The effects of nebivolol on P wave duration and dispersion in patients with coronary slow flow

Koroner yavaş akımlı hastalarda nebivololün P dalga süresi ve dispersiyonuna etkileri

Yılmaz Güneş, Mustafa Tuncer, Ünal Güntekin, Yemlihan Ceylan

Department of Cardiology, Faculty of Medicine, Yüzüncü Yıl University, Van, Turkey

Abstract

Objective: Coronary slow flow (CSF) is characterized by delayed opacification of coronary arteries in the absence epicardial occlusive disease. P wave duration and dispersion have been reported to be longer in patients with CSF. Nebivolol, besides its selective beta$_1$-blocking activity, causes an endothelium dependent vasodilatation through nitric oxide release. In this study, we searched for the association between left ventricular diastolic functions and atrial conduction dispersion, the effects of nebivolol on P wave duration and dispersion in patients with CSF.

Methods: This prospective case-controlled study included 30 patients having CSF and 30 subjects having normal coronary arteries in coronary angiography. The patients were evaluated with 12-leads electrocardiography and echocardiography before and three months after treatment with nebivolol. The difference between maximum and minimum P wave durations was defined as P-wave dispersion (PWD). Early diastolic flow (E), atrial contraction wave (A) and E deceleration time (DT) and isovolumetric relaxation time (IVRT) were measured. Unpaired and paired t-tests, Chi-square test, Mann-Whitney's U-test and Pearson correlation analysis were used in statistical analysis.

Results: Compared to control group maximum P wave duration (Pmax) (104.3±12.2 vs. 93.4±9.8 msec, p<0.001) and PWD (35.0±8.6 vs. 24.8±5.4 msec, p<0.001), DT (245.4±54.9 vs. 198.0±41.7 msec, p<0.001) and IVRT (112.9±20.8 vs. 89.5±18.2 msec, p<0.001) were significantly longer and E/A ratio (0.89±0.27 vs. 1.27±0.27, p<0.001) was lower in patients with CSF as compared with control subjects. There were no significant correlations of Pmax and PWD with clinical and echocardiographic variables. Systolic and diastolic blood pressures (130.5±15.5 mmHg to 117.8±12.3 mmHg and 84.5±9.8 mmHg to 75.0±6.2 mmHg, p<0.001), Pmax (to 98.7±11.7 msec, p=0.038), PWD (to 21.3±5.1 msec, p<0.001) and DT (to 217.3±41.4 msec, p<0.001) and IVRT (to 101.2±17.4 msec, p<0.001) significantly decreased and E/A ratio (to 1.1±0.23, p<0.001) significantly increased after treatment with nebivolol. Correlation analysis revealed that the change in PWD was not significantly correlated with any of the clinical and echocardiographic variables including decrease in blood pressures.

Conclusions: Coronary slow flow is associated with prolonged P wave duration and dispersion and impaired diastolic filling. Nebivolol may be helpful in restoration of these findings. P wave duration and dispersion may not be associated with left ventricular function parameters in patients with CSF. *(Anadolu Kardiyol Derg 2009; 9: 290-5)*

Key words: Coronary slow flow, nebivolol, P wave dispersion

Özet

Amaç: Koroner yavaş akım (KYA) epikardiyal tıkayıcı bir hastalık olmaksızın koroner arterlerde opaklaşmanın gecikmesi ile karakterizedir. P dalga süresi ile dispersiyonunun KYA olan hastalarda uzadığı bildirilmiştir. Nebivolol, beta$_1$-bloker aktivitesinin olması yanı sıra, nitrik oksit salınımı ile endotele bağımlı vazodilatasyona yol açar. Bu çalışmada KYA olan hastalarda sol ventrikül diyastolik fonksiyonları ile atriyal iletim dispersiyonu arasındaki ilişkiyi ve nebivololün P dalga dispersiyonu (PWD) üzerindeki etkilerini araştırdık.

