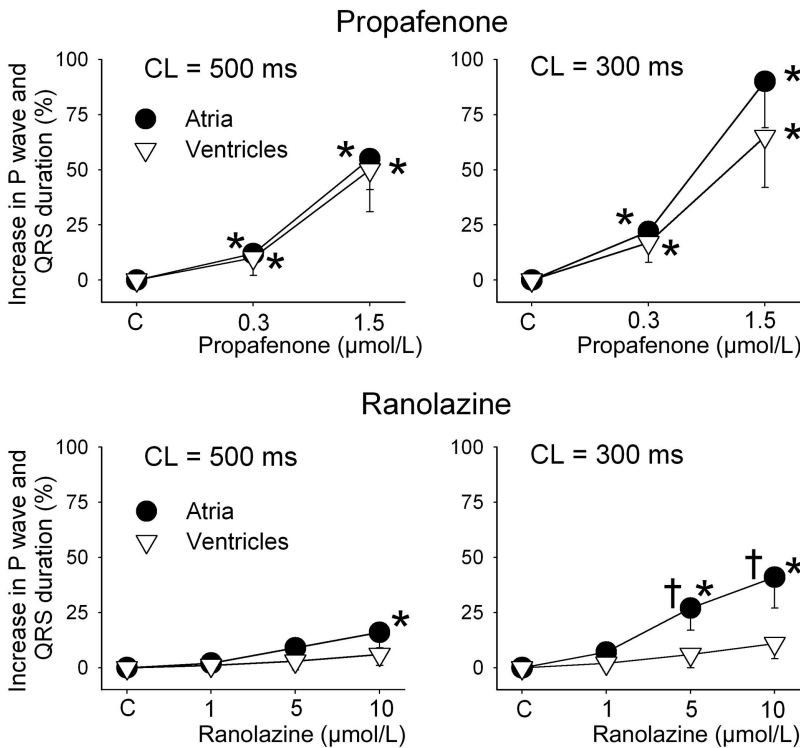


Fig. 5. Rate-dependent effects of propafenone (top) and ranolazine (bottom) on conduction times in atrial and ventricular preparations. Atrial and ventricular conduction times were estimated by measuring by the duration of P-wave and QRS complexes of ECG recordings from coronary-perfused atrial and ventricular preparations. *, $p < 0.05$ versus respective control. †, $p < 0.05$ versus values in ventricles. $n = 6-10$.

TABLE 1

Ranolazine (10 μM) vs. propafenone (1.5 μM) to suppress Ach (0.5 μM)-mediated persistent AF in the isolated canine coronary-perfused right atria
 APD₉₀ and ERP data presented were obtained from the pectinate muscle region of coronary-perfused atria at a CL of 500 ms. Shortest S₁-S₁ is the shortest CL permitting 1:1 activation (at a DTE $\times 2$ determined at a CL of 500 ms). $n = 6-12$.

	APD ₉₀	ERP	Shortest S ₁ -S ₁	Induction of Persistent AF	Termination of Persistent AF	Prevention of AF Recurrence
	<i>ms</i>			<i>%</i>		
ACh	45 ± 9	51 ± 7	64 ± 8	100 (10/10)	0 (0/10)	
ACh + ranolazine	69 ± 16*	112 ± 23*†	163 ± 46*	18 (2/11)	66 (8/12)	75 (6/8)
ACh + propafenone	83 ± 23*	142 ± 37*†	241 ± 69*	14 (6/7)	80 (8/10)	100 (8/8)

* $P < 0.05$ vs. values at ACh alone.
 † $P < 0.05$ vs. APD₉₀.

the inhibition of late I_{Na} does not directly affect peak I_{Na} -mediated parameters such as V_{max} , PRR, and DTE.

Propafenone is a well studied and clinically used class IC antiarrhythmic agent, which suppresses AF and prevents its recurrence, largely because of its ability to potently block early I_{Na} (Fuster et al., 2011). Within a therapeutic range of concentrations, in addition to I_{Na} , propafenone produces relatively mild inhibition of I_{Kr} , I_{to} , I_{Ca} , and β -adrenoreceptors (Grant, 1996). We demonstrate an effect of propafenone to potently depress I_{Na} -mediated parameters in both atrial and ventricular preparations at moderate to slow pacing rates. This is in sharp contrast to the effects of ranolazine that produces a potent depression of I_{Na} -mediated parameters only in atria. However, the anti-AF efficacy of ranolazine was only slightly less than that of propafenone (Table 1).

