The Electrophysiological Properties of Ranolazine: A Metabolic Anti-Ischemic Drug or an Energy-Efficient Antiarrhythmic Agent?

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Ranolazine, a newer anti-ischemic agent that appears to induce a more efficient utilization of adenosine triphosphate at the cellular level, has been shown to be clinically beneficial in patients with chronic stable angina. More recently, the antiarrhythmic effects of the drug have been described in patients with acute coronary syndromes, as well as in those with atrial fibrillation, when combined with other agents. Experimentally, the predominant inhibitory effects on late I_{Na}, I_{Ca}, $I_{Na\text{-}Ca}$, and I_{Ks}, with little or no effect on I_{to} or I_{K1}, have been demonstrated. Different experimental models have shown the potential beneficial effect of the drug in both supraventricular and ventricular arrhythmias. Interestingly, despite its potential prolongation of the QT interval, ranolazine does not appear to induce ventricular arrhythmias in animal models. Whether the antiarrhythmic effect is secondary to a more efficient energy production by the cardiac cell or by its direct effect on ion channels is still unclear. The effect of ranolazine on other ionic currents, as well as its potential as a clinically relevant antiarrhythmic agent, still needs to be studied.

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Originally synthesized as an anti-ischemic compound, amiodarone is now recognized as a powerful and widely used antiarrhythmic agent originally classified as a class III agent.[1-3] The currently well described multiclass effects of this agent are probably responsible for its relative efficacy and cardiac safety profile when compared with other class III agents.[4-6]

Ranolazine, a newer metabolic anti-ischemic agent, appears to shift myocardial adenosine triphosphate (ATP) production from fatty acid β-oxidation to a

more oxygen-efficient carbohydrate oxidation, thereby reducing the oxygen required for cardiac excitation-contraction coupling with a consequent reduction in myocardial ischemia.[7-11] Its ability to improve chronic severe angina has been demonstrated in randomized clinical trials when used as a single agent or in combination with β-blockers or calcium channel blockers.[12,13] Interestingly, as with previous antiarrhythmic agents originally conceived to treat myocardial ischemia, ranolazine also affects cellular ionic currents, affecting the cardiac action potential (AP) in different ways in normal and diseased myocardium (Table 1).[14-16] Whether the electrophysiological effects of ranolazine are independent or secondary to a more efficient energy utilization by the myocardium remains unexplained.

This article reviews the electrophysiological properties of ranolazine in both the normal and diseased myocardium, and discusses the theoretical potential clinical applications of an energy-efficient ionic channel-modulating agent.

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Novel Antianginal Drugs: Mechanisms of Action

Classic medical therapies for angina pectoris aim to improve oxygen supply and decrease myocardial oxygen demand.[17] Novel therapies have been developed that target ischemia at the cellular level to ameliorate the symptoms of the disease. Ivabradine, a new agent that specifically blocks the pacemaker current (I_f) and consequently lowers the heart rate, was proven effective in improving exercise tolerance in patients with stable angina.[18] The protective effect of opening the ATP-sensitive potassium channels both in the plasma membrane (K_{ATP}) and in the mitochondria (Mito K_{ATP}) has been studied both in animals models and in humans using the K_{ATP} opener nicorandil.[19-21] By opening K_{ATP}, this agent hyperpolarizes the cell membrane and promotes smooth muscle relaxation and vasodilatation.[21] Moreover, experiments performed independently in neurons and cardiac myocytes suggested that by opening the mitochondrial isoform (Mito K_{ATP}), nicorandil was capable of preventing oxidative stress induced apoptosis.[22,23] The net clinical effect of this agent is likely secondary to a combined effect on both K_{ATP} and Mito K_{ATP} channels. Trimetazidine, a partial inhibitor of fatty acid oxidation,[24,25] has also been used for the treatment of chronic angina.[26-28] Although the electrophysiological effects of this drug have not been fully characterized yet, shortening of the QTc interval with trimetazidine has been described.[29]

The multiple mechanisms of action of ranolazine are reviewed in detail here. The antianginal effect of the drug seems to be secondary to a combination of (1) a shift to ATP production from fatty acid β-oxidation to a more efficient carbohydrate oxidation (thereby reducing myocardial oxygen consumption[7]), and (2) an inhibitory effect on the late sodium current (Late I_{Na}).[30] This reduced sodium influx results in an increased

