Clinical Studies

Efficacy of Nebivolol on Flow-Mediated Dilation in Patients With Slow Coronary Flow

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SUMMARY

Slow coronary flow (SCF) is the phenomenon of slow progression of angiographic contrast in the coronary arteries in the absence of stenosis in the epicardial vessels in some patients presenting with chest pain. There are no definite treatment modalities for patients with SCF. Our aim was to investigate the efficacy of nebivolol in patients with slow coronary flow by monitoring its effects on endothelial function and different markers of inflammation. Forty-two patients (16 females, 26 males; mean age, 55 ± 10) with slow coronary flow (SCF) were included in the study. After baseline assessment, the patients were administered nebivolol 5 mg once daily. After 12 weeks of nebivolol therapy, the biochemical and ultrasonographic examinations were repeated. Chest pain relief was detected in 38 patients after treatment (90%). Systolic and diastolic blood pressure and high sensitive CRP were significantly decreased after nebivolol therapy. Among brachial artery dilation variables that reflect endothelial function, basal resistive index (RI), post-flow mediated dilation RI, and post-nitrate mediated dilation RI were significantly decreased after therapy. Nebivolol is effective at improving endothelial function in patients with SCF. It controls chest pain, decreases CRP, and has favorable effects on brachial artery dilation variables in patients with coronary slow flow. (Int Heart J 2009; 50: 545-553)

Key words: Nebivolol, Coronary slow flow

SLOW coronary flow (SCF) is the phenomenon of slow progression of angiographic contrast in the coronary arteries in the absence of stenosis in the epicardial vessels in some patients presenting with chest pain.[1)] SCF was first described in 1972 and is observed in approximately one percent of the patients undergoing coronary angiography.[2)] Although the pathophysiological mechanisms of SCF remain uncertain, it has recently been reported that coronary endothelial dysfunction plays an important pathogenetic role in patients with SCF.[3)] New evidence has also indicated that inflammation may be involved in the development of SCF phenomenon.[4)]

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Received for publication March 11, 2009.

Revised and accepted May 15, 2009.

There are no definite treatment modalities for patients with SCF. Conventional antianginal therapy is of limited value in the chronic management of these patients.[5,6] Nebivolol, a selective beta 1-receptor blocker that has vasodilating properties attributable to its ability to increase NO bioactivity,[7] has been found to reverse endothelial dysfunction. The aim of the present study was to investigate the efficacy of nebivolol in patients with slow coronary flow by monitoring its effects on endothelial function variables and different markers of inflammation.

Methods

Study population: The present prospective study was conducted in the Department of Cardiology of Düzce Medical School, Düzce University. Forty-two patients (16 females, 26 males; mean age, 55 ± 10 years) with documented SCF in coronary angiography were enrolled. All of the patients had had chest pain and had been referred to our catheterization laboratory for evaluation by coronary angiography. All patients underwent coronary angiography, which showed normal epicardial coronary arteries and left ventricular systolic function. A diagnosis of SCF was made based on Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC). Subjects with any of the following were excluded; a known allergy for nebivolol, coronary artery stenosis, coronary artery spasm, coronary artery ectasia, myocardial dysfunction, history of myocardial infarction, left ventricular dysfunction, left ventricular hypertrophy, atrial fibrillation, myocardial or pericardial disease, systemic disorders, or liver or renal insufficiency. Past medical history and current medications were recorded and a detailed physical examination was performed. Vascular endothelial function was determined noninvasively using a brachial artery flow-mediated dilation (FMD) method. After baseline assessment, the patients received nebivolol 5 mg once daily. All biochemical and ultrasonographic examinations were repeated after 12 weeks of nebivolol therapy. The medications being taken by the patients were not altered during the study.

Ethical information: Every patient signed an informed consent form and the Düzce University ethics committee approved the study.

