The effects of nebivolol on fibrinolytic parameters in mild and moderate hypertensive patients

Bahman Tarighi MD¹, Turhan Kurum MD FESC¹, Muzaffer Demir MD², Sen Nur Azcan BS²

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BACKGROUND: The aim of the present study was to investigate the effects of nebivolol (5 mg daily) on plasma levels of hemostatic and fibrinolytic endothelial function markers in mild or moderate hypertensive patients.

METHODS AND RESULTS: Thirty-five (22 female, 13 male; mean $\pm$ SD 54.7 $\pm$ 11.3 years of age) mild and moderate hypertensive patients were included the study. The mean systolic blood pressure [BP] was 160 mmHg (range 150 mmHg to 165 mmHg) and the mean diastolic BP was 100 mmHg (range 90 mmHg to 100 mmHg). Plasma tissue plasminogen activator antigen (tPA-Ag), plasminogen activator inhibitor type 1 antigen (PAI-1-Ag), PAI-1 activity, tPA-Ag/PAI-1-Ag index, fibrinogen and euglobulin lysis time were determined before and after two months of therapy. tPA-Ag and PAI-Ag levels were measured by ELISA. After this period, treatment with nebivolol (5 mg/day) in all patients was associated with a significant decrease in systolic BP and diastolic BP ($P < 0.001$ for each), heart rate ($P < 0.01$), fibrinogen ($P < 0.005$) and euglobulin lysis time ($P < 0.01$). The tPA-Ag and tPA-Ag/PAI-1-Ag index levels were increased significantly ($P < 0.001$ for each) in all patients, but the PAI-1-Ag ($P > 0.05$) and PAI-1 activity ($P > 0.05$) did not show significant change. In the present study, there was no correlation between decreases in arterial BP and decreases in fibrinolytic parameters ($P > 0.05$), but there was a positive, statistically significant correlation between fibrinogen and body mass index ($P < 0.001$).

CONCLUSIONS: The results indicated that, compared with no treatment, a two-month treatment trial with nebivolol was associated with a more favourable modification of hemostatic and fibrinolytic status in addition to antihypertensive effects.

Key Words: Fibrinolytic system; Hypertension; Nebivolol

The vascular endothelium is a metabolically active paracrine organ. It regulates thrombogenicity, vascular tone, leukocyte adhesion, and platelet and smooth muscle function (1). While normal endothelium is in a nonthrombotic state, deterioration of the vascular endothelium results in the synthesis and release of procoagulant and anticoagulant substances from the disrupted vascular endothelium (2,3).

One of the major risk factors for atherosclerosis is hypertension. Most of the studies on hypertensive subjects have shown that hypertension is associated with cardiovascular abnormalities marked by oxidative stress induction, endothelial dysfunction and derangement of the normal hemostatic and fibrinolytic balance (4-6). Optimal blood pressure (BP) control

Les effets du nébivolol sur les paramètres relatifs à la fibrinolyse dans l'hypertension artérielle légère ou modérée

CONTEXTE : La présente étude avait pour but de déterminer les effets du nébivolol (5 mg par jour) sur la concentration sanguine de marqueurs endothéliaux de l'hémostase et de la fibrinolyse chez des patients atteints d'hypertension artérielle (HTA) légère ou modérée.

MÉTHODE ET RÉSULTATS : Trente-cinq sujets (22 femmes et 13 hommes; âge moyen $\pm$ écart-type : 54,7 $\pm$ 11,3) atteints d'HTA légère ou modérée ont participé à l'étude. La pression artérielle systolique (PAS) moyenne était de 160 mm Hg (150-165 mm Hg) et la pression artérielle diastolique (PAD) moyenne, de 100 mm Hg (90-100 mm Hg). Il y a eu mesure des taux d'antigènes de l'activateur tissulaire du plasminogène (A-ATP) et d'antigènes de l'inhibiteur de l'activateur du plasminogène de type 1 (A-IAP-1), du degré d'activité de l'IAP-1, de l'indice A-ATP/A-IAP-1, de la concentration de fibrinogène et du temps de lyse de l'euglobuline avant et après un traitement d'une durée de deux mois. Les taux d'A-ATP et d'A-IAP ont été mesurés selon la méthode ELISA. Après la période d'essai, le traitement au nébivolol (5 mg par jour) a été associé, chez tous les patients, à une diminution significative de la PAS ($p < 0,001$), de la PAD ($p < 0,001$), de la fréquence cardiaque ($p < 0,01$), de la concentration de fibrinogène ($p < 0,005$) et du temps de lyse de l'euglobuline ($p < 0,01$). Une augmentation significative du taux d'A-ATP et de l'indice A-ATP/A-IAP-1 ($p < 0,001$ chacun) a été observée chez tous les sujets, mais le taux d'A-IAP-1 ($p > 0,05$) et l'activité de l'IAP-1 ($p > 0,05$) n'ont pas montré de variation importante. Aucune corrélation n'a été établie entre la diminution de la pression artérielle et la diminution des paramètres relatifs à la fibrinolyse ($p > 0,05$) dans la présente étude, mais une possible corrélation statistiquement significative a été observée entre la concentration de fibrinogène et l'indice de masse corporelle ($p < 0,001$).

