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Effective suppression of atrial fibrillation by ivabradine: Novel target for an established drug?

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ABSTRACT

Background: Ivabradine is an inhibitor of mixed Na^+-K^+-currents and routinely administered in chronic heart failure. Clinical studies reported divergent trends regarding proarrhythmic and antiarrhythmic effects in atrial fibrillation (AF).

Methods and results: In 12 isolated rabbit hearts AF was induced in 7 of 12 hearts (13 episodes) under baseline conditions by a standardized protocol employing atrial burst pacing. Thereafter, a combination of acetylcholine and isoproterenol was employed to enhance AF occurrence. Monophasic action potential recordings showed a decrease of atrial action potential duration (aAPD,-37 ms, $p < 0.05$) and atrial effective refractory period (aERP;-39 ms, $p < 0.05$) after infusion of both acetycholine (1 μM) and isoproterenol (1 μM) as compared with baseline. This led to induction of AF in 11 of 12 hearts (124 episodes). Simultaneous infusion of ivabradine (3 μM) led to a significant reduction of AF (6 of 11 hearts, 63 episodes). Ivabradine induced an increase of aAPD (+9 ms) and aERP (+30 ms, $p < 0.05$) leading to a marked increase of atrial post-repolarization refractoriness (aPRR), defined as the difference of aERP and aAPD (+21 ms, $p < 0.05$).
Results were compared to 10 rabbits treated with flecainide. Flecainide treatment also induced a significant increase of aPRR and resulted in induction of AF in 6 of 10 hearts (58 episodes) while 9 of 10 hearts were inducible during sole treatment with acetylcholine and isoproterenol (129 episodes).

Conclusion: In the present experimental study, administration of ivabradine reduced inducibility of AF and therefore may represent a supplemental therapeutic option in AF. Of note, its antiarrhythmic efficacy was comparable to the established agent flecainide.

1. Introduction

Rhythm control of atrial fibrillation (AF) still remains challenging although a few new antiarrhythmic drugs have been introduced recently. The limited efficacy of rhythm control therapy is attributed to the complexity of the substrate as a result of atrial remodeling in chronic AF [1]. Current guidelines for patients with heart failure recommend amiodarone as the only pharmacologic option in patients with severe structural heart disease and a significantly reduced left ventricular function [2]. Different antiarrhythmic drugs, in particular traditional sodium channel inhibitors, are disadvised due to an increased rate of proarrhythmia and/or an increased mortality in heart failure patients. Other novel agents like vernakalant are not available for chronic treatment. These aspects underline the demand for innovative therapeutic options to ameliorate rhythm control of AF [3].

Ivabradine is an inhibitor of the pacemaker current (I_f) designed to reduce heart rate without any negative inotropic effects [4]. Of note, ivabradine also exerts relevant effects on human ether-a-go-go-related-gene (hERG) currents. This was observed in patch-clamp experiments as well as in intact guinea pig hearts where a prolongation of ventricular repolarization by ivabradine occurred [5]. This effect results from a prolongation of phase-3 of cardiac repolarization [6]. In an in vivo pig model a combination of ivabradine with the late sodium current inhibitor ranolazine resulted in a remarkable reduction of ventricular rate in the presence of AF [7]. In accordance, sole treatment with ivabradine may induce a rate-dependent reduction of ventricular rate during AF. This was reported in experimental [8] as well as in clinical settings [9,10]. Furthermore, a reduction of ischemia-reperfusion-related ventricular arrhythmias mediated by ivabradine treatment was observed in experimental animal models [11,12]. These electrophysiological characteristics suggest a potential antiarrhythmic effect in AF.

Clinical studies and meta-analyses displayed divergent trends regarding potential proarrhythmic or antiarrhythmic effects of ivabradine in AF. In a meta-analysis of clinical trials including >

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21,500 patients AF was reported to be a more common side effect of ivabradine treatment than previously suspected with a relative risk of 1.15 [13]. This trend was confirmed in a more recent meta-analysis including >40,000 patients [14] and was also observed in the SIGNIFY-study in which ivabradine in patients with stable coronary heart disease did not improve clinical outcome [15]. In contrast, treatment with ivabradine in addition to standard therapy was associated with a reduced incidence of AF in patients after coronary bypass surgery [16].

The rationale of the present study was to investigate the direct electrophysiologic actions of ivabradine on the level of the atrium in an established experimental model of atrial fibrillation [17,18] in comparison to the established antiarrhythmic agent flecainide [19].

2. 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).

