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Electrophysiological Basis for the Antiarrhythmic Actions of Ranolazine

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Abstract

Ranolazine is an FDA-approved anti-anginal agent. Experimental and clinical studies have shown that ranolazine has anti-arrhythmic effects in both ventricles and atria. In the ventricles, ranolazine can suppress arrhythmias associated with acute coronary syndrome, long QT, heart failure, ischemia, and reperfusion. In atria, ranolazine effectively suppresses atrial tachyarrhythmias and fibrillation (AF). Recent studies have shown that the drug may be effective and safe in suppressing AF when used as a pill-in-the pocket approach, even in patients with structurally compromised hearts, warranting further study. The principal mechanism underlying ranolazine's antiarrhythmic actions is thought to be primarily via inhibition of late I_{Na} in the ventricles, and via use-dependent inhibition of peak I_{Na} and I_{Kr} in the atria. Short and long term safety of ranolazine has been demonstrated in the clinic, even in patients with structural heart disease. This review summarizes the available data regarding the electrophysiological actions, and anti-arrhythmic properties of ranolazine in preclinical and clinical studies.

Keywords

Antiarrhythmic drugs; pharmacology; electrophysiology; atrial fibrillation; ventricular arrhythmias; ventricular fibrillation; ventricular tachycardia; Bradyarrhythmias

A. Ion Channel Currents

Ranolazine is known to inhibit a number of ion currents (e.g., I_{Na} , I_K , $I_{Ca,L}$) that are important for the genesis of the transmembrane cardiac action potential.^{1–5} Table 1 summarizes the concentrations of ranolazine that cause 50% inhibition (IC_{50} values) of the various ion currents. In ventricular myocytes, the two ion currents most sensitive to ranolazine are the late/sustained/persistent sodium current (late I_{Na}) and the rapidly activating delayed-rectifier potassium current (I_{Kr}). In atrial myocytes, in addition to block of I_{Kr} and late I_{Na} , ranolazine inhibits the early or peak sodium channel current (peak I_{Na}).^{4, 5}

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A.1 Peak and Late Sodium Current (I_{Na})

The inhibition by ranolazine of I_{Na} , peak and late, is voltage- and frequency-dependent, tissue-specific (atria vs. ventricles), and possibly species-specific. The differential potencies of ranolazine to inhibit peak and late I_{Na} have been characterized in canine ventricular myocytes isolated from non-failing and failing hearts³ and in human embryonic kidney cell line HEK-293 expressing the human $Na_v1.5$ gene.⁶ Ranolazine inhibits peak I_{Na} (tonic block) in ventricular myocytes from non-failing hearts and failing hearts with similar IC_{50} values (potencies) of 294 and 244 μM , respectively. In comparison, the potency of ranolazine to inhibit late I_{Na} (tonic block) in myocytes from failing hearts is approximately 6.5 μM ,³ a value similar (5.85 μM) to that reported by Antzelevitch et al.¹ in canine ventricular myocytes isolated from normal hearts (Table 1). Thus, in canine ventricular myocytes, tonic block of late I_{Na} is observed at concentrations of ranolazine that are about 30 to 38-fold lower than required to cause tonic inhibition of peak I_{Na} . In ventricular myocytes of mice expressing the ΔKPQ mutation (LQT-3), ranolazine was found to inhibit peak and late I_{Na} with potencies of 135 μM and 15 μM , respectively, resulting in a differential potency of approximately 9-fold.⁷ Whether species and/or experimental conditions account for the differential potency ratio of ranolazine to inhibit peak vs. late I_{Na} (30 to 38-fold in canine vs. 9-fold in the LQT3 mouse) is not known. Whereas ranolazine inhibition of late I_{Na} is well within the therapeutic range of concentrations of 2 to 8 μM , inhibition of peak I_{Na} in the ventricles occurs well beyond the therapeutic range.^{1, 8}

In contrast to the lower potency of ranolazine to block peak I_{Na} in ventricular cells, the drug potently inhibits peak I_{Na} in atrial cells.^{4, 6} Ranolazine blocks late I_{Na} in atrial myocytes as well.⁵

A comprehensive study of the concentration and frequency-dependent inhibition (or use-dependent block; UDB) of peak and late I_{Na} by ranolazine in human wild type (WT) and LQT3 mutant (R1623Q) $Na_v1.5$ channels stably expressed in HEK-293 cells has been carried out.^{9, 10} The potencies of ranolazine to block peak I_{Na} and late I_{Na} increase with the stimulating frequency, but the selectivity of ranolazine for inhibiting late relative to peak I_{Na} is maintained at both low (0.1 Hz, tonic block) and high frequencies (5.0 Hz, UDB). In WT, the IC_{50} values of ranolazine to reduce peak I_{Na} , at stimulating frequencies of 0.1 and 5.0 Hz are 427 ± 35.21 μM and 154.01 ± 17.81 μM respectively, whereas in the R1623Q mutant, they are reported to be 95.32 ± 2.25 μM and 24.60 ± 2.46 μM , respectively.¹⁰ The endogenous late I_{Na} of the R1623Q mutant, which is 2- to 3-fold greater than in the WT, was inhibited by ranolazine with IC_{50} values of 7.45 ± 0.11 μM and 1.94 ± 0.01 μM at 0.1 Hz and 5.0 Hz, respectively.¹⁰ These findings suggest that inhibition of late I_{Na} by ranolazine will be greater at faster (i.e., tachycardia) than at normal heart rates in pathological conditions in which this current is augmented. The inhibition of peak I_{Na} by ranolazine is also dependent on membrane potential. In HEK-293 cells expressing $Na_v1.5$, the IC_{50} values for ranolazine to reduce the amplitude of peak I_{Na} were 428 ± 35 μM , 209 ± 9 μM and 35 ± 5 μM at holding potentials -120 mV, -100 mV and -80 mV, respectively.⁹ Hence, inhibition of peak I_{Na} by ranolazine is expected to be greater in depolarized myocytes.

