Heart failure (HF) and atrial fibrillation (AF) frequently coexist and can promote each other. Pharmacological options for rhythm control of patients with HF are limited to amiodarone and dofetilide in the United States and amiodarone in the European Union.1 These agents cause cardiac and extracardiac adverse effects in many cases. There is a critical need for safer and more effective pharmacological rhythm control treatments of AF in the setting of HF. Most clinically available antiarrhythmic agents are not recommended in patients with AF who also have HF, because of the risk of induction of ventricular proarrhythmia. This limitation can be minimized with the use of atrial-selective agents.²,³

Clinical Perspective on p 633

The actions of ranolazine to produce atrial-selective electrophysiological effects, enabling it to suppress AF without inducing ventricular arrhythmias, have been demonstrated in several healthy canine and porcine models.⁴,⁵ In the present study, we investigated the electrophysiological and anti-AF effects as well as ventricular proarrhythmic potential of a clinically relevant concentration of ranolazine (5 μmol/L) in coronary-perfused right atrial and left ventricular preparations isolated from the hearts of dogs with HF.

Background—There is a critical need for safer and more effective pharmacological management of atrial fibrillation (AF) in the setting of heart failure (HF).

Methods and Results—This study investigates the electrophysiological, antiarrhythmic, and proarrhythmic effects of a clinically relevant concentration of ranolazine (5 μmol/L) in coronary-perfused right atrial and left ventricular preparations isolated from the hearts of HF dogs. HF was induced by ventricular tachypacing (2–6 weeks at 200–240 beats per minute; n=17). Transmembrane action potentials were recorded using standard microelectrode techniques. In atria, ranolazine slightly prolonged action potential duration but significantly depressed sodium channel current–dependent parameters causing a reduction of maximum rate of rise of the action potential upstroke, a prolongation of the effective refractory period secondary to the development of postrepolarization refractoriness, and an increase in diastolic threshold of excitation and atrial conduction time. Ranolazine did not significantly alter these parameters or promote arrhythmias in the ventricles. Ranolazine produced greater inhibition of peak sodium channel current in atrial cells isolated from HF versus normal dogs. A single premature beat reproducibly induced self-terminating AF in 10 of 17 atria. Ranolazine (5 μmol/L) suppressed induction of AF in 7 of 10 (70%) atria. In the remaining 3 atria, ranolazine reduced frequency and duration of AF.

Conclusions—Our results demonstrate more potent suppression of AF by ranolazine in the setting of HF than previously demonstrated in nonfailing hearts and absence of ventricular proarrhythmia. The data suggest that ranolazine may be of benefit as an alternative to amiodarone and dofetilide in the management of AF in patients with HF. (Circ Heart Fail. 2014;7:627-633.)

Key Words: anti-arrhythmia agents ■ arrhythmias, cardiac ■ electrophysiology ■ pharmacology ■ sodium channel blockers

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Original Article

Ranolazine Effectively Suppresses Atrial Fibrillation in the Setting of Heart Failure

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Background—There is a critical need for safer and more effective pharmacological management of atrial fibrillation (AF) in the setting of heart failure (HF).

Methods and Results—This study investigates the electrophysiological, antiarrhythmic, and proarrhythmic effects of a clinically relevant concentration of ranolazine (5 μmol/L) in coronary-perfused right atrial and left ventricular preparations isolated from the hearts of HF dogs. HF was induced by ventricular tachypacing (2–6 weeks at 200–240 beats per minute; n=17). Transmembrane action potentials were recorded using standard microelectrode techniques. In atria, ranolazine slightly prolonged action potential duration but significantly depressed sodium channel current–dependent parameters causing a reduction of maximum rate of rise of the action potential upstroke, a prolongation of the effective refractory period secondary to the development of postrepolarization refractoriness, and an increase in diastolic threshold of excitation and atrial conduction time. Ranolazine did not significantly alter these parameters or promote arrhythmias in the ventricles. Ranolazine produced greater inhibition of peak sodium channel current in atrial cells isolated from HF versus normal dogs. A single premature beat reproducibly induced self-terminating AF in 10 of 17 atria. Ranolazine (5 μmol/L) suppressed induction of AF in 7 of 10 (70%) atria. In the remaining 3 atria, ranolazine reduced frequency and duration of AF.

