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Comparison of ivabradine and metoprolol tartrate impact on the heart rate variability in patients with angina pectoris

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Abstract

Background: Heart rate variability (HRV) is an effective way to estimate heart rate (HR) autonomic regulation. In some cardiovascular diseases increased sympathetic activity (low frequency spectral power of HRV) was shown to be an unfavorable risk factor which could be downregulated by beta-blockers. There are only few data on I_f-blocker ivabradine impact on HRV parameters and direct comparison between beta-blockers and ivabradine in relation to HRV was not conducted. The purpose of the study was to compare the impact of I_f-blocker ivabradine and metoprolol tartrate on autonomic control of nervous system HR control in patients with stable angina pectoris.

Methods: Effects of ivabradine 7.5 mg and 50 mg metoprolol tartrate HRV were estimated in 33 patients with angina pectoris in the open-labeled randomized, controlled, crossover design and acute pharmacological test study. HRV was determined for 10 minutes in supine position before and after 4h the each test drug according to randomization.

Results: Equal negative chronotropic impact for ivabradine and metoprolol was shown, the effect increased with HR upraise and was positively correlated with baseline HR. Both ivabradine and metoprolol produced downregulating effect of sympathetic tone, but the effect of ivabradine was more significant. However, metoprolol decreased the total power parameter and the value of adaptation.

Conclusions: In patients with angina pectoris I_f-blocker ivabradine downregulation of sympathetic status in comparison with beta-blocker metoprolol tartrate effect was firstly shown.

Keywords: Heart rate variability, ivabradine, metoprolol, CHD

Introduction

Heart rate variability (HRV) is accessible, informative and efficient way to estimate the balance of sympathetic and parasympathetic nervous system of the heart [1]. Some HRV parameters correlate with the frequency of unfavorable cardiovascular events [2,3] and are used to assess the patients' state, to predict outcomes and to optimize therapy [4]. Coronary heart disease (CHD), especially after myocardial infarction (MI), results in sympathetic and parasympathetic nervous systems heart rate (HR) regulation and correspondingly, HRV imbalance caused by upregulation of low-frequency (LF) and downregulation of high frequency (HF) domain decreases [5]. Therefore, in CHD, especially after MI, the drugs positively affecting HRV are more favorable [2]. Several cardiovascular drugs such as beta-blockers (BB), angiotensin-

converting enzyme inhibitors and angiotensin receptor blockers have proved to modulate HRV [4]. The classical ones are BBs, which not only reduce the HR, but also normalize the above mentioned balance of sympathetic/parasympathetic system of HR regulation by upregulating HF and, on the contrary, by downreguling LF and very LF components [6-8].

Ivabradine is a unique drug from the group of I_f-blockers, selectively decreasing HR [9,10]. According to the guidelines, it could be used in stable angina pectoris and chronic heart failure in patients with high HR especially in case of BB contraindications and lack of BB efficacy, also in combination with the last one [11]. Actual absence of clinical efficacy in non-heart failure patients with CHD in SIGNIFY (Study assessInG the morbidity-mortality beNefits of the If inhibitor ivabradine in

patients with coronary artery disease) study [12] and on the contrary, positive effect of ivabradine on the cardiovascular end-points in BEAUTIFUL (MorBidity-mortality EvAlUaTion on the I$_f$ Inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) [13] and SHIFT [14] studies require further clarification. Over the past years the data on ivabradine impact on HRV appeared. Belal et al., (2013) [15] in the small study involving 15 volunteers showed that ivabradine could promote earlier onset and more significant modulation of neural control of cardiovascular system. However, until now no contrastive comparisons of BB and I$_f$-blockers impact on HRV have been shown. Joanides et al., (2006) [16] compared the effects of ivabradine and nonselective BB propranalol on the various hemodynamic parameters, including autonomic regulation of cardiovascular system, in 10 healthy volunteers. It was shown that both Iva and propranolol increased HF component as well as HF/LF ratio. However, from the clinical point of view the small number of patients and healthy volunteers but not CHD participants restricted the value of study.

In the present paper the direct comparison of BB and If-blocker on cardiac autonomic status in patients with CHD was performed. The purpose of the study was to compare the effects of I$_f$-blocker ivabradine with BB metoprolol tartrate on HRV in patients with stable angina pectoris in the open-labeled randomized controlled trial with crossover design and acute pharmacological test.

Methods

33 patients with CHD and angina pectoris in stable state and good BB compliance participated in the study.