Ranolazine is structurally similar to some local anesthetics (LA) and appears to interact with the same binding site in the inner pore of the cardiac sodium channel (NaCh).⁷ This is supported by the finding that the effects of ranolazine to inhibit peak and late I_{Na} are significantly reduced by mutation of residue F1760 in the LA binding site in the S6 helical transmembrane segment of domain IV of the NaCh.⁷

A.2 Rapidly Activating Delayed Rectifying K⁺ Current (I_{Kr})

I_{Kr} encoded by the human Ether-à-go-go-Related Gene (hERG) plays a major role in cardiac repolarization. Inhibition of this current is associated with prolongation of the cardiac action potential and QT interval. In canine left ventricular (LV) myocytes, ranolazine causes a concentration-dependent inhibition of I_{Kr} with an IC₅₀ of 11.5 μM (Table 1). Inhibition of I_{Kr} by ranolazine explains the effect of the drug to prolong ventricular and atrial action potential (AP) duration (APD) and the small QT_c interval prolongation observed in clinical trials.¹¹ In HEK-293 cells stably expressing hERG K⁺ channels (I_{hERG}), ranolazine causes a time- and voltage-dependent, but frequency independent block of peak tail I_{hERG} at -20 mV with an IC₅₀ of 12 μM,¹² nearly identical to that of I_{Kr} in canine ventricular myocytes.¹ The development and recovery from I_{hERG} block by ranolazine has rapid kinetics.¹² I_{hERG} block develops within milliseconds (<80 msec), depending on the concentration of ranolazine, and recovery from block is complete within 200 msec at -80 or -100 mV.¹² In comparison, other I_{Kr} blockers (e.g., E-4031, dofetilide) have slow kinetics for the development of inhibition (hundreds of milliseconds), which is frequency-dependent, and recovery from block, is slow or irreversible.¹³

A.3 L-Type Calcium Current (I_{Ca,L})

Ranolazine is a weak inhibitor of I_{Ca,L}. In canine ventricular myocytes, ranolazine inhibits peak and late I_{Ca,L} with an IC₅₀ of 296 and 50 μM, respectively (Table 1). Within the therapeutic concentration range of 2 to 8 μM, ranolazine reduces late I_{Ca,L} by 25 to 30%.¹ In guinea pig ventricular myocytes, ranolazine at concentrations of 3 and 30 μM reduced the amplitude of I_{Ca,L} by 8±2% and 13±3% respectively.¹⁴ In another study in guinea pig myocytes 10 and 100 μM ranolazine caused a small 2.4% and 17.3% inhibition of the basal I_{Ca,L}.¹⁵ In the same study, 10 μM ranolazine inhibited isoproterenol-stimulated I_{Ca,L} by 47.6%,¹⁵ likely due to a β-adrenergic receptor blocking activity of ranolazine.¹⁶ Consistent with these relatively weak effects on I_{Ca,L}, the effects of ranolazine on Ca²⁺-dependent cardiac, vascular and smooth muscle functions, such as contractility, atrioventricular (AV) nodal conduction, heart rate and direct vasodilation are small or not observed at concentrations ≤ 10 μM.¹⁴

A.4 Other Ion Currents

In canine and guinea pig ventricular myocytes, ranolazine at concentrations as high as 100 μM has no effect on I_{K1},^{1, 14} which explains the lack of effect of ranolazine on the resting membrane potential of ventricular and atrial myocytes.^{1, 4, 14} Likewise, ranolazine has a minimal effect on the transient outward potassium current (I_{to}), causing approximately a 10±2% reduction in the amplitude of I_{to} at a concentration of 50 μM¹ and has no significant effect on I_{Kur} in canine atrial cells (Zygmunt and Antzelevitch, unpublished observation).

The Na-Ca exchange current (I_{NCX}) of canine ventricular myocytes is weakly inhibited by ranolazine with a potency of 91 μM (Table 1). In a recent abstract Soliman et al.¹⁷ reported that in intact neonatal rat cardiac myocytes, ranolazine directly inhibits the reverse mode of NCX_{1.1}. In the same study, the IC₅₀ of ranolazine to inhibit the reverse mode of recombinant NCX_{1.1} was 40.8±3.9 μM. To our knowledge, the effects of ranolazine on I_f, I_{Ca-T} and I_{K-ATP} have not been determined. However, based on the known effects of ranolazine on cardiac action potentials and heart function (e.g., APD duration, normal automaticity), it is unlikely that ranolazine will have a major effect on these currents.