Definition of slow coronary flow: Coronary flow was quantified by a single independent observer, who was blinded to the clinical details of the individual participants, using the corrected thrombosis in myocardial infarction frame count (TFC) method.[8] The first frame was defined as the frame in which concentrated dye occupies the full width of the proximal coronary artery lumen, touching both borders of the lumen, and indicates forward motion down the artery.[8] The final frame counted is that in which the contrast first reaches the distal predefined landmark branch without the necessity for full opacification.[8] The left

anterior descending artery (LAD) frame counts were corrected by dividing by 1.7 to derive the corrected TFC as described before. All participants with a corrected TFC greater than two SDs from the normal published range for the particular vessel were accepted as having SCF, while those who had corrected TFC that fell within the SD of the published normal range were considered to have normal coronary flow. After assessment of coronary flow in the coronary arteries using the corrected TFC method, for each group the mean corrected TFC, which is the mean value of the frame count in the LAD, circumflex artery, and right coronary artery, was obtained from the participants with SCF and the participants with normal coronary flow.[8)]

Measurement of endothelial function: The vascular endothelial function was determined noninvasively by flow-mediated dilation (FMD), which is the most frequently used assessment method. All subjects were studied in the morning, having abstained from alcohol, caffeine, and food for 12 hours. Optimal imaging of the brachial artery was obtained and a resting scan was recorded using a Doppler ultrasound (Hitachi EUB-6500; Ibaraki, Japan, with a 7.5-MHz probe). All of the ultrasonographic assessments were performed by the same blinded radiologist. A single blinded radiologist performed all of the ultrasonographic assessments. Pretreatment and posttreatment basal values of diameter, resistive index (RI), flow volume, and Vmax (maximum velocity) were obtained for each patient, and recorded in follow-up forms. RI is a commonly used vascular resistance parameter, particularly in tortuous vascular structures in order to minimize the interindividual or intraindividual variability, for its reliability in repeated measurements [RI = (Vmax − end diastolic velocity) Vmax].

After the basal values were obtained, the cuff of the sphygmomanometer was inflated to a pressure of 250 mmHg (with a pressure 50 mmHg above the systolic arterial pressure), and the supply of blood from the brachial artery was stopped and maintained at this position for 5 minutes. The cuff was then rapidly deflated to induce a reactive hyperemia in the brachial artery. Recording continued until 1 minute after deflation of the cuff. The measurements were obtained with the greatest diameter. The % difference between the postreactive hyperemic diameter and the basal diameter was considered as flow-mediated vasodilatation (FMD): [FMD = 100 × (posthyperemic diameter − basal diameter)/basal diameter].

Following the reactive hyperemia, the patient rested for 10 minutes. After administration of sublingual nitroglycerine (NTG) (0.3 mg) and a 5-minute wait for the maximal effect, Doppler measurements were repeated at the initially marked site. The % difference between the postnitrate diameter and the basal diameter was considered as nitrate-mediated dilation (NMD): [NMD = 100 × (postnitrate diameter − basal diameter)/basal diameter].

Reproducibility: The reproducibly of FMD has been extensively studied and is well established.[9-11] It has been shown that with a proper technique it has a reproducibly with an accuracy comparable to that of IVUS.[9] To ensure high reproducibility, however, it is recommended that study designs incorporate a single tester to ensure that subjects are scanned by the same individual each visit.[11] Therefore, in the present study a single blinded radiologist performed all of the ultrasonographic assessments. Intraobserver variability was assessed by performing the measurements under the same basal conditions. Observer variability was defined as the absolute difference between two observations and expressed as the concordance correlation coefficient. The intraobserver concordance correlation coefficient for basal RI was 0.99 [95% CI 0.980 to 0.995]. The coefficients for post FMD RI and post NMD RI were 0.985 [95% CI 0.972 to 0.991] and 0.993 [95% CI 0.986 to 0.995] respectively.

Statistical analyses: The analyses were performed using SPSS 10.0 (SPSS for Windows, Chicago, IL). Data are expressed as the mean ± SD. Before and after treatment comparison analyses were performed using the paired samples *t*-test. *P* values < 0.05 were considered significant.

