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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Decreased risk of ventricular arrhythmias with treatment of nebivolol in patients with coronary slow flow

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Abstract

Background: Coronary slow-flow (CSF) is an angiographic phenomenon characterised by delayed opacification of vessels in the absence of any evidence of obstructive epicardial coronary disease. QT interval dispersion (QTD) reflects regional variations in ventricular repolarisation and cardiac electrical instability and has been reported to be longer in patients with CSF.

Aim: To examine QT duration and dispersion in patients with CSF and the effects of nebivolol on these parameters.

Methods: The study population included 67 patients with angiographically proven normal coronary arteries and CSF, and 38 patients with angiographically proven normal coronary arteries without associated CSF. The patients were evaluated with 12-lead electrocardiography, and echocardiography before and three months after treatment with nebivolol.

Results: Compared to the control group QTcmax and QTcD were significantly longer in patients with CSF ($p = 0.036$, $p = 0.019$, respectively). QTcD significantly correlated with the presence of CSF ($r = 0.496$, $p < 0.001$). QTcmax ($p = 0.027$), QTcD ($p = 0.002$), blood pressure ($p = 0.001$), and heart rate ($p < 0.001$) values significantly decreased after treatment with nebivolol.

Conclusions: Coronary slow flow is associated with increased QTD. Nebivolol reduced increased QTD in patients with CSF after three months.

Key words: coronary slow flow, nebivolol, QT dispersion

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INTRODUCTION

Coronary slow flow (CSF) phenomenon is a microvascular disease diagnosed by detection of slow passage of the contrast agent in the absence of epicardial occlusive disease, in which many aetiological factors such as microvascular and endothelial dysfunction and small vessel disease have been implicated [1].

QT-interval parameters, in particular heart rate-corrected QT (QTc) interval duration, are presumed markers of increased cardiovascular risk and provide important prognostic information in clinical practice [2]. QT dispersion (QTD) is defined as the inter-lead variability in the duration of the QT interval in the 12-lead electrocardiogram (ECG). This parameter can be used to assess the homogeneity of cardiac repolarisation and autonomic function [3].

Nebivolol is a new beta-blocker and besides its selective beta1-blocking activity causes an endothelium-dependent vasodilatation through nitric oxide release [4]. Nebivolol also dilates coronary resistance micro arteries and increases coronary flow reserve [4]. Thus it might be especially useful in the treatment of CSF through improvement of endothelial function and dilatation of small and large coronary arteries.

It has been shown that CSF has been associated with increased QTD [5]. However, to the best of our knowledge, the effects of nebivolol on QT interval and dispersion in patients with CSF have not been investigated in the literature.

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METHODS

Study group

Out of 614 patients describing stable angina pectoris or having non-ST elevation acute coronary syndrome, 67 patients with angiographically proven CSF but normal epicardial coronary arteries and 38 healthy individuals were selected from patients who had undergone diagnostic coronary arteriography because of suspected coronary artery disease and were found to have normal epicardial coronary arteries without CSF. Coronary slow flow was defined according to the Thrombolysis in Myocardial Infarction frame count (TFC) method, and the individuals with a TFC greater than two standard deviations (SD) from the published normal range for the particular vessel were accepted as having CSF. 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 pre-excitation, atrioventricular conduction abnormalities, and those taking medications known to alter cardiac conduction were excluded from the study. The patients were evaluated with echocardiography and 12-lead ECG before and three months after treatment with nebivolol (5 mg/day). The study was approved by hospital Ethics Committee according to the Declaration of Helsinki, and patients gave written, informed consent.

Echocardiography

The echocardiography examination was performed at rest, with the patient in left lateral decubitus position, using a commercially available echocardiography 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 distally to the mitral valve leaflets according to current recommendations. Left ventricular ejection fraction was calculated via modified biplane Simpson's method from apical four- and two-chamber views. 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 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.

Electrocardiography

Twelve-lead ECGs were obtained at rest, with 20 mm/mV amplitude and 50 mm/s rate with standard lead positions. ECGs were manually measured by the use of a magnifying glass by two blinded cardiologists having no information about the patients. QT intervals were taken beginning from the onset of the QRS complex to the end of the T wave, which was defined as its return to the T and P wave duration on ECG baseline. If U-waves were present, the QT interval was measured to the nadir of the curve between the T- and U-waves. The R-R interval was measured and used to compute the heart rate and to correct QT interval (QTc) with Bazett's formula. QTcD was determined as the difference between the maximum and minimum QTc interval in different leads. All measurable ECG leads were used in QTcD calculations. No patient had less than nine measurable leads. The intraobserver and interobserver variations for measurements were less than 5% and were non-significant.