CONCLUSIONS : Outre ses effets antihypertenseurs, l'essai de traitement au nébivolol, d'une durée de deux mois, a été associé à une modification favorable des marqueurs de l'hémostase et de la fibrinolyse par rapport à l'absence de traitement.

in hypertensive patients does not always lead to restoration of normal endothelial function, and drugs with comparable BP-lowering effects do not counteract hypertension-induced endothelial dysfunction to a similar degree (7).

Nebivolol is a selective beta₁-adrenergic receptor antagonist that relaxes vascular smooth muscle by nitric oxide- and cyclic GMP-dependent mechanisms (8). Nebivolol reverses endothelial dysfunction in essential hypertension (9). The direct effect of nebivolol on endothelial function as assessed by the measurement of plasminogen activator inhibitor type 1 antigen (PAI-1-Ag), PAI-1 activity, tissue plasminogen activator antigen (tPA-Ag), tPA-Ag/PAI-1-Ag index, fibrinogen and euglobulin lysis time (ELT) has not been reported. The

¹Department of Cardiology; ²Department of Haematology, Trakya University School of Medicine, Edirne, Turkey

Correspondence: Dr Turhan Kurum, Department of Cardiology, Trakya University School of Medicine, Gullapoglu Yerleskesi, 22030 Edirne, Turkey. Telephone 90-535-396-1964, fax 90-284-235-7652, e-mail atkurum@trakya.edu.tr

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TABLE 1
Demographic data of study subjects before and after treatment

Characteristic	Baseline	After 2 months	P
Age, years (mean ± SD)	54.7±11.3		
Sex (male/female)	13/22		
Smokers, %	14		
Body mass index, kg/m ² (mean ± SD)	29.4±5.4	28.7±5.2	NS
High-density lipoprotein cholesterol, mg/dL (mean ± SD)	42.8±7.9	41.4±8.1	NS
Triglycerides, mg/dL (mean ± SD)	133.6±47	138±52	NS
Fasting blood sugar, mg/dL (mean ± SD)	104±11	102±10	NS

NS Not significant

aim of the present study was to investigate the effects of nebivolol on plasma levels of hemostatic and fibrinolytic markers in mild and moderate hypertensive patients.

METHODS

Patients and study protocol

A total of 37 patients with uncomplicated essential hypertension and no contraindications to beta-blockers were recruited. Informed consent was obtained. Full clinical and laboratory evaluation was carried out to exclude patients with secondary hypertension. Hypertension was diagnosed when patient systolic BP was 140 mmHg or higher, and/or diastolic BP was 90 mmHg or higher on at least three occasions. Clinical evaluation consisted of a routine physical examination and three BP measurements taken 10 min after arriving at the clinic, using the same arm and positioning during each assessment. A sphygmomanometer was used to measure systolic and diastolic BP (Korotkoff phases I and V). A physical examination and electrocardiogram were conducted for each patient. Heart rate was measured using a standard electrocardiogram under the same conditions by calculating the average of 10 R-R intervals. Patients were weighed wearing only light clothing, without shoes, and height was measured. Body mass index (BMI) was calculated as weight divided by the square of height. Exclusion criteria included signs or symptoms of heart failure, coronary artery disease, valvular heart disease, atrial fibrillation or any other arrhythmias, atrioventricular conduction abnormalities, sinus bradycardia (less than 50 beats/min), history of stroke or transient ischemic attack, chronic obstructive pulmonary disease, hepatic insufficiency and severe obesity (BMI higher than 36 kg/m²). Each patient underwent routine laboratory examinations of serum and urine, obtained in a fasting state. Plasma triglyceride, high- and low-density lipoprotein, and total cholesterol levels were analyzed by a standard technique. Patients were prescribed a beta-blocker – nebivolol 5 mg/day (10,11). If systolic BP remained at 140 mmHg or higher, or if diastolic BP remained at 90 mmHg or higher after four weeks of treatment, an angiotensin-converting enzyme inhibitor was added to the regimen and the subject was excluded from the study. Thereafter, patients were examined in an outpatient clinic at baseline and two, four, six and eight weeks after the start of nebivolol monotherapy.

