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Baseline intrinsic heart rate and response to ivabradine treatment in patients with inappropriate sinus tachycardia

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Abstract

Background: Treatment with ivabradine became a new therapeutic alternative for patients with inappropriate sinus tachycardia (IST). The aim was to determine a relation between intrinsic heart rate (IHR) and response to ivabradine treatment.

Methods: Twenty-seven patients (mean age 37 ± 11; 23 women) with symptomatic IST despite medical treatment were recruited into the study. Resting ECG, 24-hr ECG monitoring (24hECG), exercise treadmill test, and symptoms evaluation were performed initially and after 60 days on ivabradine. IHR was acquired at baseline after pharmacological autonomic blockade.

Results: Nineteen patients (70%) were classified as abnormal IHR group (AIHR) while eight showed normal IHR (NIHR). No significant differences in ECG parameters were found between NIHR and AIHR subgroups, while baseline exercise capacity was higher in AIHR patients (10.9 vs. 9.5 METs, $p < .05$). Ivabradine treatment resulted in significant reduction in resting heart rate, average 24hECG heart rate, improvement in exercise capacity and reduction of symptoms in both subgroups. Nevertheless, favorable influence of ivabradine was significantly more exaggerated in AIHR subgroup (HR 116 vs. 90 bpm, av. HR 98 vs. 79 bpm, 10.9 vs. 13.6 METS, EHRA score 3.1 vs. 1.1, $p < .001$ for all) than in NIHR patients (HR 112 vs. 98 bpm, av. HR 97 vs. 88 bpm, 9.5 vs. 11.1 METs, EHRA score 3.1 vs. 1.9; $p < .05$ for all).

Conclusions: Intrinsic heart rate may be useful in predicting response to ivabradine in patients with IST. More intense response to ivabradine in patients with AIHR may be attributed to different pathophysiological mechanisms underlying IST in AIHR and NIHR groups.

KEYWORDS

heart rate, inappropriate sinus tachycardia, ivabradine

1 | INTRODUCTION

Inappropriate sinus tachycardia (IST) is defined as a syndrome characterized by a sinus heart rate higher than 100 bpm at rest with a mean 24-hr heart rate higher than 90 bpm, which is associated with distressing symptoms of palpitations (Sheldon et al., 2015). The syndrome is associated neither with structural heart disease nor provoked by secondary causes of elevated sinus rate (Krahn, Yee, Klein, & Morillo, 1995; Olshansky & Sullivan, 2013). It is usually considered to be a rare cardiac pathology with unknown prevalence. An elevated sinus heart rate was found in approximately 1% of patients enrolled in the OPERA study (Still et al., 2005), however, both, symptomatic and asymptomatic individuals were included. The mechanism of IST is not precisely understood and is postulated to be multifactorial and complex. An enhanced sinus node activity and/or impaired sympathovagal balance seems to be the major players (Sheldon et al., 2015). Treatment options include both pharmacological and invasive approaches. Traditionally used negative chronotropic agents (beta-blockers and calcium antagonists) are often ineffective or not well-tolerated (Ptaszynski, Kaczmarek, Ruta, Klingenheben, & Wranicz, 2013). Therefore, the I_f-blocker ivabradine has recently been proposed as a promising alternative for IST patients (Abed, Fulcher, Kilborn, & Keech, 2016).

The aim of this study was to evaluate the therapeutic efficacy of ivabradine in relation to sinus node function determined by intrinsic heart rate (IHR) in patients suffering from IST despite medical treatment with negative chronotropic drugs.

2 | METHODS

Twenty-seven consecutive patients (aged 24–53 av. 36 ± 11 years) with symptomatic IST nonresponsive to previous treatment were enrolled into a study. The population consisted mainly of women (23/27, 85%). Diagnosis of IST was based on the latest guidelines (Sheldon et al., 2015). Potential secondary causes of sinus tachycardia had been excluded with thorough diagnostics of specialists in internal medicine, cardiology, and endocrinology. Only two individuals had arterial hypertension (2%), and no other important comorbidities were found. No structural abnormalities were found in echocardiography (average left ventricular ejection fraction was 62 ± 8%).

The study was performed in accordance with Declaration of Helsinki. Local bioethical committee of Medical University approved the trial, and all patients gave informed consent.