In summary, considering that the mean peak plasma concentration of ranolazine achieved at the two FDA approved doses, 500 and 1,000 mg bid, are 1,126 ng/mL (2.6 μM) and 2,477 ng/mL (5.8 μM), late I_{Na+} and I_{Kr} are the currents most likely to be significantly inhibited by ranolazine in ventricular myocytes, although inhibition of late I_{Ca-L} may also contribute to

ranolazine's electrophysiological actions. In atrial cells, the electrophysiological effects of ranolazine are likely to be mediated primarily via inhibition of peak I_{Na} and I_{Kr} , but inhibition of late I_{Na} is also likely to contribute.

B. Transmembrane Ventricular and Atrial Action Potential

B.1 Resting Membrane Potential (RMP)

Ranolazine has no effect on the RMPs of canine and guinea pig ventricular myocytes, guinea pig papillary muscles, canine Purkinje fibers or canine atrial preparations,^{1, 4, 14} which is consistent with the lack of effect of the drug on inward rectifier potassium channel current (I_{K1}).

B.2 Action Potential Amplitude, Overshoot, and Rate of Rise of Upstroke (V_{max})

In canine epicardial (Epi) and M cells as well as in Purkinje fibers, ranolazine at concentrations $\leq 50 \mu M$ has minimal or no effect in AP amplitude and overshoot,¹ but does depress AP amplitude and V_{max} at higher concentrations in ventricular and Purkinje preparations.¹ In contrast, ranolazine significantly depresses V_{max} in atria at concentrations within the therapeutic range, particularly at rapid activation rates (Figure 1).^{4, 18}

B.3 Action Potential Duration (APD)

The effect of ranolazine on APD of ventricular myocytes is mediated by its effect to inhibit late I_{Na} ($IC_{50} = 6 \mu M$) and I_{Kr} ($IC_{50} = 12 \mu M$). Because these two currents have opposing effects on APD, the net effect of ranolazine on APD depends on their relative contribution to repolarization at any given time/condition, and on the cell type (e.g., ventricular Epi-, M cell, Purkinje fiber, atrial crista terminalis, pectinate muscle, or pulmonary vein (PV)).^{1, 4, 18} In M cells and Purkinje fibers, where late I_{Na} and APD are relatively large and long, respectively, ranolazine causes a concentration-dependent abbreviation of APD at slow pacing rates. When late I_{Na} is increased and APD is prolonged, as in myocytes isolated from the LV of $\Delta KQT3$, failing or hypertrophic hearts (HF and LVH), or cells exposed to ATX-II, veratridine, or angiotensin II,¹⁹ ranolazine abbreviates APD. Similarly, when I_{Kr} is inhibited (e.g., by drugs, hERG mutations) and APD is prolonged, the physiologic late I_{Na} , although small, contributes significantly to ventricular repolarization, so that its inhibition by ranolazine results in abbreviation of APD.²⁰ Under these conditions, the effects of ranolazine to inhibit late I_{Na} are not only important for regulation of APD, but also for dispersion of ventricular repolarization and beat-to-beat variability of APD. The effect of ranolazine to prolong epicardial but abbreviate M cell APD results in a reduction of transmural dispersion of repolarization (TDR).¹ This effect of ranolazine is particularly pronounced when TDR is augmented following exposure to I_{Kr} blockers such as E-4031 or late I_{Na} agonists such as ATX-II.²⁰

Reduced repolarization reserve due to an enhanced late I_{Na} , reduced I_{Kr} or both, accompanying pathological conditions (e.g., HF, LVH) is associated with a marked increase in beat-to-beat variability of APD in isolated ventricular myocytes, isolated perfused hearts and whole heart *in situ*. Ranolazine has been shown to reduce the beat-to-beat variability of APD under these conditions.²¹ At heart rates equivalent to resting sinus rhythm (in canine CL ~ 500 ms), ranolazine causes no significant changes in APD_{50-90} in canine LV M cell and epicardial preparations, while still causing significant abbreviation of APD_{50-90} in Purkinje fibers.⁴

Ranolazine significantly prolongs atrial but not ventricular APD_{90} at a CL of 500 ms (Figure 1).⁴ It is noteworthy that I_{Kr} inhibition with E-4031 also produces atrial-selective

prolongation of APD and effective refractory period at normal and rapid activation rates.^{22, 23}

C. Refractoriness and Excitability

C.1 Effective refractory period (ERP), post-repolarization refractoriness (PRR), diastolic threshold of excitation (DTE), and Conduction time (CT)

Ranolazine prolongs ERP, increases DTE, and slows conduction velocity exclusively or predominantly in atria.^{4, 18} The ranolazine-induced prolongation of atrial ERP is due both to prolongation of APD and development of PRR. In the ventricles, ranolazine does not induce PRR. Atrial-selective prolongation of ERP and increased DTE as well as slowing of conduction velocity have also been demonstrated in *in vivo* pigs.^{24, 25} These changes in DTE, CT, PRR, and $V_{\max}$ are all due to ranolazine-mediated depression of peak I_{Na} . A number of factors are thought to contribute to the atrial selectivity of ranolazine to suppress sodium channel (NaCh)-mediated parameters, including a more depolarized RMP in atria, a more negative half-inactivation voltage ($V_{0.5}$), and a more gradual phase 3 of the atrial action potential that leads to reduction or elimination of the diastolic interval in atria, particularly at rapid activation rates (Figure 1, for review see ²⁶).

