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The Impact of Third-Generation Beta-Blocker Antihypertensive Treatment on Endothelial Function and the Prothrombotic State

Effects of Smoking

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Background: The significance of β-blockers in the treatment of cardiovascular diseases is well established. The effect of vasodilating β-blockers on endothelial function and prothrombotic state has not been investigated.

Methods: The study comprised 550 consecutive patients with uncomplicated essential hypertension. They were treated with celiprolol, carvedilol or nebivolol monotherapy (171, 179, and 200 patients, respectively), achieving comparable blood pressure reduction. Plasma levels of fibrinogen and homocystine and serum levels of plasminogen activator inhibitor–1 (PAI-1) were obtained before and 6 months after initiation of treatment.

Results: The three drugs differentiated in regard to homocystine ($P < .00001$) and fibrinogen level changes ($P = .00003$), but not (P = NS) in PAI-1 change. In smokers, differentiation was found in all three parameters ($P = .0002$, $P = .001$, and $P = .006$ for fibrinogen, PAI-1, and homocystine, respectively), but in nonsmokers differentiation was found only in homocystine change ($P = .00003$). In smokers, fibrinogen, PAI-1, and homocystine were reduced more ($P = .002$, $P = .0009$, and $P < .0001$, respectively) than in nonsmokers in the whole study cohort. The effect of nebivolol was more prominent in smokers than nonsmokers in reducing all three parameters ($P = .0001$, .003, and .003, respectively), whereas in celiprolol and carvedilol-treated groups, differentiation between smokers and nonsmokers was significant ($P = .00003$ and .01, respectively) only in homocystine level change.

Conclusions: In hypertensive smokers, nebivolol resulted in a significant decrease of plasma PAI-1, fibrinogen and homocystine. Celiprolol also significantly affected these parameters but to a lesser degree, whereas carvedilol had no significant favorable action. In nonsmokers, homocystine was reduced significantly by nebivolol. We conclude that smoking status should be a determinant of antihypertensive treatment choice. Am J Hypertens 2004;17:582–589 © 2004 American Journal of Hypertension, Ltd.

Key Words: Hypertension, third-generation beta blockers, endothelial function, prothrombotic state.

Arterial hypertension (AH) comprises a major risk factor for atherosclerotic disease such as coronary artery disease and stroke. The pathophysiologic mechanisms by which arterial hypertension exerts its deleterious effects on the cardiovascular system have not been fully elucidated.

The significance of β-blockers in the treatment of cardiovascular diseases including coronary artery disease, arterial hypertension, and heart failure is well documented. Emerging evidence suggests that the so-called third-generation, vasodilating β-blockers are characterized by additional beneficial effects on the vasculature, in addition to their β-blocking properties.[1] Recent studies indicate that third-generation β-blockers reverse endothelial dysfunction and oppose oxidant stress in the vascular system.[2,3] Especially for nebivolol, accumulating evidence suggests that this compound has a unique action profile that is not shared by the other drugs in this group and that results in beneficial effects on endothelial function, enhancing nitric oxide (NO) bioavailability.[4]

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Endothelial dysfunction is currently recognized as a feature of patients with arterial hypertension and is also shared by other cardiovascular risk factors.[5] Vascular endothelium is a metabolically active paracrine organ with a pivotal role in the regulation of thrombogenicity, vascular tone, leukocyte adhesion, and platelet and smooth muscle function. Endothelial impairment of the coronary and peripheral vessels has been associated with increased incidence of cardiovascular events[6] and is interrelated with a pathologic prothrombotic/fibrinolytic balance. Moreover, optimal blood pressure (BP) control in hypertensive patients does not always lead to restoration of normal endothelial function, and drugs with comparable BP-lowering effects do not counteract the hypertension-induced endothelial dysfunction in the same degree.[7]

Despite the fact that blood vessels in hypertensive individuals are exposed to high BP, surprisingly the complications of hypertension are mainly thrombotic rather than hemorrhagic in nature. The prothrombotic and hypercoagulable potential that accompanies AH[8] is currently under thorough investigation. Moreover, the role of several biochemical parameters coupled with the endothelial fibrinolytic mechanisms and their putative implication in the progression of atherosclerotic disease is continuously underscored.