Yöntemler: Prospektif, vaka-kontrollü bu çalışmaya koroner anjiyografide KYA saptanan 30 hasta ve koroner arterleri normal bulunan 30 birey alındı. Hastalar nebivolol tedavisinden önce ve üç ay sonra 12-derivasyonlu elektrokardiyografi ve ekokardiyografi ile değerlendirildiler. Maksimum ve minimum P dalga süreleri arasındaki fark PWD olarak tanımlandı. Erken diyastolik akım (E), atriyal kasılma dalgası (A), E deselarasyon zamanı (DT) ile izovolumetrik gevşeme zamanı (IVRT) ölçüldü. İstatistiksel analizde t-testleri, Ki-kare testi, Mann-Whitney U-testi ve Pearson korelasyon analizi kullanıldı.

Bulgular: Kontrol grubuna göre KYA olan hastalarda maksimum P dalga süresi (Pmax) (104.3±12.2 karşın 93.4±9.8 msn, p<0.001), PWD (35.0±8.6 karşın 24.8±5.4 msn, p<0.001), DT (245.4±54.9 karşın 198.0±41.7 msn, p<0.001), IVRT (112.9±20.8 karşın 89.5±18.2 msn, p<0.001) anlamlı olarak daha uzun, E/A oranı (0.89±0.27 karşın 1.27±0.27, p<0.001) daha düşüktü. Pmax ve PWD ile klinik ve ekokardiyografik parametreler arasında anlamlı korelasyon bulunmadı. Nebivolol tedavisinden sonra sistolik ve diyastolik kan basınçları (130.5±15.5 mmHg'den 117.8±12.3 mmHg'ye ve 84.5±9.8

Address for Correspondence/Yazışma Adresi: Yılmaz Güneş, MD, Yüzüncü Yıl University, Faculty of Medicine, Cardiology Department, Van, Turkey
Phone: +90 432 216 47 09 Fax: +90 432 216 83 52 E-mail: yilmazleman@yahoo.com

mmHg'den 75.0±6.2 mmHg'ye, p<0.001) ile Pmax (98.7±11.7 msn'ye, p=0.038), PWD (21.3±5.1 msn'ye, p<0.001), DT (217.3±41.4 msn'ye, p<0.001) ve IVRT (101.2±17.4 msn'ye, p<0.001) anlamlı olarak azalırken E/A oranı (1.1±0.23'e, p<0.001) yükseldi. Korelasyon analiziyle PWD'deki değişim ile kan basıncındaki düşme dahil olmak üzere klinik ve ekokardiyografik parametreler arasında anlamlı ilişki bulunmadı.

Sonuç: Koroner yavaş akım uzamış P dalga süresi, P dalga dispersiyonu ve diyastolik dolum bozukluğu ile ilişkilidir. Nebivolol bu bulguların düzeltilmesinde faydalı olabilir. Koroner yavaş akım olgularında P dalga süresi ve dispersiyonu sol ventrikül diyastolik fonksiyonları ile ilişkili olmayabilir. *(Anadolu Kardiyol Derg 2009; 9: 290-5)*

Anahtar kelimeler: Koroner yavaş akım, nebivolol, P dalga dispersiyonu

Introduction

Coronary slow flow (CSF) is a phenomenon characterized by delayed opacification of coronary arteries in the absence of epicardial occlusive disease, in which many etiological factors such as microvascular and endothelial dysfunction and small vessel disease have been implicated (1-4).

P-wave dispersion (PWD) is defined as the difference between the longest and the shortest P-wave duration recorded from multiple different surface electrocardiogram (ECG) leads. Several studies used this ECG marker in various clinical settings and particularly in the assessment of risk of atrial fibrillation (AF) (5-8). P wave duration and dispersion have been reported to be longer in patients with CSF (9, 10).

Nebivolol is a new beta-blocker and besides its selective $beta_1$-blocking activity causes an endothelium dependent vasodilatation through nitric oxide release (11). Nebivolol also dilates coronary resistance microarteries and increases coronary flow reserve (12, 13). Thus it might be especially useful in the treatment of CSF through improvement of endothelial function and dilatation of small and large coronary arteries. However, the relationship of nebivolol and atrial conduction dispersion are not well elucidated.