Statistical analysis

All tests were performed in the SPSS program for Windows, version 18.0 (Chicago, IL, USA). Quantitative variables are expressed as mean ± SD, and qualitative variables as numbers and percentages. Differences between independent groups were assessed by t-tests for quantitative data and χ^2 test for qualitative variables. Mann-Whitney's U-test was used for variables without normal distribution. The relation between QT variables and clinical and echocardiographic variables was assessed using Pearson correlation analysis. The changes in parameters after treatment were compared using paired t-test. The relation between the change in QT variables after treatment and clinical and echocardiographic variables was assessed by Pearson correlation analysis. A two-tailed p value < 0.05 was considered significant.

RESULTS

Baseline clinical characteristics and two-dimensional echocardiographic data, except IVRT, were similar between CSF patients and control groups. However, QTcmax and QTcD were significantly longer in CSF patients than in the control group ($p = 0.036$, $p = 0.019$, respectively) (Table 1, Fig. 1). QTcD significantly correlated with the presence of CSF ($r = 0.496$, $p < 0.001$). QTcmax ($p = 0.027$), QTcD ($p = 0.002$), blood pressure ($p = 0.001$), and heart rate ($p < 0.001$) values significantly decreased after treatment with nebivolol (Table 2, Fig. 2).

DISCUSSION

This study demonstrated that the CSF phenomenon is associated with prolonged QT interval duration and increased QT dispersion and restoration of these parameters with treatment of nebivolol.

QT dispersion, defined as the difference between maximum and minimum QT interval measured on the surface ECG, is regarded as a measure of regional ventricular repolarisation abnormalities [3]. Previous studies have shown that healthy subjects exhibit a small degree of QTD [6]. However, increased QTD has been linked to increased heterogeneity of ventricular repolarisation, implicated in the genesis of potentially lethal ventricular arrhythmias, and has been associated with an adverse prognosis in a variety of patient populations [7].

Slow runoff dye in the coronary arteries during selective coronary angiography is known as slow coronary artery flow

Table 1. Comparison of the baseline clinical characteristics of the study population

	CSF group (n = 67)	Control group (n = 38)	P
Age [years]	53.3 ± 9.9	49.9 ± 8.8	0.08
Male	38 (61.2%)	33 (65.7%)	0.67
Smoking	27 (40.3%)	11 (28.9%)	0.29
Hypertension	9 (15.5%)	8 (21.1%)	0.41
Diabetes mellitus	4 (5.9%)	0 (0%)	0.29
Systolic BP [mm Hg]	130.4 ± 10.9	124.6 ± 8.01	0.11
Diastolic BP [mm Hg]	81.7 ± 4.4	79.4 ± 6.2	0.26
Body mass index [kg/m^2]	25.4 ± 2.9	23.7 ± 2.6	0.09
Heart rate [bpm]	80.7 ± 8.8	78.37.7	0.16
Total cholesterol [mg/dL]	182.6 ± 38.8	186.8 ± 24.9	0.53
Triglyceride [mg/dL]	180.1 ± 87	157.2 ± 49.2	0.23
Left atrium [mm]	33.5 ± 4.3	32.5 ± 3.1	0.242
LVEF	63 ± 3.6	64.5 ± 3.6	0.058
Deceleration time [ms]	216.8 ± 30.1	200 ± 36.1	**0.026**
IVRT [ms]	113.6 ± 19.7	101.3 ± 17.6	**0.012**
E/A ratio	O.9 ± 0.4	1.2 ± 0.3	**0.038**
TFC LAD	49.9 ± 18.9	23.8 ± 4.7	**< 0.001**
TFC RCA	53.7 ± 25.4	21.6 ± 3.4	**< 0.001**
TFC Cx	50.7 ± 19.7	22.2 ± 3.3	**< 0.001**
QTcmax [ms]	459.3 ± 59.2	421.2 ± 52.9	**0.036**
QTcmin [ms]	396.5 ± 45.7	373.4 ± 47.6	< 0.105
QTcD [ms]	62.6 ± 21.5	47.9 ± 10.9	**< 0.019**

BP — blood pressure; CSF — coronary slow flow; Cx — circumflex artery; IVRT — isovolumetric relaxation time; LAD — left anterior descending artery; LVEF — left ventricular ejection fraction; RCA — right coronary artery; TFC — Thrombolysis in Myocardial Infarction frame count; QTc — corrected QT interval; QTcD — corrected QT interval dispersion