Among these substances, fibrinogen, plasminogen activator inhibitor–1 (PAI-1) and homocystine (Hcy) are of potential interest. Their levels are significantly higher in AH.[9,10] Blood levels of these parameters increase when normal endothelial function is impaired, although their relation to increased cardiovascular risk is now unquestionable.

The direct effect of antihypertensive treatment with third-generation vasodilating β-blockers on endothelial function as assessed by the measurement of PA1-1, fibrinogen, and Hcy has not been investigated. We hypothesized that such drugs could possibly have beneficial and perhaps inhomogeneous effects on these parameters. Moreover, because cigarette smoking is a habit that is highly prevalent among hypertensive individuals and that is also related to endothelial dysfunction, high prothrombotic potential, and thus increased risk of cardiovascular disease,[11,12] the differential effects of third-generation vasodilating β-blockers on the parameters of interest according to smoking status were also examined.

Methods

A total of 853 consecutive patients with uncomplicated essential hypertension and no contraindication to β-blockers were recruited, after informed consent was obtained. Full clinical and laboratory evaluation was carried out to exclude patients with secondary hypertension. Patients with acute or chronic inflammatory disease, endocrinopathy, diabetes mellitus, renal insufficiency (creatinine >1.5 mg/dL), chronic obstructive or other lung disease, malignancy, history of cerebrovascular event, heart failure, coronary artery disease, sinus bradycardia (<55 beats/min) or tachycardia (>100 beats/min), ventricular arrhythmia or atrioventricular conduction disturbance, severe obesity (body mass index [BMI] >36 kg/m^2), poor compliance, or drug-related side effects were also excluded. After a 2-week washout period, BP was determined in three different visits 1 week apart. At every visit, systolic BP and diastolic BP in the sitting position were measured. A mercury sphygmomanometer was used, with three readings 1 min apart, and mean values were calculated.

All patients included in the final cohort were responders to β-blocker monotherapy (diastolic BP <90 mm Hg or drop in diastolic BP of >10 mm Hg). To achieve goal BP, β-blocker dose was doubled in 30% of patients, and in 20% of patients low-dose hydrochlorothiazide (HCTZ, 12.5 mg once daily) was added as well. Patients who needed the addition of another antihypertensive agent for BP control were excluded from the study.

Thus, the study finally comprised 550 patients (302 men and 248 women, mean age 55.0 years, 32.9% smokers), who were randomized to 6 months of antihypertensive treatment with β-blockers: celiprolol 200 mg, carvedilol 12.5 mg, or nebivolol 5 mg once daily.

Characteristics of patients in each β-blocker group are listed in Table 1. Age, body mass index (BMI), and waist-to-hip (W/H) ratio were similar in the three groups (P = NS). Women were represented to similar degrees in the carvedilol and nebivolol group, whereas they were the majority in the celiprolol group. The percentage of patients receiving antihypertensive drugs before entering the study was higher in the celiprolol-treated group, but this was not statistically significant. The rest of the patients were newly diagnosed with hypertension or were on lifestyle modification for hypertension at the time of their recruitment. Smoking and impaired glucose tolerence (serum glucose 126 to 200 mg/dL 2 h after a 75-g glucose load) incidence was higher in the celiprolol group. The overall percentage of obese patients (BMI >27) was higher in carvedilol group, although patients with central obesity were fewer in that group. Nonetheless, the differences were not significant.

Fibrinogen, PAI-1, and Hcy levels were measured before and 6 months after treatment, after an overnight fast. Plasma fibrinogen was measured by nephelometry method (BN II, Dade Behring, Marburg, Germany; lower limit of detection 30 mg/dL, intra- and inter-coefficient of variation [CV] 2.7% and 2.6%, respectively), plasma Hcy by micro-ELISA (AXSYM, Abbott, Oslo, Norway; lower limit of detection 0.80 μmol/L, intra- and inter-CV 2.1% and 2.2%, respectively), whereas for serum PAI-1 activity, chromogenic method (BCT, Dade Behring; lower limit of detection 0.5 IU/mL, intra- and inter-CV <4% and 3% to 6%, respectively) was used.