RESULTS

The general characteristics of the patients are presented in Table I. A comparison of clinical and biochemical variables before and after nebivolol treatment is presented in Table II. Chest pain relief was detected in 38 patients after treatment (90%). Systolic and diastolic blood pressure and high sensitive CRP

Table I. Demographic, Biochemical, and Angiographic Characteristics of the Patients

Age (years)	55 ± 10
Male/female	26/16
Height (cm)	164 ± 17
Weight (kg)	81 ± 14
Waist circumference (cm)	99 ± 16
Hypertension	25
Diabetes	7
Hyperlipidemia	13
Smoker	14
Systolic BP (mmHg)	135 ± 16
Diastolic BP (mmHg)	81 ± 11
Glucose (mg/dL)	108 ± 20
Creatinine (mg/dL)	0.8 ± 0.16
CTFC for LAD	60 ± 12
TFC for Cx	38 ± 10
TFC for RCA	39 ± 11

CTFC indicates corrected TIMI frame count; LAD, left anterior descending artery; Cx, circumflex artery; and RCA, right coronary artery.

Table II. Comparison of Clinical and Biochemical Variables Before and After Nebivolol Treatment

	Before treatment (mean ± SD)	After treatment (mean ± SD)	*P*
Systolic BP (mmHg)	135 ± 16	127 ± 11	0.001
Diastolic BP (mmHg)	81 ± 11	75 ± 9	0.003
Total cholesterol (mg/dL)	169 ± 33	161 ± 38	0.293
LDL cholesterol (mg/dL)	88 ± 33	81 ± 28	0.342
HDL cholesterol (mg/dL)	47 ± 19	43 ± 9	0.289
Triglyceride (mg/dL)	185 ± 87	184 ± 111	0.967
HsCRP (mg/dL)	5.6 ± 4.4	3.9 ± 3.6	0.001
Hemoglobin (g/dL)	13 ± 2	13 ± 2	0.05
WBC	6500 ± 1800	6400 ± 1600	0.642
Platelet (1 × 1000)	199 ± 51	189 ± 38	0.078
Mean platelet volume (fL)	9.6 ± 0.8	9.6 ± 0.9	0.521
Sedimentation (mm)	29 ± 36	29 ± 42	0.963

Table III. Comparison of Variables Related to Flow-Mediated and Nitrate Dependent Brachial Artery Dilatation

	Before treatment (mean ± SD)	After treatment (mean ± SD)	*P*
Basal diameter (mm)	4.18 ± 0.64	4.24 ± 0.52	0.53
Post-FMD diameter (mm)	4.38 ± 0.72	4.46 ± 0.56	0.44
FMD (%)	4.56 ± 10.7	4.66 ± 8	0.57
Post-NMD diameter (mm)	4.55 ± 0.64	4.63 ± 0.55	0.34
NMD (%)	9.4 ± 10.7	9.77 ± 7.2	0.84
Basal RI	0.92 ± 0.07	0.88 ± 0.06	0.014
Post FMD RI	0.90 ± 0.06	0.86 ± 0.06	0.003
Post NMD RI	0.90 ± 0.07	0.86 ± 0.06	0.01
Basal (L/min)	569.1 ± 209.4	563.0 ± 139.7	0.862
Post FMD flow volume (L/min)	635.2 ± 219.6	633.1 ± 203.4	0.96
Post NMD flow volume (L/min)	674.8 ± 194.9	675.1 ± 178.3	0.99

FMD indicates flow-mediated dilatation; NMD, nitrate-mediated dilatation; RI, resistive index; and SD, standard deviation.