Conclusions—Our results demonstrate more potent suppression of AF by ranolazine in the setting of HF than previously demonstrated in nonfailing hearts and absence of ventricular proarrhythmia. The data suggest that ranolazine may be of benefit as an alternative to amiodarone and dofetilide in the management of AF in patients with HF. (Circ Heart Fail. 2014;7:627-633.)

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confirmed by hemodynamic and histopathologic changes as well as other clinical signs, such as lethargy, dyspnea, and edema. This model recapitulates many features of clinical HF (including LV systolic and diastolic dysfunctions).

Pacemaker implantation for right VTP was performed at the Cornell University Hospital for Animals (Ithaca, NY) using previously described protocols. After recovering from the procedure (1–2 days), they were transported to Masonic Medical Research Laboratory. Within 2 days of arrival at Masonic Medical Research Laboratory, the dogs were continuously paced at 200 to 240 beats per minute for a period of 2 or 6 weeks. The dogs were constantly monitored for clinical signs of HF and followed by a licensed veterinarian weekly. Pulse rate was monitored daily and a 12-lead ECG was recorded weekly to ensure proper pacing.

After 2 to 6 weeks of VTP, the HF dogs (aged ≥1 year) were anticoagulated with heparin and anesthetized with pentobarbital (with an initial dose of 30–35 mg/kg intravenously, and if needed, an additional dose of 15–20 mg/kg intravenously was used). After loss of corneal reflex, the chest was opened via a left thoracotomy, the heart was deca
ded and perfused through the ostium of the right coronary artery; the LV wedge was perfused through a diagonal branch of the left anterior descending coronary artery. Unperfused tissue was removed with a razor blade. Cut ventricular and atrial branches were ligated with silk thread. The preparations were then transferred to a temperature-controlled bath and arterially perfused with Tyrode solution by use of a roller pump. For both atrial and ventricular preparations, the composition of the Tyrode solution was (in mM): NaCl 129, KCl 4, NaHPO₄ 0.9, NaHCO₃ 20, CaCl₂ 1.8, MgSO₄ 0.5, and d-glucose 5.5, buffered with 95% O₂ and 5% CO₂ (37.0±0.5 °C).

Transmembrane action potential (AP) recordings were obtained either differentially or referenced to ground using floating glass microelectrodes (2.7 mol/L KCl, 10–25 mol/L DC resistance) connected to a high-input impedance amplification system. A pseudo-ECG was recorded using 2 electrodes consisting of Ag/AgCl half cells placed in the Tyrode solution bathing the preparation, 1.0 to 1.2 cm from the 2 opposite sides of the atrial or ventricular coronary-perfused preparations. Diastolic threshold of excitation (DTE) was determined by increasing stimulus intensity in 0.01 mA steps. Effective refractory period (ERP) was measured by delivering premature stimuli after every tenth regular beat at a pacing cycle length (CL) of 500 (with 5 ms resolution; stimulation with a 2× DTE amplitude). Postpolarization refractoriness (PPR) was recognized when ERP exceeded 90% AP duration (APD₉₀) in the ventricle and APD₉₀ in atria. Note that, at baseline, ventricular ERP coincides with APD₉₀ whereas atrial ERP generally coincides with APD₉₀. Conduction velocity was measured from the duration of QRS in ventricles and P wave on the pseudo-ECG at a level of representing 30% of QRS or P-wave amplitude in isolated preparations. In contracting perfused preparations, a large variability in maximum rate of rise of the AP upstroke (V'ₕₚₚ) measurements is normally encountered at any given condition, primarily because of variability in the amplitude of phase 0 of the AP, which strongly determines Vₕₚₚ values. Vₕₚₚ changes were determined by comparing the largest Vₕₚₚ recorded before and after addition of ranolazine. The shortest S−Sₚₚ permitting 1:1 activation was measured by progressively shortening pacing CL starting from a CL of 500 ms (at 2× DTE determined at a CL=500 ms).