Mean value and standard deviation of variables, at baseline and after therapy, were calculated and compared using the paired Student t test. Comparison among drug groups and between smokers and nonsmokers was per-

Table 1. Patient characteristics

	Celiprolol	Carvedilol	Nebivolol
n (M/F)	171 (81/90)	179 (106/73)	200 (115/85)
Age (y)	55.1 ± 10.2	55.1 ± 12.5	54.6 ± 12.6
Previous drug use (%)*	57.3	49.7	51
Systolic BP (mm Hg)	162.7 ± 9.9	162.8 ± 13.8	163.3 ± 13.1
Diastolic BP (mm Hg)	103.4 ± 5.0	102.6 ± 6.8	102.4 ± 6.1
Body mass index (kg/m^2)	27.8 ± 3.8	28.0 ± 4.0	28.1 ± 3.6
Waist/hip ratio	0.848 ± 0.074	0.855 ± 0.067	0.863 ± 0.059
IGT (%)	17.5	15.6	15.5
Diabetes mellitus (%)	3.5	4.5	6.0
Obesity (%)†	53.8	58.7	55.5
High W/H ratio (%)‡	35.7	29.1	42.5
Smokers (%)	39.2	29.6	30.5

* Patients on antihypertensive treatment before entering the study.
† Body mass index >27.
‡ W/H = waist/hip ratio >0.9 in men, >0.8 in women.
BP = blood pressure; IGT = impaired glucose tolerance; M/F = males/females.

formed after analysis of variance. A value of $P < .05$ was considered to be significant. Statistical analysis was done using the SPSS package for Windows, version 10.0 (SPSS, Chicago, IL).

Results

BP Response

At baseline, BP was comparable among the three groups (P = NS; Table 1). After 6 months of treatment, BP decreased in all three groups to the same degree (P = NS). Systolic and diastolic BP decreased from 163 ± 10/103 ± 5 to 127 ± 9/84 ± 3 mm Hg, from 163 ± 14/103 ± 7 to 127 ± 9/83 ± 4 mm Hg and from 163 ± 13/102 ± 6 to 126 ± 9/83 ± 4 mm Hg in the celiprolol-, carvedilol-, and nebivolol-treated groups, respectively (all $P < .001$).

Whole Study Cohort

In the whole population, the three drugs differed in regard to Hcy ($F = 14.1$, $P < .00001$) and fibrinogen level changes ($F = 10.75$, $P = .00003$), but not in PAI-1 change ($F = 2.45$, $P = .09$; Table 2). Plasma homocystine levels decreased from 11.93 to 11.71 μmol/L ($P = .01$) in the celiprolol group, from 11.39 to 11.26 μmol/L ($P = .3$) in the carvedilol group, and from 11.98 to 11.07 μmol/L ($P < .00001$) in the nebivolol group. Plasma fibrinogen level changes were from 309 to 299 mg/dL ($P = .001$), from 304 to 309 mg/dL ($P = .2$), and from 316 to 304 mg/dL ($P = .0002$) in the respective groups. The PAI-1 values changed from 2.79 to 2.65 IU/mL ($P = .003$), from 2.71 to 2.73 IU/mL ($P = .3$) and from 2.94 to 2.79 IU/mL ($P < .00001$) in the celiprolol, carvedilol, and nebivolol groups, respectively.

Smokers

In smokers, drug effects differed in all three parameters measured ($P = .0002$, $P = .001$ and $P = .006$ for fibrinogen, PAI-1, and Hcy, respectively; Table 2). Nebivolol was the drug that decreased fibrinogen plasma levels the most, by 8.6% (from 319 to 291 mg/dL $P < .00001$). Celiprolol decreased fibrinogen by 4.9% (from 321 to 304 mg/dL, $P = .005$) while carvedilol had no effect (from 318 to 315 mg/dL, $P = .4$). Similarly, nebivolol reduced PAI-1 activity by 9.4% (from 2.94 to 2.68 IU/mL, $P < .00001$) and celiprolol by 5.4% (from 3.17 to 3.00 IU/mL, $P = .0003$), whereas carvedilol had no effect (from 2.86 to 2.83 IU/mL, $P = .4$). All three drugs reduced Hcy plasma levels in smokers, by 15.2% (from 12.92 to 11.30 μmol/L $P < .00001$), 6.7% (from 12.96 to 12.30 μmol/L, $P = .00001$), and 6.4% (from 12.74 to 12.04 μmol/L, $P = .04$) for nebivolol, celiprolol, and carvedilol, respectively.

