Ivabradine Improves Heart Rate Variability in Patients with Nonischemic Dilated Cardiomyopathy

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Abstract

Background: Ivabradine is a novel specific heart rate (HR)-lowering agent that improves event-free survival in patients with heart failure (HF).

Objectives: We aimed to evaluate the effect of ivabradine on time domain indices of heart rate variability (HRV) in patients with HF.

Methods: Forty-eight patients with compensated HF of nonischemic origin were included. Ivabradine treatment was initiated according to the latest HF guidelines. For HRV analysis, 24-h Holter recording was obtained from each patient before and after 8 weeks of treatment with ivabradine.

Results: The mean RR interval, standard deviation of all normal to normal RR intervals (SDNN), the standard deviation of 5-min mean RR intervals (SDANN), the mean of the standard deviation of all normal-to-normal RR intervals for all 5-min segments (SDNN index), the percentage of successive normal RR intervals exceeding 50 ms (pNN50), and the square root of the mean of the squares of the differences between successive normal to normal RR intervals (RMSSD) were low at baseline before treatment with ivabradine. After 8 weeks of treatment with ivabradine, the mean HR (83.6 ± 8.0 and 64.6 ± 5.8, $p < 0.0001$), mean RR interval (713 ± 74 and 943 ± 101 ms, $p < 0.0001$), SDNN (56.2 ± 15.7 and 87.9 ± 19.4 ms, $p < 0.0001$), SDANN (49.5 ± 14.7 and 76.4 ± 19.5 ms, $p < 0.0001$), SDNN index (24.7 ± 8.8 and 38.3 ± 13.1 ms, $p < 0.0001$), pNN50 (2.4 ± 1.6 and 3.2 ± 2.2 %, $p < 0.0001$), and RMSSD (13.5 ± 4.6 and 17.8 ± 5.4 ms, $p < 0.0001$) substantially improved, which sustained during both when awake and while asleep.

Conclusion: Our findings suggest that treatment with ivabradine improves HRV in nonischemic patients with HF. (Arq Bras Cardiol. 2014; 103(4):308-314)

Keywords: Anti-Arrhythmia Agents / therapeutic use; Heart Rate; Cardiomyopathy, Dilated.

Introduction

Chronic heart failure (CHF) is a major public health problem and a substantial clinical, social, and economic burden, requiring repeated hospitalization and causing a substantial reduction in the quality of life of patients[1]. Despite the advances in medicine, prognosis remains poor for patients with CHF, with a 7-year mortality rate of 75%[2]. For CHF with reduced left ventricular ejection fraction, the latest heart failure guidelines have extended the treatment possibilities by incorporating ivabradine, a novel specific heart rate-lowering agent that acts specifically on the sino-atrial node by selectively inhibiting the inward "funny" current (If) of cardiac pacemakers cells, thus preserving cardiac contractility, impulse conduction, and blood pressure[1,3-5]. In a clinical trial, it was found that lowering the heart rate of CHF patients with the help of ivabradine administration reduces morbidity and mortality[6].

Heart rate variability (HRV) is a noninvasive, practical, and reproducible measure of autonomic nervous system function. A heart rate that is variable and responsive to demands is believed to bestow a survival advantage, whereas diminished HRV may be associated with poor cardiovascular outcomes[7,8]. Available evidence suggests that reduced HRV has prognostic significance for mortality in CHF population[9-11]. Previous studies have found a 20% reduction in mortality risk with each 10-ms increase in the standard deviation of all normal-to-normal RR intervals (SDNN)[12]. Because autonomic imbalance resulting from sympathetic overactivity and parasympathetic withdrawal is a characteristic feature of CHF, we hypothesized that ivabradine may improve the vagal reflexes to the heart and reduce the sympathetic overactivity in patients with nonischemic dilated cardiomyopathy (DCM)[13]. Therefore, the aim of this study was to investigate the effects of ivabradine on heart rate variability (HRV) in patients with nonischemic DCM. This patient population was chosen in an attempt to study HRV free of a possible confounding effect of ivabradine on coronary ischemia[14].