D. Antiarrhythmic Properties and Antiarrhythmic Mechanisms

D.1 Ventricles

Arrhythmogenesis associated with reduced repolarization reserve caused by an increased late I_{Na} , reduced I_{Kr} or a combination of both, is effectively suppressed by ranolazine (Figure 2; see above Section B.3). Besides prolonging APD and destabilizing repolarization, enhanced late I_{Na} increases Na^+ influx and, via NCX, increases intracellular Ca^{2+} (Ca_i^{2+}) resulting in calcium overload. Abnormal Ca_i^{2+} handling and Ca_i^{2+} -transients lead to spontaneous release of Ca^{2+} from SR, transient inward current (I_{Ti}), delayed after depolarizations (DADs), and triggered activity. These arrhythmogenic changes occur when late I_{Na} is increased by congenital or acquired pathophysiological conditions and are reversed or prevented by ranolazine.²⁷ In ventricular myocytes from canine failing hearts, prolonged Ca_i^{2+} -transients are abbreviated and spontaneous Ca_i^{2+} release are suppressed by ranolazine and tetrodotoxin.^{28, 29} These results suggest that inhibition of late I_{Na} -induced dysregulation of Ca_i^{2+} homeostasis, manifested by spontaneous release of Ca^{++} from SR, I_{Ti} , and DADs are likely to contribute to the antiarrhythmic effects of ranolazine.^{27–29}

Results of studies conducted in both *in vitro* and *in vivo* models of arrhythmia have confirmed the antiarrhythmic properties of ranolazine. In guinea pig and rabbit isolated perfused hearts,^{30, 31} ranolazine has been shown to suppress beat-to-beat variability of APD, dispersion of ventricular repolarization, EADs, and ventricular tachycardia (VT) induced by drugs that block I_{Kr} . In the rabbit model of Torsade de Pointes (TdP) described by Carlsson et al.,³² ranolazine was found to terminate and prevent recurrence of TdP induced by clofilium, an I_{Kr} blocker (Figure 2).³³ Antoons et al.²¹ reported that in the canine chronic AV block model, TdP-induced by dofetilide, was suppressed, and short-term beat-to-beat variability of ventricular repolarization was reduced by ranolazine. Indeed, ranolazine has been reported to suppress TdP in LQT1, LQT2 and LQT3 experimental models of the long QT syndrome (LQTS) via its actions to reduce TDR.^{1, 34–38} The observed “anti-torsadogenic” effect of ranolazine can be explained by inhibition of the physiologic late I_{Na} that albeit small, becomes a major contributor of ventricular repolarization when I_{Kr} is inhibited.²⁰ Additional evidence for the antiarrhythmic activity of ranolazine are the findings that in closed-chest anesthetized pigs instrumented for programmed electrophysiological testing, ranolazine at concentrations of ~9 μM significantly prolonged right ventricular effective refractory period, increased the threshold for induction of repetitive ventricular

extrasystoles (RE) and ventricular fibrillation (VF) but not the threshold for defibrillation (DFT).³⁹ In the same study, ranolazine also significantly reduced, by ~40%, the ventricular vulnerable period width for induction of extrasystoles. These data raise the possibility that ranolazine may be effective in suppressing ventricular arrhythmias observed in the setting of myocardial ischemia. Indeed, ranolazine has been reported to reduce ischemia-reperfusion induced ventricular premature beats, VT, and VF in an anesthetized rat model of transient (5 min) ligation of left coronary artery, followed by reperfusion.⁴⁰ Whether inhibitions of late I_{Na} , I_{Kr} , and/or peak I_{Na} alone or combined contribute to the anti-arrhythmic effects of ranolazine on ventricular vulnerability for REs and VF in the intact porcine heart, and ischemia-reperfusion induced VT and VF in rats is not clear. However, recently Morita et al.⁴¹ reported that, in isolated-perfused hearts from aged rats, ranolazine effectively suppresses pacing-induced re-entrant AF and EAD-mediated multifocal VF, and provided strong evidence that this effect was due to inhibition of late I_{Na} . Another recent study demonstrated a potent antifibrillatory effect of ranolazine during severe coronary stenosis in the intact porcine model.⁴² This action appears to be due primarily to block of late I_{Na} and independent of coronary flow changes. There is now substantial literature describing the antiarrhythmic properties of ranolazine in various ventricular preparations, experimental conditions, and models of ventricular arrhythmia, as summarized in Table 2.

In summary, it is becoming increasingly clear that a pathologic increase in late I_{Na} contributes to development of arrhythmias via three major mechanisms: a) enhanced abnormal automaticity, b) triggered activity (due to after depolarizations), and c) re-entry. Observed suppression of ventricular arrhythmias by ranolazine, within the therapeutic concentrations of 2 to 8 μM , could be primarily ascribed to its effect to inhibit late I_{Na} and to reduce Na^+ -dependent intracellular calcium overload in the ventricle. Inhibitions of I_{Kr} , and under special circumstances (short cycle-lengths and depolarized cells as during VF) peak I_{Na} , may contribute as well.

