Synergistic Electrophysiologic and Antiarrhythmic Effects of the Combination of Ranolazine and Chronic Amiodarone in Canine Atria

Serge Sicouri, MD; Alexander Burashnikov, PhD; Luiz Belardinelli, MD; Charles Antzelevitch, PhD, FAHA

Background—Amiodarone and ranolazine have been characterized as inactivated- and activated-state blockers of cardiac sodium channel current (INa), respectively, and shown to cause atrial-selective depression of INa-related parameters. This study tests the hypothesis that their combined actions synergistically depress INa-dependent parameters in atria but not ventricles.

Methods and Results—The effects of acute ranolazine (5 to 10 µmol/L) were studied in coronary-perfused right atrial and left ventricular wedge preparations and superfused left atrial pulmonary vein sleeves isolated from chronic amiodarone-treated (40 mg/kg daily for 6 weeks) and untreated dogs. Floating and standard microelectrode techniques were used to record transmembrane action potentials. When studied separately, acute ranolazine and chronic amiodarone caused atrial-predominant depression of INa-dependent parameters. Ranolazine produced a much greater reduction in Vmax and much greater increase in diastolic threshold of excitation and effective refractory period in atrial preparations isolated from amiodarone-treated versus untreated dogs, leading to a marked increase in postrepolarization refactoriness. The drug combination effectively suppressed triggered activity in pulmonary vein sleeves but produced relatively small changes in INa-dependent parameters in the ventricle. Acetylcholine (0.5 µmol/L) and burst pacing induced atrial fibrillation in 100% of control atria, 75% of ranolazine-treated (5 µmol/L) atria, 16% of atria from amiodarone-treated dogs, and in 0% of atria from amiodarone-treated dogs exposed to 5 µmol/L ranolazine.

Conclusions—The combination of chronic amiodarone and acute ranolazine produces a synergistic use-dependent depression of INa-dependent parameters in isolated canine atria, leading to a potent effect of the drug combination to prevent the induction of atrial fibrillation. (Circ Arrhythm Electrophysiol. 2010;3:88-95.)

Key Words: atrial fibrillation ■ antiarrhythmic drugs ■ sodium channel blocker ■ electrophysiology ■ pharmacology

Ranolazine is an antianginal agent recently shown to possess antiarrhythmic activity in ventricular and atrial myocytes, including pulmonary vein (PV) sleeve preparations.1-4 Chronic amiodarone is commonly used for the treatment of ventricular and supraventricular arrhythmias, including atrial fibrillation (AF).7,8

Clinical Perspective on p 95

Recent studies have demonstrated that amiodarone is an atrial-selective, inactivated-state blocker of cardiac sodium channel activity and that ranolazine is an atrial-selective, activated-state blocker of sodium channel activity.5,9 We hypothesized that the combination of ranolazine and chronic amiodarone would act synergistically to cause potent use-dependent depression of sodium channel current (INa) in atrial but not ventricular tissues. The present study was designed to determine the electrophysiologic and antiarrhythmic effects of ranolazine in coronary-perfused right atrial and left ventricular preparations and superfused PV sleeves isolated from untreated and chronic amiodarone-treated dogs.

Methods

This investigation conforms to the Guide for Care and Use of Laboratory Animals published by the National Institutes of Health (National Institutes of Health publication No. 85-23, Revised 1996) and was approved by the Animal Care and Use Committee of the Masonic Medical Research Laboratory.

Adult mongrel dogs weighing 20 to 35 kg were anticoagulated with heparin (180 IU/kg) and anesthetized with sodium pentobarbital (35 mg/kg IV). The chest was opened via a left-thoracotomy and the heart excised and placed in a cold cardioplegic solution ([K+]0=12 mmol/L, 4°C).