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Methods

Study population

Patients with CHF of nonischemic origin were included in the present study. The age of the eligible patients ranged from 18 to 90 years. The patients had 1) a diagnosis of CHF that lasted for at least 3 months before entering the study 2) clinically stability in the 4 weeks before entering the study, which was defined by the absence of clinically significant changes in the physical signs of heart failure, absence of clinically significant changes in self-reported symptoms, and no changes in prescribed medicines during the study period, 3) a left ventricular ejection fraction of 0.35 or less as documented by echocardiography performed within the previous 3 months, 4) a sinus rhythm with a resting heart rate of ≥ 70 beats/ min (bpm) as assessed from 12-lead electrocardiogram on 2 consecutive visits, 5) absence of coronary artery disease as evaluated by coronary angiography performed within 1 year, 6) optimized and unchanged chronic heart failure medications and dosages in accordance with contemporary guideline recommendations (β-blockers, angiotensin-converting enzyme inhibitors [ACEI] and/or angiotensin II receptor blockers [ARB], diuretics as necessary) for ≥ 8 weeks before entering the study, and 7) the New York Heart Association (NYHA) functional class II to III. The cause of the heart failure was idiopathic in all patients. This patient population was specifically chosen because ivabradine shows antianginal and anti-ischemic effects in patients with ischemic dilated cardiomyopathy, which could have a confounding effect on HRV[14]. The diagnosis of left ventricular (LV) systolic dysfunction was established according to the recommendations of the American Society of Echocardiography[15].

Exclusion criteria included acute decompensated heart failure, ischemic heart disease, congenital heart disease, class 3 or higher chronic obstructive pulmonary disease (COPD), heart rate <60 beats/min, sick sinus syndrome, second-degree and third-degree atrioventricular block, active myocarditis, atrial fibrillation or flutter, severe or uncontrolled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg), diabetes mellitus, autonomic neuropathy, known severe liver disease or renal disease, and thyroid disorders.

Study protocol

Patients who fulfilled the inclusion criteria underwent 24-h Holter monitoring for HRV analysis before ivabradine treatment was initiated. Ivabradine was administered along with background cardiovascular therapy, which was optimized in accordance with the contemporary guideline recommendations. After the 24-h Holter monitoring, ivabradine treatment was started according to the current heart failure guidelines. Titration of ivabradine was performed as reported elsewhere[6]. The starting dose of ivabradine was 5 mg twice daily. After a 2-week titration period, the dose was increased to 7.5 mg twice daily unless the resting heart rate was ≤60 bpm. If the resting heart rate was < 50 bpm or the patient experienced signs or symptoms related to bradycardia, the dose was reduced to 2.5 mg twice daily. If the heart rate was between 50 and 60 bpm, the dose was maintained at 5 mg twice daily. Follow-up visits took place once every 2 weeks. At each follow-up visit, clinician either maintained or increased the drug dose. The 24-h Holter monitoring was repeated during the 8th week of ivabradine treatment. The study was approved by the local ethics committees and adhered to the Declaration of Helsinki. Informed consent was obtained from all subjects before the start of the study.

Holter analysis

All patients who fulfilled the inclusion criteria underwent a 24-h electrocardiographic monitoring before ivabradine treatment and at 8 weeks while on treatment with ivabradine. A six-channel digital Holter recorder (DMS 300-3A Digital Holter Recorder, California, USA) with built-in flash memory that was scanned by a computer was used for monitoring all patients. The patients were asked to continue their normal activities and their normal sleep-wake rhythm during the ambulatory electrocardiographic monitoring and were provided with a diary in which they were asked to record the sleep timings. The tapes were analyzed by a cardiologist. The HRV measurements were obtained using a commercially available Holter software program (CardioScan 12.0, DMS, USA). After the computerized primary analysis, all recordings were edited manually for eliminating from supraventricular, ventricular ectopy and artifacts. Recordings lasting for at least 22 h and having sufficient quality for evaluation were included in the analysis. When these criteria were not met, the recordings were repeated. The time domain parameters were assessed from the Holter recordings following the recommendations of the European Society of Cardiology and the North American Society of Pacing Electrophysiology[7]. The following time domain indices of HRV were measured: (1) The mean of all normal RR intervals in ms (RR, ms); (2) the standard deviation of all normal to normal RR intervals (SDNN, ms); (3) the mean of the standard deviation of all normal to normal RR intervals for all 5-min segments (SDNN index, msec); (4) the standard deviation of 5-min mean RR intervals (SDANN, ms), (5) the percentage of successive normal RR intervals exceeding 50 ms (pNN50, %), and (6) the square root of the mean of the squares of the differences between successive normal-to-normal RR intervals (RMSSD, ms).