Only highly symptomatic IST patients who experienced nonresponsiveness or poor tolerance of standard medical treatment were recruited for therapy with ivabradine. Majority of patients (85%) was previously treated with beta-blockers, and the remaining 15% with calcium channel antagonists. Invasive treatment with ablation of arrhythmia substrate has not been considered. Previous antiarrhythmic medication had to be discontinued for a period of at least five half-times, and a baseline clinical assessment was performed prior to the first dose of ivabradine. The initial dose of ivabradine was 5 mg BID and during following 14 days was up-titrated to 7.5 mg BID. That treatment was continued at least for next 60 days. At the end of this period, a clinical reassessment was performed. Figure 1 shows a study design.

The clinical assessment, both at baseline and at the end of the follow-up, consisted of electrocardiographic tests (12-lead resting electrocardiogram, 24-hr ambulatory ECG monitoring and exercise treadmill test) and IST-related symptoms scoring. Ambulatory resting electrocardiogram served to evaluate resting heart rate which was included in further analyses.

Ambulatory 24-hr ECG monitoring was performed with Medilog Darwin Holter platform (Schiller Co.). The recordings were postprocessed according to the routine of care in our center. After excluding the presence of other important arrhythmias, the crucial for IST diagnosis values—average heart rate, daytime heart rate, and maximal heart rate—were estimated and used for further evaluation.

Treadmill exercise test (TET) was performed using GE Case V.6.51 (General Electrics). Following a fasting period of at least 3 hr, all patients underwent exercise testing according to the standard Bruce protocol. Exercise capacity was assessed as oxygen consumption estimated in metabolic equivalents (METs).

Intrinsic heart rate was measured after autonomic denervation achieved by intravenous bolus injection of atropine (0.04 mg/kg) and propranolol (0.2 mg/kg). The value was calculated according to the Jose formula [IHR = 118.1 − (0.57*age) ± 15%] (Jose & Collison, 1970). Upper normal limit of IHR was calculated as 1.15*IHR. According to the values of IHR the patients were divided into two subpopulations: abnormal IHR (AIHR) group and normal IHR (NIHR) group. The interrelations of vagal (*n*) and sympathetic

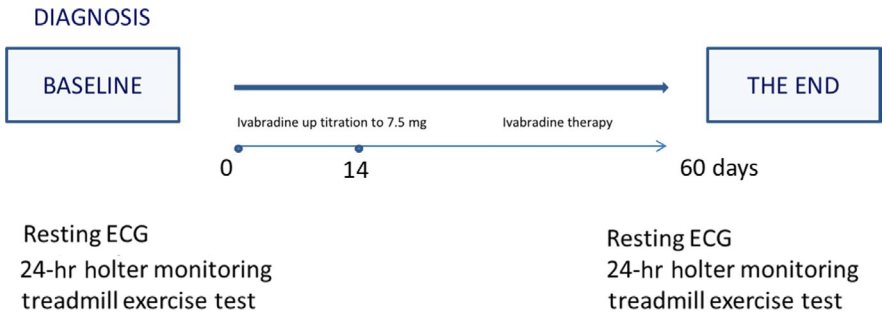

FIGURE 1 Study design

TABLE 1 Heart rate and exercise tolerance parameters

	Abnormal IHR *N* = 19 (Group AIHR)			Normal IHR *N* = 8 (Group NIHR)		
	Baseline	**Ivabradine**	***p*-value**	**Baseline**	**Ivabradine**	***p*-value**
Resting HR [bpm]	116.1 ± 5.1	90.2 ± 8.8	<.001	112.0 ± 9.4	97.8 ± 4.7	<.010
Mean HR (24 hr-HM) [bpm]	98.6 ± 4.7	79.6 ± 9.3	<.001	97.3 ± 6.0	88.0 ± 6.4*	<.050
Daytime HR (24 hr-HM) [bpm]	108.6 ± 4.7	86.3 ± 4.8*	<.001	106.0 ± 3.5	96.3 ± 3.9*	<.001
Maximal HR (24 hr-HM) [bpm]	151.9 ± 7.9	131.0 ± 8.3	<.001	147.7 ± 10.3	125.8 ± 9.1	<.001
Exercise tolerance (TET) [METs]	10.9 ± 1.3*	13.6 ± 0.8*	<.001	9.5 ± 0.4*	11.1 ± 1.1*	<.050
Resting sympathovagal balance	0.74 ± 0.03*	NA	NA	1.01 ± 0.11*	NA	NA
Symptoms score (EHRA)	3.05 ± 0.78	1.11 ± 0.46	<.010	3.13 ± 0.83	1.88 ± 0.64*	<.010

Abbreviations: 24h-HM, 24-hr Holter monitoring; bpm, beat-per-minute; HR, heart rate; METs, metabolic equivalents of task; TET, treadmill exercise test.
*Significant difference ($p < .05$) between group AIHR and NIHR (exact statistics values in text).