Arterially Perfused Atrial and Ventricular Preparations

In vitro experiments were performed using isolated arterially perfused canine right atrial (RA) and left ventricular (LV) coronary-perfused wedge preparations (~3.0×1.2×1.2 cm). The methods used for isolation and perfusion of these preparations have been...
Effects of Ranolazine on APD, ERP, and DTE

Under control conditions, coronary-perfused atrial ERP was coincident with the APD value at 75% repolarization (APD$_{75}$), whereas ventricular ERP was coincident with APD$_{90}$. APD and ERP were significantly longer in both atrial and ventricular preparations isolated from chronic amiodarone-treated dogs, compared with the respective tissues isolated from nontreated animals (Figure 1). Amiodarone-induced APD and ERP prolongation was greater in atria versus ventricles. ERP increased to a greater degree than APD in both atria and ventricles, particularly in the atria, due to development of postrepolarization refactoriness (PRR = ERP − APD).

In atrial preparations (Figure 1A), addition of ranolazine (5 μmol/L) slightly prolonged APD$_{75}$ in either untreated controls (from 154 ± 11 to 159 ± 9 ms; P = 0.245) or chronic amiodarone atria (from 183 ± 7 to 189 ± 9 ms; P = 0.156) but significantly prolonged ERP in untreated (from 158 ± 18 to 190 ± 24 ms, P < 0.05) and chronic amiodarone (from 217 ± 9 to 258 ± 50 ms, P < 0.01). Ranolazine alone produced a 21-ms increase in PRR, whereas chronic amiodarone alone increased PRR by 39 ms. The combination of the two produced a synergistic effect, increasing PRR by 69 ms. In marked contrast, addition of ranolazine produced no significant change in either APD or ERP in ventricular wedge preparations isolated from untreated or chronic amiodarone-treated dogs (Figure 1B). Ventricular PRR did not increase at all with ranolazine alone and only modestly with the combination of ranolazine and chronic amiodarone treatment (28 ms). Both treatments alone or combined caused produced an atrial-preferential prolongation of ERP and PRR.

Ranolazine (5 μmol/L) reduced $V_{\text{max}}$ of atrial AP to a much greater extent in atrial preparations isolated from chronic amiodarone-treated dogs (Figure 1A). Amiodarone (5 μmol/L) produced substantial prolongation of APD and ERP in atrial preparations isolated from untreated controls (from 183 ± 7 to 189 ± 9 ms; P = 0.156) but significantly prolonged ERP in untreated (from 158 ± 18 to 190 ± 24 ms, P < 0.05) and chronic amiodarone (from 217 ± 9 to 258 ± 50 ms, P < 0.01). Ranolazine alone produced a 21-ms increase in PRR, whereas chronic amiodarone alone increased PRR by 39 ms. The combination of the two produced a synergistic effect, increasing PRR by 69 ms. In marked contrast, addition of ranolazine produced no significant change in either APD or ERP in ventricular wedge preparations isolated from untreated or chronic amiodarone-treated dogs (Figure 1B). Ventricular PRR did not increase at all with ranolazine alone and only modestly with the combination of ranolazine and chronic amiodarone treatment (28 ms). Both treatments alone or combined caused produced an atrial-preferential prolongation of ERP and PRR.

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Effects of Ranolazine on Activation Failure in Atrial Versus Ventricular Preparations

In coronary-perfused atrial preparations, the shortest pacing CL permitting a 1:1 response was 129 ± 8 ms in untreated controls, 221 ± 39 ms with chronic amiodarone treatment, 234 ± 29 ms after acute ranolazine treatment alone (5 μmol/L), and 325 ± 34 ms after combined chronic amiodarone and ranolazine treatment (5 μmol/L) (*P < 0.01 versus either treatment alone) (Figure 4 and the Table), reflecting reduced excitability and accentuated PRR. In the presence of acetylcholine (0.5 μmol/L), the shortest pacing CL permitting a 1:1 response was 71 ± 12 ms in untreated controls, 136 ± 22 ms with chronic amiodarone treatment, 94 ± 31 ms with acute ranolazine treatment alone, and 205 ± 34 ms with chronic amiodarone + ranolazine treatment.