Table 1
Main Ionic Currents Responsible for the Normal Cardiac Action Potential

Current	Abbreviation	Primary Function	Gene
Inward Na^+	I_{Na}	Phase 0 depolarization	*SCN5A*
Inward Ca^{++}	I_{Ca}	Phase 2 plateau Excitation/contraction coupling	DHP receptor
Na^+/Ca^{++} exchanger	$I_{Na/Ca}$	Calcium extrusion during diastole	*NCX*
Outward K^+	I_{K1}	Maintaining phase 4 resting potential	*Kir2.x*
Transient outward K^+ 1 and 2	$I_{to,1}$ and $I_{to,2}$	Spike/dome shape of action potential	*Kv4.x*
Rapid-activated outward K^+ current	I_{Kr}	Repolarization	*HERG/Mirp*
Slow-activated outward K^+ current	I_{Ks}	Repolarization	*KvLQT1/minK*

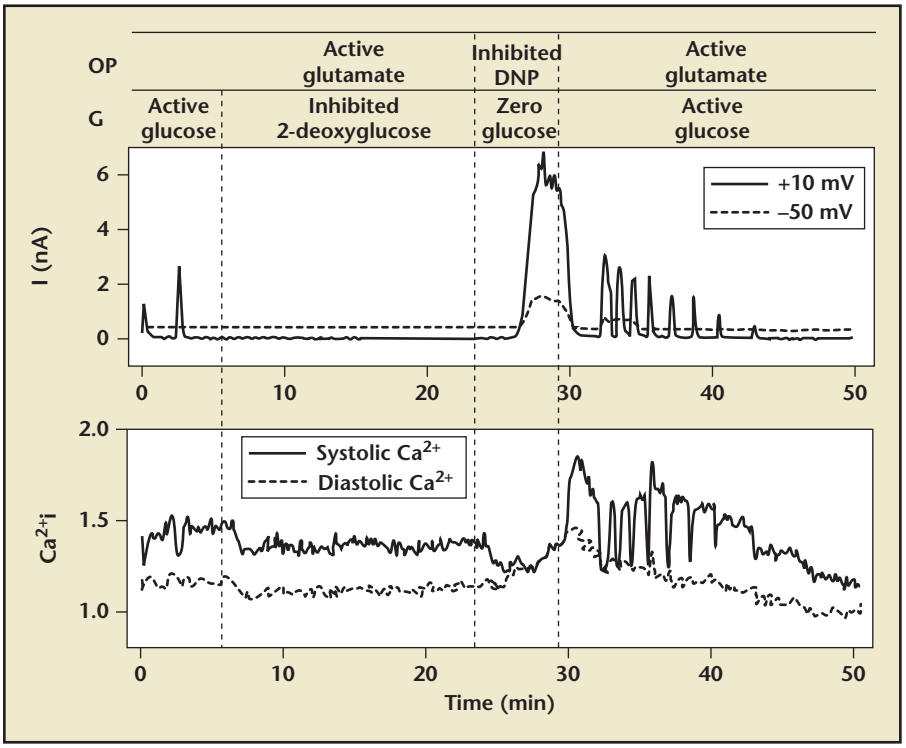
extrusion of intracellular calcium by the sodium/calcium exchanger (NCX) and less oxygen consumption.[30]

Ischemia, Energy Utilization, and Myocardial Electrophysiology

Under basal conditions, approximately 90% of myocardial ATP production is devoted to myocardial contraction and relaxation, a vital process that occurs over 3 billion times during an individual lifespan. This critical oxygen-dependent process is initiated by a timely orchestrated process, cardiac excitation-contraction coupling.[31] After accepting the intimate relationship between myocardial excitability with the high maintenance (ATP) cardiac contractility, it becomes easy to understand why ischemia has profound changes in cardiac electrophysiology and often leads to lethal arrhythmias.[32]

Changes in ionic currents such as inward sodium current (I_{Na}), inward calcium current (I_{CaL}), AP duration, and calcium transient linked to oscillations in energy metabolism, have been described in guinea pig ventricular myocytes by O'Rourke and associates (Figure 1).[33] As hypothesized by the authors, these changes in shape and duration of the AP regionally in the myocardium can be responsible for an increased susceptibility to arrhythmias.[33] These changes in myocardial ionic currents secondary to alterations in the cell metabolism are likely initiated by ATP-sensitive currents such as those generated by ATP-sensitive potassium channels ($I_{K,ATP}$). More recently, Akar and coworkers[34] elegantly described the relationship between mitochondrial inner membrane potential ($\otimes\neg_m$) and postischemic abnormal excitability and ventricular arrhythmias in whole guinea pig hearts. In their work, by blocking the mitochondrial inner membrane anion channel with 4′-chlordiazepam and preventing depolarization of $\otimes\neg_m$, they were able to prevent ischemia-reperfusion–induced arrhythmias.[34] This novel proposed antiarrhythmic strategy targeting the energy regulating organelle of the cell further supports the link between energy utilization and arrhythmogenesis. Altogether, these experimental findings support the concept of an intimate relationship between mitochondrial energy metabolism and electrophysiological changes that can be responsible in the genesis of clinically relevant arrhythmias.

