Inhibition of the cardiac late sodium current with eleclazine protects against ischemia-induced vulnerability to atrial fibrillation and reduces atrial and ventricular repolarization abnormalities in the absence and presence of concurrent adrenergic stimulation

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BACKGROUND Myocardial ischemia carries dual risk for initiating atrial and ventricular arrhythmias that can be exacerbated by adrenergic stimulation.

OBJECTIVE The purpose of this study was to investigate whether selective inhibition of the cardiac late sodium current (I_{Na}) with eleclazine decreases susceptibility to ischemia-induced atrial fibrillation (AF) and atrial and ventricular repolarization abnormalities before and after epinephrine infusion.

METHODS In chloralose-anesthetized, open-chest, male Yorkshire pigs (n = 12), atrial and ventricular ischemia was induced by partial occlusion of the left circumflex coronary artery proximal segment to reduce flow by 75%. Epinephrine (0.5 μg/kg IV bolus over 1 minute; n = 6) was infused before and at 2 hours after eleclazine (0.9 mg/kg IV bolus over 15 minutes).

RESULTS Left circumflex coronary artery occlusion significantly increased ventricular dispersion of repolarization (T-wave alternans [TWA] by 861%, T-wave heterogeneity by 286%, T_{peak}–T_{end} interval by 74%) and atrial repolarization alternans (TWA_a) by 2850% and lowered AF threshold by 65%. Eleclazine reduced the ischemia-induced surge in TWA by 81% ($P = .007$), T-wave heterogeneity by 23% ($P = .035$), and T_{peak}–T_{end} by 28% ($P = .014$), suppressed the ischemia-induced surge in atrial TWA_a by 64% ($P = .002$), and reduced the ischemia-induced fall in AF threshold to 20%. It shortened baseline QT interval by 6% ($P < .001$), JT interval by 8% ($P < .001$), and atrial action potential duration (PTa) by 8% ($P = .002$). Similar beneficial effects of eleclazine were observed after epinephrine infusion without reducing contractility ($P = .054$).

CONCLUSION Selective inhibition of cardiac late I_{Na} with eleclazine confers dual protection against vulnerability to ischemia-induced AF and reduces atrial and ventricular repolarization abnormalities before and during adrenergic stimulation without negative inotropic effects.

KEYWORDS Atrial fibrillation; Repolarization; Alternans; Heterogeneity; Epinephrine; Late sodium current

(Heart Rhythm 2016;13:1860–1867)

Introduction

Ischemic heart disease carries a risk for both malignant ventricular arrhythmias and atrial fibrillation (AF).[1–3] Pharmacologic management of these conditions is particularly challenging because of the complexity of factors responsible for arrhythmogenesis in the atria and ventricles. The problem is compounded by the fact that some drugs currently used for rhythm control in AF can promote ventricular proarrhythmia, including torsades de pointes.[4]

The safety profile of ranolazine (Gilead Sciences, Palo Alto, CA) and its effectiveness in suppressing both atrial and ventricular arrhythmias, as demonstrated in the 6500–patient Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndrome–Thrombolysis

This study was funded by a grant from Gilead Sciences to Beth Israel Deaconess Medical Center (Dr. Verrier, Principal Investigator). Ms. Justo and Mr. Fuller received support from the Science without Borders Program of Brazil administered by CAPES, the Brazilian Coordinating Office for the Advancement of Higher Education. Dr. Belardinelli and Dr. Rajamani were employees of Gilead Sciences, the company that supported this study. Drs. Verrier and Nearing received royalties from Georgetown University and Beth Israel Deaconess Medical Center for intellectual property on the Modified Moving Average method for TWA analysis, which was licensed to GE Healthcare and was used in this study. **Address reprint requests and correspondence:** Dr. Richard L. Verrier, Harvard Medical School, Beth Israel Deaconess Medical Center, Division of Cardiovascular Medicine, Harvard–Thorndike Electrophysiology Institute, 99 Brookline Ave, RN-301, Boston MA 02215-3908. E-mail address: rverrier@bidmc.harvard.edu.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2016.06.020

in Myocardial Infarction 36 (MERLIN-TIMI 36) trial, has drawn attention to a novel mode of antiarrhythmic action.[5,6] Specifically, ranolazine, which has as its main action inhibition of late I_{Na}, appears to protect against arrhythmias largely by suppressing this highly arrhythmogenic current. Enhancement of late I_{Na} predisposes to early and delayed afterdepolarization-mediated triggered activity and reentry due to increased spatiotemporal dispersion of repolarization under diverse experimental conditions.[7–9] There is suggestive evidence that the main basis for the salutary action of late I_{Na} inhibition during myocardial ischemia is blunting of excess increase in intracellular levels of sodium, which in turn through reverse-mode effects on the sodium/calcium exchanger can reduce cytosolic calcium below arrhythmogenic levels.[7–9] However, because at therapeutic plasma levels ranolazine not only inhibits late I_{Na} but also blocks peak I_{Na} and I_{Kr}, the relative contributions of these actions on the effects of ranolazine need to be taken into account.

