Antifibrotic effects of Ivabradine for myocardium in ischemic chronic heart failure

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Abstract
Heart failure (HF) is the end stage of most diseases of the cardiovascular system and is a major cause of morbidity and mortality. Ivabradine (Iva) – the new medication with sinus If-channels inhibition effects. Nowadays Iva is present in ESC recommendation for HF and chronic coronary disease management. The purpose of study was to evaluate of potential antifibrotic effects of Ivabradine for myocardium in case of chronic heart failure. On twelve-week-old male Rattus Norvegicus L. rats, weighing 220–240 g, HF were modeling. This study shows that Ivabradine treatment of rats with HF prevented anatomical remodeling. Such beneficial effects of Ivabradine on cardiac remodeling open new clinical perspectives for the treatment of severe HF.

Keywords: heart failure, ivabradine, myocardial remodeling

1. Introduction
Heart failure (HF) is the end stage of most diseases of the cardiovascular system and is a major cause of morbidity and mortality. About 26 million adults worldwide are living with HF, leading some to describe it as a global pandemic [1]. Coronary artery disease (CAD) is the main reason of HF. Increased resting heart rate (HR) is a risk factor for coronary artery disease, HF and mortality [2]. Several studies have shown the benefits of lower HR on cardiovascular mortality and morbidity in different patient populations [3, 4].

Ivabradine (Iva) reduces HR by a direct effect on the sinoatrial node. It is an inhibitor of the specific F channels (funny channels) [5], which controls the electrical pacemaker activity in the sinoatrial node. Iva is deprived of inotropic and direct vasodilating effects [6].

The beneficial effects of Iva have been shown during an early functional remodeling following myocardial infarction (MI). Indeed, a 3-mo treatment by Iva, started 7 days after MI in rats, increases stroke volume and preserves cardiac output despite the HRR [7]. Recently, a 1-mo Iva treatment started 1 day after MI was shown to improve maximal myocardial perfusion and coronary reserve in rat hearts likely via the reduction of periarteriolar collagen [8].

Although the efficacy of Iva in the treatment of myocardial ischemia and angina has been shown, small quantities of studies have directly evaluated its potential benefits on ventricular and remodeling in the context of ischemic HF.

The purpose of study was to evaluate of potential antifibrotic effects of Ivabradine for myocardium in case of chronic heart failure.

2. Material and Methods
Experiments were conducted according to “Guide for the Care and Use of Laboratory Animals” (National Institutes of Health, Publication No. 85-23, Revised 1996) and had the agreement of the local Ethics Committee. Twenty of twelve-week-old male Rattus Norvegicus L. rats, weighing 220–240 g, were used. They had free access to a standard rat diet in an aerated box. Heat at 37 °C. HF was induced by a subcutaneous injection of Isoprenaline hydrochloride (Sigma-Alorich, Germany) twice with 24-hours interval in dose of 80 mg/kg [10].

All animals were divided into 2 groups: 10 rats – control group and 10 rats were treated by Iva (Coraxan, Les Laboratories Servier, France) in dose 10 mg/kg daily during 1 month.

Rats were anesthetized by a ketamine (80 mg/kg)-xylazine (5 mg/kg) and decapitazied. An equatorial section of the heart was frozen in embedding medium. Cardiac cryosections (7 mm thick) were stained with picrosirius red F3BA, and the interstitial collagen volume fraction was blindly quantified on five sections per heart (8–10 fields/section) as described [11]. Pervascular collagen content was measured as described [11].

Data are expressed as means ± SE. The difference between the control and Iva-treated groups
at each phase of the study were assessed using two-way repeated-measures analysis of variance. When significant differences between groups were found, a pairwise multiple comparison procedure using Bonferroni t-tests were performed at each time point. All tests were performed using Statistika 12 software (StatSoft). When indicated, a t-test was used for comparison between groups. P < 0.05 was considered as significant.

3. Results and Discussion. The polymorphic morphology changes were observed in Iva-treated group of rats. In many slides we founded of hypertrophic cardiomyocytes with big-size nuclei and slim and distorted cells (Fig. 1). The places of homogenization and enlightenments, perinuclear edema and single vacuoles were identified.

Many cardiomyocytes were with wave-like distortion, places of constriction and expansion. In stroma – proliferation of gentle connective tissue with presence of few fibroblasts. In general, all cardiomyocytes were with clear contours: nuclei are isomorphic. We identified of clear transverse strip on the longitudinal sections.

In second group rats we usually didn’t founded of places of the big sizes connective tissue proliferation, but the frequent finding was polygonal interstitial fibrosis loci. The net-like growth of gently fibrosis tissue were often founded with good vascularization. The main feature was absence of cellular distortion andatrophy.

It’s known, that MI induces important cardiac remodeling, including fibrosis of the remote myocardium and myocyte hypertrophy (12). One remarkable result is the decrease of ventricular interstitial fibrosis that was observed in Iva and MI rats compared with MI rats. Previously, Iva was shown to prevent the collagen accumulation in the post-MI ventricle (8). However, this prevention was observed while Iva was initiated at 7 days post-MI. The major finding herein is that Iva was able to decrease and/or stop the accumulation of collagen in the LV remote part even when Iva was started long ago from the MI, a decreased fibrosis known to be beneficial on cardiac function (13). This is a significant advance for the potential use of this drug in clinical practice, since we may anticipate that numerous patients with HF will have an already-established cardiac fibrosis, which continues to expand.

4. Conclusion. This study shows that Ivabradine treatment of rats with HF prevented anatomical remodeling. Such beneficial effects of Ivabradine on cardiac remodeling open new clinical perspectives for the treatment of severe HF.

5. References

Fig. 1. Myocardiocytes in Iva-treated rats with HF.

Fig. 2. The net-like proliferation of connective tissue in Iva-treated rats.
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