The echocardiographic parameters dynamics in patients with chronic heart failure managed by Ivabradine

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Abstract
Cardiac remodelling is central to the pathophysiology of heart failure (HF) and is an established prognostic factor in patients with HF. Left ventricular (LV) enlargement has been shown to be associated with an increased risk for adverse cardiac events, while reduced LV ejection fraction (LVEF) is a powerful predictor of cardiovascular outcomes and all-cause mortality. Patients were randomly allocated to ivabradine or placebo, superimposed on background therapy for HF. Complete echocardiographic data at baseline and 6 months were available for 180 patients with ischemic HF and sinus rhythm. Ivabradine is effective medicine for improving the main cardio-hemodynamic parameter in patients with ischemic heart failure.

Keywords: heart failure, coronary artery disease, echocardiography, Ivabradine

1. Introduction
Despite striking improvement in the prognosis and survival in patients with coronary artery disease (CAD), hypertension, and congenital heart disease, the prevalence of chronic heart failure (HF) is still growing worldwide [1, 2, 3]. The prognosis of HF is relatively poor, with 25% mortality at 1 year and 50% mortality at 5 years (NYHA IV HF: 80% mortality at 5 years) - worse than that of many cancers [1]. Several pathogenetic mechanisms appear to be operative in HF. These include increased hemodynamic overload, ischemia-related dysfunction, ventricular remodeling, excessive neurohumoral stimulation, abnormal myocyte calcium cycling, excessive or inadequate proliferation of the extracellular matrix, accelerated apoptosis, and genetic mutations [2, 4, 5]. Biomarkers released as a consequence of myocardial stretch, imbalance between formation and breakdown of extracellular matrix, inflammation, and renal failure are useful in the identification of the pathogenetic mechanism and, when used in combination, may become helpful in estimating prognosis and selecting appropriate therapy. Promising new therapies that are now undergoing intensive investigation include an angiotensin receptor neprilysin inhibitor, a naturally-occurring vasodilator peptide, a myofilament sensitizer and several drugs that enhance Ca++ uptake by the sarcoplasmic reticulum [6, 9]. Cell therapy, using autologous bone marrow and cardiac progenitor cells, appears to be promising, as does gene therapy [7, 8]. Chronic left ventricular assistance with continuous flow pumps is being applied more frequently and successfully as destination therapy, as a bridge to transplantation, and even as a bridge to recovery and explantation. While many of these therapies will improve the care of patients with HF, significant reductions in prevalence will require vigorous, multifaceted, preventive approaches.

Ivabradine is a new therapeutic agent designed to reduce heart rate at rest and during exercise by selective inhibition of a novel receptor (If channel) located on the pacemaker-cell membrane within the sinoatrial node. As such, ivabradine joins a list of rate-limiting medications already available to prescribers for the control of heart rate in CAD and HF with systolic dysfunction [10]. The data for ivabradine influence for echocardiographic parameters in patients with ischemic HF are controversial.

The purpose of this study was to investigate the possible influence of ivabradine for echocardiographic parameters in patients with ischemic heart failure.

2. Material and Methods
180 patients with ischemic HF and sinus rhythm were observed. In accordance to treatment all patients were divided into four groups:
I group – basic treatment (89 patients); II group (91 patients) - basic treatment and Ivabradine (Coraxan, Les Laboratoires Servier Industrie, France) – 5 or 7.5 mg twice a day (depends of heart rate).

Echocardiography was performed at baseline and within 6 months. All measurements were made according to the recommendations of the American Society of Echocardiography (ASE) and the European Association of Echocardiography. The study was performed in accordance with the Helsinki Declaration and Good Clinical Practice Guideline. The study was approved by the local ethics committee and written informed consent was obtained from all patients. Categorical variables are presented as percentages, whereas continuous variables are presented as mean (M) and standart error of mean (m) if normally distributed, or as median and interquartile range (Me [IQR]), if not. Categorical variables were compared by the χ² test and continuous variables by the t test or the Mann–Whitney U test. A p value of <0.05 was considered statistically significant. All tests were 2-sided. Analyses were performed with Statistica system software, version 12.0.

3. Results and Discussion
The average age of observed patients with HF was (67.98±12.06) years. Any significant changes in left atrium diameter were founded in both groups during management period (see table). At the end of observation the significant dynamics of end-diastolic size (EDS), end-systolic size (ESS), end-diastolic volume (ESV), end-systolic volume were observed. In all cases we founded the improving of these values. However, the difference compared basic treatment group was insignificant. Ivabradine showed the more strong influence for improving of ejection fraction of left ventri cle (LVEF): from (49.13±0.98) % to (52.31±1.02) % (p<0.01) compared basic group: from (48.87±1.11) % to (49.97±0.89)%(p<0.05).

The SHIFT echocardiographic substudy showed more strong effects of ivabradine on left ventricular (LV) remodelling in HF. Complete echocardiographic data at baseline and 8 months were available for 411 patients (ivabradine 208, placebo 203). Treatment with ivabradine reduced LVESVI (primary substudy endpoint) vs. placebo [−7.0 ± 16.3 vs. −0.9 ± 17.1 mL/m²; difference (SE), −5.8 (1.6), 95% CI −8.8 to −2.7, p < 0.001]. The reduction in LVESVI was independent of beta-blocker use, HF aetiology, and baseline LVEF. Ivabradine also improved LV end-diastolic volume index (~7.9 ± 18.9 vs. −1.8 ± 19.0 mL/m², p= 0.002) and LVEF (+2.4 ± 7.7 vs. −0.1 ± 8.0%, p < 0.001). The incidence of the SHIFT primary composite outcome (cardiovascular mortality or hospitalization for worsening HF) was higher in patients with LVESVI above the median (59 mL/m²) at baseline (HR 1.62, 95% CI 1.03–2.56, p = 0.04). Patients with the largest relative reductions in LVESVI had the lowest event rates.

4. Conclusion
Ivabradine is effective medicine for improving the main cardio-hemodynamic parameter in patients with ischemic heart failure.

5. References