The encouraging findings with ranolazine have led to the development of more potent and selective inhibitors of cardiac late I_{Na}. In particular, the investigational agent GS-458967 has been shown both *in vitro*[10–12] and in large animal models to exhibit antiarrhythmic properties.[13,14] Currently, a new agent, eleclazine (dihydrobenzoxazepinone, formerly GS-6615; Gilead Sciences, Palo Alto CA), is undergoing active clinical evaluation with respect to several conditions with presumed elevation in late I_{Na} (Clinicaltrials.gov identifiers NCT02104583, NCT02291237, and NCT02300558), including in patients with long QT syndrome type III (LQT3; NCT01849003), in whom it is relatively free of side effects and is well tolerated.[15] Eleclazine reduces cardiac late I_{Na} in atrial[16] and ventricular tissue[12] and has minimal effects on other cardiac ion channels, including peak I_{Na}, I_{CaL}, I_{Ks}, and I_{Kr}.[12]

The goals of the present study were to examine the effects of eleclazine on vulnerability to ischemia-induced AF and atrial and ventricular repolarization abnormalities without and with concurrent adrenergic stimulation in an intact porcine model. The rationale for superimposing an adrenergic challenge on occlusion-induced myocardial ischemia is that sympathetic nervous system activity is an established trigger of arrhythmic events in patients with ischemic heart disease.[17–19] Newly developed techniques were applied, including measurement of PT_a, an index of atrial action potential duration, and repolarization alternans of the atria (TWA_a).[20] The translational potential of the findings of the present study is further enhanced by the measurement of ventricular T-wave heterogeneity (TWH) using a new method that has been shown to predict sudden cardiac death in the Health Survey 2000 study of 5600 subjects representative of the adult Finnish population.[21]

Methods

Experimental preparation

This study conformed to the *Guide for the Care and Use of Laboratory Animals* and to the *Position of the American Heart Association on Research Animal Use* as well as to the Declaration of Helsinki. The protocol was approved by the Institutional Animal Care and Use Committee of Beth Israel Deaconess Medical Center. Male Yorkshire pigs (N = 12) weighing 41 ± 0.7 kg (mean ± SEM) were studied. The pigs were preanesthetized with telazol (4.7 mg/kg IM) and then anesthetized with alpha-chloralose (80 mg/kg IV bolus followed by 24 mg/kg/h IV continuous infusion).

Methodologies

The catheterization methods for cardiac pacing, monitoring systemic and left ventricular blood pressure, electrocardiographic recording, assessment of repolarization alternans[13,14,16,22] and heterogeneity,[13,16,21] and drug delivery[23] are presented in the Online Supplemental Material, along with the description of analysis of plasma and tissue drug concentrations.

Myocardial ischemia induction

The experimental protocol is shown in Figure 1. A maximum of 4 left circumflex (LCx) coronary artery occlusions to reduce flow by 75% for 6 minutes was performed in each animal. The first was a preconditioning occlusion, and the second, performed 20 minutes thereafter, provided the baseline values for comparison with drug effects. Recovery periods followed each stenosis. In all animals, after the second occlusion, eleclazine (0.9 mg/kg IV bolus over 15 minutes) was infused via the left femoral vein. The third and fourth occlusions were at 60 and 120 minutes after the start of the drug infusion. Parameters were measured at baseline and from minutes 2 to 4 of occlusions during right atrial pacing at 150 bpm. In 6 pigs, after the end of the pacing period, AF threshold testing was performed. In the remaining 6 pigs, epinephrine was administered. We have demonstrated the absence of attenuation in response to repeated occlusions in this model.[13]

Adrenergic stimulation

Epinephrine (0.5 μg/kg IV bolus over 1 minute) was administered both before and during ischemia. The effects of epinephrine on T-wave alternans (TWA) and TWA_a were analyzed across a 2-minute period immediately after the start of the 1-minute epinephrine infusion.

Statistical analysis

The effects were analyzed using paired *t* tests with Bonferroni correction for multiple comparisons. All data are reported as mean ± SEM, and $P < .05$ was considered significant.

Results

Pharmacokinetic and hemodynamic response to eleclazine

The plasma level of eleclazine reached its peak concentration at 15 minutes after drug infusion (2179 ± 312.5 nM) and