In this study, we aimed to investigate the association of left ventricular diastolic functions and atrial conduction dispersion and the effects of nebivolol on P wave dispersion in patients with CSF.

Methods

Patients and study design

This prospective case-controlled study included 30 patients with angiographically proven CSF but otherwise normal epicardial coronary arteries and 30 healthy subjects selected from patients who had undergone diagnostic coronary arteriography because of suspected coronary artery disease and were found to have normal epicardial coronary arteries other than CSF. The reason for coronary angiography was typical angina in 24 (80.0%) patients and positive treadmill test in 6 (20.0%) patients in CSF group. Of the patients having normal coronary arteries 6 (20.0%) had typical angina, 16 (53.3%) had positive treadmill test and 8 (26.7%) had perfusion defect in myocardial scintigraphy. Coronary slow flow was defined according to the TIMI frame count (TFC) method, and the subjects with a TFC greater than 2 standard deviations (SD) from the published normal range for the particular vessel were accepted as having CSF (14). Patients with a history of congestive heart failure, coronary artery disease including spasm, plaque, or ectasia, valvular heart disease, hyperthyroidism, chronic obstructive pulmonary disease, ventricular preexcitation, atrioventricular conduction abnormalities and those taking medications known to alter cardiac conduction and/or having antiischemic effects were excluded from the study. The patients were evaluated with echocardiography and 12-leads electrocardiography before and three months after treatment with nebivolol (5 mg/day). The study was approved by hospital Ethic Committee according to Declaration of Helsinki and patients gave written informed consent.

Echocardiography

The echocardiographic examination was performed at rest, with the patient at left lateral decubitis position, using a commercially available echocardiographic device (Vivid 3, General Electric) with a 3 MHz transducer, by two experienced echocardiographers who were blinded to the clinical data. Using M-mode echocardiography, long-axis measurements were obtained at the level distal to the mitral valve leaflets according to current recommendations (15). Left ventricular (LV) ejection fraction was calculated via modified biplane Simpson's method from apical four and two chamber views. Left ventricular mass (LVM) was measured by using Devereux formula (16). The pulsed Doppler sampling volume was placed between the tips of the mitral valve leaflets to obtain maximum filling velocities. Early diastolic flow (E), atrial contraction signal (A) and E deceleration time (DT) were measured. Isovolumetric relaxation time (IVRT) was determined as the interval between the end of the aortic outflow and the start of the mitral inflow signal. Intra-observer and inter-observer coefficients of variation for echocardiographic measurements were less than 10% and nonsignificant.

Electrocardiography

Twelve-lead ECGs were obtained at rest, with 20 mm/mV amplitude and 50 mm/sec rate with standard lead positions. The ECGs were manually measured by the use of a magnifying glass by two blinded cardiologists having no information about the patients. The beginning of the P wave was defined as the point where the initial deflection of the P wave crossed the isoelectric line, and the end of the P wave was defined as the point where the final deflection of the P wave crossed the isoelectric line. The difference between maximum and minimum P wave duration (Pmax and Pmin) was defined as PWD. Intra-observer and inter-observer coefficients of variation for P wave variables were less than 5% and nonsignificant.

Statistical analyses

All tests were performed in the SPSS program for Windows, version 10.0 (Chicago, IL, USA). Quantitative variables are expressed as mean±standard deviation (SD), and qualitative variables as numbers and percentages. Differences between independent groups were assessed by t-tests for quantitative data and Chi-square test for qualitative variables. Mann-Whitney's U-test was used for variables without normal distribution. Relation between P wave variables and clinical and echocardiographic variables were assessed using Pearson correlation analysis. The changes in parameters after treatment were compared using paired t-test. The relation between the change in PWD after treatment and clinical and echocardiographic variables was assessed by Pearson correlation analysis. A two-tailed p value of <0.05 was considered significant.

Sample size determination

To detect a difference of 8.8 msec between groups with a 5-msec SD within groups, given an a value of 0.05 and a power of 80%, the sample size was determined to be 24 subjects. Therefore, a sample size of 30 patients was chosen as a conservative estimate of an adequate sample size required for this study.

