The effect of nebivolol on P wave duration and dispersion in patients with Behçet's disease; a prospective single-arm controlled study

Behçet hastalığında nebivololün P dalga süresi ve P dalga dispersiyonuna etkisi; prospektif, tek grup kontrollü çalışma

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ABSTRACT

Objective: Behçet's disease (BD) is a chronic multi-system disease presenting with recurrent oral and genital ulceration, and relapsing uveitis. Left ventricular diastolic dysfunction, ventricular arrhythmia and sudden cardiac death have been documented in BD. P wave dispersion (PD) has been reported to be associated with inhomogeneous and discontinuous propagation of sinus impulses. PD has been reported to be longer in patients with BD. Nebivolol, besides its selective beta1-blocking activity, causes an endothelium dependent vasodilatation through nitric oxide release. In this study, we searched for the effects of nebivolol on P wave duration and dispersion in patients with BD.

Methods: This study was designed as prospective single-arm controlled study. We prospectively studied 35 Behçet's patients who were diagnosed according to the International Study Group criteria. Patients received 5 mg nebivolol per day for 3 months. The patients were evaluated with 12-leads electrocardiography at baseline and after for 3-month therapy. The difference between maximum and minimum P wave durations was defined as PD. The paired samples t test, Wilcoxon test were used for statistical analysis.

Results: A significant decrease was observed in PD after therapy period (62.85±21.62 vs. 44.28±18.03 msec, p=0.001). No adverse effects were observed in treatment period.

Conclusion: BD is associated with prolonged P wave duration and dispersion. We have shown for the first time that nebivolol causes a significant decrease in maximum P wave duration and PD in patients with BD. However, further comprehensive studies are needed to determine the long-term effects of nebivolol. *(Anadolu Kardiyol Derg 2013; 13: 682-7)*

Key words: Behçet's disease, nebivolol, P wave dispersion

ÖZET

Amaç: Behçet hastalığı (BH), tekrarlayıcı oral ve genital ülserasyon ve üveit atakları ile karakterize, kronik multisistemik bir hastalıktır. BH'da sol ventrikül diyastolik disfonksiyonu, ventriküler aritmi ve ani kardiyak ölüm vakaları bildirilmiştir. P dalga dispersiyonu (PD)'nun, sinüs uyarılarının homojen olmayan ve kesintili yayılımı ile ilişkili olduğu gösterilmiştir. PD'nin BH'da daha uzun olduğu gösterilmiştir. Selektif beta 1 bloker olan nebivolol, nitrik oksit salınımı sayesinde endotel bağımlı vazodilatasyon yapar. Bu çalışmada, BH'da nebivololün P dalga süresi ve PD üzerindeki etkisini araştırdık.

Yöntemler: Bu araştırma prospektif, tek grup kontrollü çalışma olarak tasarlandı. Çalışmaya Uluslararası Çalışma Grubu kriterlerine uyan 35 BH alındı. Hastalara 3 ay süreyle 5 mg/gün nebivolol verildi. Hastalar başlangıçta ve 3 aylık tedavi sonrasında 12 kanallı elektrokardiyografi ile değerlendirildi. Maksimum ve minimum P dalga süresi arasındaki fark PD olarak belirlendi. Paired samples t-test, Wilcoxon testi istatistiksel değerlendirme için kullanıldı.

Bulgular: Tedavi sonrasında PD'da belirgin azalma izlendi (62.85±21.62'e karşı 44.28±18.03 msn, p=0.001). Tedavi süresinde herhangi bir yan etki izlenmedi.

Sonuç: BH uzamış P dalga süresi ve PD ile ilişkilidir. Çalışmamızla ilk kez nebivololün BH'da P dalga süresinde ve PD'da belirgin azalma yaptığını gösterdik. Ancak nebivololün uzun dönem etkilerini saptayabilmek için daha kapsamlı çalışmalara ihtiyaç vardır.
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Anahtar kelimeler: Behçet hastalığı, nebivolol, P dalga dispersiyonu

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Introduction

Behçet's disease (BD) is a chronic inflammatory vasculitic disease, multi-systemic by nature, characterized by recurrent oral aphthous ulcers, genital ulcers and uveitis attacks (1). In addition to major triad of this disease, it is reported that the involvement of skin, articular, central nervous system, gastrointestinal system, pulmonary system and cardiovascular system is likely (2). Although it is rarely reported in BD, cardiac involvement affects the prognosis of this disease and leads to increase in mortality (2). Cardiac involvement may emerge in the form of endocarditis, myocarditis, pericarditis, intracardiac thrombus, endomyocardial fibrosis, coronary arthritis, myocardial infarction, conduction system disturbances and valvular heart disease (3). Most recently, endothelial dysfunction, left ventricular (LV) diastolic dysfunction and cardiac-dependent sudden death cases have been reported (4, 5).