D.2 Atria

Ranolazine has been shown to terminate atrial arrhythmias and prevents their initiation in several experimental models.^{4, 18, 24} Ranolazine (10 μM) has been shown to be very effective in suppressing persistent vagally-mediated AF and preventing its induction in canine isolated coronary-perfused atria (Figure 3).⁴ Ranolazine also prevents the induction of β -adrenergically-mediated AF in coronary-perfused canine atria exposed to ischemia and reperfusion (Figure 3).⁴ In canine isolated pulmonary vein preparations, ranolazine (5–10 μM) suppresses the common triggers of AF initiation (i.e., DAD and late phase 3 EAD activity) (Fig. 4).^{18, 43} In isolated atrial guinea pig myocytes, DADs and EADs induced by an increase of late I_{Na} and automaticity induced by hydrogen peroxide (H_2O_2) are effectively suppressed by ranolazine.^{27, 44} Ranolazine (~9 μM) significantly shortens vagally-mediated AF in porcine hearts *in vivo*.²⁴ Table 3 summarizes studies demonstrating an effect to ranolazine to suppress atrial arrhythmias in both experimental and clinical settings.

The antiarrhythmic mechanism underlying the effect of ranolazine to suppress AF includes several factors. The principal factor entails block of peak I_{Na} , which reduces excitability, thus leading to use-dependent prolongation of ERP, due to development of PRR. The net result is failure of rapid activation of the atria (Figure 3). The effect of ranolazine to prolong APD_{90} in atria, secondary to its action to block I_{Kr} , serves to synergize the effect of the drug to block peak I_{Na} by reducing the diastolic interval, during which the NaCh recovers from drug block (Figure 1). As a result of its action to block peak and late I_{Na} , ranolazine reduces intracellular calcium activity (Ca_i), thus suppressing DAD-and EAD-mediated triggers of AF (Figure 4).¹⁸

Recent studies conducted in canine coronary-perfused atrial and ventricular preparations have shown a remarkable synergism when a relatively low concentration of ranolazine (5 μ M) is combined with either chronic amiodarone or acute dronedarone, leading to atrial-selective depression of I_{Na} -dependent parameters and effective suppression of AF (Figs. 4 and 5).^{43, 45} Individually, dronedarone or a low concentration of ranolazine prevented the induction of AF in 17% and 29% of preparations, respectively. In combination, the 2 drugs suppressed AF and triggered activity and prevented the induction of AF in 9 of 10 preparations (90%). Thus, low concentrations of ranolazine and dronedarone produce relatively weak electrophysiological effects and weak suppression of AF when used separately but when combined exert potent synergistic effects, resulting in atrial-selective depression of sodium channel-dependent parameters and effective suppression of AF.

The role of late I_{Na} inhibition by ranolazine in the management of AF is less well understood. Normalization of repolarization by block of late I_{Na} under conditions of prolonged repolarization in ventricles (such as LQTS and HF) can be readily understood (as discussed above; see Figure 2). AF occurrence is commonly associated with a significant abbreviation of atrial repolarization. Under these conditions, a specific block of late I_{Na} is expected to further abbreviate APD, thus promoting AF. However, enhanced late I_{Na} has been reported in atrial myocytes from patients with chronic AF⁵, and prolonged atrial APD has been reported in a number of diseases associated with AF occurrence such as congestive HF,⁴⁶ atrial dilatation^{47, 48} and LQTS.⁴⁹ Furthermore, in murine hearts from Δ KPQ-SCN5A mice, prolonged atrial AP and repolarization is associated with atrial tachyarrhythmias and AF that can be reversed by flecainide via, most likely, inhibition of late I_{Na} .^{50, 51} AF initiation in these conditions may be prevented by abbreviation of APD by block of late I_{Na} . Thus, inhibition of late I_{Na} may contribute to suppression of AF triggers by reducing Ca_i , secondary to the decrease in intracellular sodium activity (Na_i).⁴⁶⁻⁴⁹

D.3 Atrial-selective sodium channel block as a strategy for AF suppression

A property of antiarrhythmic agents to specifically or selectively inhibit ion channels in atria is desirable in the management of AF in order to minimize the risk of ventricular pro-arrhythmia. The discovery in 2007 of important distinctions between atrial and ventricular sodium channels⁴ led to the identification of atrial-selective sodium channel blockers, including ranolazine and amiodarone.^{43, 52, 53} In canine coronary-perfused atrial and ventricular preparations as well as superfused PV preparations, ranolazine depresses sodium channel-mediated parameters, including V_{max} , DTE, CT, and induces PRR selectively in atria.^{4, 18} At concentrations causing little to no electrophysiological changes in ventricles (10 μ M), ranolazine effectively suppresses AF in canine atria and DAD/EAD in PV preparations.^{4, 18} Available data indicate that agents that block I_{Na} with relatively rapid kinetics tend to be atrial-selective and with slow kinetics are not (for review see²⁶). Current understanding of the those that block I_{Na} mechanisms of atrial selectivity of I_{Na} blockers as well as potential applications of atrial-selective I_{Na} block for AF rhythm control are discussed in detail in recent reviews.^{26, 53, 54}

E. Clinical Studies

E.1 Safety of Ranolazine

In multiple clinical studies ranolazine has demonstrated a relatively good clinical safety profile.^{11, 55, 56} Despite its effect to block I_{Kr} and prolong the QT interval, ranolazine does not induce TdP arrhythmias and, in fact, suppresses long QT-related ventricular arrhythmias in all long QT experimental models tested, including LQT1, LQT2 and LQT3.^{21, 30, 33, 35} The principal protective mechanism of ranolazine against TdP is its potent inhibition of late I_{Na} , which opposes the APD- and TDR-prolonging effects of I_{Kr} block.³⁵

Both acute and long-term treatment with ranolazine has been shown to be safe in patients, even in those with cardiac structural abnormalities, including severe acute coronary syndrome, history of myocardial infarction, and congestive heart failure.^{55, 56} Ranolazine's safety is due in large part to the atrial selectivity of its action to block peak I_{Na} .^{26, 54} Thus, the available data suggest that ranolazine can be safe and effective in suppressing a wide variety of cardiac arrhythmia syndromes.