Results

Baseline clinical characteristics and two dimensional echocardiographic data including left atrial diameter and LV ejection fraction were similar between CSF patients and control groups. However, DT, IVRT and P max and PWD were significantly longer and E/A ratio was lower in CSF patients (p<0.001 for all) (Table 1).

Among clinical and echocardiographic variables Pmax and PWD significantly and positively correlated only with the presence of CSF (r=0.448, p<0.001 and r=0.584, p<0.001).

E/A ratio (p<0.001) and Pmin (p=0.005) significantly increased and blood pressure, heart rate, DT, IVRT, Pmax and PWD values significantly decreased (p<0.001) after treatment with nebivolol (Table 2, Fig. 1). The change in PWD after treatment was not significantly correlated with any of the baseline characteristics including age, gender, hypertension, diabetes, smoking, BMI, heart rate, blood pressure, LVEF, DT, IVRT, cardiac dimensions and LVM and the amount of decrease in blood pressures.

All the patients were free of angina after treatment.

Table 1. Baseline clinical characteristics of the study population

Parameters	CSF group (n=30)	Control group (n= 30)	*p
Age, years	55.5±13.1	53.4±14.3	0.568
Male sex, n(%)	21 (70.0)	16 (53.3)	0.144
Diabetes mellitus, n(%)	5 (16.7)	2 (6.7)	0.424
Hypertension, n(%)	10 (33.3)	8 (26.7)	0.779
Smoking, n(%)	9 (30.0)	12 (40.0)	0.589
BMI, kg/m^2	25.9	24.9	0.138
Heart rate, bpm	79.0±10.9	75.5±7.6	0.149
Systolic BP, mmHg	130.5±15.5	128.3±17.0	0.609
Diastolic BP, mmHg	84.5±9.8	85.8±10.7	0.617
LVEF, %	61.3±3.1	62.3±4.4	0.316
LVM, gr	220.7	202.7	0.150
LA diameter, mm	35.1±5.4 3.4 (2.7-4.6)	33.5±2.6 3.35 (2.8-3.7)	0.140
DT, msec	245.4±54.9 230 (176-340)	198.0±41.7 180 (170-340)	<0.001
IVRT, msec	112.9±20.8 110 (75-150)	89.5±18.2 80 (75-140)	<0.001
E/A ratio	0.89±0.27 0.80 (0.56-1.80)	1.27±0.27 1.37 (0.55-1.57)	<0.001
TFC LAD	38.3±10.9 35.5 (24-80)	29.7±1.5 30 (28-32)	<0.001
TFC RCA	46.6±23.7 46 (18-130)	23.4±1.5 24 (20-26)	<0.001
TFC Cx	41.5±11.1 40 (24-66)	24.7±1.5 24 (22-28)	<0.001
Pmax, msec	104.3±12.2 100 (80-120)	93.4±9.8 95 (80-110)	<0.001
Pmin, msec	69.3±10.1 60 (60-80)	68.6±9.0 67 (58-90)	0.768
PWD, msec	35.0±8.6 40 (20-40)	24.8±5.4 20 (20-34)	<0.001

Data are presented as Mean±SD, Median (Mimimum-Maximum) values and proportion/percentage

*Chi-square test, unpaired t-test and Mann Whitney U test

BP - Blood pressure, BMI - Body mass index, CSF - Coronary slow flow, Cx - circumflex artery, DT - deceleration time, IVRT - isovolumetric relaxation time, LA - left atrial, LAD - left anterior descending artery, LVEF - left ventricular ejection fraction, LVM - left ventricular mass, PWD - P wave dispersion, RCA - right coronary artery, TFC - TIMI frame count

Discussion

The present study suggests that LV diastolic functions are impaired and P wave duration and dispersion are increased in CSF patients and treatment with nebivolol is associated with normalization of these parameters. No significant correlation was found between PWD and diastolic function parameters in this setting.