P wave dispersion (PD) is defined as the difference between the longest and the shortest P wave duration recorded from multiple different surface electrocardiography (ECG) leads. Prolonged P wave duration and PD have been reported to represent an increased risk for atrial fibrillation (AF), and are also related with stable angina pectoris, acute coronary syndromes, coronary slow flow phenomenon, hypertrophic cardiomyopathy (6-8). Increased P wave duration and PD have been reported in patients with BD (9, 10).

Nebivolol is a selective beta-adrenergic blocker with vasodilatory property. This vasodilatory action depends on its potentiating effect on the bioactivity and levels of nitric oxide (11, 12). There is no study in the literature that investigated how nebivolol affects P wave duration and PD in patients diagnosed with BD.

In the present study, we analyzed the effect of nebivolol on P wave duration and PD in patients with BD.

Methods

Study design

This study was designed as a prospective single-arm controlled (patients are self-controls) study

Study population

A total of 35 consecutive patients who were examined at the dermatology polyclinic of Erciyes University Faculty of Medicine between January 2008 and August 2008 and fulfilled the International Study Group's criteria for BD, were recruited prospectively (13). The inclusion criteria were ultrasonographically documented endothelial dysfunction evaluated with flow-mediated dilatation method and a stable condition (14, 15). Exclusion criteria were as follows: (1) impaired cardiopulmonary function, defined as the occurrence of respiratory failure, pulmonary infection or congestive heart failure; (2) coronary artery disease, defined as having a typical angina pectoris, history of a prior myocardial infarction, presence of a positive stress test or positive coronary angiographic findings; (3) valvular disease, atrial fibrillation, atrioventricular block or congenital heart disease; (4) hypertension, diabetes, dyslipidemia low-density lipoprotein (LDL) cholesterol >160 mg/dL, total cholesterol >240 mg/dL, triglyceride >200 mg/dL), using antihypertensives, antidiabetics and lipid-lowering treatment; (5) chronic alcoholism and smoking; (6) malignancy, hyperthyroidism and hypothyroidism; (7) use of any vasoactive drug; (8) renal and liver insufficiency; (9) vitamin B12 or folic acid deficiency; (10) active phase of BD clinically. No subjects were under antiarrhythmic, digitalis, beta blocker or calcium channel blocker medication.

Study protocol

Patients were given 5 mg/day nebivolol. The patients were evaluated with 12-leads ECG before and three months after treatment with nebivolol. The patients were observed for any adverse effects. Written informed consent was obtained from each subject, and institutional Ethic Committee approved the study protocol according to Declaration of Helsinki.

P wave dispersion measurements on 12-lead ECGs

Twelve-lead ECGs were obtained after a 10-minute rest, with 20 mm/mV amplitude and 50 mm/sec rate with standard lead positions in a supine position. Twelve-lead ECGs recording was repeated at the end of the 3-months treatment period. ECGs were manually measured by the use of a ×10 magnifying glass by the same cardiologist having no information about the patients. The P wave duration was measured in all leads from the beginning of the P wave, defined as the point where the initial deflection of the P wave crossed the isoelectric line, to the end of the P wave, defined as the point where the final deflection of the P wave crossed the isoelectric line. The difference between maximum and minimum P wave durations (Pmax and Pmin) was defined as PD. Patients with measurable P waves in nine or fewer electrocardiographic leads were excluded from the study. Intra-observer coefficient of variation for P wave variables were less than 5% and nonsignificant.