(*m*) effects on sinus rate can be defined with the *Rosenblueth and Simeone* formula (HR = *m***n**IHR) (Rosenblueth & Simeone, 1934). Cardiac sympathovagal balance (SVB), which combines influence of both parts of autonomic system on heart rate, was calculated according to the following equation SVB = *m**n = HR*IHR^{-1} (Bootsma, Swenne, Janssen, Cats, & Schalij, 2003; Goldberger, 1999; Opthof, 2000). SVB was calculated for HR recorded at rest—resting SVB—and for daytime activity period—daytime SVB. If the sympathetic tone overdrives the parasympathetic one the SVB value is higher than 1.

The complaints related to IST were classified with EHRA scoring system adopted from atrial fibrillation, as described previously (Ptaszynski, Kaczmarek, Ruta, Klingenheben, Cygankiewicz, et al., 2013). Score 1 was given to patients who were asymptomatic. If symptoms related to IST troubled patient but did not affect one's daily activity the score was 2. While IST provoked symptoms which affected daily activity or led to its discontinuation were categorized as score 3 or 4, respectively.

Statistical analysis was performed using Statistica software (ver. 12; StatSoft Inc.). Continuous variables are expressed as mean ± standard deviation. The Student's *t* test and Mann-Whitney test were applied for between group comparison, accordingly to data distribution. Categorical variables are presented as frequency. The chi-square test and its modification were used to compare categorical data. Values of $p < .05$ were considered statistically significant.

3 | RESULTS

All 27 patients completed the study. Ivabradine was titrated up to 7.5 mg BID in all subjects. Side effects on ivabradine were not observed.

Intrinsic heart rate in the study population was significantly higher than upper normal limit according to age (143.1 ± 21.4 vs. 112.0 ± 5.0 bpm; $p < .001$). Abnormal IHR was recorded in majority of the patients (19 pts, 70%). Their IHR was increased if compared to the rest of the study population (156.3 ± 5.6 vs. 111.6 ± 7.5 bpm, $p < .001$). Both groups were similar with regard to age (33.1 ± 5.8 vs. 37.4 ± 8.1, respectively for NIHR and AIHR, $p = .19$) as well as sex distribution (male to female proportion: 1/7 vs. 2/17, $p = .54$).

Resting heart rate was comparable in both groups (NIHR vs. AIHR: 112.0 ± 9.4 vs. 116.1 ± 5.5 bpm; $p = .15$). Similarly, there were no important differences between patients with normal and abnormal IHR in terms of average, maximal and daytime heart rate assessed in 24-hr Holter monitoring (Table 1). Analysis of the resting SVB revealed that the sympathetic tone slightly overdrove the parasympathetic one in patients with normal IHR, which was not observed in individuals with abnormal IHR (1.01 ± 0.11 vs. 0.74 ± 0.03, $p < .001$). An average SVB for daytime activity was significantly higher in patients with normal IHR (0.95 ± 0.08 vs. 0.70 ± 0.03, $p < .001$).

Despite lack of significant differences in heart rate profile between both groups, exercise capacity assessed with TET was significantly higher in patients from AIHR group (10.9 ± 1.2 bpm vs. 9.8 ± 0.3 METs; $p < .001$).

Ivabradine therapy resulted in a heart rate reduction in both groups (Table 1), but the decrease was significantly higher in AIHR patients (25.9 ± 10.0 vs. 14.3 ± 8.0 bpm; $p < .05$; Figure 2). All analyzed parameters obtained from 24-hr ECG Holter monitoring and treadmill exercise tolerance changed favorably on treatment in both groups (Table 1). However, higher decrement in daytime heart rate (22.3 ± 4.8 vs. 9.8 ± 3.0 bpm; $p < .001$) and increase in exercise tolerance (2.7 ± 1.1 vs. 1.3 ± 1.6 METs; $p < .001$) were noted in the group of abnormal IHR (Figure 2).

As outlined above, all patients complained of palpitations at baseline. Moreover, 22 patients (81%) suffered exercise intolerance and more than half of them (14 pts, 52%) had paroxysmal dyspnea. One-third of the population reported presyncope (8 pts, 30%) or syncope (2 pts, 7%). All patients complained of symptoms at least 12 months prior to inclusion (mean 38; maximum 84 months). In the majority of the patients (16 pts, 60%), these symptoms significantly limited their normal activity (EHRA score 3 and 4).