E.2 Ventricular arrhythmias

Consistent with its action to block late I_{Na} in the ventricle, ranolazine has been shown to cause a dose-dependent abbreviation of the QT_c interval in patients with the LQT3 type of the LQTS, a monogenic disorder in which the electrophysiologic phenotype is due to an increase in late I_{Na} .⁵⁷ Ranolazine, at a plasma concentration of 2,074 ng/mL (~4 μ M), caused a mean abbreviation of QT_c ranging from 22 to 40 ms from time-matched baseline QT_c values.⁵⁷ Each 1,000 ng/mL of ranolazine (i.e., ~2 μ M) was associated with a 24 ms QT_c abbreviation, with no change in PR interval or QRS duration.⁵⁷ The lack of effect of ranolazine on PR interval and QRS duration are in keeping with the findings that ranolazine, at therapeutic concentrations, does not significantly inhibit peak I_{Na} in the ventricle.

Although data from the MERLIN-TIMI 36 study failed to demonstrate efficacy in patients with non ST-segment elevation acute coronary syndrome (NSTE ACS), data from 6 days of continuous ECG monitoring showed that ranolazine significantly suppressed episodes of non-sustained VT of ≥ 8 beats ($p < 0.001$).⁵⁸ These findings are supportive of further studies specifically designed to address this hypothesis that ranolazine has antiarrhythmic effects in the ventricle.

E.3 Atrial arrhythmias

To date, no well controlled, large randomized studies have been conducted evaluating the effect of ranolazine to suppress atrial arrhythmias. In a secondary analysis from the MERLIN-TIMI 36 trial, ranolazine treatment was associated with a significant reductions of supraventricular tachyarrhythmias ($p < 0.001$) as well as a 30% reduction in new onset AF ($p = 0.08$). Subsequently, results of a number of small exploratory clinical studies have shown an anti-AF efficacy of ranolazine in termination of paroxysmal AF as well as in prevention of postoperative AF.^{59–62} In an exploratory (not placebo-randomized control) clinical study, ranolazine was found to be more effective than amiodarone in preventing post-operative AF (AF incidence was 15 vs. 25%, respectively).⁶²

The “pill-in-the-pocket” method has long been utilized for the acute termination of paroxysmal AF on an out-of-hospital basis, using agents such as propafenone and flecainide.⁶³ The “pill-in-the-pocket” approach has proved to be an effective (approx. 80% AF suppression), convenient, and a patient-friendly approach, but it has a limited application because agents like flecainide and propafenone are contraindicated in patients with structurally-compromised hearts, which comprise the majority of AF patients. Recent exploratory clinical studies suggest that a single dose of 2000 mg ranolazine may be effective as a “pill-in-the-pocket” approach, converting 77% of AF patients, including patients with structural cardiac abnormalities, with no significant adverse reactions.^{60, 61} Considering the safety of ranolazine in patients with structural heart disease,^{55, 56} the “pill-in-the-pocket” approach utilizing ranolazine may have a much wider applicability than previously used Class Ic antiarrhythmic agents (i.e., propafenone and flecainide). The results of these studies are encouraging, but larger and multicenter clinical trials to evaluate the efficacy and safety of ranolazine in the management of patients with AF are needed.

Future Directions

Despite growing experimental and clinical evidence that ranolazine possesses antiarrhythmic activity, no randomized placebo-controlled clinical trial has specifically tested this hypothesis. Randomized placebo-controlled clinical trials examining the efficacy of ranolazine against atrial and ventricular arrhythmias are warranted. One such clinical trial planned to start in the first half of 2011, is a study designed to determine the effect of ranolazine to reduce implantable cardiovascular-defibrillator shocks in high-risk patients for VT and VF. This is an NIH funded study sponsored by the University of Rochester: ClinicalTrials.gov Identifier: NCT01215253; Wojciech Zareba, Principal Investigator.

Recent trends in the management of patients with AF and cardiovascular co-morbidities (e.g. HF) indicate a shift from electrically-derived objectives, such as rate or rhythm control, to reductions in morbidity and mortality.⁶⁴ The majority of patients with AF have a number of coexisting diseases such as hypertension, heart failure, coronary artery diseases, myocardial ischemia, diabetes, etc, which can be more serious than AF itself. These diseases often develop independently of AF, but may promote AF, and be aggravated by AF. Comprehensive treatment of AF and AF-associated diseases or consequences as well as co-existing morbidities would be preferable. In this respect, our recent experimental results showing synergistic electrophysiologic and anti-AF effects of the combination of ranolazine and dronedarone (described in D2) may be of particular interest. Dronedarone, a derivative of amiodarone, was approved by the FDA for the treatment of AF (for reduction of hospitalization). The anti-AF efficacy of dronedarone appears to be low,^{65, 66} clearly inferior to that of amiodarone,⁶⁷ but its safety, as of this writing, appears to be superior to that of amiodarone.^{65, 67} During clinical development (e.g. ATHENA Trial), dronedarone was associated with a number of positive electrical and non-electrical effects in patients with AF, including reduction in hospitalizations, stroke, blood pressure, acute coronary syndrome, AF occurrence, and ventricular rate during AF.^{68, 69} Ranolazine, in addition to its antiarrhythmic actions, reduces ischemia.^{11, 56} Considering these non-electrical beneficial effects of dronedarone and ranolazine, their clinical safety profiles, and the synergistic anti-AF efficacy of their combination (demonstrated in experimental models⁴³), the use of a fixed dose combination of these two drugs holds promise to not only be a safe and efficacious therapy for AF but may also prove to be clinically beneficial beyond suppression of AF.