The electrophysiological effects of both propafenone and ranolazine at clinically relevant concentrations, pacing rates, and temperature are caused largely by the inhibition of peak I_{Na} and I_{Kr} . The functional potency of these drugs to inhibit peak I_{Na} and I_{Kr} depends critically on the heart chamber studied as well as pacing rate. Physiologically relevant IC₅₀ values for the comparison of ranolazine and propafenone are not available at present. Previous studies have reported IC₅₀

values for ranolazine inhibition of peak I_{Na} of 285 ± 170 and 286 ± 150 μM for atrial and ventricular cells, respectively; however, the data were obtained at a slow pacing rate, 15°C, and -140 mV holding potential (Zygmunt et al., 2011). Judging from the effects of the drugs on peak I_{Na} -mediated parameters (V_{max} , PRR, DTE, etc.), the potency of propafenone to block peak I_{Na} in the ventricles is much greater than that of ranolazine. Differences in the relative potency of the two agents to suppress peak I_{Na} in the atria is less obvious, particularly at a CL of 300 ms. The potency of propafenone and ranolazine to inhibit I_{Kr} seems approximately comparable in that both agents produce a similar prolongation of APD₉₀ in atria and no change in the ventricles.

The ranolazine data reported in the current study are very similar to those previously published by our group (Burashnikov et al., 2007) (both studies were conducted in canine coronary-perfused right atrial preparations and used similar experimental protocols). Atrioventricular electrophysiological differences on the effect of propafenone are poorly investigated, but the available data are consistent with the results of the present study. Propafenone reduces V_{max} and induces PRR similarly in atrial and ventricular guinea pig superfused preparations (Delgado et al., 1985). 1-[3-(Phenylethyl)-

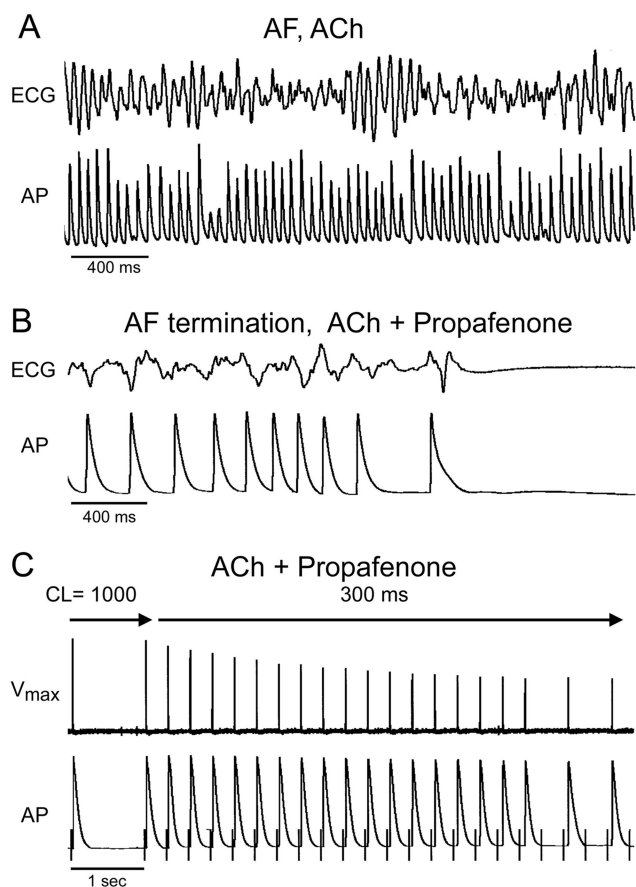


Fig. 6. Propafenone suppresses AF and prevents induction/reinduction of the arrhythmia in coronary-perfused right atria. A, persistent AF induced in the presence of ACh (0.5 μ M). B, propafenone (1.5 μ M) terminates the arrhythmia. C, attempt to reinduce AF fails because of development of use-dependent block of sodium channels (evident from progressive reduction in V_{max}), leading to the development of postrepolarization refractoriness and 2:1 activation failure.

2-benzofuryl]-2-(propylamino)-ethanol hydrochloride (GE-68), an analog of propafenone, selectively prolongs atrial APD, but depresses V_{max} to a similar extent in atrial and ventricular guinea pig superfused preparations (Lemmens-Gruber et al., 1997).

Propafenone is used for both conversion of paroxysmal AF and long-term maintenance of sinus rhythm in AF patients with relatively healthy hearts (Alboni et al., 2004; Fuster et al., 2011). One of the clinical uses of propafenone is in the so-called “pill-in-the pocket” approach (Alboni et al., 2004). A disadvantage of propafenone is that its use is contraindicated in patients with structural heart disease (conditions encountered in many patients with AF) because of the risk of induction of life-threatening ventricular arrhythmias. Clinical studies suggest that a single dose of 2000 mg of ranolazine may be effective as a pill-in-the-pocket approach, converting 77% of AF patients, including patients with structural cardiac disease, with no significant adverse reactions (Murdock et al., 2009, 2010). Considering the safety of ranolazine in patients with structural heart diseases (Koren et al., 2007; Wilson et al., 2009), the pill-in-the-pocket approach using ranolazine may prove to have a much wider applicability than previously used class IC antiarrhythmic agents (i.e., propafenone and flecainide).