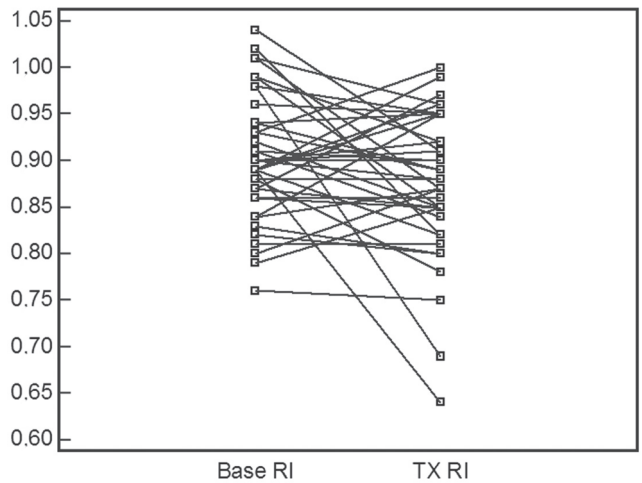

Figure 1. Individual changes in basal resistive index after treatment with nebivolol (Base RI: resistive index at baseline, TX RI: resistive index after treatment).

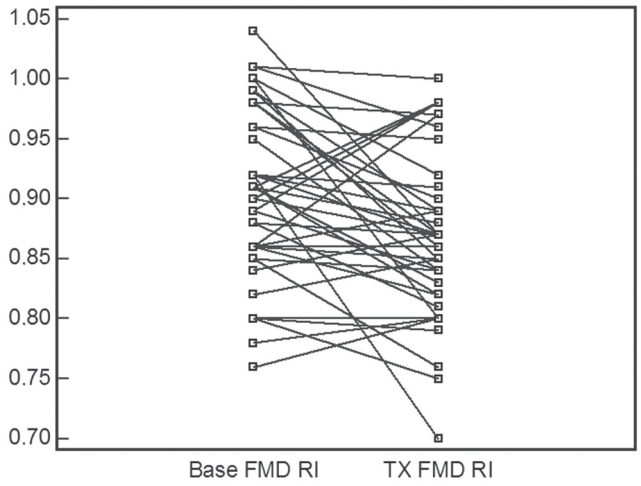

Figure 2. Individual changes in flow mediated resistive index after treatment with nebivolol (Base FMD RI: flow mediated resistive index at baseline, TX FMD RI: flow mediated resistive index after treatment).

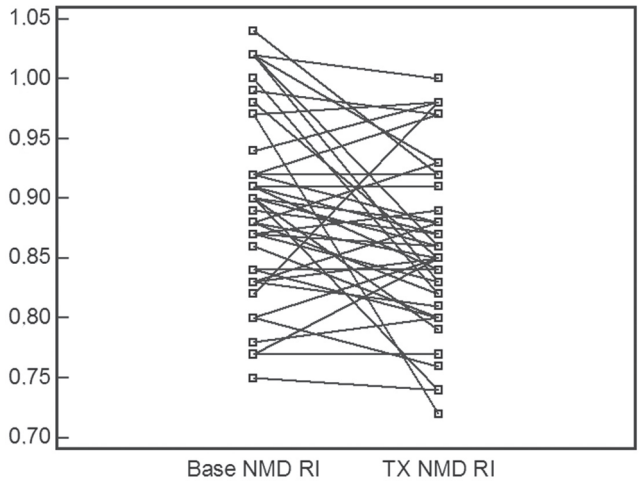

Figure 3. Individual changes in nitrate mediated resistive index after treatment with nebivolol (Base NMD RI: nitrate mediated resistive index at baseline, TX NMD RI: nitrate mediated resistive index after treatment).

were significantly decreased after therapy. Flow-mediated and nitrate dependent brachial artery dilation variables, reflecting endothelial function are shown in Table III. The mean values of brachial artery diameter at baseline, after flow mediated dilation, or after nitrate mediated dilation did not change significantly after treatment. Mean flow volumes did not change as well. However, a statistically significant difference was found in basal RI values after treatment with

nebivolol compared to the pretreatment values (0.92 ± 0.07 versus 0.88 ± 0.06; *P* : 0.014). Similarly, the differences were statistically significant for the post-FMD and post-NMD values (0.90 ± 0.06 versus 0.86 ± 0.06; *P* : 0.003 and 0.90 ± 0.07 versus 0.86 ± 0.06; *P* : 0.01 respectively). Individual changes for basal RI, post-FMD RI and post-NMD RI are demonstrated in Figures 1-3.