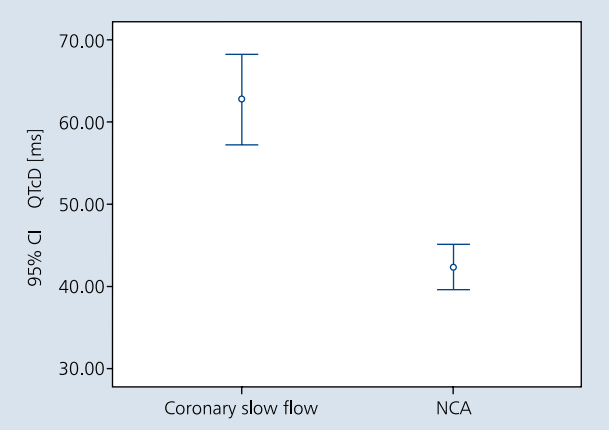

Figure 1. Error bar of correct QT interval dispersion (QTcD) in patients with coronary slow flow and control group; NCA — normaly coronary artery

and its exact pathophysiological mechanism is not known. Different theories have been postulated about the cause of small vessel dysfunction based on observations including microvascular tone dysfunction, endothelial thickening in small vessels [8], patchy fibrosis in the biopsy specimen taken from the right ventricle [9], impaired endothelial release of nitric oxide [10], and endothelial inflammation [11].

Small clinical series and individual case reports have shown that CSF phenomenon may cause angina, myocardial ischaemia, and infarction [12, 13]. In the TIMI-IIIA study, the incidence of CSF was approximately 4% among patients who presented with unstable angina and had no or insignificant epicardial coronary artery disease [14]. Furthermore, some authors have shown exercise-induced ST-segment depression in patients with CSF without obstructive coronary artery disease [12]. In patients with ischaemic heart disease, an increase in QTcD has been shown in patients with both acute ischaemia and chronic ischaemic heart disease [5]. Therefore, ischaemia at the microvascular level may be a reason behind the increased QT dispersion and prolonged QT interval.

On the other hand, it is well known that coronary vascular tone is modulated by autonomic nervous system control, and coronary adrenergic hyperactivity may account for the primary reduction in coronary blood flow and the chest pain. Moreover, previous studies have suggested abnormally high small vessel resistance and increased microvascular tone as

Table 2. Comparison of pre- and post-treatment values of some variables in patients with coronary slow flow

	Baseline	Third month	P
QTcmax [ms]	459.3 ± 59.2	446.1 ± 47.3	**0.027**
QTcmin [ms]	396.5 ± 45.7	388.9 ± 44	0.118
QTcD [ms]	62.6 ± 21.5	54.4 ± 11	**0.002**
Heart rate [bpm]	80.7 ± 8.8	75 ± 8.5	**< 0.001**
Systolic BP [mm Hg]	130.4 ± 10.9	125.1 ± 7.5	**0.002**
Diastolic BP [mm Hg]	81.7 ± 4.4	78.8 ± 3.5	**0.001**
Left atrium [mm]	33.5 ± 4.3	32.5 ± 3.8	0.199
LVEF	63 ± 3.6	63.1 ± 4.1	0.944
Deceleration time [ms]	216.8 ± 30.1	207.7 ± 22.2	0.091
IVRT [ms]	113.6 ± 19.7	107.5 ± 17	0.096
E/A ratio	0.9 ± 0.4	1.1 ± 0.3	0.064

Abreviations as in Table 1

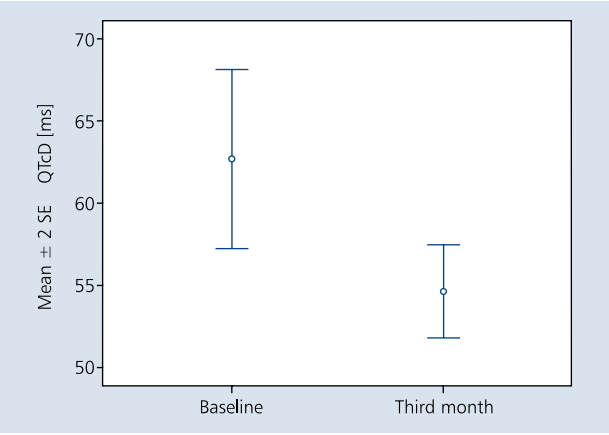

Figure 2. Error bar for pre- and post-treatment correct QT interval dispersion (QTcD) values

the cause of CSF [8]. Patients with CSF had higher adrenalin and noradrenalin levels when compared to patients with normal coronary flow, and TFC was reported to be positively correlated with adrenalin and noradrenalin levels [15]. These findings suggest that adrenergic hyperactivity might have an impact on CSF pathogenesis.