Statistical analysis

Statistical analyses were performed using the SPSS software, version 17.0 (SPSS for Windows 12.0, Chicago, Ill). All data were tested for normal distribution using the Kolmogorov–Smirnov test. Continuous variables were presented as mean and standard deviation, and categorical variables as frequency and percentage. Changes in the time indices of HRV were tested by paired samples t-test for normally distributed data and two related samples test (Wilcoxon Signed Rank test) for non-normally distributed data. All p values were two-tailed and values less than 0.05 were considered to indicate statistical significance.

Results

Initially, a total 60 patients were included in the study. Twelve patients were excluded prematurely from the study

because of visual side effects of ivabradine (2 patients), excessive bradycardia (4 patients), and lost during follow-up (6 patients). Fourth-eight patients completed the study and were included in the analysis. Baseline characteristics of the study population and their HRV parameters are listed in Table 1. The average age was 70.9±10.6 years. There were 27 men and 21 women and all study participants were white. Mean left ventricular ejection fraction was 23.0±5.4 %. The mean dosage of ivabradine was 5.8±1.6 mg twice daily at 8 weeks. Acceptable Holter recordings were collected for 100% of the population both at baseline and at 8 weeks. A total of 5 Holter recordings at baseline and 4 Holter recordings after ivabradine treatment were made for enhanced quality.

In our cohort of idiopathic dilated heart failure patients with low ejection fractions, the mean RR interval, SDNN, SDANN, SDNN index, pNN50, and RMSSD were markedly low at baseline (Table 1). After 8 weeks of treatment with ivabradine, the mean RR interval, SDNN, SDANN, and SDNN index increased significantly (Table 2). Parameters of parasympathetic activity, pNN50 and RMSSD, also increased after ivabradine administration (Table 2). This significant increase in time domain indices of HRV observed after ivabradine administration was persisted both when the patient was awake and while asleep (Table 3).

Discussion

To our knowledge, this is the first study that assessed the effect of ivabradine on time domain indices of HRV in patients with advanced heart failure. The main finding of our study is that incorporating ivabradine in the treatment regimen of CHF patients who are in sinus rhythm with a heart rate of ≥70 bpm and are treated with guideline-based background therapy (including maximally tolerated β-blockade) substantially improves HRV. Our results showed that this improvement persisted both when the patient was awake and while asleep.

Ivabradine is a novel heart rate-lowering agent, which modulates the spontaneous diastolic depolarization in the sino-atrial node[16]. The spontaneous slow diastolic depolarization drives membrane potential toward a threshold that triggers an action potential. The rate of spontaneous diastolic depolarization is significantly influenced by If, a mixed sodium–potassium current involving ion movement across the f-channels[17]. Ivabradine directly and selectively inhibits the If current, reducing the diastolic depolarization time and heart rate. The specificity of ivabradine for the If current ensures that ivabradine has no direct effects on myocardial contractility (or relaxation), ventricular repolarization, or intracardiac conduction. Thus, ivabradine has no negative inotropic or lusitropic effect[3,4]. Clinical trials have consistently demonstrated that lowering the heart rate by administering ivabradine improves left ventricular (LV) functions, exercise capacity, and quality of life of patients and reduces mortality in nonischemic and ischemic heart failure patients independent of the dose of the β-blocker[6,18-21]. Therefore, the new Guidelines of the European Society of Cardiology recommend the use of ivabradine in heart failure patients with a sinus rhythm of at least 70 bpm[1].