In ACh-pretreated preparations, burst pacing induced AF in 100% of controls from untreated animals (10 of 10), in 16% (1 of 6) of atria isolated from chronic amiodarone-treated dogs, in 75% (3 of 4) of atria treated with ranolazine (5 μmol/L) only, and in 0% (0 of 4) in preparations with combined chronic amiodarone and ranolazine (5 μmol/L) treatments.

Similar depression of excitability was observed in PV sleeve preparations. Figure 5 shows use-dependent depression of V\text{max} and action potential in PV sleeves. The addition of 5 μmol/L ranolazine caused a marked reduction in V\text{max} and excitability resulting in 4:3 and 4:1 activation failure at CLs of 1000 and 300 ms. Addition of 10 μmol/L ranolazine produced complete activation failure in the PV sleeve preparation.
Acceleration-induced activation failure was not observed in ventricular wedge preparations isolated from the LV wedge of chronic amiodarone-treated dogs either in the absence or presence of ranolazine (5 and 10 μmol/L; Figure 6).

The marked rate-dependent depression of \( I_{Na} \) in PV sleeve preparations, as reflected by the use-dependent decrease in \( V_{\text{max}} \), led to activation failure at slower rates in chronic amiodarone-treated preparations. This effect was much more accentuated in the presence of ranolazine; Figure 7 shows composite data of the effect of ranolazine on the BCL at which 1:1 activation failure first occurred in pulmonary vein sleeves (Figure 7A) and LV wedge (Figure 7B) preparations isolated from untreated and chronic amiodarone-treated dogs. In untreated preparations, ranolazine (10 μmol/L) induced a significant increase in the BCL at which activation failure occurred in PV but not LV wedge preparations. Chronic amiodarone induced a significant increase in both PV sleeve and LV wedge preparations but a much greater increase in PV sleeves. The combination of chronic amiodarone and ranolazine produced a remarkable synergistic increase in the BCL, permitting 1:1 activation in PV sleeves, with little additional effect in the ventricular wedge preparations.

### Effects of Acute Ranolazine and Chronic Amiodarone on Triggered Activity Induced by Early Afterdepolarizations and Delayed Afterdepolarizations

Previous studies have shown that ranolazine (10 μmol/L) alone suppresses late phase 3 early afterdepolarizations (EADs), delayed afterdepolarizations (DADs), and triggered activity elicited by exposure of the PV sleeves to ACh+isoproterenol, or high \([Ca^{2+}]_{o}\) + rapid pacing and that chronic amiodarone is capable of preventing the appearance...
of DADs, late phase 3 EADs, and triggered activity induced at fast rates in PV sleeves in 80% of PV sleeve preparations exposed to ACh, isoproterenol, high [Ca\(^{2+}\)]\(_o\) or their combination.\(^1\) In the present study, neither DADs nor late phase 3 EADs were observed in PV sleeves in the presence of combined ranolazine and chronic amiodarone (n=6).

**Discussion**

The results of the present study indicate that the combination of chronic amiodarone and relatively low concentrations of acute ranolazine (therapeutic range, 2 to 8 \(\mu\)mol/L) produces a synergistic use-dependent depression of sodium channel–

dependent parameters including \(V_{\text{max}}\), DTE, PRR, and 1:1 activation in isolated canine atria (coronary-perfused right atria and superfused left atrial PV sleeve preparations), leading to a much more potent effect of the drug combination to prevent the induction of AF. Importantly, LV preparations were much less affected by the drug combination. Altogether, the data show a marked atrial selectivity of combined acute ranolazine and chronic amiodarone to depress sodium channel–dependent parameters.