Inclusion criteria
- Written informed consent
- Stable angina pectoris
- Stable dose of BB before the study
- Body mass index 19-30 kg/m^2

Exclusion criteria
- Arterial hypotension with systolic BP<90 mm Hg
- Acute coronary syndrome
- HR <60 and >90 beats/min before the study
- NYHA IV
- Diabetes mellitus
- Atrial fibrillation, atrial flutter, AV-block of II-III degree
- Actual comorbidities
- Myocardial infarction in the past
- Fever, sepsis, myocarditis

Comparators
I$_f$-blocker ivabradine 7.5 mg (Procoralan, Servier, France) and BB metoprolol tartrate 50 mg (Egilok, "Gedeon Richter", Hungary) were chosen for comparison. Both drugs have comparable half-life (12 hours) and the peak of serum concentration (3-4h).

The doses were chosen to decrease heart rate equipotentially.

Study design
Prospective, open-labeled, short-term, controlled, crossover and acute pharmacological test design has been applied. After obtaining the written informed consent, physical examination (height, weight), auscultation, heart rate, systolic and diastolic blood pressure (SBP and DBP) were estimated. After enrolling in the study patients discontinued using BB for 2 days (washout period) but continued taking other cardiovascular drugs. HRV was estimated in supine position for 10 minutes with "Sphygmacor" (AtCor, Australia) device, and then the patients were randomized. Every patient has equal probability 1/2 to be included in two groups according to software based random number generator. According to the randomization, participants received ivabradine 7.5 mg (group 1) or metoprolol 50 mg (group 2) once per os. In 3.5-4h, at the peak of drug concentration in serum, patients' HRV was re-estimated (Investigation 2). At least after 2 days the "crossover" test was performed in which the patients previously received 50 mg of metoprolol (Group 2), then they were given ivabradine 7.5 mg and vice-versa. Investigations 3 and 4 were conducted similar to the 1st and the 2nd ones (**Figure 1**).
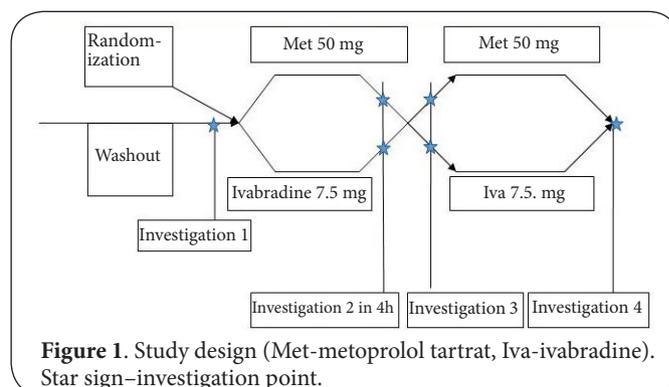

Figure 1. Study design (Met-metoprolol tartrat, Iva-ivabradine). Star sign–investigation point.

During the analysis the following HRV indicators were calculated: standard deviation of all R-R intervals–SDNN; square root of the mean squared differences of successive normal NN intervals–RMSSD; LF (low frequency), HF (high frequency) wave spectrums, the total power (TP) and the ratio of low and high frequency waves–LF/HF.

No side and adverse effects (bradycardia, sinus tachycardia, arrhythmias, collapse, etc.) were identified during the research.

Differences between the groups were assessed with Student's t-test for paired variables and the nonparametric Wilcoxon signed-rank test. A value of p<0.05 was considered to be significant.

Local bioethical committee of Bashkir State Medical University approved the study.

Results
33 ambulatory patients (16 men and 17 women, aged 56-75 years)

with CHD and current diagnosis "angina pectoris" in sinus rhythm and NYHA I-III and without myocardial infarction in the past were enrolled in the study. All the patients signed informed consent. In the **Table 1** the basic features of the study group are presented.

Table 1. Characteristics of the patients.

Parameters	Values
N	33
M/W	16/17
Age, years	64.9±0.94
Weight, kg	74.3±1.7
Height, cm	168.8±0.64
BMI, kg/m^2	26.08±1.14
NYHA function class:	
I	11
II	20
III	2

The patients were randomized to receive firstly ivabradine (group 1, 16 patients) and metoprolol (group 2, 17 patients) firstly. **Table 2** presents the baseline vital (HR, SBP, DBP) and HRV parameters before the first investigation (pre-dose). No significant difference was found between the groups at the baseline.

Table 2. Baseline vital and HRV parameters in groups 1 and 2.