Small clinical series and individual case reports have shown that CSF phenomenon may cause angina, myocardial ischemia, and infarction (17-20). A recent study has shown that CSF might be the cause of transient myocardial underperfusion in patients with angina and normal coronary arteries. Compared to microvascular angina patients without CSF this phenomenon was associated with increased mortality and development of significant coronary artery disease at long term. (21). This is in accordance to another study showing a worse prognosis in patients with endothelial dysfunction having chest pain and normal angiograms (22). Therefore, patients with normal coronary arteries and CSF should deserve a more careful follow-up.

Table 2. Comparison of baseline and post-treatment with nebivolol echocardiographic and electrocardiographic values

Variables	Baseline	Third month	*p
Heart rate, bpm	79.0±10.9	64.9±9.2	<0.001
Systolic BP, mmHg	130.5±15.5	117.8±12.3	<0.001
Diastolic BP, mmHg	84.5±9.8	75.0±6.2	<0.001
DT, msec	245.4±54.9	217.3±41.4	<0.001
IVRT, msec	112.9±20.8	101.2±17.4	<0.001
E/A ratio	0.89±0.27	1.1±0.23	<0.001
Pmax, msec	104.3±12.2	98.7±11.7	0.038
Pmin, msec	69.3±10.1	77.3±12.6	0.005
PWD, msec	35.0±8.6	21.3±5.1	<0.001

Data are presented as Mean±SD
*Paired t-test
DT - deceleration time, IVRT - isovolumetric relaxation time, PWD - P wave dispersion

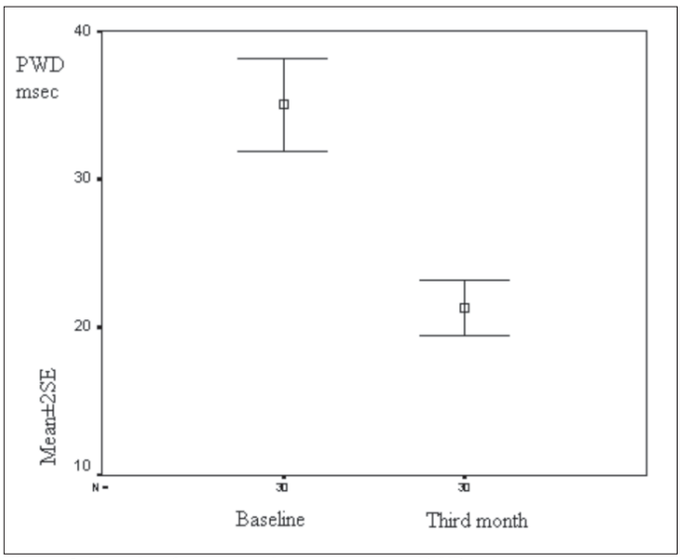

Figure 1. Error bar for pre- and post-treatment PWD values
PWD - P wave dispersion, SE - standard error

Several studies showed that PWD has a predictive value for AF, which is characterized by inhomogeneous and discontinuous atrial conduction in patients with various conditions (5-8). Increased heterogeneity of refractoriness, which is present in ischemia, may be a substrate for AF (23). Accordingly, it has been shown that myocardial ischemia increased P-wave duration and PWD (24-26). Thus, one possible mechanism for the increase in PWD and PW duration may be microvascular ischemia in these patients.

Previous studies have suggested abnormally high small vessel resistance and increased microvascular tone as the cause of CSF (1, 3, 21). Sympathetic stimulation has a major role in regulating coronary arterial tonus. Patients with CSF had higher adrenalin and noradrenalin levels when compared to patients with normal coronary flow and TIMI frame count was reported to be positively correlated with adrenalin and noradrenalin levels suggesting that adrenergic hyperactivity might have an impact on CSF pathogenesis (28). P wave duration and PWD have been reported to be influenced by the autonomic tone, which induces changes in the velocity of impulse propagation (29). In patients with microvascular angina an impaired autonomic control with reduced vagal tone and a shift toward sympathetic predominance has been described (30-32). It has also been reported that increased sympathetic activity causes a significant increase in PWD (33). Therefore, the other mechanism responsible for increase in PWD and P-wave duration in CSF phenomenon may be altered cardiac autonomic nervous control.