Nonsmokers

In nonsmokers, difference in drug effects was found in relation to Hcy change ($F = 10.7$, $P = .00003$); celiprolol and carvedilol had no effect on plasma levels ($P = .3$ for both), whereas nebivolol decreased Hcy by 5.7% (from 11.57 to 10.96 μmol/L, $P < .00004$). Minor ($P = .04$) or no ($P = .49$) differences were found for fibrinogen and PAI-1 values, respectively (Table 2).

Smokers Versus Nonsmokers

Baseline values of fibrinogen, PAI-1, and Hcy were higher in smokers than in nonsmokers ($P < .0001$; Table 3). Irrespectively of drug treatment, all three parameters were reduced more ($P = .002$, $P = .0009$, and $P < .00001$, respectively) in smokers than in nonsmokers. The decrease was significant for all three parameters in smokers ($P = .00008$, $P < .00001$, and $P < .00001$, respectively); in nonsmokers such a reduction was not found for fibrinogen ($P = .45$) or was weakly significant for PAI-1 and Hcy ($P = .04$ and 0.03).

The effect of nebivolol was more prominent in smokers than nonsmokers in reducing all three parameters ($P =$

Table 2. Pre- and post-treatment values and percentage changes (%Δ) of fibrinogen (in mg/dL), PAI-1 (in IU/mL), and homocystine (in μmol/L) levels according to treatment and smoking status

	Celiprolol				Carvedilol				Nebivolol				*P* (among groups)
	Pre	**Post**	**%Δ**		**Pre**	**Post**	**%Δ**		**Pre**	**Post**	**%Δ**		
Nonsmokers		**(*n* = 104)**		***P***		**(*n* = 126)**		***P***		**(*n* = 139)**		***P***	
Fibrinogen	302	295	−1.7 ± 14.6	.11	298	307	4.9 ± 22.9	.1	315	309	−0.5 ± 15.6	.1	.04
PAI-1	2.54	2.42	−0.8 ± 29.3	.08	2.64	2.69	3.7 ± 22.1	.3	2.94	2.83	0.9 ± 33.7	.006	.49
Hcy	11.26	11.32	0.4 ± 8.5	.3	10.82	10.93	0.9 ± 14.2	.3	11.57	10.96	−5.7 ± 14.3	.00004	.00003
Smokers		**(*n* = 67)**		***P***		**(*n* = 53)**		***P***		**(*n* = 61)**		***P***	
Fibrinogen	321	304	−4.9 ± 9.1	.005	318	315	2.8 ± 22.3	.4	319	291	−8.6 ± 11.2	< .00001	.0002
PAI-1	3.17	3.00	−5.4 ± 9.4	.0003	2.86	2.83	0.1 ± 17.7	.4	2.94	2.68	−9.4 ± 12.9	< .00001	.001
Hcy	12.96	12.30	−6.7 ± 10.9	.00001	12.74	12.04	−6.4 ± 17.0	.04	12.92	11.30	−15.2 ± 21.4	< .00001	.006
All		**(*n* = 171)**		***P***		**(*n* = 179)**		***P***		**(*n* = 200)**		***P***	
Fibrinogen	309	299	−3.0 ± 12.8	.001	304	309	4.3 ± 22.7	.2	316	304	−3.0 ± 14.9		.00003
PAI-1	2.79	2.65	−2.6 ± 23.6	.003	2.71	2.73	2.6 ± 20.9	.3	2.94	2.79	−2.3 ± 29.3	< .00001	.09
Hcy	11.93	11.71	−2.4 ± 10.1	.01	11.39	11.26	−1.3 ± 15.4	.3	11.98	11.07	−8.6 ± 17.3	< .00001	< .00001

Smokers Versus Nonsmokers	***P***	***P***	***P***
Fibrinogen	.09	.34	.0001
PAI-1	.13	.21	.003
Hcy	.00003	.01	.003

Hcy = homocystine; PAI-1 = plasminogen activator inhibitor–1.