Parameters	Groups		
	All, n=33	**Ivabradine (group 1), n=16**	**Metoprolol (group 2), n=17**
SBP, mm Hg	132.9±1.9	133±3.4	131.3±2.5
DBP, mm Hg	84.8±1.3	84.6±2.4	ó84±1.6
HR, beat/min	73.4±1.2	74.9±2	72.4±1.2
SDNN, msec	54.3±11.8	32.9±4.4	63.1±20.0
RMSSD, msec	33.0±6.9	20.9±4.1	35.1±10.9
LF, msec^2	293.4±83.6	276.7±85	310.2±82.3
HF, msec^2	274.1±100.4	252.7±98	295.5±125.4
Total, msec^2	1189.9±324.9	1166.5±324.6	1213.4±325.3
LF/HF	3.21±0.9	2.5±0.5	3.92±1.4

After the investigation the above mentioned parameters for each studied drug were calculated. In group 1 (with ivabradine) there was a change of the vital HRV parameters between investigations 1 and 2 and in group 2 those between 3 and 4 were summarized (**Table 3**). Accordingly, in group 2 (with metoprolol) there were changes of parameters between investigations 3 and 4, and in group 1 the changes between

the 1st and the 2nd ones were revealed.

As a result, HR decreased significantly in the study with ivabradine, namely from 72 to 65 beats/min (CI 78-68, p=0.001) and with metoprolol it went down from 72 to 65 beats/min (CI 70-64, p=0.001, **Figure 2**). Thus, the drugs showed comparable negative chronotropic effects. In particular, ivabradine, as well as the metoprolol, did not reduce SBP and DBP (p=0.114 and p=0.577 for ivabradine and p=0.129 and p=0.196 for metoprolol). As in ivabradine, so in metoprolol effect (Δ/min) increased with HR rise (**Figure 3**). There was similar decrease in HR in both groups (p=0.400 between groups), and no change in BP (p=0.114 for SBP and p=0.796 for DBP between groups). Such results enabled the comparison of both drugs' impact on the state of autonomic nervous system of heart rate regulation defined by the HRV. As it is presented in **Figure 3**, after the tests the effect (Δ/min) of both drugs increased with HR rise.

LF spectral power reflects the tone of parasympathetic nervous system [**4**].

Ivabradine reduced significantly LF domains of HRV in absolute values (Δ=−53.0 msec^2, p=0.020), but not in relative (Δ=−2.2%, p=0.614). Metoprolol had greater effect, reducing both absolute and relative value of HF domain (Δ=−131.5 msec^2, p=0.011 and −15.9%, p=0.006). The comparison of HF domain absolute values affirmed the above-mentioned changes, i.e., metoprolol induced greater decrease (p=0.019, **Table 3**).

The total power parameter reflects adaptation potential of the heart. TP had tendency to decrease in ivabradine (Δ=143 msec^2, p=0.424), and it was downregulated significally by metoprolol (Δ=380 msec^2, p=0.006).

The ratio LF/HF showed the tendency to increase in iva-bradine group (Δ=0.25 msec^2, p=0.338), and to decrease in metoprolol group (Δ=−1.18 msec^2, p=0.332), reflecting change in symphathic/parasymphathic status under the drugs influence.

The remaining parameters SDNN, RMSSD are used tradi-tionally for prolonged ECG analysis (24h or 48h recording). Also, metoprolol and ivabradine showed expectedly insig-nificant trend to decrease them (p>0.05).
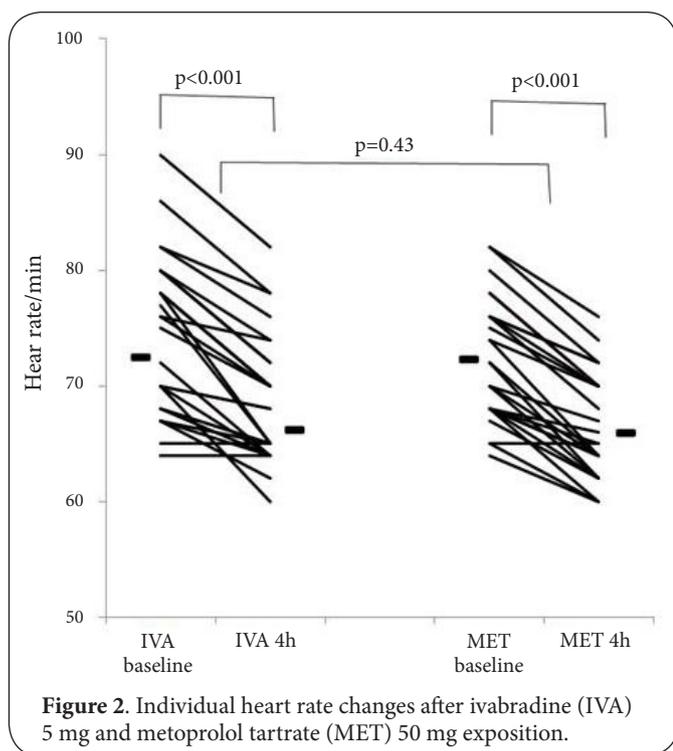
Discussion