Figure 1. *Influence of metabolic modulators on oscillations of $I_{K,ATP}$ and transients. Effects of glycolytic inhibition [10 μM 2-deoxyglucose], uncoupling mitochondrial energy production [0.2 μM dinitrophenol (DNP)], and recovery from inhibition on oscillations in current (upper panel) and systolic Ca^{2+} (lower panel). The combined effects of external and internal substrates and inhibitors on oxidative phosphorylation (OP) and glycolysis (G) are indicated above. Reproduced with permission from O'Rourke B et al.[33]*



Basic Electrophysiologic Effects of Ranolazine

The basic electrophysiologic effects of ranolazine were meticulously studied by Antzelevitch and colleagues in canine wedge preparations.[14] Using the voltage clamp technique in isolated myocytes they demonstrated that ranolazine inhibited I_{Kr} (IC_{50} = 11.5 μM), late I_{Na}, (IC_{50} = 5.9 μM), late I_{Ca} (IC_{50} = 50 μM), peak I_{Ca} (IC_{50} = 296 μM), $I_{Na\text{-}Ca}$ (IC_{50} = 91 μM), and I_{Ks} (17% at 30 μM). Remarkably, it caused little or no inhibition of I_{to} or I_{K1} (Figures 2 and 3). In canine wedge preparations, ranolazine induced a concentration-dependent prolongation of the AP duration of epicardial cells, and abbreviation of M cells, resulting in a reduction or no change in transmural dispersion of repolarization (TDR).[14]

The role of early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs) in triggered arrhythmias has been described by Marban and coworkers.[35] In their study, using ferret papillary muscles, they were able to potentiate EADs

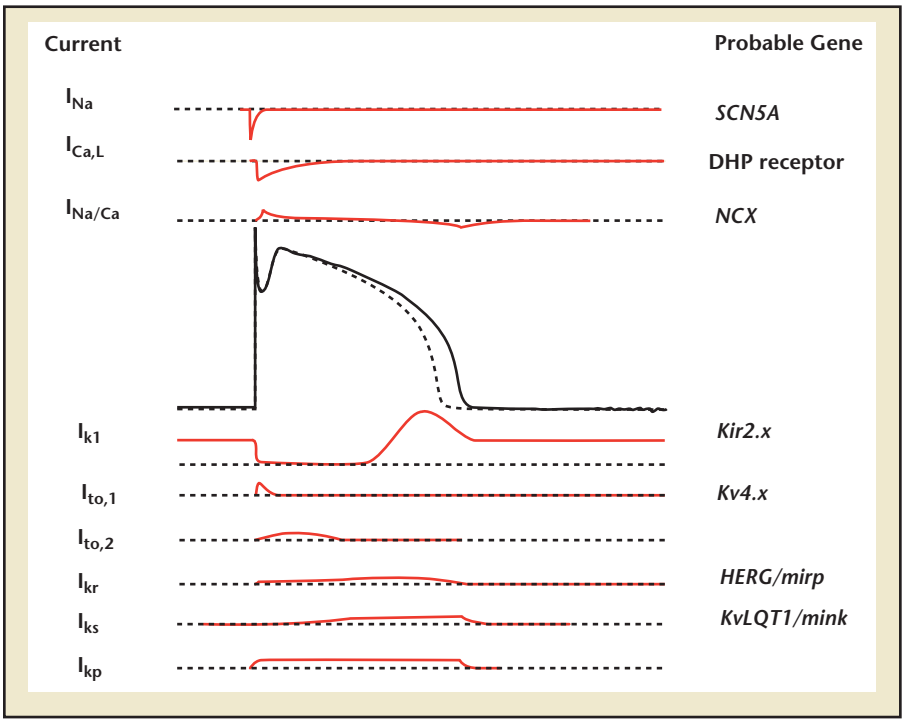


Figure 2. *Schematic representation of major ionic currents with respective coding genes influencing the cardiac myocyte action potential. Ranolazine predominantly affects late I_{Na}, I_{Ca}, I_{Na-Ca}, and I_{Ks}, with little or no effect on I_{to} or I_{K1}.*