Future research using new chemicals that are more potent, efficacious, specific (for NaChs) and selective (for late I_{Na} vs. peak I_{Na}) than ranolazine, are likely to further our understanding of the role of late I_{Na} in the genesis of AF and other cardiac arrhythmias.

Abbreviations

AF	atrial fibrillation
late I_{Na}	late sodium channel current
I_{Kr}	rapidly activating delayed-rectifier potassium current
peak I_{Na}	peak sodium channel current
UDB	use-dependent block
WT	wild type
LA	local anesthetics
hERG	ether-à-go-go-related gene

AP	action potential
APD	action potential duration
I_{hERG}	hERG K ⁺ channel current
LV	left ventricle
I_{Ca,L}	L-Type calcium channel current
AV	atrioventricular
I_{to}	transient outward potassium current
I_{NCX}	Na-Ca exchange current
RMP	resting membrane potential
I_{K1}	inward rectifier K ⁺ channel current
Epi	epicardial
PV	pulmonary vein
HF	heart failure
LVH	left ventricular hypertrophy
TDR	transmural dispersion of repolarization
ERP	effective refractory period
PRR	post-repolarization refractoriness
DTE	diastolic threshold of excitation
CT	conduction time
NaCh	sodium channel
I_{Ti}	transient inward current
DADs	delayed after depolarizations
VT	ventricular tachycardia
TdP	Torsade de Pointes
LQTS	long QT syndrome
RE	repetitive ventricular extrasystoles
VF	ventricular fibrillation
DFT	threshold for defibrillation
Ca_i	intracellular calcium activity
Na_i	intracellular sodium activity
AADs	antiarrhythmic drugs
NSTE ACS	non ST-segment elevation acute coronary syndrome
I_f	funny pacemaker current
I_{Ca-T}	T-type calcium channel current
I_{K-ATP}	ATP-sensitive potassium channel current.

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Figure 1.

Ranolazine produces a much greater rate-dependent inhibition of the maximal action potential upstroke velocity (V_{max}) in atria than in ventricles. Shown are V_{max} and action potential (AP) recordings obtained from coronary-perfused canine right atrium and left ventricle before (C) and after ranolazine (10 μ M). Ranolazine prolongs late repolarization in atria, but not ventricles (due to I_{Kr} inhibition²³) and acceleration of rate leads to elimination of the diastolic interval in the atrium. Reprinted from *J Electrocardiol*, Vol 42, Antzelevitch C, Burashnikov A, Atrial-selective sodium channel block as a novel strategy for the management of atrial fibrillation, 543–548, 2009, with permission from Elsevier.

Figure 2.

Ranolazine (200 $\mu\text{g/kg/min}$) abbreviates ventricular repolarization and suppresses Torsade de Pointes (TdP) arrhythmias in anesthetized rabbit. Shown are representative ECG and left ventricular endocardial monophasic action potential (MAP) tracings. Repolarization was prolonged and TdP was induced by the combination of methoxamine (15 $\mu\text{g/kg/min}$) and clofilium (100 ng/kg/min). Modified with permission from Wang WQ, Robertson C, Dhalla AK, Belardinelli L. Antitortadogenic effects of ({+/-})-N-(2,6-dimethyl-phenyl)-(4[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazine (ranolazine) in anesthetized rabbits. *J Pharmacol Exp Ther*, 325(3):875–881.

Figure 3.

Ranolazine suppresses AF and/or prevents its induction in two experimental models involving isolated canine arterially-perfused right atria. **A:** Persistent ACh (0.5 μM)-mediated AF is suppressed by ranolazine (10 μM). AF initially converts to flutter and then to sinus rhythm. **B:** ERP measured at a CL of 500 ms is 140 ms. Attempts to re-induce AF fail because ranolazine-induced depression of excitability leads to 1:1 activation failure soon after CL is reduced from 500 to 200 ms (right panel). **C:** Rapid-pacing induces non-sustained AF (48 sec duration) following ischemia/reperfusion plus isoproterenol (Iso, 0.2 μmol/L) (left panel). Ranolazine (5 μM) prevents pacing-induced AF due to 1:1 activation failure (right panel). In both models, ranolazine causes prominent use-dependent induction of PRR.

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Figure 4.