Echocardiographic examination

All patients included in the study underwent a transthoracic echocardiography. Transthoracic echocardiographic examinations are carried out by using a Vivid 7 Dimension® (GE Vingmed Ultrasound AS, N-3190 Horten, Norway) echocardiography device and a 2.5 MHz transducer. Measurements are made in a left-side decubitis position after a rest time of 5 minutes through standard parasternal long axis, short axis, apical four and five chamber view windows. In cross-section located immediately beneath mitral valve in parasternal long axis views, interventricular septum thickness (IVS), left ventricular (LV) posterior wall thickness (PW), LV end-systolic diameter (LVESD) and LV end-diastolic diameter (LVEDD) are measured through M-mode examination. In parasternal long axis view, left atrium (LA) size

is measured through M-mode examination. Left ventricular ejection fraction (LVEF) is calculated by biplane Simpson method from apical four-chamber and two-chamber views according to the suggestion of the American Society of Echocardiography (16). All echocardiographic measurements were calculated from an average of 3 consecutive cardiac cycles. Left ventricular mass was calculated with the Devereux equation (17) and was indexed to body surface area. All echocardiographic measurements were performed by the same examiner, who was blinded to the clinical and biochemical data. Intra-observer coefficient of variation for echocardiographic measurements were less than 10% and nonsignificant.

Laboratory methods

Blood samples were taken for renal and liver function tests, high-sensitive C-reactive protein (hs-CRP) (Dade-Behring, Deerfield, IL, USA) and erythrocyte sedimentation rate (ESR) after a 12 hours overnight fasting.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences, version 13.0 (SPSS Inc., Chicago, IL, USA). Deviation from normality was evaluated by Kolmogorov-Smirnov test. Data were expressed as the mean±SD and median (minimum-maximum). To assess the effects of nebivolol, we used paired samples t-test for the continuous variables with normal distribution, while the Wilcoxon test was employed for the continuous variables outside the normal distribution. Pearson correlation analysis used to analyze the correlation. All probability values were two-tailed, and a value <0.05 was considered statistically significant.

Results

Demographic and clinical results

Twenty (57%) of the enrolled patients were female and 15 (43%) were male. Mean age was 38.0±10.8 years. The mean disease duration of BD was 8.3±5.7 years. Body mass index was 26.8±4.9 kg/m^2. Pre-treatment values of patients were as follows: heart beat rate (HR) 78.4±9.6 beats/min, systolic blood pressure (SBP) 123.4±11.9 mmHg and diastolic blood pressure (DBP) 79.8±9.5 mmHg. Baseline clinical and echocardiographic characteristics are listed in Table 1.

After three months of treatment HR and DBP reduced significantly (p<0.05 for both), while no change in SBP was observed (Table 2). Similarly changes in LVEF, LVMI and left atrium dimension were insignificant (p>0.05). Before medical treatment, mean hs-CRP level of patients was 6.02±6.10 mg/L (median: 3.84 mg/L, minimum: 3.02 mg/L, maximum: 34.70 mg/L). Following three months of treatment with nebivolol, mean hs-CRP level was 5.48±4.73 mg/L (median: 3.24 mg/L, minimum: 3.02 mg/L, maximum: 23.60 mg/L). Reduction in post-treatment hs-CRP level was not statistically significant compared to pre-treatment level (p>0.05). Mean sedimentation rate of patients before nebivolol treatment was 21.08±13.04 mm/hr. Repeated measurements of sedimentation after treatment revealed a mean value of 18.14±10.07 mm/hr. Change in the mean sedimentation rates following nebivolol treatment was not statistically significant (p>0.05).

Effects of nebivolol on Pmax, Pmin and PD

After three months treatment period showed a significant reduction in Pmax and PD (Table 2, Fig. 1). However, there was no statistically significant difference between the values of Pmin measured before and at the end of the nebivolol therapy (Table 2). Before the treatment period, the correlation analysis showed a relation between PD and LV mass index (r=0.478, p=0.004). No adverse effects were observed in treatment period.

Discussion

Our study showed that nebivolol treatment produces significant reduction in Pmax and PD in patients with BD.

BD, a multisystemic inflammatory disorder, has been associated with a number of cardiovascular dysfunctions, including endomyocardial fibrosis of the right heart, atrial fibrillation, ventricular arrhythmias and sudden cardiac death. Cardiac involvement can manifest with apparent symptoms or can be subclinical. In recent studies, P wave abnormalities have been demonstrated in patients with BD (9, 10, 18). AF is the most common type

Table 1. Baseline clinical, echocardiographic and electrocardiographic characteristic of the study population

Age, years	38.0±10.8
Disease duration, years	8.3±5.7
BMI, kg/m^2	26.8±4.9
SBP, mmHg	123.4±11.9
DBP, mmHg	79.8±9.5
Heart beat rate, beats/min	78.4±9.6
LVDd, mm	45.9±4.4
LVSd, mm	30.4±3.2
LVEF, %	63.0±3.8
Left atrium, mm	30.5±4.3
LVM, g	152.6±45.9
LVMI, g/m^2	85.0±19.5
Pmax, msec	123.14±13.45 121.37 (100-160)
Pmin, msec	60.28±20.07 59.13 (40-120)
PD, msec	62.85±21.62