Laboratory measurements

Measurements of fibrinolytic and hemostatic variables, and routine laboratory examinations of serum and urine were performed in a fasting state between 08:00 and 11:00, after 15 min of rest in

the supine position, and were repeated after eight weeks of treatment with nebivolol to evaluate the short-term effects on fibrinolysis and the hemostatic state. Plasma triglyceride, total cholesterol, and high-density and low-density cholesterol lipoprotein levels were measured enzymatically with an autoanalyzer (Synchron LX 20, Beckman Coulter, USA) using the spectrophotometric method.

The levels of tPA-Ag (IMUBIND tPA ELISA, American Diagnostica Inc, USA; normal range in healthy men is less than 9 ng/mL) and PAI-1-Ag (IMUBIND PAI-1 ELISA, American Diagnostica Inc; normal range in healthy men is 2 ng/mL to 47 ng/mL, with a lower limit of detection of 0.5 U/mL) were determined in citrated samples by ELISA. PAI-1 activity was assessed by commercially available kits using the spectrophotometric method (Spectrolyse [pL] PAI, American Diagnostica Inc; lower limits of detection for healthy men and women 20 to 49 years of age are 8.2±6.2 ng/dL and 7.0±5.9 ng/dL, respectively, and lower limit of detection for healthy men and women 50 to 59 years of age is 12.8±12.1 ng/dL). Plasma fibrinogen levels were determined with a one-stage clotting assay kit (Fibri-Prest 2, Diagnostica Stago, France). The tPA-Ag/PAI-1-Ag index was calculated, and ELT was determined by classical methods.

Statistical analysis

Classical statistical analysis was performed to examine differences in the distribution of variables. Numerical variables were tested for normal distribution by the Kolmogorov-Smirnov test. Comparison among groups was made by a paired sample *t* test for normally distributed data and a nonparametric Wilcoxon signed rank test for non-normally distributed data. Measurements of the association between two variables were made by Pearson correlation analysis for normally distributed data or Spearman correlation analysis for non-normally distributed data. Normally distributed variables were shown as mean ± SD and non-normally distributed variables were shown as median (25% and 75% percentiles). In the present study, data were analyzed using the Minitab packet program (release 13, Minitab Inc, USA).

RESULTS

Of the initial 37 patients with hypertension who were treated with nebivolol, 35 patients continued to receive nebivolol 5 mg/day alone and two patients were excluded from further study because of poor BP control (*n*=1) or a personal reason (*n*=1). Thirty-five ambulatory patients with borderline to mild hypertension (22 female, 13 male, mean age ± SD 54.7±11.3 years) who visited the Trakya University School of Medicine (Edirne, Turkey) from January 2004 to February 2005 were selected. Patient characteristics are summarized in Table 1.

After two months of treatment, systolic and diastolic BP decreased from 160 mmHg (range 150 mmHg to 165 mmHg) to 130 mmHg (range 130 mmHg to 140 mmHg) (*P*<0.001), and from 100 mmHg (range 90 mmHg to 100 mmHg) to 80 mmHg (range 70 mmHg to 90 mmHg) (*P*<0.001), respectively. There was a significant reduction in heart rate after nebivolol treatment (8.8 beats/min in the mean two-month period, *P*<0.01) (Table 2). Nebivolol decreased fibrinogen from 292.34±40.36 mg/dL to 276.68±46.15 mg/dL (*P*<0.01), increased tPA-Ag from 9.28 ng/dL (7.97 ng/dL to 10.17 ng/dL) to 12.89 ng/dL (10.33 ng/dL to 13.99 ng/dL, *P*<0.001), reduced ELT from 114.57±15.97 min to 106.80±11.28 min (*P*<0.01), and increased the tPA-Ag/PAI-1-Ag index from 0.10 (range 0.08 to 0.11) to 0.12 (range 0.10 to 0.13) (*P*<0.001) (Table 3). There

