Antifibrillatory effect of ranolazine during severe coronary stenosis in the intact porcine model

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BACKGROUND Clinical evidence suggests that the antianginal agent ranolazine has antiarrhythmic properties, but its effects on vulnerability to ventricular fibrillation (VF) and T-wave alternans (TWA) during coronary artery stenosis have not been measured.

OBJECTIVE We investigated whether the antiarrhythmic effect of ranolazine during acute coronary stenosis could be quantified by measuring VF threshold and TWA magnitude.

METHODS Electrode catheters placed in the left ventricular apex were used to determine VF threshold during ventricular pacing at 130 beats/min, and TWA was quantified from epicardial electrograms using modified moving average method (N = 18). Left anterior descending coronary flow was reduced with a balloon occluder by 75% for 10 minutes. The I_{Kr} blocker E-4031 was used to distinguish effects of late I_{Na} and I_{Kr} inhibition by ranolazine.

RESULTS Before stenosis, ranolazine and E-4031 increased VF threshold from 32 ± 4 mA to 46 ± 4 mA (mean ± SEM), $P = .02$, and from 33 ± 5 mA to 40 ± 9 mA, $P = .02$, respectively. During stenosis, ranolazine increased VF threshold from 19 ± 2 mA to 33 ± 3 mA ($P = .02$), whereas E-4031 decreased VF threshold from 21 ± 3 mA to 15 ± 3 mA ($P = .02$). The ischemia-induced increase in TWA was suppressed by ranolazine but not by E-4031, consistent with effects of these agents on VF threshold.

CONCLUSION Ranolazine exerts significant antifibrillatory effects during coronary stenosis through direct effects on cardiac electrical properties independent of coronary flow. Ranolazine's antifibrillatory action during myocardial ischemia does not appear to be mediated by blockade of I_{Kr} but rather by inhibition of late I_{Na}. TWA changes paralleled vulnerability to VF as indicated by VF threshold testing.

KEYWORDS Antiarrhythmic agents; Myocardial ischemia; Sodium; T-wave alternans; Ranolazine; Ventricular fibrillation threshold

ABBREVIATIONS **APD** = action potential duration; **LAD** = left anterior descending; **MMA** = modified moving average; **TWA** = T-wave alternans; **VF** = ventricular fibrillation

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Introduction

In disease states such as ischemia and heart failure, late inward sodium current (late I_{Na}) is enhanced, leading to an increase in intracellular levels of sodium.[1–3] This effect increases the activity of the reverse mode of the sodium–calcium exchanger and thereby increases cytosolic levels of calcium, an action that impairs mechanical relaxation and predisposes to cardiac arrhythmias by eliciting calcium release from the sarcoplasmic reticulum, and, in the case of heart failure, by prolongation of the ventricular action potential.

Ranolazine is a recently introduced antianginal drug that exerts its effects predominantly by blocking late I_{Na}. Ranolazine decreased the incidence of ventricular tachycardia in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN TIMI 36) trial.[4] Consistent with this finding, ranolazine has also been shown to increase markedly the thresholds for repetitive extrasystole and ventricular fibrillation (VF) in a large animal model.[5] To our knowledge, the antiarrhythmic effects of ranolazine during coronary stenosis have not been investigated in a large animal model. In addition to the inhibition of late I_{Na}, ranolazine at therapeutic plasma concentrations

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also blocks the rapid component of delayed rectifier potassium current (I_{Kr}) albeit to a lesser extent than late I_{Na}.[2] The relative contributions of blockade of late I_{Na} and I_{Kr} in terms of vulnerability to VF either at baseline or during coronary artery stenosis are unknown.

T-wave alternans (TWA) is an electrocardiographic phenomenon indicating an electrically unstable myocardial substrate.[6] This beat-to-beat alternation in the shape, amplitude, or timing of the ST-segment and the T wave is due to fluctuations in the morphology and duration of the action potential. TWA has been found to predict sudden cardiac death and cardiovascular and total mortality independent of standard risk factors in relatively low-risk populations[7] as well as in higher-risk groups.[8] Extensive evidence in animals during coronary artery occlusion and in humans during angioplasty indicates that provocation of myocardial ischemia increases TWA magnitude.[9] Ischemia-induced increases in TWA magnitude have been shown in experimental studies to parallel heightened susceptibility to ischemia- or reperfusion-induced VF or ventricular tachycardia.[9] The presence of TWA is thought to be arrhythmogenic, because it can reflect beat-to-beat alternation in action potential morphology and duration, which can be out-of-phase in different regions of the myocardium, referred to as discordant alternans.[10,11] Discordant alternans is conducive to VF because this condition establishes steep heterogeneous repolarization gradients that can predispose to reentry and wavebreak.[10–12] No prior study has assessed whether the protective effect of ranolazine during myocardial ischemia could be tracked by concomitant changes in VF threshold and in TWA.