The equilibration period for the preparations once placed in the bath was 30 to 60 minutes. The electrophysiological parameters were measured at a pacing CL of 500 ms before and after addition of ranolazine (5 μmol/L) to the coronary perfusate. Tissues were exposed to ranolazine for ≥15 minutes before start of data collection. Electrophysiological data from atrial preparations were largely obtained from the endocardial pectinate muscle areas. Ventricular AP data were obtained from immediate subendocardial region and DTE and ERP from the endocardial surface. Programmed electric stimulation (a single premature stimulation, with amplitude of stimulation of 2× DTE) was used to induce atrial and ventricular arrhythmias. In some atrial preparations, rapid atrial pacing (CL=80–100 ms for 3–10 seconds) was also used to induce atrial arrhythmias.

Single Isolated Myocytes

Single myocytes were obtained by enzymatic dissociation of the left atria obtained from normal and tachypaced hearts. Whole-cell sodium channel current (Iₙᵥ) was recorded in low external Na⁺ at 15°C to ensure adequate voltage control. Experiments were performed using a MultiClamp 700A (Molecular Devices, Sunnyvale, CA). Command voltages were delivered, and data were acquired via a DigiData 1322 computer interface using the pCLAMP 9 program suite (Molecular Devices) with data stored on a computer hard disk. Patch pipettes were pulled from borosilicate glass (1.5-mm outer diameter and 1.1-mm inner diameter) on a model PP-830 vertical puller (Narishige Instruments, East Meadow, NY). The electrode resistance was 0.9 to 2.0 mol/Ω when filled with the internal solution. The membrane was ruptured by applying negative pressure and series resistance compensated by 70% to 80%. Whole-cell current data were acquired at 10 to 50 kHz and filtered at 5 kHz. Currents were normalized to cell capacitance.

The external solution used in the voltage-clamp experiments contained (in mM/L) 2 CaCl₂, 10 glucose, 1 MgCl₂, 40 NaCl, 120 N-methyl-D-glucamine, and 10 HEPES, with pH adjusted to 7.4 with HCl. CaCl₂ (300 μmol/L) was added to the external solution to block Ca²⁺ current and to partially reduce Iᵥ. The pipette solution contained (in mM/L) 1 MgCl₂, 5 NaCl, 145 Cs-aspartate, 10 HEPES, 5 EGTA, and 5 MgATP. pH was adjusted to 7.1 with CsOH. Peak Iᵥ was evaluated using a square depolarization pulse to −10 mV for 100 ms at holding potential of −140 to −20 mV for 5 seconds, applied once every 10 seconds. In addition, recordings of Iᵥ were made ≤5 minutes after rupture to minimize the effects of the time-dependent negative shift of steady-state inactivation that occurs in conventional voltage-clamp experiments.

Drugs

Ranolazine (Gilead Sciences, Foster City, CA), dissolved in distilled water, was prepared fresh as a stock of 5 μmol/L before each experiment.

Statistics

Statistical analysis was performed using a paired and unpaired Student t test and 1-way repeated measures or multiple comparison ANOVA followed by Bonferroni test, as appropriate. All data are expressed as means±SD. Statistical significance was assumed at P<0.05.