Discussion

In this prospective study, we have shown that nebivolol effectively controls chest pain in patients with SCF. Furthermore, it decreased inflammation and had beneficial effects on endothelial function in this patient group.

Nebivolol is a beta1-adrenoreceptor antagonist, which in contrast to other selective beta1-adrenergic receptor antagonists possesses peripheral vasodilator properties specifically related to microcirculation, which are attributed largely to endothelial nitric oxide (NO).[9] The antioxidant properties of nebivolol are regarded as an important mechanism for its endothelium-protective effects since this action contributes to increase NO bioavailability.[12] Endothelial dysfunction is a generalized process affecting both central and peripheral arteries in a parallel manner. Endothelial dysfunction in the brachial artery is related to the presence of endothelial dysfunction in the coronary arteries; while it is a predictor of cardiovascular events in patients with CAD.[13] Endothelial function measured by means of flow-mediated dilatation (FMD) of the brachial artery is also significantly impaired in patients with SCF.[3] It has been suggested that FMD is predominantly due to endothelial release of nitric oxide (NO). There was a strong and inverse relationship between TFC and percentage of FMD in patients with SCF, thereby suggesting that endothelial NO activity is impaired in these patients. Lekakis, *et al* compared the efficacy of nebivolol and atenolol on endothelial function in the brachial artery in patients with coronary artery disease (CAD) and found that nebivolol but not atenolol improved endothelial dysfunction in patients with CAD.[14] Korkmaz, *et al* reported a significant change in the resistive index value following flow-mediated vasodilatation in patients with hypertension after treatment with nebivolol.[15] They speculated that significant change in the RI value in the absence of an increase in FMD can be a more sensitive parameter than FMD in the determination of endothelial dysfunction. Staub, *et al* reported that the RI value of the internal carotid artery is as important as the intima-media thickness of the common carotid artery in predicting cardiovascular mortality and morbidity.[16] The RI value is a hemodynamic parameter and an indirect way of detecting atherosclerosis. Although we have failed to show a significant change in brachial artery diameter or flow after nebivolol treatment, there was a statistically significant reduction in brachial artery resistive index

after therapy, suggesting that nebivolol improves endothelial dysfunction in patients with SCF and RI may show this improvement in the earliest period.

Recently, an inflammation mechanism has also been suggested to be involved in SCF phenomenon. Turhan, *et al* found that the serum ICAM-1, VCAM-1, and E-selectin concentrations of patients with SCF were significantly higher than those of control subjects with normal coronary flow.[4] Lee, *et al* reported that the plasma concentration of CRP and IL-6 concentration were increased, and were positively correlated with TIMI frame count in patients with SCF compared with normal coronary flow subjects. Among the inflammatory markers, a large amount of data has indicated that high-sensitive CRP (hsCRP) is a sensitive marker of underlying systemic inflammation and is increased among men and women at risk for future cardiovascular events.[17] In our study, nebivolol also effectively decreased hsCRP levels after 3 months of therapy. Statins are well known drugs that decrease hsCRP.[18] Caliskan, *et al* showed that atorvastatin improves coronary flow reserve in patients with SCF.[19] These results also indicate an important link between inflammation and SCF.

In conclusion, nebivolol seems to be a good alternative in the treatment of patients with SCF and the present study is the first one investigating its efficacy in patients with SCF. The results are concordant with the pathophysiological clues reflecting the importance of endothelial function and inflammation in slow flow phenomena.

Limitations of the study: The study design is an open label, is not randomized, and does not have a control group. The lack of repeat angiographic measurements is another limitation.

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