The objectives of the present study were to determine: (1) the effect of ranolazine on vulnerability to VF as assessed by VF threshold testing before and during severe coronary artery stenosis; (2) whether ranolazine's effects on vulnerability to VF are reflected in parallel changes in TWA; and (3) whether ranolazine's I_{Kr} blocking effect contributes to the changes in VF threshold and TWA.

Methods

Experimental preparation

This study conformed 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 our institutional animal use committee. Data were gathered from male Yorkshire pigs (N = 21) weighing 31.3 ± 2.0 kg (mean ± SD). Three animals were lost due to difficult resuscitation after VF. The animals were preanesthetized with telazol (4.7 mg/kg, intramuscularly) and then anesthetized with isoflurane (1.5% to 2.0% by inhalation). Arterial pO_2, pCO_2, and pH were maintained in the physiologic range with the use of a constant volume-cycled respirator (Harvard Apparatus, Holliston, MA) and supplemental oxygen through endotracheal intubation. The right femoral artery and vein were cannulated with 8-F introducer sheaths using the Seldinger technique. Arterial blood pressure was continuously monitored from a femoral arterial sheath, and intravenous fluids along with investigational drugs were administered through a femoral vein. The left carotid artery was cannulated for ventricular pacing and electrical testing. An electrocardiogram was recorded with a Prucka Cardiolab workstation (GE Medical Systems, Milwaukee, WI). A hydraulic balloon occluder (Docxs, Inc., Ukiah, CA) was positioned around a proximal segment of the left anterior descending (LAD) coronary artery (Figure 1). LAD flow was determined using a Doppler flow probe (Transonic, Inc., Ithaca, NY) positioned proximally to the balloon occluder.

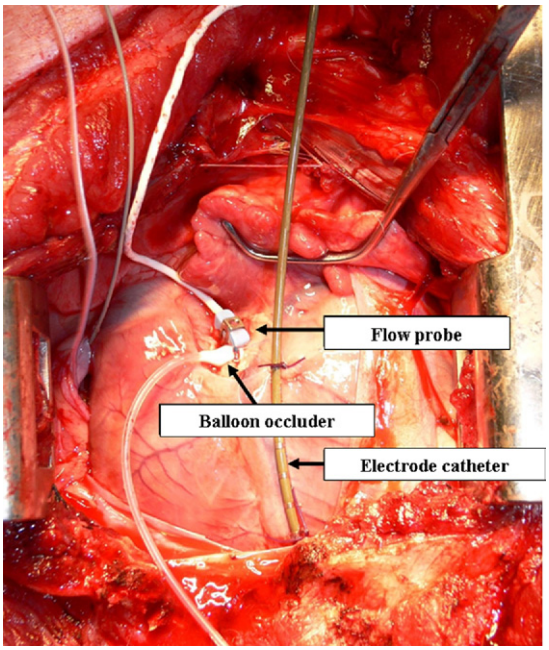

Figure 1 Experimental model. Balloon occluder around left anterior descending (LAD) coronary artery reduced flow by 50% or 75%, measured by flow probe. An electrode catheter was positioned in the LAD territory.

Study protocol

All animals were subjected to preconditioning ischemia induced by decreasing the LAD coronary artery flow by 50% for 5 minutes. In a pilot series (N = 6), we examined the effects of moderate 50% reduction of LAD flow on ranolazine-induced changes in TWA. In the final animal of the pilot series and in 12 subsequent pigs, VF threshold testing was performed 4 times after preconditioning. The first test was performed without ranolazine at normal coronary flow. The second test was during 10-minute LAD coronary artery flow reduction by 75% from baseline (25 ± 2 ml/min) to ~5 to 9 ml/min (n = 13). The third VF threshold test was performed without stenosis at 30 minutes after the start of ranolazine or E-4031 infusion. The fourth test was carried out during 10-minute 75% flow reduction at 20 minutes after ranolazine or E-4031 infusion. Testing during flow reduction was always initiated after 4 minutes of myocardial ischemia. Ranolazine (Gilead Palo Alto, Inc., Palo Alto, CA) was administered as a 2.4-mg/kg intravenous bolus over 1 minute followed by a continuous infusion