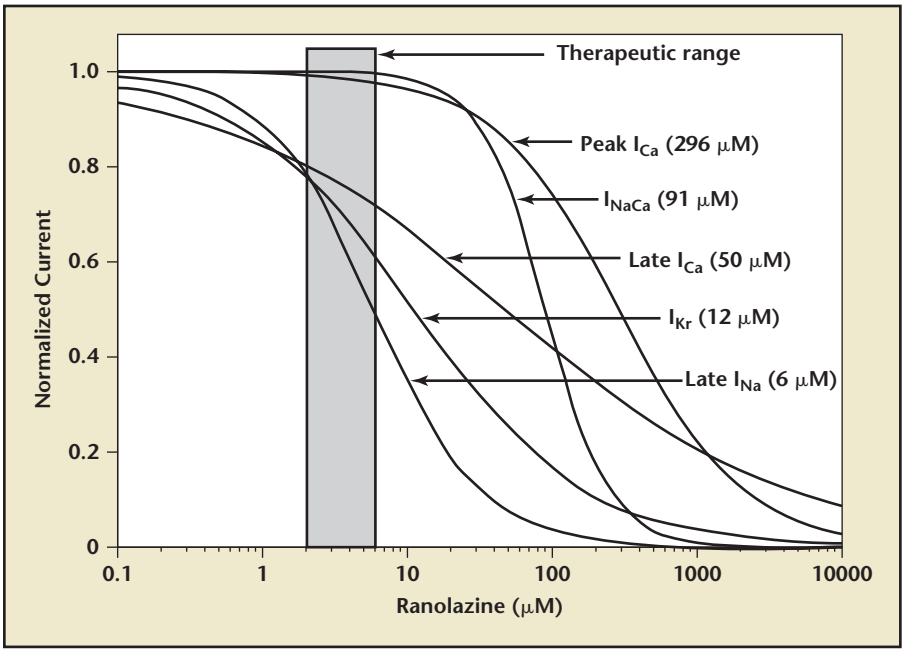


Figure 3. *Summary of the concentration-response relationships for the effect of ranolazine to inhibit inward and outward ion channel currents in canine ventricular myocytes. Numbers inside the parentheses are IC_{50} values for the effect of ranolazine on the respective currents. Reproduced with permission from Antzelevitch C et al.*[14]

with the L-type Ca^{2+} channel-specific agonist BAY K8644, and abolish those by nitrendipine (3-20 μM). They were able to inhibit DADs by intracellular Ca^{2+} chelators (BAPTA or quin2). In this seminal study, they established the importance of external Ca^{2+} influx through the L-type Ca^{2+} channel in EAD-induced triggered arrhythmias.[35]

The effects of ranolazine on other ionic currents that could also be responsible for EADs and the genesis of ventricular arrhythmias have yet to be investigated. For example, different isoforms of hyperpolarization-activated cyclic nucleotide-gated channels responsible for the pacemaker current (I_f) have been found to be increased in severely hypertrophied or failing rat hearts.[36] In these pathologic conditions, I_f could be responsible for EADs and lethal ventricular arrhythmias. One of the possible explanations of the minimal incidence of polymorphic ventricular tachycardia with amiodarone even with extreme prolongation of the QT interval might be the inhibitory effects on I_f in the diseased ventricle. Whether ranolazine shares this property with amiodarone or not has yet to be determined.

Ranolazine as a Potential Antiarrhythmic Agent

Increased automaticity from the pulmonary veins (PVs) has been shown to play an important role in the genesis of atrial fibrillation (AF).[37] Recently, Sicouri and coworkers[38] were able to demonstrate in canine PV preparations the antiarrhythmic effect of ranolazine (2-10 μM) prolonging the effective refractory period and slowing conduction. In the same study they were able to suppress late phase-3 EADs, DADs, and triggered activity. More recently, the electrophysiological effects of ranolazine when combined with the new agent dronedarone were studied in canine isolated perfused preparations by Burashnikov and associates.[39] In this experimental model, low doses of dronedarone (10 μM) and ranolazine (5 μM) were evaluated separately or in combination. Separately,