Table 3. Pre- and post-treatment values and percentage changes (%Δ) of fibrinogen, PAI-1, and homocystine levels according to smoking status, in the whole population

	Pre	Post	%Δ	*P*
Nonsmokers (n = 369)				
Fibrinogen	306	304	1.0 ± 18.4	.45
PAI-1	2.73	2.67	1.4 ± 28.9	.04
Hcy	11.23	11.05	−1.7 ± 13.3	.03
Smokers (n = 181)				
Fibrinogen	319	303	−3.9 ± 15.4	.0008
PAI-1	3.00	2.84	−5.1 ± 13.9	< .00001
Hcy	12.88	11.89	−9.5 ± 17.2	< .00001
Smokers *v* nonsmokers				
Fibrinogen	P < .0001		P = .002	
PAI-1	P < .0001		P = .0009	
Hcy	P < .0001		P < .00001	

Hcy = homocystine; PAI-1 = plasminogen activator inhibitor–1.

.0001, .003, and .003 for fibrinogen, PAI-1, and Hcy, respectively), whereas in the celiprolol- and carvedilol-treated groups (Fig. 1), differentiation between smokers and nonsmokers was significant only for Hcy decrease (P = .00003 and .01, respectively; Table 2).

Discussion

Arterial hypertension is a major risk factor for atherosclerosis; it exerts its deleterious effects on the cardiovascular system by inducing oxidative stress, endothelial dysfunction, and by deranging the normal prothrombotic/fibrinolytic balance. Thus, AH is linked to abnormal arterial endothelium-dependent vasodilation, inasmuch as it impairs endothelial NO availability.[5] Oxidative stress seems to be of great importance, because the superoxide anion, which is the main free radical counteracting NO, is produced in greater amounts in hypertensive individuals.[13] Finally, emerging evidence suggests that AH can promote a prothrombotic state partly because of impaired fibrinolysis.[8]

The main findings of our study are as follows. First, smoking is associated with higher baseline values of PAI-1, fibrinogen, and Hcy. Second, irrespective of BP-lowering and β-blocking potency, vasodilating β-blockers have beneficial effects on the endothelial performance and thrombotic state of AH patients, and this is influenced by smoking status. Third, nebivolol exhibits a more favorable effect on these parameters compared with celiprolol and carvedilol. This differentiation is accentuated in the tobacco-using subgroup of the hypertensive population.

In this context, we should emphasize that except for the documented beneficial impact of carvedilol treatment in patients with chronic heart failure,[14] at the moment there are no clinical outcome data from large trials concerning vasodilating β-blockers, and their potential benefits are therefore speculative at this time. Moreover, despite the increased cardiovascular risk conferred upon patients with elevated levels of PAI-1, fibrinogen, and Hcy,[15–17] there is no evidence that decreasing these parameters is beneficial.

In the present study, all three vasodilating β-blockers decreased BP to the same degree after a 6-month treatment period. The percentages of patients in each drug group and smoking status group who needed the addition of HCTZ to achieve optimal BP control were not different, even though chronic low-dose HCTZ treatment does not seem to have a substantial effect on endothelial function in AH patients.[7] Although diuretics increase serum PAI-1 levels,[18] only a small percentage of the patients enrolled in the present study received HCTZ, and these patients were homogeneously distributed among the three treatment arms, minimizing any putative implication of BP reduction per se or the coadministration of the diuretic agent with regard to our results.

The substance PAI-1 is a physiologic inhibitor of fibrinolysis, as it reduces clot lysis by preventing the tissue plasminogen activator from acting on its substrate, plasminogen, thus providing links with thrombosis. Elevated serum PAI-1 is regarded as a marker of endothelial dysfunction[19] and predicts future cardiovascular risk.[15] Fibrinogen comprises an essential element of the coagulation pathway and serves as a marker of inflammation. Plasma fibrinogen concentration is increased in hypertensive patients.[9] Furthermore, it is associated with the presence and severity of target organ damage,[20] whereas hyperfibrinogenemia is considered as an independent risk factor for atherosclerotic disease.[16] Levels of Hcy have been found to correlate with systolic BP,[10] whereas mild to moderate elevation of its plasma concentration is associated with endothelial dysfunction and increased cardiovascular morbidity.[17] High Hcy levels are related to increased production of reactive oxygen species,[21] thus decreasing the bioavailability of NO. Moreover, hyperhomocystinemia affects adversely the normal fibrinolytic pathways.[22]