The modulation of the elevated HR and the use of BB are the cornerstone of CAD and AP treatment [**11**]. BB, especially highly selective ones, are the "gold standard" of rhythm-controlled therapy [**17**]. At the same time, BB have several contraindications, such as AV-block, bronchial asthma, peripheral arterial disease, etc. Furthermore, in some cases, for example in hypotension or resistive tachycardia the use of other pulse-downregulating drugs is required. Some studies such as REACH (The REduction of Atherothrombosis for Continued Health) showed no advantage of BB over ivabradine the on the primary endpoints in patients with AP in the absence of past myocardial infarction [**16**]. Taking into account the widespreading use of I$_f$-blocker ivabradine in the clinical practice, its significant antianginal effect and minimal number of side effects [**9,19**], the choice

Table 3. Comparison of Met and Iva effect on HR, BP and HRV.

Parameter	Baseline	Ivabradine	pΔ Iva	Baseline	Metoprolol	pΔ Metoprolol	pΔ $_{individual}$ Ivabradine-Metoprolol
SBP, mm Hg	130 (120;140)	130(120;140)	0.114	130(120;140)	130(120;130)	0.129	0.134
DBP, mm Hg	80(80;90)	80(80;80)	0.577	80(80;90)	80(80;80)	0.196	0.796
HR, beat/min	72(68;78)	65(64;70)	0.001	72(68;76)	65(64;70)	0.001	0.429
SDNN, ms	28.1(18.9;40.2)	24.5(17.0;37.5)	0.581	30.6(18.8;63.2)	23.7(20.4;41.8)	0.155	0.155
RMSSD, ms	17.8(10.0;29.5)	16.1(8.1;29.5)	0.371	22.6(9.2;42.1)	16.4(12.0;22.6)	0.140	0.556
Ptotal, ms^2	595(326;1028)	452(251;983.5)	0.424	926(366;1322)	546(262;554)	0.006	0.015
LF, ms^2	145.0(60.5;216.0)	93.0(49.5;187.0)	0.020	220.0(89.0;796.2)	88.5(52.5;221.5)	0.011	0.019
HF, ms^2	86.0(27.0;354.0)	134.5(16.0;485.0)	0.808	105.0(39.0;443.5)	77.5(26.0;148.5)	0.215	0.423
LF%	60.9(51.7;73.8)	63.1(49.9;72.1)	0.614	72.6(62.0;78.5)	56.7(49.6;70.1)	0.019	0.056
LF/HF	1.92(1.03;4.28)	2.17(1.39;4.49)	0.338	2.62(1.96;2.96)	1.44(0.98;2.24)	0.332	0.124

P.s. Data are presented as Median (25% quartile; 75% quartile). HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SDNN: Standard deviation of NN intervals; square root of the mean squared differences of successive normal NN intervals-RMSSD; LF: Low frequency; HF: High frequency spectral power and the ratio of waves of low and high frequency-LF/HF

Figure 2. Individual heart rate changes after ivabradine (IVA) 5 mg and metoprolol tartrate (MET) 50 mg exposition.

Figure 3. Heart rate dynamics after ivabradine (IVA)/ metoprolol (MET) exposure. Linear trend line: - - -ivabradine, ----- metoprolol.