Results

Isolated Coronary-Perfused Atrial and Ventricular Preparations

A single premature beat reproducibly induced self-terminating AF or atrial flutter (AFl) in 10 out of 17 atrial HF preparations (Figure 1; Table 1). Electric and structural characteristics of atria that did and did not develop AF have been reported previously. The average duration of the vulnerable period, defined as the range of diastolic intervals during which a single extra-stimulus could induce AF, was 36±23 ms (n=10). The addition of ranolazine (5 μmol/L) to the coronary perfusate completely prevented the induction of arrhythmias in 7 of the 10 atria. In the remaining atrial preparations (n=3), the arrhythmia generally became slower and briefer and the duration of vulnerable
Ranolazine (5 μmol/L) terminated the arrhythmia and depressed excitability resulting in failure of 1:1 activation at a cycle length of 300 ms, thus preventing reinduction of the arrhythmia. Pacing artifacts are seen on the action potential (AP) tracing.

The actions of ranolazine on electrophysiological parameters were determined in the atrial preparations that reproducibly developed AF/AFl (n=10). Figures 2 and 3 summarize the effect of ranolazine at RA sites displaying a short ERP. These were the sites of briefest refractoriness where a prematurely initiated premature beat (that initiate AF/AFl) or the maintenance of rapid activation (Figure 1B).

The longest atrial fibrillation/flutter (AF/AFl) episode recorded in each atrium was taken for calculation of AF/AFl duration.

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Duration, s</th>
<th>Vulnerable Window, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>109±178</td>
<td>36±23</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>4.0±4.3*</td>
<td>13±6</td>
</tr>
</tbody>
</table>

The longest atrial fibrillation/flutter (AF/AFl) episode recorded in each atrium was taken for calculation of AF/AFl duration.

*P<0.05 vs control (paired t test; 3 atria that develop AF both before and after ranolazine).

Isolated Atrial Myocytes

We next investigated the effect of ranolazine to inhibit peak \( I_{Na} \) in atrial myocytes isolated from HF versus normal dogs. In the absence of drug, \( I_{Na} \) density was smaller in cells isolated from HF dogs (Figure 4A–4D). Ranolazine (10 μmol/L) produced significantly greater inhibition of peak \( I_{Na} \) in atrial cells isolated from the dogs with HF. The efficacy of ranolazine-induced block of \( I_{Na} \) was greater at −90 mV than at −120 mV in both normal and HF atrial cells.

The reduction in peak \( I_{Na} \) because of ranolazine may be because of a shift in Na⁺ channel availability. Therefore, we next evaluated steady-state inactivation using a standard prepulse test protocol in the absence and presence of 10 μmol/L.
ranolazine. Peak current after a 5-second prepulse was normalized to the maximum current and plotted as a function of the prepulse voltage, and a Boltzman function was fitted to the data. For atrial cells, \( V_{1/2} \) in absence and presence of ranolazine was \(-84.5\pm0.15 \) and \(-87.1\pm0.18 \) mV, respectively (\( P<0.05 \)); for ventricular cells, \( V_{1/2} \) in absence and presence of ranolazine was \(-77.0\pm0.34 \) and \(-77.4\pm0.20 \) mV (\( P=0.32 \)).

**Discussion**

Our data demonstrate that ranolazine at a relatively low concentration (5 \( \mu \)mol/L), well within the therapeutic range of the drug, causes marked atrial-selective electrophysiological effects and is effective in preventing induction of AF in canine HF. Moreover, ranolazine did not induce ventricular arrhythmias in the setting of HF. Our experimental data suggest that ranolazine may be safe and effective for rhythm control management of AF in patients with HF.

**Atrial-Selective Electrophysiological Effect of Ranolazine in Canine HF**

Previous in vitro and in vivo studies have demonstrated atrial-selective effects of ranolazine (5–10 \( \mu \)mol/L) to block peak \( I_{Na} \), and depress peak \( I_{NaK} \)-mediated parameters in healthy cardiac preparations. The present study demonstrates that a relatively low concentration of ranolazine (5 \( \mu \)mol/L) has a more potent atrial-selective effect to prolong ERP and PRR and to depress \( I_{Na} \) in a diseased model of nonischemic dilated cardiomyopathy induced by 2 to 6 weeks of VTP compared with healthy controls.