Symptoms related to IST were beneficially reduced on ivabradine in whole study population (EHRA score 3.08 ± 0.78 to 1.33 ± 0.62, $p < .001$) and in each subgroup (Table 1). The frequency of all

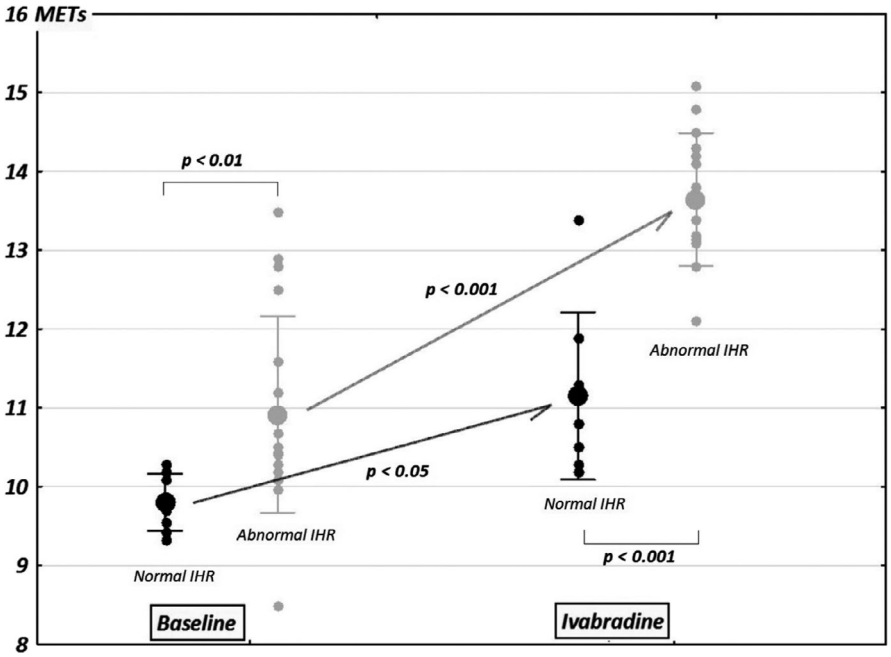

FIGURE 2 Exercise capacity measured with treadmill exercise test

symptoms that were recorded decreased significantly on treatment. However, accidentally registered syncope was observed as often before as after onset of the medication. The majority of the patient from group of abnormal IHR became asymptomatic on ivabradine (18 of 19 pts, 95%). In contrast, significantly more patients with normal IHR remained symptomatic, although less severely, despite the treatment (6 of 8 pts, 75%; p = .001).

4 | DISCUSSION

Inappropriate sinus tachycardia is an infrequent arrhythmia observed more often in 30- to 40-year-old women (Krahn, Yee, Klein, & Morillo, 1995; Olshansky & Sullivan, 2013), which corresponds well with characteristics of our study population.

Mechanism of IST is deemed to be multifactorial. An increased automaticity of sinus node was found by Morillo et al. (1994) in a group of six patients. Similarly, Leon et al. (2005) described that the majority of IST patients (seven out of eight) had IHR higher than predicted. Contrasting data were reported by Bauernfeind et al. (1979) and Nwazue et al. (2014), who obtained values of IHR within normal range but disclosed significantly impaired sympathovagal balance. These authors concluded that main mechanism of elevated sinus rate was related to sympathetic tone predominance over vagal one. Bauernfeind's series of IST patients consisted of seven individuals of which five were evaluated to have insufficient vagal drive and two excessive sympathetic tone. In our previous analysis in a larger group of patients with IST (Ptaszynski, Kaczmarek, Klingenheben, et al., 2013), approximately 1/3 to 1/4 of the patients had abnormal results of noninvasive autonomic tests indicating complex autonomic dysregulation. The present study revealed that the majority of IST patients (70%) had increased automaticity of the sinus node. The remaining patients had IHR within normal range, and tachycardia was more likely provoked by imbalance between sympathetic and vagal tone. A calculated SVB in this subgroup was shifted toward sympathetic predominance. Interestingly, Morillo et al. (1994) reported that an increased sinus node activity can be combined with autonomic disorder disclosed as an impaired baroreflex gain. Molecular bases of IST including autoimmune reactions and channelopathies have been recently studied (Baruscotti, Bianco, Bucchi, & DiFrancesco, 2016). Chiale et al. (2006) disclosed a high prevalence of beta-receptors autoantibodies in patient with IST, which was not observed in healthy volunteers. This study was shown that these antibodies stimulated production of cAMP dependent on beta-receptors. Levels of cAMP are one of mechanisms which influence the I_f availability (Baruscotti et al., 2016). Baruscotti et al. (2017) elegantly demonstrated a link between R524Q mutant of hyperpolarization-activated cyclic nucteotide-gated (HCN4) protein and increased sensivity of I_f channels to cAMP. These authors provided the first evidence of gain-of-function HCN4 mutation. Up to their paper, all known mutations of HCN4 were loss-of-function with leading phenotype of sinus bradycardia (Di Francesco, 2013). The findings of previously published papers altogether with our analysis support the hypothesis that IST is a pathology of heterogenous and complex mechanism with two leading components: increased automaticity of sinus node and autonomic dysregulation.