Data are expressed as mean±standard deviation and median (minimum-maximum).
BMI - body mass index, DBP-diastolic blood pressure, LVDd - left ventricular diastolic diameter, LVEF - left ventricular ejection fraction, LVM- left ventricular mass; LVMI - left ventricular mass index, LVSd - left ventricular systolic diameter, msec- millisecond; mm-millimeters, Pmax - maximum P wave duration, Pmin - minimum P wave duration, PD - P wave dispersion, SBP - systolic blood pressure

Table 2. Clinical, echocardiographic and electrocardiographic values before and after nebivolol treatment

Variables	Before treatment	After treatment	*p
SBP, mmHg	123.4±11.9	121.2±11.0	0.14
DBP, mmHg	79.8±9.5	75.5±9.9	0.01
Heart beat rate, beats/min	78.4±9.6	71.4±8.7	<0.001
LVEF, %	63.0±3.8	63.4±3.7	0.33
Left atrium, mm	30.5±4.3	28.3±8.6	0.16
LVMI, g/m^2	85.0±19.5	82.6±14.3	0.24
Pmax, msec	123.14±13.45 121.37 (100-160)	106.57±18.46 104.73 (80-160)	<0.001
Pmin, msec	60.28±20.07 59.13 (40-120)	62.28±17.16 61.05 (40-100)	0.4
PD, msec	62.85±21.62	44.28±18.03	0.001

Data are expressed as mean±standard deviation and median (minimum-maximum).
*- paired samples t-test and Wilcoxon test
DBP - diastolic blood pressure, LVEF - left ventricular ejection fraction, LVMI - left ventricular mass index, mm-millimeters, msec - millisecond, Pmax - maximum P wave duration, Pmin - minimum P wave duration, PD - P-wave dispersion, SBP - systolic blood pressure

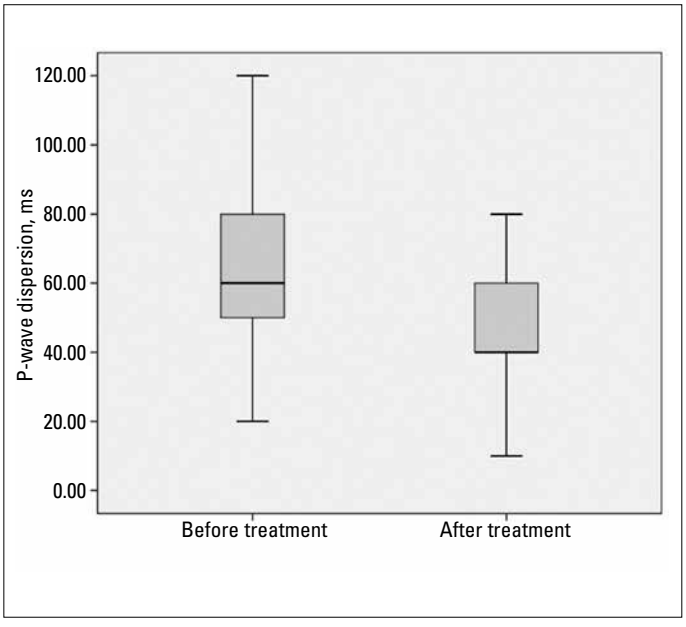

Figure 1. P wave dispersion before and after nebivolol treatment

of tachyarrhythmia encountered in clinical practice and is associated with increased morbidity and mortality (19). Systemic inflammation plays a significant role in AF pathogenesis (20).

In recent studies, atrial involvement has shown in patients with BD. Aktürk et al. (21) found that LA mechanical functions and volumes were impaired in BD who have no clinical evidence for cardiovascular disease. In a study of Karabağ et al. (22) atrial electromechanical delay (EMD) duration, a non-invasive predictor of AF, were investigated in patients with BD and interatrial and intra-atrial EMD found to be increased in patients with BD compared with the control group.