2.1. Preparation of hearts for perfusion

The experimental method of rabbit heart isolation has been described in previous studies [17,20]. In short, rabbits were euthanized with sodium thiopental (200–300 mg i.v.). After midsternal incision and opening of the pericardium, the intact hearts were removed and directly positioned in an ice-cold Krebs-Henseleit solution (composition in mM: $CaCl_2$ 1.80, KCl 4.70, KH_2PO_4 1.18, $MgSO_4$ 0.83, NaCl 118, $NaHCO_3$ 24.88, Na-pyruvate 2.0 and D-glucose 5.55). The aorta was cannulated, the pulmonary artery was incised, and the spontaneously beating hearts were perfused at constant flow (52 ml/min) with tempered (36.8 to 37.2 °C) Krebs-Henseleit solution. Perfusion pressure

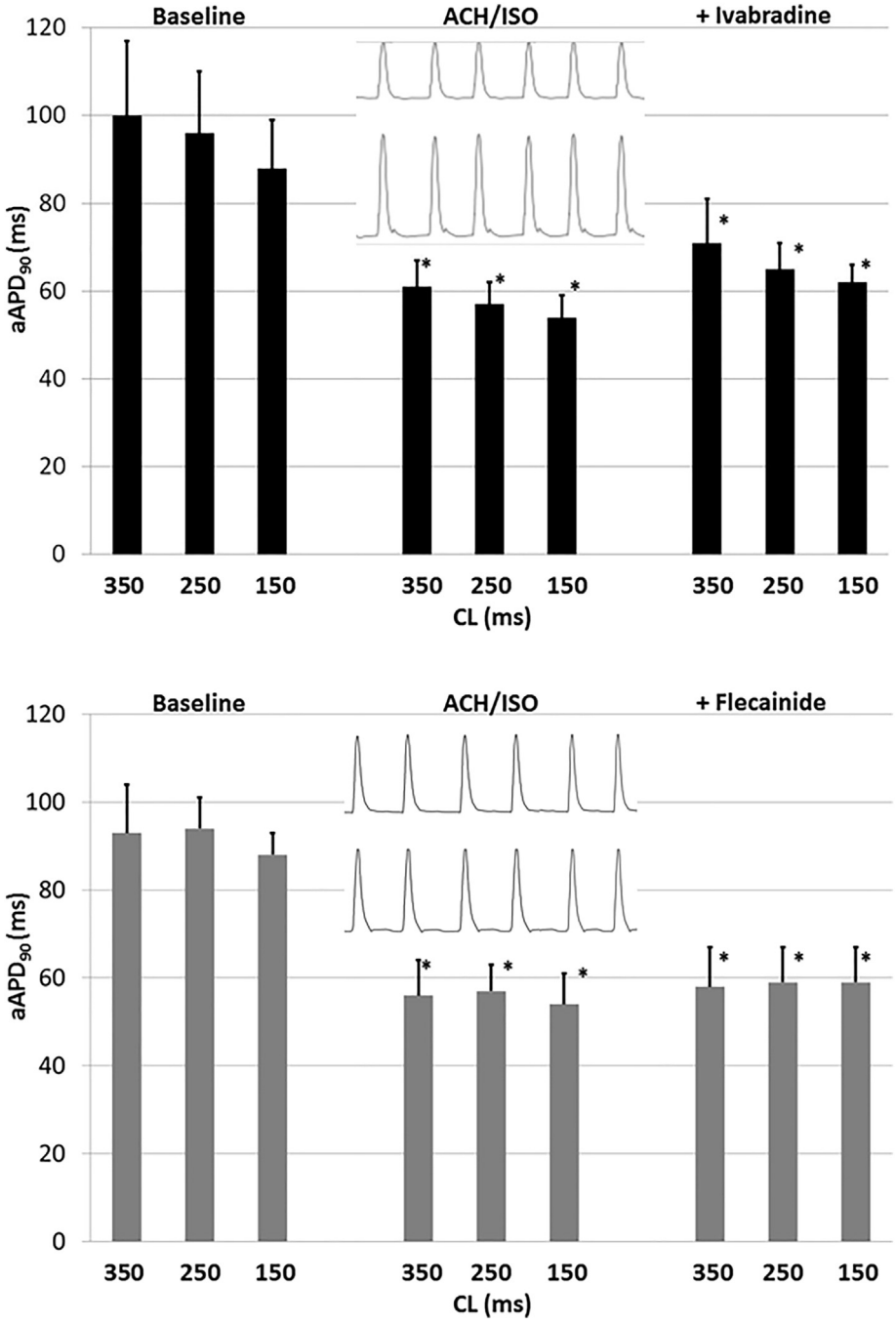

Fig. 1. Effects of ivabradine (black) or flecainide (grey) application on $aAPD_{90}$. (* = $p < 0.05$ as compared with baseline). Top center: exemplary atrial monophasic action potential recordings.

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