Surprisingly, patients that differed in the underlying IST mechanism were indistinguishable in routine electrocardiographic nor demographical features. Those with normal IHR had significantly lower exercise capacity but ranges of this parameter overlapped between both subgroups. The difference in TET performance between studied subpopulations puzzles well to the concept of two leading mechanisms of IST. It seems to be highly possible that the IST patients with sympathetic overbalance at rest have less capacity to additionally recruit more sympathetic activation during physical effort.

Even though IST is a relatively benign illness, there are some patients who manifest debilitating symptoms and therefore require treatment (Olshansky & Sullivan, 2013). Traditionally, first-line medical therapy was based on negative chronotropic drugs, mainly beta-blockers and calcium channels antagonists (Abed et al., 2016). As these agents were often poorly tolerated or ineffective other modes of treatment were applied, including catheter- and surgically based invasive modifications of sinus node region (Marrouche et al., 2002) or new pharmaceutics, recently ivabradine (Romeo et al., 2011; Sette, Martino, Lioy, & Calo, 2010). There is now growing evidence for use of ivabradine for IST treatment (Abed et al., 2016; Wilson & Crook, 2009). Initially, ivabradine was an alternative or additional option to beta-blockers and calcium channels antagonists (Goldberger, 1999). One small randomized trial compared ivabradine to placebo in patients with IST disclosing its beneficial effect in terms of heart rate reduction and symptom improvement (Cappato et al., 2012). Our data are in agreement with observations by other authors in terms of reduction of heart rate and improvement of IST-related symptoms. The favorable rate controlling effect was observed in both analyzed subgroups; however, significantly higher decrease of resting and daytime heart rate (26 vs. 14 bpm and 22 vs. 10 bpm, respectively) was noted in patients with excessive automaticity of sinus node. The rate reduction in patients with abnormal IHR is expectable on basis of previous experiences (Cappato et al., 2012; Ptaszynski, Kaczmarek, Ruta, Klingenheben, & Wranicz, 2013) and consistent with ivabradine's mechanism of actions. However, a profitable reaction registered in patients with sympathovagal imbalance is not trivially obvious. As there is no evidence of ivabradine influence on autonomic nervous system the sinus rate decrease may be assigned to the effector suppression. It is possible that in patients with autonomic dysregulation there is also component of relatively excessive sinus node function. Such complex mechanisms of IST were suggested by Morillo et al. (1994). Profound analysis of our results disclosed that patients classified to group with normal sinus node function had IHR values within reference range but approaching the upper limit of normal. Thus, the reduction of moderately overactive automaticity of sinus node seems to be a reasonable explanation.

A beneficial effect of ivabradine on reduction of IST-related symptoms has been reported previously (Annamaria et al., 2016; Mathew, Po, & Thadani, 2018). There was a significant reduction in the level of symptoms in both of presently investigated subpopulations. Almost all patients with excessive sinus node automaticity were asymptomatic on treatment. In contrast, the majority of patients with autonomic dysregulation reported residual symptoms. As the remaining symptoms were observed despite effective heart rate reduction, which showed also Marrouche et al. (2002), these complaints could be attributed to dysautonomia.

4.1 | Study limitation

The sample size of the present study is small; however, the syndrome is relatively rare in a general population. Another limitation is also the design of the study, which is an observational, off-label, nonrandomized study. Generally, the reproducibility of autonomic tests is moderate mainly due to complex physiological aspects and factors.

In conclusion, baseline intrinsic heart rate has an impact on response to ivabradine treatment in patient with inappropriate sinus tachycardia. Patients with abnormal intrinsic heart rate had higher decrease of heart rate and more favorable reduction of symptoms. The most probable explanation for the different effect of ivabradine therapy is heterogeneous pathomechanism of IST, which needs further investigations.

CONFLICT OF INTEREST

No conflict of interest to declare for all authors.

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