of rhythm-controlling drug is relevant. Further comparison of these drug classes should be considered not only by rate-reducing and antianginal effects, but also by the impact on HRV. HRV is generally accepted as an indicator of sympathetic/parasympathetic tones balance and predictor of unfavorable cardiovascular and other events. Positive impact of BB on HRV on reducing sympathetic tone of nervous system and increasing of parasympathetic was repeatedly shown. In particular, Wennerblom B. et al., (1998) [20] showed that
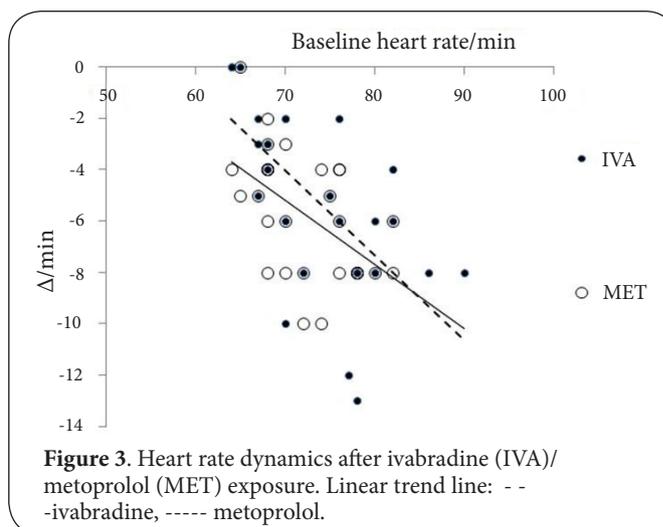
metoprolothe in the dosage of 100 mg per day reduced the tone of the sympathetic nervous system, improved prognosis for the disease in patients with AP with II-III NYHA functional class. In the study of Targoński R. et al., (2009) [21] it has been revealed that the evening dose of BB was better for their impact on the autonomic balance than the morning one.

At the same time, there are only few small studies on impact of I$_f$-blocker ivabradine on HRV in compare with BB. We conducted open-labeled, randomized, controlled trial with crossover design and acute pharmacological test to evaluate the effect of the I$_f$-blocker ivabradine and BB metoprololtartrate on the HRV in 33 patients with angina pectoris. As a result, in the group with ivabradine and metoprolol HR significantly reduced to 7.0 beats/min, i.e., negative chronotropic effect of the both drugs was comparable Ivabradine, as well as metoprolol, did not change SBP and DBP. Both drugs

decr-eased sympathetic activity by decreasing LF domain but for metoprolol the effect was greater. While for metoprolol such conclusion was expected because of the widely known sympathetic downregulating activity of BB by reducing positive inotropic and chronotropic effects of catecholamine mediating through b1-b2-adrenergic receptors and adreno-dependent relaxation of vascular smooth muscle cells [22], no data on the direct effect of ivabradine on sympathetic activity have been obtained for ivabradine. In our opinion, the reduction of sympathetic influences on the autonomic regulation of the heart may be associated with a reduction of myocardial ischemia by feedback mechanism (**Figure 4**).

The additional advantage of ivabradine is the absence of TP

Figure 4. Possible downregulating mechanism of ivabradine impact on sympatic nervous system.
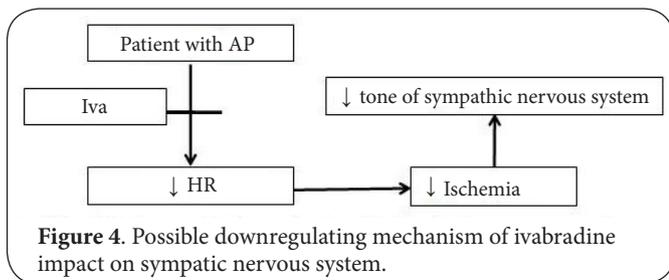
decrease observed in metoprolol treatment, which reflects the adaptation resource of the heart.

Recent randomized clinical trials indicate ivabradine's anti-nginal effects comparable with BB and some calcium antag-onists [23-25]. Ivabradine prolongs diastole more than BB [26], which is critical for myocardial oxygen supply. Having given the presence of specific contraindication to BB (atrioventricular block, bronchial asthma), the additional impact on the vege-tative status of HR can support indications for use of ivabradine at stable angina pectoris.

Conclusions

In prospective, open-labeled, short-term, controlled, crossover with acute pharmacological test design patients with coronary heart disease and angina pectoris having received both metoprolol tartrate and ivabradine 7.5 per os decreased equally heart rate. The effect attenuated with the heart rate upraises.

Both metoprolol tartrate 50 mg and ivabradine 7.5 mg showed a cardioprotective effect on HRV by downregulating LF domain and reducing sympathetic activity (more significant for metoprolol). For ivabradine this fact can be explained by decrease of ischemia by feedback mechanism.

Metoprolol, but not ivabradine decreased the total power parameter of heart rate variability.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	NSZ	RHZ	EOT	SZZ
Research concept and design	✓	✓	✓	✓
Collection and/or assembly of data	✓	✓	✓	✓
Data analysis and interpretation	✓	✓	✓	✓
Writing the article	✓	✓	✓	✓
Critical revision of the article	✓	✓	✓	✓
Final approval of article	✓	✓	✓	✓
Statistical analysis	✓	✓	✓	✓

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