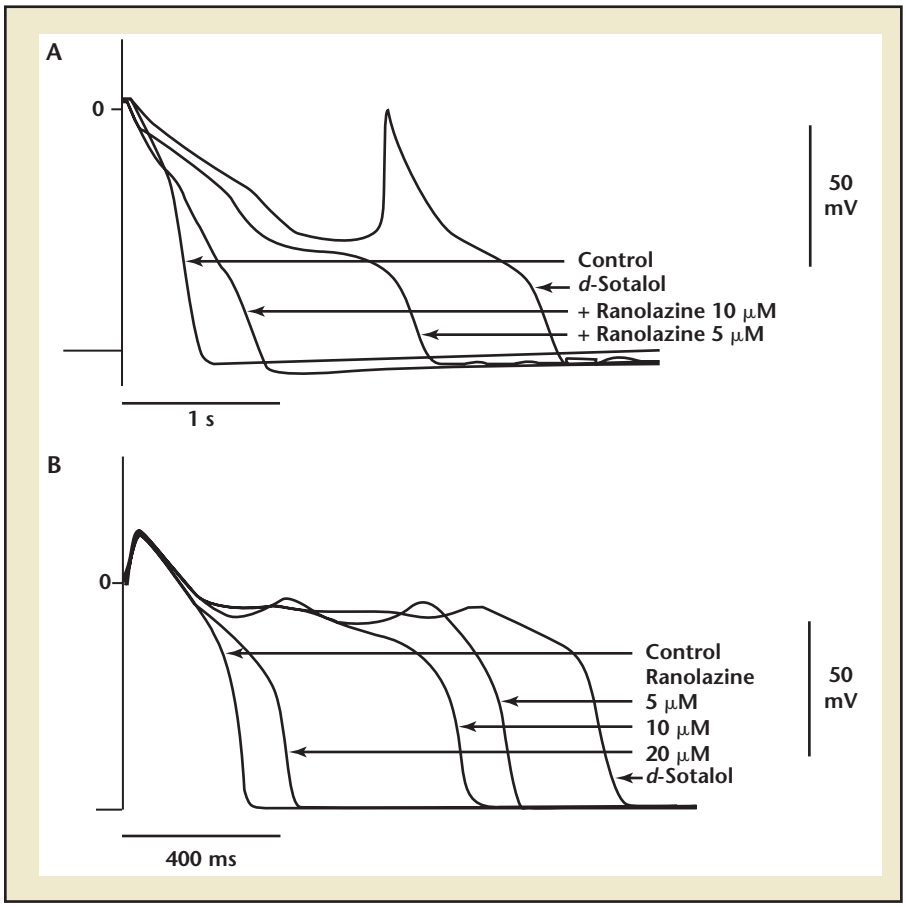


Figure 4. *Ranolazine inhibits* d*-sotalol-induced early afterdepolarizations in Purkinje* **(A)** *and M-cell preparations* **(B).** *Reproduced with permission from Antzelevitch C et al.*[14]

dronedarone (10 μM) or low concentrations of ranolazine (5 μM) prevented the induction of AF in 17% and 29% of the preparations, respectively. Interestingly, both agents combined suppressed AF, triggered activity, and prevented the induction of AF in 9 of 10 preparations (90%).[39]

In experiments performed using pseudo-electrocardiograms (ECGs) in canine wedge preparations, ranolazine (10 μM) prolonged the QT interval by 20 ms but had no impact on TDR. Extrasystolic activity or torsades de pointes (TdP) were not observed spontaneously nor after programmed stimulation.[14] Interestingly, at a concentration of 5 to 20 μM suppression of EADs and reduction in the increase in TDR provoked by the selective I_{Kr} blocker, *d*-sotalol was observed (Figure 4).[14] These experimental findings support the protective effect of ranolazine against arrhythmias induced by agents capable of prolonging the AP at the cellular level, a determinant of the QT of the surface ECG.

Timothy syndrome is a genetic systemic disorder characterized by QT prolongation and ventricular arrhythmias caused by mutations in Ca(V)1.2, with the resulting gain of function of the L-type calcium current ($I_{Ca,L}$).[40] In a pharmacologic model of $I_{Ca,L}$ augmentation with the agonist Bay K8644, Sicouri and coworkers[40] were able to prolong the QT interval, increase transmural dispersion of repolarization, and induce spontaneous or rapid pacing-provoked ventricular tachycardia. These effects were suppressed by a clinically significant concentration (10 μM) of ranolazine.