Discontinuous and inhomogeneous propagation of sinus impulses in atrial myocardium play a major role in initiation of atrial reentry. These distribution properties of sinus impulses in atrial myocardium can be stated by two simple electrocardiographic parameters recently. Pmax is an indicator of interatrial conduction disorder and inhomogeneous, non-uniform atrial conduction is assessed by PD (23). Prolongation of intra-atrial and interatrial conduction time and inhomogeneous propagation of sinus impulses are known electrophysiological characteristics of atria prone to fibrillation (23, 24).

Accordingly, many investigators have searched the PD in many cardiac diseases to determine whether it is useful or not to predict the risk of AF. Based on the available data obtained from these investigations, PD may be considered as a non-invasive electrocardiographic marker to predict the risk of AF, especially in some cardiovascular disorders as cardiomyopathy, rheumatic mitral stenosis, ischemic heart disease, hypertension, and paroxysmal AF which characterized with a high prevalence of AF (7, 8, 25-31).

Several studies have demonstrated that PD, which is considered to be a risk factor for AF, is higher in patients with BD than control subjects (9, 10), AF and prolonged PD is related with ongoing inflammation and endothelial damage/dysfunction (32-35). Like most of the vasculitic pathologies, inflammation, the endothelial damage and dysfunction are apparently associated with the etiopathogenesis of BD. In the active stage of the disease, a high systemic inflammatory activity is observed in the circulation or the vascular tissue (36-38).

Recent studies have demonstrated that nebivolol produces a significant reduction in maximum duration and dispersion of the P wave in patients with coronary slow flow and hypertensive patients (6, 39). The specific effect of nebivolol on atrial conduction has not been previously studied in patients with BD. In our study, the effect of nebivolol on atrial conduction was assessed in patients with BD showing prolonged P wave duration and PD. We have observed significant reduction in Pmax and PD with nebivolol therapy for 3-month period. These results may be a guide to therapeutic approach for patients with BD.

There are several possible mechanisms by which nebivolol might reduce the prolongation of the maximum duration and dispersion of the P wave. Beta-blockers enhance ventricular filling, lengthen duration of diastole, decrease atrial pressure and dilatation, reduce atrial ischemia and fibrosis and thereby may improve stretch related arrhythmogenic mechanisms (39). Consistent with this data, beta-blockers have been shown to be effective in prevention of postoperative AF, in adrenergically mediated AF, and in reducing relapse rates of AF following cardioversion (40-42). BD patients have been found to have increased sympathetic and decreased parasympathetic modulation (43). Tükek et al. (44) have reported that increased sympathetic activity causes a significant increase in PD. So, it is reasonable to suggest that the decrease in maximum P wave duration and PD measured at the end of the nebivolol therapy may be related with the attenuation

of the actions of the sympathetic nervous system on atrial electrical physiology. Nebivolol promote nitric oxide bioactivity and vasodilatation by inhibiting oxidative stress and inflammation (45). Furthermore, nebivolol reduced coronary artery smooth muscle cell growth (46, 47). CRP decreases NO release by showing effects on the enzyme nitric oxide synthase. Increased hs-CRP levels have been shown in BD and CRP levels may decrease with nebivolol therapy (14). Studies have demonstrated that CRP is interrelated and associated with interatrial electromechanical delay and AF (48, 49). In our study, a decrease in hs-CRP values was observed with nebivolol therapy but the hs-CRP reduction did not reach a statistically significant level. The lack of a statistically significant reduction in hs-CRP values was thought to have resulted from the low number of study patients and the enrollment of patients during the clinically inactive phase by their Behçet's Disease Activity Index. Improved nitric oxide bioactivity, reduced oxidative stress and inflammation, inhibition of smooth muscle cell growth with nebivolol therapy may improve ischemia induced prolongation of atrial conduction.

Study limitations

Our study has some limitations. Small number of the patients included in the study is one of the major limitations. Another major limitation is that this is a single arm study without placebo group. The follow up period is relatively short to assess the clinical impact of BD on arrhythmia development and the preventive effects of nebivolol treatment. Larger studies and longer term follow-up should strengthen the value of the results. P wave measurements were performed manually on the standard paper ECG. A digitized measurement method for P wave parameters would be more accurate. However, our method has been used in previous studies (7, 23, 26, 39).

Conclusion

We have shown for the first time that nebivolol therapy causes a significant decrease in PD, indicating increased risk for AF, in patients with BD. Although it is our belief that the significant results of our study will shed a light on the ways of treatment of BD, we are also of the opinion that these results must be further supported clinically by prospective studies performed on a higher number of patients.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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