The HRV analysis is a well-established and noninvasive tool for monitoring the autonomic control of the heart[7]. A heart rate that is variable and responsive to demands is believed to bestow a survival advantage, whereas reduced HRV may be associated with poor cardiovascular health and outcomes[7]. Therefore, alterations in cardiac autonomic control as measured by HRV may define subgroups with higher risk for cardiovascular morbidity and mortality[22]. Analysis of HRV has recently been used to evaluate the cardiac autonomic control both in normal subjects and in subjects with a wide variety of cardiac and noncardiac disorders[23-29]. Of these cardiac disorders, nonischemic DCM is associated with an increase in the sympathetic tone (with increased plasma norepinephrine) and a withdrawal in vagal tone. In this group

Table 1 – Baseline characteristics of the study population

Demographic parameters	
Age, years	70.9 ± 10.6
Women, n (%)	21 (43)
BMI, kg/m^2	26.6 ± 3.3
Duration of HF, years	6.3 ± 1.8
Hypertension, n (%)	25 (52)
Cigarette smoking, n (%)	9 (19)
Previous stroke, n (%)	3 (6)
Cardiac parameters	
SBP, mmHg	110.5 ± 9.4
DBP, mmHg	72.2 ± 7.9
Left ventricular ejection fraction, %	23.0 ± 5.4
eGFR, mL/min	75.3 ± 10.9
NYHA class II, n (%)	20 (42)
NYHA class III, n (%)	28 (58)
Background medications, n (%)	
β-blocker	46 (96)
Target dose of β-blocker	25 (52)
ACE inhibitor and/or ARB	45 (94)
Diuretics (excluding antialdosterone)	44 (91)
Antialdosterone diuretics	26 (54)
Statin	8 (16)
Amiodarone	9 (19)
Cardiac glycosides	8 (16)
Devices	
ICD	4 (8)
CRT	3 (6)

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; CRT: cardiac resynchronization therapy; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HF: heart failure; ICD: implantable cardioverter defibrillator; NYHA: New York Heart Association; SBP: systolic blood pressure

Table 2 – Changes in time domain HRV indices of the study population before and after ivabradine treatment

Variable	Before treatment	After treatment	Change. %
HR, bpm	83.6 ± 6.0	64.6 ± 5.8†	– 33.3
RR interval, ms	713 ± 74	943 ± 101†	+ 34.1
SDNN, ms	56.2 ± 15.7	87.9 ± 19.4†	+ 58.5
SDANN, ms	49.5 ± 14.7	76.4 ± 19.5†	+ 56.3
SDNN index, ms	24.7 ± 8.8	38.3 ± 13.1†	+ 55.3
RMSSD, ms	13.5 ± 4.6	17.8 ± 5.4†	+ 35.2
pNN50, %	2.4 ± 1.6	3.2 ± 2.2†	+ 43.3

†p < 0.0001 between before and after treatment
bpm: beats per min; HR: mean heart rate; HRV: heart rate variability; pNN50: percentage of successive normal RR intervals exceeding 50 ms; RMSSD: the square root of the mean of the squares of the differences between successive normal-to-normal RR intervals; RR: mean RR interval; SDANN: the standard deviation of 5-min mean RR intervals; SDNN: the standard deviation of all normal-to-normal RR intervals; SDNN index: the mean of the standard deviation of all normal to normal RR intervals for all 5-min segments.

Table 3 – Changes in time domain HRV indices of the study population when awake and while asleep before and after ivabradine treatment

Variable	Awake			Asleep		
	Before treatment	After treatment	Change. %	Before treatment	After treatment	Change. %
HR, bpm	89.2 ± 8.9	68.6 ± 7.5†	– 31.2	79.7 ± 7.7	61.4 ± 5.5‡	– 22.5
RR interval, ms	656 ± 86	848 ± 66†	+ 29.9	748 ± 82	956 ± 105‡	+ 28.5
SDNN, ms	51.7 ± 13.1	80.6 ± 18.1†	+ 57.0	49.0 ± 16.4	70.4 ± 19.5‡	+ 46.3
SDANN, ms	46.3 ± 13.9	71.0 ± 19.8†	+ 54.0	44.2 ± 14.9	66.3 ± 21.7‡	+ 50.4
SDNN index, ms	22.8 ± 8.0	34.9 ± 12.2†	+ 53.4	22.2 ± 10.3	32.2 ± 13.3‡	+ 48.9
RMSSD, ms	11.0 ± 3.2	14.1 ± 3.8†	+ 29.2	17.0 ± 4.9	24.3 ± 6.0‡	+ 45.7
pNN50, %	2.1 ± 1.6	2.7 ± 2.3†	+ 32.9	3.5 ± 1.9	5.1 ± 2.5‡	+ 58.7

†p < 0.0001 between before and after treatment in awake period; ‡p < 0.0001 between before and after treatment in asleep period. bpm: beats per min; HR: mean heart rate; HRV: heart rate variability; HRV abbreviations as in Table 2.

of patients, markedly reduced HRV has been observed, which coincides with the severity of CHF as well as being a significant prognostic factor for morbidity and mortality[9,10,12].