Accordingly, prolonged QT interval is regarded as a marker of imbalanced distribution of sympathetic nervous system activity on the heart, indicating that the autonomic neural tone is an important determinant of QT interval duration and dispersion [16, 17]. Moreover, increased QTD was found to be correlated with increased sympathetic activity and decreased parasympathetic activity in healthy volunteers [18]. Thus, changes in autonomic neural tone may be another reason for the prolonged QT interval and increased QTD.

Drugs acting on the 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 ischaemia. It has been shown that treatment with nebivolol significantly improved angina, exercise capacity, and diastolic and regional systolic functions in patients with CSF [19, 20]. Nebivolol has also been shown to be associated with improved endothelial function in patients with CSF [21]. Furthermore, it has been shown that atenolol reduced QTc and QTcD only in patients with microvascular angina, but not in normal subjects [22]. Therefore, symptomatic improvement induced by atenolol in these patients may be partly related to reduction of abnormally augmented sympathetic tone. Nebivolol is a novel, potent, and selective beta1-adrenergic receptor-blocker with endothelium-dependent nitric oxide-modulating properties, and it might be especially useful for improving coronary flow reserve due to its vasodilating properties on the small and large coronary arteries [4]. The marked vasodilating effect of nebivolol in human coronary micro vessels is well established [4]. The nitric oxide-releasing and vasodilating properties of nebivolol in coronary micro vessels may also underlie its beneficial effects in patients with ischaemic and dilated cardiomyopathies [23].

Recently it has been shown that inflammation may be involved in the development of CSF phenomenon, and treatment of CSF with nebivolol effectively decreased high sensitivity C-reactive protein [24]. Furthermore, recent studies have also demonstrated an inflammatory background of ventricular arrhythmias [25]. Therefore, inhibition of sympathetic activity, increase in coronary flow through vasodilatation of coronary microcirculation with improvement in ischaemia, and positive effects on inflammation may be the possible explanations for improvement of symptoms and shortening of QT interval and dispersion with nebivolol.

Limitations of the study

The 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 QT interval measurements may be criticised.

CONCLUSIONS

Coronary slow may be associated with prolonged QT interval and increased QT dispersion. Nebivolol may be helpful in restoration of QTD in CSF through inhibition of sympathetic activity, improvement in ischaemia through vasodilatation of coronary microcirculation with endothelium dependent nitric oxide release, and positive effects on inflammation.

Conflict of interest: *none declared*

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Wpływ terapii nebiwololem na zmniejszenie ryzyka komorowych zaburzeń rytmu u chorych ze zwolnionym przepływem wieńcowym

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Streszczenie

Wstęp: Zwolniony przepływ wieńcowy (CSF) jest zjawiskiem angiograficzne cechującym się opóźnieniem opacyfikacji tętnic wieńcowych przy braku jakichkolwiek cech choroby wieńcowej w obrazie tętnic nasierdziowych. Dyspersja odstępu QT (QTD) odzwierciedla regionalne zróżnicowanie w zakresie repolaryzacji komór i elektryczną niestabilność miokardium. Doniesienia wskazują, że QTD przybiera większe wartości u chorych z CSF.

Cel: Celem niniejszej pracy była ocena czasu trwania i dyspersji odstępu QT u chorych z CSF oraz wpływu nebiwololu na te parametry.

Metody: Do analizy włączono 67 chorych, u których w badaniu angiograficznym potwierdzono prawidłową budowę tętnic wieńcowych i wykazano CSF, oraz 38 pacjentów, u których zarówno budowa tętnic wieńcowych, jak i przepływ wieńcowy zostały ocenione w angiografii jako prawidłowe. U wszystkich chorych przed rozpoczęciem leczenia nebiwololem i po 3 miesiącach stosowania leku wykonano 12-odprowadzeniowe badanie elektrokardiograficzne i badanie echokardiograficzne.

Wyniki: U chorych z CSF czas trwania odstępów QTcmax i QTcD był istotnie dłuższy niż u osób z grupy kontrolnej (odpowiednio $p = 0,036$ i $p = 0,019$). Długość odstępu QTcD istotnie korelowała z obecnością CSF ($r = 0,496$; $p < 0,001$). Po leczeniu nebiwololem stwierdzono znamienne skrócenie odstępów QTcmax ($p = 0,027$) i QTcD ($p = 0,002$) oraz zmniejszenie ciśnienia tętniczego ($p = 0,001$) i częstości rytmu serca ($p < 0,001$).

Wnioski: Zwolniony przepływ wieńcowy wiąże się ze zwiększoną QTD. Stosowanie nebiwololu spowodowało redukcję zwiększonej QTD u chorych z CSF po 3 miesiącach.

Słowa kluczowe: zwolniony przepływ wieńcowy, nebiwolol, dyspersja odstępu QT

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