Combination of ranolazine (5 μM) and dronedarone (10 μM) eliminates delayed afterdepolarization (DAD)-induced triggered activity in canine PV sleeve preparations. **A:** Isoproterenol (1 μM) and high calcium (5.4 mM) induce DAD and DAD-induced triggered activity. Ranolazine (5 μM) eliminates the triggered activity, but not the DAD. Washout of ranolazine restores the triggered response followed by a DAD. Dronedarone (10 μM) eliminates the triggered response, but the DAD persists. The combination of ranolazine and dronedarone eliminates all DAD activity and induces 2:1 activation failure; an increase of stimulus intensity restores 1:1 activation, but not the DAD. **B:** In another preparation, the same protocol yielded multiple triggered beats. Ranolazine is seen to abolish all of ectopic activity, but not the DAD, whereas dronedarone (5 μM) reduces the number of triggered responses. A single triggered beat followed by a DAD persists. The combination of ranolazine and dronedarone eliminates all DAD activity and induces 2:1 activation failure; an increase of stimulus intensity restores 1:1 activation, but not the DAD. Basic cycle length (BCL) = 120 ms (A) and 150 ms (B). Modified from J Am Coll Cardiol, Vol 56, Burashnikov A, Sicouri S, Di Diego JM, Belardinelli L, Antzelevitch C, Synergistic effect of the combination of dronedarone and ranolazine to suppress atrial fibrillation, 1216–1224, 2010 with permission from Elsevier.

Figure 5.

Atrial-selective induction of post-repolarization refractoriness (PRR) by ranolazine (Ran), dronedarone (Dron) alone and in combination (PRR was approximated by the difference between effective refractory period (ERP) and action potential duration measured at 70% repolarization (APD₇₀) in atria and between ERP and APD measured at 90% repolarization (APD₉₀) in ventricles; ERP corresponds to APD₇₀₋₇₅ in atria and to APD₉₀ in ventricles.

A: Shown are superimposed action potentials demonstrating relatively small changes with dronedarone and ranolazine and their combination. **B:** Summary data of atrial-selective induction of PRR. Ventricular data were obtained from epicardium and atrial data from endocardial pectinate muscle (PM). n=7–8. * p<0.05 vs. respective control (C). † p<0.05 vs. washout. ‡ p<0.05 vs. Dron 10. # p<0.05 vs. respective ERP. ** - p<0.05 - change in ERP induced by combination of Ran and Dron (from washout) vs. the sum of changes caused by Ran and Dron independently (both from washout). CL = 500 ms. Reprinted from J Am Coll Cardiol, Vol 56, Burashnikov A, Sicouri S, Di Diego JM, Belardinelli L, Antzelevitch C, Synergistic effect of the combination of dronedarone and ranolazine to suppress atrial fibrillation, 1216–1224, 2010 with permission from Elsevier.

Table 1

Summary of the potency of ranolazine to inhibit cardiac ion channel currents in canine left ventricular myocytes

Ion Currents	IC ₅₀ values (μM)
A. Inward	
Peak I _{Na}	294 ^a
Late I _{Na}	5.9
Peak I _{Ca,L}	296
I _{Na-Ca} (reverse mode)	91
B. Outward	
I _{Kr}	11.5
I _{Ks}	17% at 30 μM
I _{K1}	No effect
I _{To}	No effect

All data from Antzelevitch et al,¹ except peak I_{Na}^a which is from Undrovinas et al.³

IC₅₀ = concentration of ranolazine that causes 50% inhibition (potency)

Note: The magnitude of effect of ranolazine on peak and late I_{Na} is voltage, frequency, and tissue-dependent (see text for details).

Table 2

Summary of pathological conditions, pharmacological agents, toxins known to elicit ventricular arrhythmias* that are suppressed by ranolazine

Reactive Oxygen Species ^{41, 70, 71}
Class III antiarrhythmic agents (e.g., dofetilide, sotalol, amiodarone) ^{1, 21, 30, 33, 72–75}
Non-cardiovascular drugs that cause TdP (moxifloxacin, cisapride, etc.) ^{31, 35}
Late I_{Na} agonists (toxins and pharmacological agents) ^{2, 29, 30, 72, 75, 76}
Pharmacological agents (e.g., bayK 8644, Ouabain, Angiotensin II) ^{19, 77, 78}
High CO_2 (e.g., acidosis) ⁷⁹
LQT2 iPS cell ⁸⁰
Ventricular myocytes from failing hearts (ischemia- or tachycardia-induced HF) ^{3, 28, 81}
Ischemic hearts (pre-clinical) ⁴⁰
Ischemic and non-ischemic hearts (clinical) ^{58, 82–84}
Severe acute coronary artery stenosis (pre-clinical) ⁴²

* Includes ventricular ectopic beats and tachycardia, beat-to-beat variability of ventricular repolarization, abnormal automaticity, and triggered activity caused by early and delayed afterdepolarizations.

Table 3

Summary of atrial tachyarrhythmias and bradyarrhythmias suppressed by ranolazine.

Vagally-mediated AF in isolated canine atria and in pig in vivo ^{4, 24}
β -adrenergically-mediated AF in canine atria exposed to ischemia/reperfusion ⁴
DAD- and EAD-induced triggered activity in canine isolated PV ¹⁸ and human RA trabeculae ⁵
DAD and EAD activity as well as automaticity in isolated atrial guinea pig myocytes ^{27, 44}
EAD-induced atrial arrhythmias in LQT3 mouse ⁸⁵
Bradyarrhythmia in LQT3 mouse ⁷⁶
Bradyarrhythmias (clinical) ⁵⁸
Supraventricular tachycardia (clinical) ⁵⁸
New onset of AF (clinical) ⁵⁸
Paroxysmal AF (clinical) ^{59–61}
Post-operative AF (clinical) ⁶²