Atrial-Selective APD Prolongation Potentiates Atrial Selectivity of I_{Na} Block. The primary anti-AF mechanism of propafenone and ranolazine in our study is related to the action of these drugs to block the peak sodium channel current, I_{Na} , especially at fast atrial rates. The prolongation of APD₉₀ in atria by both agents probably contributes to the anti-AF effect of these agents both directly and indirectly (i.e., by enhancing the block of early I_{Na} ; Fig. 4). Atrial-selective prolongation of APD₉₀ by ranolazine and propafenone is likely caused by their effect to block I_{Kr} (Grant, 1996; Antzelevitch et al., 2004). Indeed, specific I_{Kr} block with *N*-[4-[1-[2-(6-methylpyridin-2-yl)ethyl]piperidine-4-carbonyl]phenyl] (E-4031) produces atrial-predominant prolongation of APD₉₀ and ERP in canine preparations at a CL of 500 ms (Burashnikov et al., 2008). A similar atrial-predominant effect of I_{Kr} blockers to prolong ERP has been demonstrated in vivo in both canine and porcine hearts (Spinelli et al., 1992; Wiesfeld et al., 1996). It is also noteworthy that neither propafenone (Gross and Castle, 1998) nor ranolazine (A. C. Zygmunt and C. Antzelevitch, unpublished work) block I_{Kur} and I_{Kur} inhibition abbreviates instead of prolonging APD₉₀ in “healthy” atria (Burashnikov et al., 2004; Wettwer et al., 2004).

Atrial-selective prolongation of APD₉₀ induced by propafenone and ranolazine contributes to the abbreviation of the diastolic interval at rapid pacing rates in atria but not ventricles (Fig. 4). Because much of the recovery of the sodium channels from block occurs during the diastolic interval (Whalley et al., 1995), the atrial-selective prolongation of APD₉₀ enhances the effect of both drugs to depress I_{Na} and I_{Na} -mediated parameters in atria at rapid rates, thus potentiating their effects to suppress AF.

Atrial Selectivity of I_{Na} Blockers: Rapid versus Slow Dissociation Kinetics? Both propafenone and ranolazine are predominantly open-state sodium channel blockers (Whalley et al., 1995; Wang et al., 2008; Zygmunt et al., 2011). Amiodarone and AZD1305 are also atrial-selective sodium channel blockers (Burashnikov et al., 2008, 2010). Although amiodarone is primarily an inactivated-state sodium channel blockers (Whalley et al., 1995), AZD1305 is a potent tonic blocker (i.e., inhibits sodium channel at the resting state) (Burashnikov et al., 2010). Ranolazine produces little to no tonic block at normal resting membrane potential (Zygmunt et al., 2011). Thus, the available data suggest that preferential binding to a given state of the channel (i.e., open, inactivated, or resting) does not necessarily determine atrial selectivity of I_{Na} blockers. The unbinding kinetics of propafenone and ranolazine seem to play a determining role. Propafenone dissociates slowly ($\tau \geq 8$ s; Whalley et al., 1995), whereas ranolazine dissociation is relatively rapid ($\tau = 1.6$ s; Burashnikov et al., 2007). Consistent with this hypothesis, amiodarone, which has been shown to be an atrial-selective sodium channel blocker (Burashnikov et al., 2008), unbinds rapidly from the sodium channel (Whalley et al., 1995). Other factors that contribute to atrial-selective inhibition of I_{Na} include a more negative voltage dependence of steady-state inactivation of the sodium channels, a more positive resting membrane potential, and a much slower phase 3 of the action potential in atria versus ventricles (for detailed discussion see Burashnikov and Antzelevitch, 2008a, 2009, 2010).

Study Limitations. Extrapolation of our results obtained from in vitro to in vivo animal models or the clinic should be

done with great caution. The absence of autonomic and hormonal influences, which can significantly modulate cardiac electrophysiology and thereby the pharmacological response to drugs, are among the limitations of in vitro preparations. In addition, our experiments were carried out using “healthy” atria and ventricles, whereas AF normally occurs in electrically and structurally remodeled atria. Atrial remodeling can significantly affect pharmacological responses.

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Authorship Contributions

Participated in research design: Burashnikov and Antzelevitch.

Conducted experiments: Burashnikov.

Contributed new reagents or analytic tools: Burashnikov, Belardinelli, and Antzelevitch.

Performed data analysis: Burashnikov and Antzelevitch.

Wrote or contributed to the writing of the manuscript: Burashnikov, Belardinelli, and Antzelevitch.

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