In the present study, baseline values of fibrinogen,

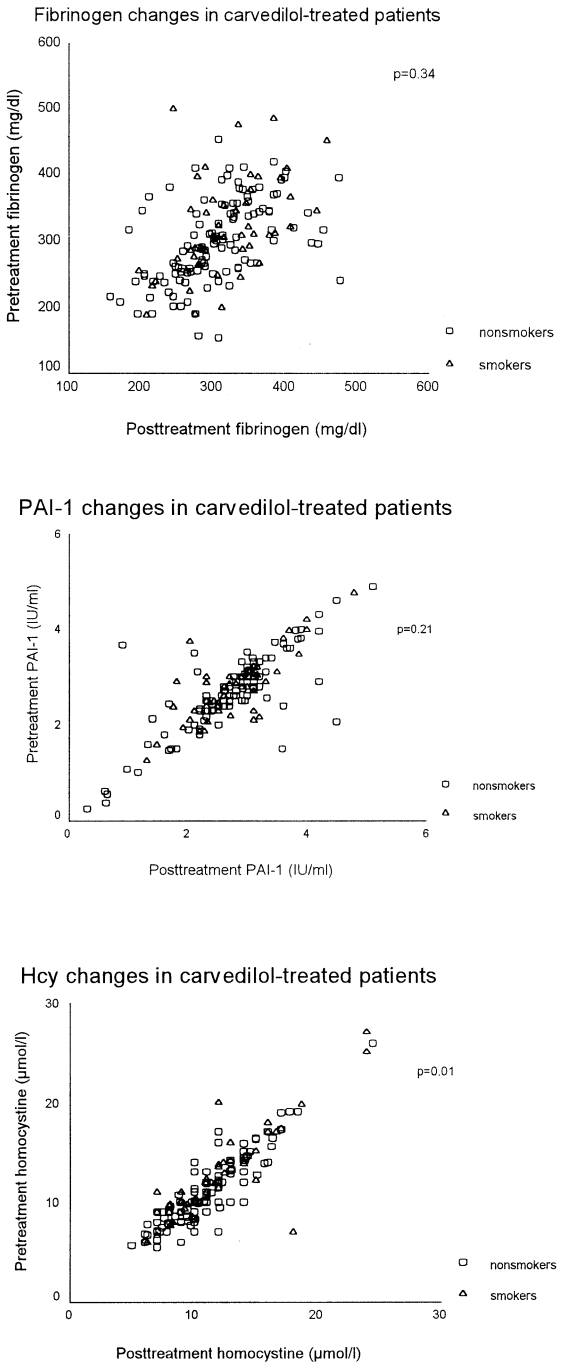

FIG 1. Fibrinogen, plasminogen activator inhibitor–1 (PAI-1), and homocystine (Hcy) level changes in carvedilol-treated patients according to smoking status.

PAI-1, and Hcy were significantly higher in smokers than in nonsmokers in all three groups. Concerning fibrinogen and Hcy, our findings are consistent with a recent study that established a strong, positive, independent, dose–response relationship between cigarette smoking and the two above-mentioned parameters.[23] Conversely, we found that baseline PAI-1 levels are higher in smokers, a finding not supported by other investigators. Two relevant studies did not show any differentiation in PAI-1 levels according to smoking status.[24,25] These studies (one of them carried out in vitro) do not necessarily oppose our own, because these investigators examined a small number of subjects and, more importantly, because they referred to nonhypertensive populations. This unfavorable effect of smoking on endothelial performance and thrombotic potential could be anticipated on the basis of the acknowledged effects of smoking. Beside the direct toxic effects on endothelial cells, smoke, and its toxic products carbon monoxide and nicotine also promote oxidant stress and production of reactive oxygen species, decrease NO release, raise Hcy,[10] and increase blood coagulability and platelet aggregation.[11]

It seems that smoking—one of the most important modifiable risk factors for atherosclerosis—acts additively to AH in increasing all three of these biochemical parameters. Moreover, data from previous studies indicate that the beneficial effects of β-blockers in controlling BP and reducing cardiovascular events in hypertensive patients are largely attenuated in patients who smoke.[26,27] Taking into consideration the association of these parameters with cardiovascular risk, it is prudent to convince these patients to quit smoking.