Ranolazine (5 \( \mu \)mol/L) did not significantly prolong repolarization in either atria and ventricles isolated from the hearts of dogs with HF; an effect generally consistent with that observed in healthy canine atria and ventricles. This effect seems to be because of the fact that ranolazine blocks both depolarizing late \( I_{Na} \) and repolarizing rapidly activating \( K^+ \) currents, which act to abbreviate and prolong APD.

Ranolazine (5–10 \( \mu \)mol/L) is known to produce APD abbreviation in ventricular cells when APD is significantly prolonged (APD, \( \geq 500 \) ms; in the conditions of long QT syndrome and ischemic HF at slow pacing rates). It is noteworthy that late \( I_{Na} \) is increased in ischemic HF model. Whether late \( I_{Na} \) is altered in nonischemic HF, used in the present study, remains to be established.

**Antiarrhythmic Potential and Safety of Ranolazine in HF**

Ranolazine, originally introduced as an antianginal agent, has a significant antiarrhythmic potential in both ventricles and atria. In atria, the primary antiarrhythmic action is most likely because of block of peak \( I_{Na} \), whereas in the ventricles it is because of block of late \( I_{Na} \). A low prevalence of ventricular arrhythmias in our current study (3 out of 17 wedges) precluded us from a proper evaluation of antiarrhythmic potential of ranolazine. The limited data obtained indicate that ranolazine (5 \( \mu \)mol/L) may be effective in preventing ventricular arrhythmias in the setting of HF.

An important result of our study is that ranolazine did not induce ventricular proarrhythmia in our canine HF model. The lack of proarrhythmic effect in the ventricles is likely because of the relatively minor effects of ranolazine on peak \( I_{Na} \)-mediated parameters in the ventricles of dogs with HF. The high propensity of ventricles for development of \( I_{Na} \) block–induced proarrhythmia is well recognized, but generally limited to agents that dissociate slowly from the cardiac sodium channel. Ranolazine has rapid unbinding kinetics. The lack of effect of ranolazine to induce major QT prolongation or Torsade
de Pointes is consistent with the results of previous clinical and experimental investigations. Indeed, ranolazine has been repeatedly demonstrated to suppress early afterdepolarizations and torsade de Pointes in various experimental models. 

Ranolazine was more effective in preventing the induction of AF in atria from dogs with HF than from healthy dogs. At a concentration of 5 μmol/L, ranolazine prevents the induction of persistent AF in our vagal model in 29% of atria. In comparison, this concentration of the drug prevented induction of AF/AFl in 70% of atria from dogs with HF. This greater effect of ranolazine to suppress AF in the HF model than in the non-HF acetylcholine AF model is consistent with the greater effect of 5 μmol/L ranolazine to alter sodium channel–mediated parameters in the former than in the latter AF model (Table 2). It is also consistent with a greater efficacy of ranolazine to inhibit peak INa in HF versus healthy atrial cells (Figure 4). Acetylcholine markedly abbreviates APD and ERP and hyperpolarizes the resting membrane potential. Both these factors significantly reduce the effectiveness of INa blockers but may be underestimated in the acetylcholine-mediated AF model. In the HF atria, resting membrane potential is more likely to be depolarized, which augments ranolazine’s effectiveness to inhibit peak INa.

Acetylcholine- and HF-mediated AF models are distinct. In healthy atria, acetylcholine markedly abbreviates atrial APD and ERP allowing for the induction of AF by a single premature beat or burst pacing in 100% of atria. The induced arrhythmia is commonly persistent. In the HF model of AF, all that is needed to induce AF, in the majority of cases, is a single premature beat, but, however, most episodes are non-sustained. Although the acetylcholine model is representative of vagally induced AF, the VTP-induced HF model is more clinically relevant. The antiarrhythmic efficacy of 5 μmol/L ranolazine in the HF AF model is similar to that of the ischemia/reperfusion-mediated AF model. In the ischemic model, 5 μmol/L ranolazine prevented AF induction in 60% of atria (3 of 5). In all models of AF tested, it is clear that ranolazine’s action is due largely to atrial-selective inhibition of peak INa.