TABLE 2
Systolic and diastolic blood pressure, and heart rate before and after treatment

Variable	Baseline	After 2 months	P
Systolic blood pressure, mmHg	160 (150–165)	130 (130–140)	<0.001
Diastolic blood pressure, mmHg	100 (90–100)	80 (70–90)	<0.001
Heart rate, beats/min	78 (70–92)	70 (64–80)	<0.01

Values are given as median (interquartile range)

were no differences in PAI-1-Ag (90.27 ± 22.68 ng/dL at baseline versus 87.51 ± 22.98 ng/dL after treatment, $P=0.491$) and PAI-1 activity (21.14 ± 4.67 ng/dL at baseline versus 22.99 ± 5.68 ng/dL after treatment, $P=0.234$). There were no significant differences between baseline and post-treatment BMI measurements and lipid parameters. There were positive significant correlations between BMI and fibrinogen levels ($r=0.525$, $P<0.01$) and between post-treatment diastolic BP and post-treatment PAI-1-Ag ($r=0.463$, $P<0.01$).

DISCUSSION

Vascular endothelial dysfunction may promote atherosclerosis. Therefore, an antihypertensive agent that reverses endothelial dysfunction and lowers BP may improve the prognosis of patients with hypertension. Nebivolol, a third-generation β_1 -selective and lipophilic β -blocker without sympathomimetic activity, combines β -blocking activity with nitric oxide-mediated vasodilatory properties (8,9). Nebivolol augments endothelium-dependent vasodilation in normotensive and hypertensive subjects (8,9). The antihypertensive activity of β -blockers increases during the first six to eight weeks of treatment (12). In hypertensive patients, nebivolol 5 mg/day has been shown to be an effective antihypertensive dose (10,11). In our study, we also used nebivolol (5 mg/day) for two months. A greater reduction, compared with no treatment, in BP was obtained after two months of nebivolol treatment.

Hypertension can promote a prothrombotic/fibrinolytic balance partly because of impaired fibrinolysis due to abnormal plasma levels of tPA, PAI-1, fibrinogen and other parameters in endothelial dysfunction (13,14). These levels are significantly higher in patients with hypertension (15,16). Recent reports (17–19) suggest that many of these markers are playing important roles in precipitating future vascular events, both cardiovascular disease and stroke (17). The substance PAI-1 is a physiological inhibitor of fibrinolysis, because it reduces clot lysis by preventing the tPA from acting on its substrate, plasminogen, thus providing links to thrombosis. Elevated serum levels of PAI-1 are considered to be a marker of endothelial dysfunction and predict future cardiovascular risk (18,19). Enhanced fibrinolysis may be detected by the ELT, a global test for fibrinolysis. ELT is largely dependent on the activity of both tPA and PAI. Short lysis times are indicative of increased fibrinolysis.

Conflicting results have been reported in smaller studies (20–26) regarding the effects of β -blockers on fibrinolysis. Winther (20) and Winther and Hedman (21) investigated the cardioselective agent metoprolol and the noncardioselective agent propranolol in two small hypertensive groups. The authors reported that propranolol (80 mg twice daily) significantly prolonged ELT and decreased tPA activity, while metoprolol (100 mg twice daily) had no effect. Similarly, in 10 hypertensive patients given the noncardioselective agent

TABLE 3
Fibrinolytic and hemostatic variables before and after treatment

Variable	Baseline	After 2 months	P
tPA-Ag, ng/dL	9.28 (7.97–10.17)	12.89 (10.33–13.99)	<0.001
PAI-1-Ag, ng/dL	90.27 $\pm$ 22.68	87.51 $\pm$ 22.98	NS
PAI-1 Act, ng/dL	21.14 $\pm$ 4.67	22.99 $\pm$ 5.68	NS
tPA-Ag/PAI-1-Ag index	0.10 (0.08–0.11)	0.12 (0.10–0.13)	<0.001
Fibrinogen, mg/dL	292.34 $\pm$ 40.36	276.68 $\pm$ 46.15	<0.01
Euglobulin lysis time, min	114.57 $\pm$ 15.97	106.80 $\pm$ 11.28	<0.01

