Effect of ranolazine on ventricular repolarization in class III antiarrhythmic drug-treated rabbits

Gerrit Frommeyer, MD,[*] Dennis Kaiser, MS,[*] Timo Uphaus, MS,[*] Sven Kaese, MD,[*] Nani Osada, PhD,[†] Sridharan Rajamani, PhD,[‡] Luiz Belardinelli, MD,[‡] Günter Breithardt, MD, EFESC, FACC, FHRS,[*] Lars Eckardt, MD,[*] Peter Milberg, MD[*]

From the [*]Division of Electrophysiology, Department of Cardiovascular Medicine, and [†]Department of Medical Informatics and Biomathematics, University of Münster, Münster, Germany [‡]Department of Biology, Gilead Sciences, Foster City, California.

BACKGROUND Ranolazine exhibits a synergistic effect in combination with class III drugs to suppress atrial fibrillation.

OBJECTIVE To investigate whether a combination therapy affects repolarization and provokes ventricular tachyarrhythmias (VT) in a sensitive model of proarrhythmia.

METHODS Thirty-seven rabbits were assigned to 3 groups and fed with amiodarone (50 mg/kg/d; n = 10) or dronedarone (50 mg/kg/d; n = 10) over a period of 6 weeks. A third group was used as control (n = 17). After obtaining baseline data in Langendorff-perfused control hearts, sotalol (100 μM) was administered in this group. Thereafter, ranolazine (10 μM) was additionally infused on top of amiodarone, dronedarone, or sotalol.

RESULTS Chronic treatment with amiodarone or dronedarone as well as sotalol significantly increased action potential duration at 90% repolarization (APD_{90}). Additional treatment with ranolazine further increased APD_{90} in amiodarone- and dronedarone-pretreated hearts but not in sotalol-treated hearts. Ranolazine increased postrepolarization refractoriness as compared with amiodarone or dronedarone alone owing to a marked effect on the refractory period. In contrast to amiodarone and dronedarone, acute application of sotalol increased dispersion of repolarization ($P < .05$). Additional treatment with ranolazine did not further increase spatial or temporal dispersion. After lowering extracellular [K^+] in bradycardic hearts, no proarrhythmia occurred in amiodarone- or dronedarone-treated hearts whereas 11 of 17 sotalol-treated hearts showed early afterdepolarizations and subsequent polymorphic VT. Additional treatment with ranolazine reduced the number of VT episodes in sotalol-treated hearts and did not cause proarrhythmia in combination with amiodarone or dronedarone.

CONCLUSIONS Application of ranolazine on top of class III drugs does not cause proarrhythmia despite a marked effect on ventricular repolarization. The effect of ranolazine on the repolarization reserve is associated with the lack of effect on early afterdepolarizations and dispersion of repolarization.

KEYWORDS Ranolazine; Amiodarone; Dronedarone; Postrepolarization refractoriness; Dispersion of repolarization; Proarrhythmia; Repolarization reserve

ABBREVIATIONS **APD** = action potential duration; **APD_{90}** = action potential duration at 90% repolarization; **EAD** = early afterdepolarization; **I_{Kr}** = delayed rectifier K^+ current; **I_{NaL}** = late Na^+ current; **PRR** = postrepolarization refractoriness; **VT** = ventricular tachyarrhythmias

(Heart Rhythm 2012;9:2051–2058)

Introduction

In the presence of numerous side effects and contraindications, antiarrhythmic drug therapy is limited in atrial fibrillation. Ranolazine is an antianginal drug used in ischemic heart disease. More recently, studies in experimental animal models[1] as well as clinical reports[2,3] have suggested an antiarrhythmic potential of the drug on the level of the ventricle.

An antiarrhythmic effect of ranolazine based on an atrial-selective sodium channel block was proven in isolated atrial myocytes[4] as well as in canine pulmonary vein sleeve preparations[5] and intact porcine hearts.[6] Moreover, a remarkable antiarrhythmic effect of ranolazine in atrial fibrillation has been proven in a large cohort of patients after coronary bypass surgery.[7] It also effectively converted atrial fibrillation in patients with structural heart disease and enlarged left atria.[8] Acute and long-term treatment with ranolazine as monotherapy also has been reported to be safe even in patients with structural heart disease.[9,10]

Recently, a synergistic effect of a combined antiarrhythmic therapy with amiodarone and ranolazine as well as dronedarone and ranolazine was demonstrated by Antzelevitch and

This study was supported by the Dr Peter Osypka Foundation. Dr Eckardt holds the Peter Osypka Professorship of Experimental and Clinical Electrophysiology. Dr Rajamani and Dr Belardinelli are full-time employees of Gilead Sciences. **Address reprint requests and correspondence:** Dr Peter Milberg, MD, Abteilung für Rhythmologie, Department für Kardiologie und Angiologie, Universitätsklinikum Münster, Albert-Schweitzer Campus 1, D-48149 Münster, Germany. E-mail address: milbergp@uni-muenster.de.