Rate-dependent induction of PRR contributed prominently to the anti-AF effectiveness of ranolazine (Table 2). Interestingly, whereas slowly dissociating INa blockers such as propafenone induce significant PRR in both atria and ventricles, rapidly dissociating INa blockers such as ranolazine and amiodarone are atrial-selective in their ability to induce PRR.

Frommeyer et al reported that ranolazine (10 μmol/L) effectively suppresses AF in Langendorff-perfused hearts isolated from control and VTP-induced HF rabbits. However, AF was induced by pretreatment with acetylcholine plus isoproterenol and burst pacing. In these rabbit AF models, as in our studies, anti-AF efficacy of ranolazine was associated with induction of PRR. There are several important differences between this study and our current investigation. First, we investigated the antiarrhythmic effect of ranolazine on AF induced by a single premature beat in the setting of HF without the need to use acetylcholine plus isoproterenol or burst pacing. It is noteworthy that acetylcholine, isoproterenol, and burst pacing can each induce AF in control hearts. Second, in contrast to our study, Frommeyer et al did not report the electrophysiological and anti-AF effects of ranolazine in the absence of acetylcholine plus isoproterenol, confounding the assessment of effect of ranolazine in the setting of HF. Third, we used a more clinically relevant concentration of ranolazine (ie, 5 versus 10 μmol/L used by Frommeyer et al). Fourth, we evaluated the electrophysiological effects of ranolazine in both atria and ventricles, evaluating its proarrhythmic potential. Finally, we directly measured the efficacy of ranolazine to inhibit INa in atrial myocytes isolated from control and HF dogs.

There are important differences in hemodynamic, structural, and electrophysiological parameters in dog ventricular tachypacing for 2 to 3 versus 5 to 6 weeks. Our recent study demonstrated greater AF vulnerability associated with moderate versus severe electrostructural atrial remodeling. Ranolazine prevented AF induction in 71% of atria isolated from the 2- to 3-week tachypaced group and in 66% of atria from the 5- to 6-week tachypaced group.

### Study Limitations

Patients with HF commonly present with a constellation of intra- and extracardiac diseases, with various underlying, often overlapping, causes (eg, coronary artery diseases and hypertension), and the disease commonly develops gradually. This respect, although the canine VTP-induced HF model recapitulates major HF clinical features, it does not reproduce the full spectrum of clinical phenotypes, being largely a nonischemic dilated cardiomyopathy HF model. The electrophysiological

### Table 2. More Potent Effect of Ran to Reduce AF Inducibility and Depress Sodium Channel–Dependent Parameters in HF vs Vagal non-HF Models of AF

<table>
<thead>
<tr>
<th>AF Model</th>
<th>ΔVmax</th>
<th>ΔVmaxm</th>
<th>ΔERP</th>
<th>ΔPRR</th>
<th>ΔS1–S1</th>
<th>Reduction of AF/AFI Inducibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ran 5 μmol/L in HF model</td>
<td>−18%*</td>
<td>−32%*</td>
<td>+49 ms† (+39%)</td>
<td>+40 ms†</td>
<td>+109 ms† (+81%)</td>
<td>70%</td>
</tr>
<tr>
<td>Ran 5 μmol/L in vagal non-HF model</td>
<td>−4%</td>
<td>−9%</td>
<td>+20 ms (38%)</td>
<td>+11 ms</td>
<td>+38 ms (+68%)</td>
<td>29%</td>
</tr>
<tr>
<td>Ran 10 μmol/L in vagal non-HF model</td>
<td>−7%</td>
<td>−15%</td>
<td>+57 ms (+98%)</td>
<td>+47 ms</td>
<td>+108 ms (+148%)</td>
<td>80%</td>
</tr>
</tbody>
</table>