The results of our study highlight the favorable effects of third-generation vasodilating β-blockers on vascular functions and underline the cardinal role of smoking. Nonetheless, this beneficial impact was not ubiquitous, and significant differences among the three drugs were noted regardless of the similarities in BP control achieved by all of them. This gives rise to the hypothesis that unique properties attributed to each particular molecule, and not β-blocking capacity in general, should be responsible for the different effects of these drugs.

Third-generation β-receptor blockers comprise a group of drugs that, as a rule, selectively block the β_1-adrenergic receptor (cardioselectivity) and simultaneously exhibit vasodilator properties. The physiologic background for this vasodilation is not fully understood and seems to be heterogeneous.

Carvedilol is a β_1- and β_2-receptor blocker, owing its vasodilating activity mainly to a concominant α_1-receptor blocking action.[14] Celiprolol vasodilates via two suggested mechanisms[1]: a) intrinsic sympathomimetic activity (ISA) and a resultant β_2-adrenoreceptor stimulation that accounts at least in part for its vasodilatory effect; and b) an endothelium-dependent effect through the 5-HT1A-receptor / NO pathway.[1] This route is probably also shared by nebivolol but not by carvedilol. Nebivolol, a highly cardioselective third-generation β-blocker, comprises an isomolar racemic mixture of D- and L-enantiomers. The former accounts for its β-blocking and the latter for its vasodilating properties. Nebivolol possesses vasodilating activity that is not attributed to α_1-receptor blockade but predominantly to endothelium-dependent mechanisms, given its favorable effect on the L-arginine/NO pathway.[4] Accumulating data suggest a unique pharmacologic profile of nebivolol that is not shared by other compounds in the

same category. Nebivolol augments endothelium-dependent vasodilation in normotensive[4] and hypertensive[28] subjects.

Several mechanisms have been proposed to explain the favorable impact of nebivolol on vascular function. This drug has been shown to activate the endothelial inositol phosphate, thus upregulating the endothelial NO synthase.[29] The plausible role of 5-HT1 receptor in mediating the action of nebivolol on the endothelium is currently being investigated.[1] Nebivolol also reduces the production of endothelin and blunts its action.[28] Moreover, nebivolol possesses potent antioxidant and anti-inflammatory properties.[3] The role of the increased lipophilicity of nebivolol compared with that of other vasodilating β-blockers is also questioned.[30] Finally, current experimental evidence refutes the old hypothesis that nebivolol could perhaps act as a direct NO donor.[2]

In our study, the effects of the three vasodilating β-blockers on the levels of PAI-1, fibrinogen, and Hcy were different in smokers, and nebivolol was found to decrease these levels to a greater extent. On the contrary, in nonsmokers differentiation was noted only in Hcy, which was reduced in the nebivolol-treated group. In smokers, all three parameters decreased, irrespective of treatment. Nebivolol exhibited a more beneficial profile than the other two drugs in all three parameters tested, although its effect was much more pronounced in smokers.

There are some limitations in our study. First, our population is inhomogeneous in terms of previous antihypertensive treatment use. More than one half of our patients were on such a treatment before entering the study. Although no patient received any antihypertensive drug for 2 weeks before the first BP measurement and approximately 1 month before baseline blood sample acquisition, a carry-over effect of previous drug use cannot be precluded. Second, the design of the study does not allow us to support any possible explanation for these results. It may be that the manifold intense oxidative stress–generating mechanisms induced by cigarette smoking and superimposed to an already dysfunctional endothelium due to AH, in conjunction with the potent antioxidant capacity of nebivolol, could possibly account for our results. Our finding that carvedilol had no significant favorable action cannot be easily interpreted. Perhaps its β2- and α1-blocking activity could have a role, inasmuch as they are the only properties that differentiate carvedilol from the other two drugs.

We conclude that the overall cardiovascular risk is increased in hypertensive individuals who smoke, because they have higher levels of PAI-1, fibrinogen, and Hcy than hypertensive nonsmokers. In smokers, nebivolol results in a significant decrease in these parameters. Celiprolol also significantly affects these parameters but to a lesser degree, whereas carvedilol has no significant favorable action despite comparable BP control. In nonsmokers, Hcy is affected by nebivolol only, whereas there is no correlation of fibrinogen and PAI-1 level decrease with the β-blocker used. Hypertensive patients should be encouraged to quit smoking, and smoking status should be a determinant of antihypertensive treatment choice.

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