**Pharmacological and Electrophysiological Profile of Chronic Amiodarone and Ranolazine**

Amiodarone is widely used in the treatment of both supraventricular and ventricular arrhythmias. Its mechanism of action includes inhibition of a number of cardiac ionic currents (\(I_{\text{Kr}}, I_{\text{Ks}}, I_{\text{Na}}, I_{\text{Ca-L}}, I_{\text{Ca-T}}, I_{\text{K1}}, I_{\text{K(ACh)}}, I_{\text{K(ATP)}}\)) as well as \(\alpha\)- and \(\beta\)-adrenoceptor–blocking activity.\(^8,13\) Acute amiodarone inhibits \(I_{\text{Kr}}\), whereas chronic amiodarone also leads to a reduction of \(I_{\text{Ks}}.\(^14\) Chronic amiodarone prolongs ventricular APD and QT interval.\(^9,13,15\) Both acute and chronic amiodarone have been shown to prolong the ERP more than APD, resulting in PRR.\(^16,17\) Whereas acute amiodarone reduces \(V_{\text{max}}\) and blocks \(I_{\text{Na}}\) in practically all studies (for review, see Reference 13).\(^1,15\) chronic amiodarone has been reported to either depress \(V_{\text{max}},\)\(^9,18-20\) or to cause little to no change in \(V_{\text{max}}\) in superfused ventricular muscle and Purkinje fibres.\(^13,15,19\) Ventricular conduction velocity is slowed and QRS duration is prolonged in both acute and chronic amiodarone-treated humans and animals in vivo.\(^21-23\)

Ranolazine has been shown to have a pharmacological profile similar to that of chronic amiodarone. Like amiodarone, ranolazine, although at different concentrations, causes inhibition of \(I_{\text{Na}}, I_{\text{Kr}}\) and \(I_{\text{Ca}}.\(^1,24\) Both agents have relatively rapid unbinding kinetics from the sodium channel (\(\tau=1.56\pm0.56\) and 0.3 to 1.6 seconds for ranolazine and chronic amiodarone, respectively).\(^5,13\) Like amiodarone, ranolazine produces an atrial-selective depression of \(I_{\text{Na}}\)-dependent parameters. Unlike amiodarone, which is an inactivated-state blocker of cardiac sodium channels,\(^13,25\) ranolazine is an activated-state blocker.\(^26\) We hypothesized that an atrial-selective activated-state blocker such as ranolazine would potentiate the effects of atrial selective inactivated-state blocker such as amiodarone in producing use-dependent depression of \(I_{\text{Na}}\)-mediated parameters and thus potentiate the effectiveness of amiodarone in the management of AF. Our results provide evidence in support of this hypothesis.

**Atrial-Selective Effects of Ranolazine and Chronic Amiodarone on Sodium Channel Activity**

The combination of rapid dissociation of drug from the sodium channel and an effect to preferentially prolong atrial APD, secondary to \(I_{\text{Kr}}\) block, have been suggested to be key features for atrial-selective depression of sodium channel–dependent parameters and anti-AF efficacy.\(^4,20\)

Our data indicate that the combination of ranolazine and chronic amiodarone treatment produce an atrial-selective, use-dependent depression of \(V_{\text{max}}\) and excitability that is much greater than either treatment alone and greater than the algebraic sum of the individual treatments, thus pointing to a synergism of the effects of the 2 therapies.\(^3,6,9,20\)

Under control conditions, take-off potential (TOP) of PV sleeves was \(-81\pm4, -80.6\pm4, -79.8\pm3, -77.6\pm3,\) and \(-75.6\pm3\) mV at BCLs of 2000, 1000, 500, 300, and 200 ms, respectively. Thus, a change in BCL from 2000 to 200 ms results in a 5-mV depolarization of TOP. It is difficult to record a stable RMP from vigorously contracting coronary-
perfused LV wedge preparations. However, when stable recordings were obtained during a change in rate, no changes in RMP were observed between BCL 2000 and 20 ms. Thus, average RMP in LV is more hyperpolarized at 85.3 ± 2 mV and does not depolarize appreciably at rapid rates. The difference in behavior of TOP between atrial and ventricular tissues at fast rates is attributable to the much slower action potential phase 3 in atrial versus ventricular cells. A more positive TOP clearly contributes to the greater depression of atrial versus ventricular Vmax. We have previously shown that this contributes to the atrial selectivity of agents such as ranolazine and amiodarone.