Shown are changes of average values. Data from non-HF atria are from Burashnikov et al. S−S= shortest S−S, pacing interval permitting a 1:1 activation. Pacing cycle length (CL)=500 ms (except for the shortest S−S). Vagal non-HF model=control atria exposed to acetylcholine (1.0 μmol/L). Vmax, 500–300 ms=maximum rate of rise of the action potential upstroke; (Vmax changes in percentage after acceleration of pacing rate from a CL of 500 to 300 ms. AF indicates atrial fibrillation; ERP, effective refractory period; HF, heart failure; PRR, postrepolarization refractoriness; and Ran, ranolazine.

*P<0.05 vs Ran 5 and 10 μmol/L in vagal non-HF model.
†P<0.05 vs Ran 5 μmol/L in vagal non-HF model (unpaired t test); n=10 for each.
data were obtained from isolated cardiac preparations, which do not entirely recapitulate in vivo conditions. Our measurements were obtained from the RA, and it is possible that these data may not apply to the left atrium.

Clinical Implications
Sinus rhythm is preferable in patients with HF and a history of AF, provided the anti-AF therapeutic approach is safe and effective. Current pharmacological rhythm control management of patients with HF and AF is limited to amiodarone and dofetilide. Although these agents are generally safer than other antiarrhythmics, they nevertheless cause significant adverse effects in some patients, because of development of prolonged QT intervals and Torsade de Pointes in the case of dofetilide but rarely in the case of amiodarone and because of extracardiac toxicity in the case of amiodarone.1 Because of a high risk of induction of ventricular arrhythmias in patients with structural heart diseases, propafenone and flecainide (potent I\textsubscript{Na} blockers and effective anti-AF drugs) are contraindicated in patients with HF. Available evidence indicates that ranolazine is safe for both short- and long-term administration in patients with HF,23,17 Interestingly, ranolazine’s ion channel profile is similar to that of amiodarone,2 and amiodarone, like ranolazine, is also an atrial-selective peak I\textsubscript{Na} inhibitor.22,24 In the present study, we demonstrate that ranolazine is also an atrial-selective sodium channel blocker in the setting of HF. This similarity notwithstanding, ranolazine does not have any of the severe extracardiac adverse effects of amiodarone. Propafenone and flecainide are not atrial-selective in their action to block sodium channel activity.2,21 The anti-AF efficacy of ranolazine in patients with HF is poorly studied, but available evidence indicates that this drug can be an effective anti-AF agent in patients with HF.25,26 Although the clinical antifibrillatory effect of long-term ranolazine therapy in patients has not been tested, our data suggest that ranolazine may be a better alternative to amiodarone or dofetilide in patients with HF, when taking into account both safety and anti-AF efficacy.

In an experimental vagal model of AF, we have shown a synergistic action of ranolazine and amiodarone as well as ranolazine and dronedarone to suppress AF and to atrial-selectively depress sodium channel–dependent parameters.11,27 Future studies might be directed at assessing the effectiveness of the combination of ranolazine together with low-dose amiodarone or dronedarone for the management of AF in the setting of HF.

Secondary to its inhibition of late I\textsubscript{Na} and direct effect on the myofilaments, ranolazine has been shown to ameliorate diastolic dysfunction in several HF animal and human in vitro studies.28–31 Ranolazine’s effect to improve LV diastolic dysfunction in patients with HF with preserved LV ejection fraction (often referred to as diastolic HF) is being tested in a clinical trial.32 In most patients with HF, systolic and diastolic abnormalities coexist. Diastolic dysfunction promotes AF and seems to contribute to the disease phenotype at all levels of LV ejection fraction impairment.33 Interestingly, the prevalence of AF is significantly greater in patients with HF with preserved than reduced LV ejection fraction.34 Ranolazine may be particularly useful in the management of patients with HF who have diastolic dysfunction and AF, because it has both anti-HF and anti-AF actions. As with all experimental models, the clinical relevance of our experimental data is clearly speculative, but reasonable in light of this model’s demonstrated value in predicting clinical outcomes (The Harmony Trial, Late-Breaking Clinical Trials III, The Heart Rhythm Society Meeting 2014).