In our study, the mean RR interval, SDNN, SDANN, SDNNindex, pNN50, and RMSSD were found to be low at baseline before ivabradine treatment. Our finding is consistent with the results of earlier studies[9,10]. Because impaired sympathovagal balance, characterized by the sympathetic overactivity and parasympathetic withdrawal, is considered to be a hallmark of the CHF-related morbidity and mortality, agents that improve the sympathovagal balance may be of clinical significance. A variety of drugs, including β-blockers, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and antialdosterone diuretics have been shown to suppress sympathetic overactivity and improve HRV[30-35]. Aronson et al[30] reported that β-blockers have a beneficial modulating effect on HRV in CHF patients. Bullinga et al[31] found that carvedilol therapy in patients with CHF significantly increased HRV, which was also correlated with improved hemodynamics. Jansson et al[32] have shown the beneficial effects of metoprolol and captopril on HRV. A separate study of the Tambara et al[33] found that candesartan treatment improves the cardiac autonomic balance by attenuating the sympathetic nervous activity and augmenting the parasympathetic activity in patients with CHF[33]. Tommassi et al[34] reported that lisinopril treatment enhanced HRV in patients with CHF. Further, aldosterone blockade with spironolactone was shown to lower the heart rate and improve HRV in CHF patients[35]. However, the guideline-recommended target doses of these drugs may not always be realized due to side effects such as dizziness, fatigue, bradycardia, hypotension, and persistence of symptoms[6,36,37]. Therefore, combination therapy with ivabradine appears to be valuable for patients who do not tolerate the target doses of beta-blockers, ACEIs, ARBs, and diuretics. We found that 8 weeks of ivabradine treatment increased the time domain indices of HRV in nonischemic DCM patients. This improvement was sustained both when awake and while asleep. The possible mechanisms for this improvement may include: 1) heart rate reduction with no negative effects on inotropism, which leads to the lengthening of the diastolic filling time, permitting a more complete LV filling; 2) beneficial effects on LV remodeling; 3) reducing the sympathetic influence and enhancing the vagal tone as suggested by the decrease in SDNN

and increase in pNN50 observed in our study, leading to an improvement in the sympathovagal balance; and 4) suppression of endothelial dysfunction[4,38-40].

Limitations

This study had several limitations. First, this was not a placebo-controlled, randomized study. Second, the sample size of the study was relatively small and there was no follow-up beyond 8 weeks. Therefore, the results obtained were not sufficient to analyze the association between improved HRV and morbidity and mortality. While HRV is of prognostic importance, its utility as a therapeutic target in HF patients treated with ivabradine remains uncertain after this study. Third, because only approximately half the number of patients were titrated to the recommended 7.5 mg twice daily dose of ivabradine, the effect of the treatment may be underestimated. Therefore, it is likely that the therapeutic potential and the clinical benefits of ivabradine can be further increased by the use of the full dose as recommended. Fourth, we have not measured the natriuretic peptide levels. Fifth, the heart rate turbulence and frequency domain indices of HRV were not assessed in the present study. Finally, CHF patients with NYHA class IV and COPD patients were not included in the study.

Conclusion

The present data indicate that appropriate ivabradine treatment may not only lower the heart rate induced by sympathetic overactivity but also augment the parasympathetic activity, thus improving cardiovascular autonomic regulation. This may reduce the risk for morbidity and mortality in patients with long-term CHF. Further studies with larger sample size are needed to assess the long-term beneficial effects of ivabradine treatment on HRV in patients with CHF.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Kurtoglu E, Balta S; Acquisition of data: Karakus Y, Yasar E, Cuglan B, Kaplan O, Gozubuyuk G; Statistical analysis: Balta S, Karakus Y, Yasar E, Cuglan B; Writing of the manuscript: Kurtoglu E; Critical revision of the manuscript for intellectual content: Kaplan O, Gozubuyuk G.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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