The atrial-selective effects of both chronic amiodarone and ranolazine to depress peak INa and INa-dependent parameters are thought to result from the more negative steady-state inactivation relationship for INa as well as to the much slower action potential phase 3 of atrial compared with ventricular cells. The slow phase 3 repolarization in atrial cells potentiates the effect of chronic amiodarone at rapid activation rates by abbreviating the diastolic interval and raising TOP of the next beat, thus reducing the availability of sodium channels and the number of channels in the rested state, from which the drug unbinds. Another factor that contributes to the reduced availability of peak INa in atria is the more depolarized RMP of atrial compared with ventricular cells. Intrinsically atrioventricular differences in RMP is due principally to a smaller Ik1 in atrial versus ventricular cells.

Effects on EAD- and DAD-Induced Triggered Activity in PV Sleeves

Ectopic activity arising from the PV sleeves is thought to be an important source of triggers and in some cases substrate for the development of AF. Over the past decade, radiofrequency ablation has become the treatment of choice for drug-resistant AF. Segmental PV isolation and circumferential PV ablation are procedures now commonly used to suppress refractory atrial arrhythmias, including AF.

Our results suggest that combined ranolazine and chronic amiodarone prevent the appearance of DADs, late phase 3 EADs, and triggered activity induced in PV sleeves by exposure to ACh, isoproterenol, high [Ca2+]o, or their combination. Previous studies have shown that 10 μmol/L ranolazine can suppress EADs, DADs, or triggered activity in 100% (11 of 11) of PV sleeve preparations studied and that chronic amiodarone alone is capable of preventing the appearance of DADs, late phase 3 EADs, and triggered activity induced in PV sleeves in 80% of PV sleeve preparations. Additionally, chronic amiodarone was observed to prevent ACh-induced marked abbreviation of the action potential. The combination of ranolazine and chronic amiodarone was associated with a high degree of activation failure even at relatively slow rates. Neither EAD, DAD, or reentrant activity is likely to develop under these conditions.

Study Limitations

The dose of amiodarone used in the present study (40 mg/kg/d) is larger than that typically used in the clinic, where the loading dose of amiodarone ranges from 800 to 1600 mg/d (approximately 20 to 25 mg/kg/d). Similar dosage regimens have been used in previous studies, reflecting the relatively lower sensitivity of dogs to amiodarone. Plasma or tissue concentrations of amiodarone were not measured in this study. However, tissue concentrations of amiodarone were not measured in this study. Plasma or tissue concentrations of amiodarone were not measured in this study.
amiodarone treatment (40 ng/mL) with a loading dose of 600 mg daily for 1 week, followed by 200 mg daily for a period of 7 weeks.\(^3\)

**Clinical Implications**

Most antiarrhythmic agents shown to be effective in terminating and/or preventing clinical AF or atrial flutter act primarily by reducing sodium channel current, \(I_{Na}\) (eg, propafenone or flecainide), or \(I_{Kr}\) (eg, dofetilide) or by blocking multiple ion channels (amiodarone). Use of these agents is limited by their potential ventricular proarrhythmic actions and/or organ toxicity at therapeutically effective doses.\(^2,3,4\)

Acute and chronic amiodarone are widely used in the clinical management of atrial and ventricular arrhythmias.\(^8,36,37\) Chronic amiodarone is the most effective pharmacological agent available for the maintenance of sinus rhythm after termination of AF.\(^8\) The antiarrhythmic efficacy of chronic amiodarone has been attributed to the multiplicity of effects on ion channel activity (class I, II, III and IV actions), reduction of transmural dispersion of repolarization, induction of postrepolarization refractoriness, prolongation of the excitable gap, suppression of triggered activity, and inhibition of atrial remodeling.\(^8,17,19,36,38,39\)