Conclusions
Our results indicate that ranolazine possesses potent anti-AF efficacy and does not promote ventricular proarrhythmia in a canine HF model. Ranolazine produces more potent atrial-selective depression of peak I\textsubscript{Na}-mediated parameters in atria isolated from dogs with HF than those from normal animals. Rate-dependent inhibition of peak I\textsubscript{Na} leading to the development of PRR seems to be the primary mechanism underlying the anti-AF efficacy of ranolazine in HF-mediated model of AF. In view of the clinical safety of ranolazine in patients with structural heart disease,16,17 our results suggest a need for studies specifically designed to evaluate the clinical utility of ranolazine for rhythm control of AF in patients with HF.

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Disclosures
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References


**CLINICAL PERSPECTIVE**

Heart failure (HF) and atrial fibrillation (AF) frequently coexist and can promote each other. There is a critical need for safer and more effective pharmacological management of AF in the setting of HF. Pharmacological options for rhythm control of patients with HF are limited to amiodarone and dofetilide in the United States and amiodarone in the European Union. These agents may cause cardiac and extracardiac adverse effects, including ventricular proarrhythmias. These limitations can be minimized with the use of atrial-selective agents. The present study investigates the electrophysiological, antiarrhythmic, and proarrhythmic effects of a clinically relevant concentration of ranolazine (5 μmol/L) in coronary-perfused right atrial and left ventricular preparations isolated from the hearts of HF dogs. Ranolazine had been previously shown to be an atrial-selective peak sodium channel current blocker in nonfailing hearts, effectively suppressing AF via induction of atrial-selective postrepolarization refractoriness. Our current results demonstrate that ranolazine produces more potent atrial-selective depression of peak sodium channel current–mediated parameters and more effective suppression of AF in the setting of HF than previously demonstrated in nonfailing hearts. Moreover, ranolazine induced no ventricular proarrhythmia in the setting of HF. In view of the apparent clinical safety of ranolazine in patients with structural heart disease, our results suggest that ranolazine may be of benefit as an alternative to amiodarone and dofetilide in the management of AF in patients with HF.
Ranolazine Effectively Suppresses Atrial Fibrillation in the Setting of Heart Failure
Alexander Burashnikov, José M. Di Diego, Hector Barajas-Martínez, Dan Hu, Jonathan M. Cordeiro, N. Sydney Moise, Bruce G. Kornreich, Luiz Belardinelli and Charles Antzelevitch

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/content/8/4/841.full.pdf

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In the article by Burashnikov et al, “Ranolazine Effectively Suppresses Atrial Fibrillation in the Setting of Heart Failure,” which first published online May 29, 2014, and appeared in the July 2014 issue of the journal (Circ Heart Fail. 2014; 7: 627–633. DOI: 10.1161/CIRCHEARTFAIL- URE.114.001129), several corrections were needed.

On page 628, in the methods section, the authors inadvertently wrote that “Single myocytes were obtained by enzymatic dissociation of the RA obtained from normal and tachypaced hearts.” The sentence has been changed to read, “Single myocytes were obtained by enzymatic dissociation of the left atria obtained from normal and tachypaced hearts.”

On page 630, in the last paragraph of the results section, the authors inadvertently referred to Figure 4E, which is not present in the manuscript. As such, the text “(Figure 4E)” has been deleted.

On page 630, in the figure legend for Figure 4, the authors inadvertently wrote “n=6 to 8”. The text has been corrected to read, “n=3 to 5”.

None of the errors impact the results or conclusions presented in the manuscript.

Lastly, at his request, Andy Zygmunt, PhD, has been removed as an author from the article.

These corrections have been made to the article, which is available at http://circheartfailure.ahajournals.org/content/7/4/627. The authors regret these errors.