Values are given as mean $\pm$ SD or median (interquartile range). NS Not significant; PAI-1 Act Plasminogen activator inhibitor type 1 activity; PAI-1-Ag PAI-1 antigen; tPA-Ag Tissue plasminogen activator antigen

propranolol (80 mg twice daily), ELT was prolonged and tPA activity was reduced (22). In another study (23), baseline PAI-1-Ag and PAI-1 activity, and tPA-Ag and tPA-Ag activity were unaffected by 200 mg metoprolol once daily over seven days in healthy volunteers. Teger-Nilsson et al (24) found that metoprolol, in doses of 100 mg/day to 200 mg/day over four to 21 days, decreased PAI-1 activity in healthy volunteers and patients with mild hypertension. Another noncardioselective agent, nadolol, given over seven days to 15 patients with mild hypertension did not have an effect on ELT, tPA-Ag and PAI-1-Ag during rest, as well as after isometric exercise and mental stress (25). The cardioselective agent atenolol was studied in patients with mild to moderate hypertension. Similar to the results obtained with metoprolol, administration of up to 100 mg per day of atenolol over six months did not change levels of tPA-Ag and PAI-1-Ag or PAI-1 activity (26). In another study (1), 550 consecutive patients with uncomplicated hypertension were treated with celiprolol, carvedilol or nebivolol monotherapy. Plasma levels of fibrinogen and homocysteine, and serum levels of PAI-1 decreased in the celiprolol- and nebivolol-treated groups. In the carvedilol group, these parameters also decreased, except PAI-1 levels.

Recent studies (27,28) indicate that third-generation β -blockers, especially nebivolol, reverse endothelial dysfunction. There are accumulating data suggesting that nebivolol benefits endothelial function by enhancing nitric oxide bioavailability, an effect not shared by other drugs in the third-generation class of β -blockers (8). In our study, BP control with nebivolol was followed by increases in tPA and the tPA-Ag/PAI-1-Ag index, and decreases in ELT, but not both PAI-1-Ag and PAI-1 activity.

Fibrinogen plays an essential role in the coagulation pathway and is a marker of inflammation. It strongly affects hemostasis, blood rheology, platelet aggregation and endothelial function (29). Most studies on hypertensive subjects have resulted in elevated fibrinogen levels compared with normotensive controls (30–32). Fibrinogen is also considered to be a predictor of cardiovascular events, that is, coronary artery disease and stroke (17,33). Previous studies (34–39) examining the influence of therapeutic intervention on fibrinogen plasma levels have produced conflicting results. Sufficient data do not exist to determine whether decreases in fibrinogen levels are associated with unique properties of the drugs used or whether they are directly related to BP reduction. In our study, statistically significant decreases in fibrinogen levels were observed after two months of treatment. The metabolic profile of our study group did not influence the observed fibrinogen values. Makris et al (15) studied the effects of atenolol and irbesartan (an angiotensin II

type 1 receptor antagonist) on plasma levels of hemostatic and fibrinolytic and endothelial function markers in a cohort of previously untreated hypertensive patients. They reported that the reduction of fibrinogen and PAI-1 was significantly greater in the irbesartan group than the atenolol group.

Different studies (41,42) that compared fibrinogen levels in both obese and nonobese subjects reported significantly higher fibrinogen levels in the obese subjects. Some of these reports found a significant correlation between BMI and fibrinogen (41,42). In our study, baseline fibrinogen values were within the normal range. We also found a positive correlation between BMI and fibrinogen levels. Moreover, Tomiyama et al (43) observed that fibrinogen correlated significantly with age, but there was no correlation between fibrinogen, age and other parameters analyzed in our study.

Limitation

The study period may have been too short for nebivolol administration to effect significant decreases in PAI-1-Ag and PAI-1 activation levels.

CONCLUSIONS

The present study demonstrated the beneficial effects of nebivolol on fibrinolytic abnormalities and on the procoagulative state. This effect is independent of BP-lowering effects of the drug in patients who are in the early stages of hypertension. Our results also indicate that the treatment of endothelial dysfunction should be considered in the management of patients with hypertension. These important effects may be more beneficial in the prevention of cardiovascular complications.

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