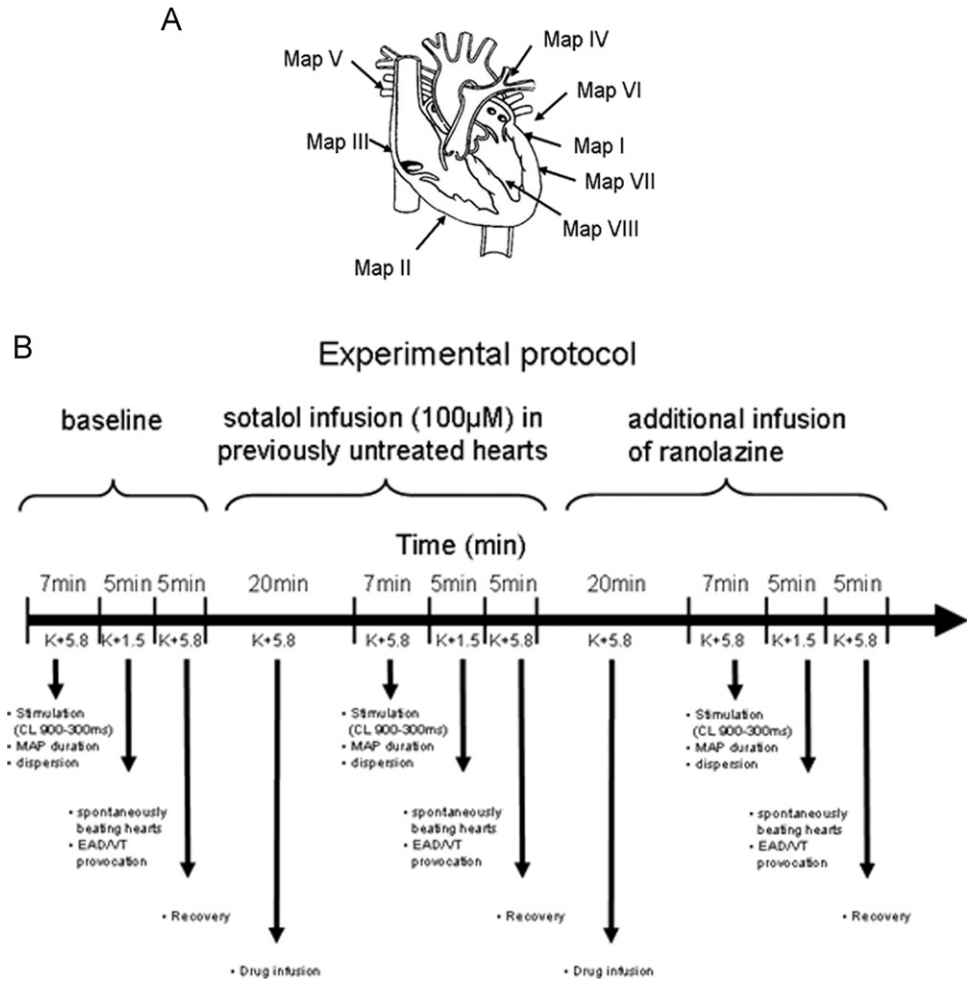

Figure 1 **A:** Position of MAP electrodes around the isolated heart. Left heart: MAP VIII = endocardial; MAP I = basis; MAP VII = midmyocardial; MAP VI = midmyocardial; MAP IV = apical. Right heart: MAP V = basis; MAP III = midmyocardial; MAP II = apical. **B:** Flowchart to illustrate the different consecutive parts of the experimental protocol. In chronically pretreated hearts, amiodarone or dronedarone replace the baseline part. No sotalol was employed in these groups. MAP = monophasic action potential.

colleagues.[11,12] The described effect, achieved through therapeutic plasma concentrations of 2–8 μM, is likely due to the inhibition of late Na^+ current (I_{NaL}) and delayed rectifier K^+ current (I_{Kr}),[13] but possibly also due to a voltage-dependent block of peak I_{Na}.[14] A combination of class III drugs with the I_{NaL} inhibitor, ranolazine, may therefore represent a new therapeutic approach in atrial fibrillation with promising perspectives. Moreover, ranolazine may amplify the relatively moderate antiarrhythmic efficacy of dronedarone in atrial fibrillation.[15]

However, ranolazine also blocks I_{Kr} with a half-maximal inhibitory concentration of 12–14 μM[14,16] and has been shown to prolong corrected QT intervals.[17] The effect of an "on-top therapy" with ranolazine has not been evaluated earlier. Combining ranolazine with class III drugs may further stress the repolarization reserve, which has been defined by Roden[18] as a patient-specific response to a repolarization-prolonging drug underlying acquired QT syndrome and could thus cause proarrhythmia. Certainly, the latter would reduce the potential future perspectives of a combined antiarrhythmic drug therapy with ranolazine. Thus, the present study was designed to examine whether an "on top" combined antiarrhythmic therapy including ranolazine causes serious proarrhythmic side effects. In a sensitive model of proarrhythmia,[19] amiodarone[20] and dronedarone[21] did not reveal proarrhythmic effects despite moderate QT prolongation. In contrast, sotalol resulted in ventricular tachyarrhythmias (VT) owing to a significant effect on repolarization reserve in the same model.[20]

Methods

All experimental protocols were approved by the local animal care committee and conformed to the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication No. 852-3, revised 1996).

Oral drug treatment and preparation of hearts for perfusion

Ten white female New Zealand rabbits (weighing 3.0–3.5 kg) received oral amiodarone treatment (50 mg/kg body weight