Ranolazine has a pharmacological profile similar to that of chronic amiodarone.\(^1,2,4\) Although clinical trials of the actions of ranolazine to suppress AF are not available as yet, results of the MERLIN trial indicate that the drug shows both ventricular and supraventricular antiarrhythmic activity. Treatment with ranolazine resulted in significantly lower incidence of ventricular tachycardia lasting \(\geq8\) beats (5.3\% versus 8.3\%; \(P=0.001\)), supraventricular tachycardia (44.7\% versus 55.0\%; \(P=0.001\)), or new-onset AF (1.7\% versus 2.4\%; \(P=0.08\)).\(^40\)

Both amiodarone and ranolazine are atrial-selective in their actions. The synergism of their combined electrophysiological and anti-AF effects may be due to their interaction with different states of the cardiac sodium channel. The potentiation by ranolazine of the anti-AF effects amiodarone may permit the use of a lower dose of amiodarone to obtain a similar outcome, thus reducing its adverse effects that limit its clinical use.\(^9\)

Clinical and experimental studies have highlighted the role of PV in the triggering of atrial arrhythmias, AF in particular.\(^41,42\) In the present study, PV-selective depression of \(I_{Na}\)-related parameters was potentiated by addition of ranolazine to chronic amiodarone, leading to activation failure at relatively long CLs and complete suppression of triggered activity. The combined effect of chronic amiodarone and acute ranolazine suggest that ranolazine may help suppress AF in patients in whom amiodarone was not effective.

The actions of chronic amiodarone plus ranolazine to produce potenti block of the sodium channels in the atria are similar to that of class IC antiarrhythmic agents such as propafenone and flecainide. However, unlike the IC agents, the electrophysiological effects of the drug combination is largely restricted to the atrial myocardium, rendering it atrial-selective.\(^4,9\) The drug combination is thus effective in terminating and preventing the induction of AF in experimental models of AF, without exerting an arrhythmogenic effect on ventricular myocardium, as is the case with putative sodium channel blockers such as propafenone.

We conclude that the combination of chronic amiodarone and relatively low concentrations of acute ranolazine produces a synergistic use-dependent depression of sodium channel–dependent parameters in isolated canine atria that lead to a potent effect of the drug combination to prevent the induction of AF.

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**Disclosures**

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**References**


**CLINICAL PERSPECTIVE**

Ranolazine is an antianginal agent recently shown to possess antiarrhythmic activity in ventricular and atrial tissues, including pulmonary vein sleeve preparations. Chronic amiodarone is commonly used for the treatment of ventricular and supraventricular arrhythmias, including atrial fibrillation. Ranolazine has been shown to have a pharmacological profile similar to that of chronic amiodarone. Like amiodarone, ranolazine produces inhibition of $I_{Na}$, $I_{Kr}$, and $I_{Ca}$. Both agents have relatively rapid unbinding kinetics from the sodium channel. Recent studies have demonstrated that amiodarone is an atrial-selective, inactivated-state blocker of cardiac sodium channel activity and that ranolazine is an atrial-selective, activated-state blocker of sodium channel activity. This study tests the hypothesis that the ranolazine and chronic amiodarone in combination synergistically depress sodium channel current in atrial but not ventricular tissues. The data presented demonstrate that the combination of chronic amiodarone and relatively low concentrations of acute ranolazine, within its therapeutic range, produces a synergistic atrial-selective use-dependent depression of sodium channel–dependent parameters that underlies a potent effect of the drug combination to prevent the induction of atrial fibrillation. These experimental data coupled with recent clinical observations suggest that additional studies specifically designed to evaluate the antiarrhythmic potential of combinations of atrial-selective sodium channel blockers may be warranted.
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