Another mechanism for increased P-wave duration and dispersion in CSF may be diastolic dysfunction associated with CSF. P wave dispersion has been shown to be increased in LV diastolic dysfunction (34). As in the present study, diastolic abnormalities in LV function have been reported in CSF phenomenon (35, 36). Several studies have demonstrated that CSF is associated with myocardial ischemia, but data are limited on how the LV functions are affected from this disease (2, 4, 17). Diastolic dysfunction without systolic dysfunction may present at an early stage of myocardial ischemia in patients with coronary artery disease, compatible with the fact that left ventricular diastolic functions are more susceptible to ischemia than systolic functions (37).

Considering the presented explanations above, drugs acting on sympathetic system, having coronary vasodilatory effects and reducing microvascular tonus may be useful in the treatment of CSF. Beta-blockers reduce oxygen consumption of the myocardium and thus, diminish myocardial ischemia. Previous clinical studies using coronary flow measurements suggest that non-selective beta-adrenergic antagonists may be associated with an increase in coronary vascular resistance and, therefore, reduce coronary flow reserve (38, 39). This phenomenon has been attributed to the unopposed alpha-adrenergic vasomotor tone. However, selective beta-blockers like metoprolol have been shown to improve myocardial perfusion by increasing coronary flow reserve (40). Beta-blockers also has been shown to be associated with improved anginal symptoms and exercise tolerance and improved LV filling in patients with microvascular angina (41,42). Furthermore, it has been showed that atenolol reduced QTc and QTd only in patients with microvascular angina, but not in normal subjects (43). Therefore, symptomatic improvement induced by atenolol in these patients (41) may be partly related to reduction of abnormally augmented sympathetic tone. Erbay et al (44) reported a favorable effect of b-blockers on Pmax and PWD through inhibition of sympathetic activity in patients with mitral stenosis. Nebivolol, a highly selective $beta_1$-adrenergic receptor-blocker with endothelium dependent nitric oxide-modulating properties, might be especially useful for improving coronary flow reserve due to its vasodilating properties on the small and large coronary arteries (11, 45, 46). The marked vasodilating effect of nebivolol in human coronary microvessels is well established (12, 13). The nitric oxide-releasing and vasodilating properties of nebivolol in coronary microvessels may also underlie its beneficial effects in patients with ischemic and dilated cardiomyopathies, particularly those

with diastolic dysfunction, given the direct lusitropic properties of nitric oxide on the myocardium (47, 48). Therefore, inhibition of sympathetic activity, increase in coronary flow through vasodilatation of coronary microcirculation with improvement in ischemia and improvement in diastolic functions may be the possible explanations for improvement of symptoms and shortening of P wave duration and dispersion with nebivolol.

Study limitations

Small number of the patients included in the study is the major limitation. The follow up period is relatively short to assess the clinical impact of CSF on arrhythmia development and the preventive effects of nebivolol treatment. Larger studies and longer term follow-up should strengthen the value of the results. Control angiography to assess the effects of nebivolol on TFC was not performed due to ethical concerns. Automated ECG measurements were not available and manual calculation of P-wave measurements may be criticized. Although, several studies have demonstrated a low error of the measurement of P wave dispersion on paper printed ECGs (6) others suggested that manual PWD measurement on paper printed ECGs obtained at a standard signal size and paper speed may have a questionable accuracy and reproducibility (49). Another limitation is that pulsed wave Doppler indices used for the evaluation of LV diastolic properties have been known to be altered by numerous factors, including loading conditions and heart heart rate (50).

Conclusions

Coronary slow flow is associated with prolonged P wave duration and dispersion and impaired diastolic filling. P wave duration and dispersion may not be associated with left ventricular function parameters in this setting. Nebivolol may be helpful in restoration of diastolic functions and P wave variables in CSF through inhibition of sympathetic activity and improvement in ischemia through vasodilatation of coronary microcirculation with endothelium dependent nitric oxide release.

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