Electrophysiological Effects of Ranolazine in Clinical Studies

Clinically, the antiarrhythmic potential of ranolazine was recently evaluated in a prospective randomized fashion in the Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction (MERLIN-TIMI) 36 trial.[41] In this study, 6500 patients with non–ST-elevation acute coronary syndrome (NSTE ACS) were followed; 6351 had interpretable Holter recordings, 3162 in the ranolazine treatment group and 3189 in the placebo treatment group. Fewer patients in the ranolazine group had ventricular tachycardia on Holter recordings lasting more than 8 beats (5.3% vs 8.3%, relative risk [RR] 0.63; $P < .001$). Also, there was less incidence of supraventricular tachycardias in the ranolazine-treated patients compared with placebo-treated patients (44.7% vs 55.0%, RR 0.81; $P < .001$). Interestingly, there were only two episodes of TdP in this trial (one in each arm).[41] As previously mentioned, the potent inhibitory effects of ranolazine on late inward sodium current (I_{Na}), can be responsible for suppressing EAD-induced triggered activity seen with other I_{Kr}-blocking agents such as sotalol.[42] The MERLIN-TIMI 36 trial findings are consistent with previous preclinical experimental data that supported the antiarrhythmic potential of this new anti-ischemic compound. Whether the clinical antiarrhythmic effect of ranolazine is confined to patients with myocardial ischemia or if it can be generalized to

nonischemic heart disease still remains to be investigated. It is extremely important to study the clinical effects of ranolazine on both supraventricular and ventricular arrhythmias in a nonischemic population to attempt to elucidate whether this effect is achieved mainly by a metabolic improvement of ischemia or a direct antiarrhythmic effect secondary to the ability of the drug to block multiple ion channels.

Ranolazine in combination with other class III agents was effective in animal models of AF.[39] No prospective randomized trial has been conducted to study the efficacy and safety of ranolazine alone or in combination with other agents for the treatment of AF. However, small, nonrandomized studies seem to indicate a potential utility of this agent for AF. A "pill in the pocket" approach, administering 2000 mg of ranolazine to 18 patients with paroxysmal AF, reported a conversion rate of 72%.[43] The results from this nonblinded, noncontrolled study need to be confirmed in a prospective, randomized fashion prior to adopting this strategy in clinical practice.

The beneficial effects of ranolazine for AF, seen both in animal models and in small clinical reports, are likely to be related to the ability of the drug to prolong the AP and refractory period in the atrial tissue, rendering the atria less susceptible to re-entry.

Conclusions

Ranolazine has clinically been shown to improve ischemia in stable angina[12,41,44,45] and has proven safe in NSTE ACS patients[44]; it also has the ability to block multiple ion channels. The drug blocks late I_{Na} and potentially underlies the I_{KR} blocking capacity to prolong QT interval without increasing transmural dispersion of repolarization, and suppresses EAD-induced triggered activity. These features make ranolazine a potential candidate to join our antiarrhythmic arsenal. This newer anti-ischemic agent may also have additional antiarrhythmic potential as-yet undiscovered. Whether the effect of this compound on cardiac electrophysiology is due to direct effects on ionic currents or secondary to changes in cardiac bioenergetics still remains to be elucidated. Dissecting this mechanism—although intellectually challenging—may not be clinically relevant given the importance of preserving cardiac excitation-contraction coupling.

Ranolazine in combination with other class III agents was effective in animal models of AF.

Over 35 years ago we learned about the electrophysiological properties of amiodarone, a compound originally synthesized as an antianginal drug, and now widely used as an antiarrhythmic agent. As history seems to repeat itself, ranolazine, a newer antianginal agent with multi-ion channel blocking activity, shares many of the antiarrhythmic effects of amiodarone. Experimental data coming from different groups elegantly describe the electrophysiological properties of this drug, as well as the potential utility in different animal models of arrhythmia. The clinical utility of ranolazine as a new antiarrhythmic agent still remains to be studied. ■

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Main Points

- Ranolazine is a novel anti-ischemic agent that promotes more efficient adenosine triphosphate utilization at the cellular level.
- Ranolazine has proven beneficial in patients with chronic stable angina, and more recently trialed in patients with acute coronary syndromes (ACS). Clinically, the drug has shown reduced incidence in ventricular tachycardia in patients with ACS.
- The drug is a multi-ion channel blocker, and potential anti-arrhythmic effects have been described in animal models of arrhythmias.
- Small, nonrandomized studies have described the potential utility of the drug for acute conversion of atrial fibrillation.
- As previously seen with other agents initially designed as anti-ischemic agents (eg, amiodarone), we may see indications for this agent beyond treating chronic stable angina in the future.

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