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Central Hemodynamics in Prehypertension: Effect of the Beta-Adrenergic Antagonist Nebivolol

Jason T. Davis, **Dalal Naqshbandi**, **Srikrishna Khandrika**, **Maple M. Fung**, **Milos Milic**, and **Daniel T. O'Connor**
Department of Medicine at the University of California, San Diego, and VA San Diego Healthcare System

Abstract

Objective—Characterize effects of the novel beta-adrenergic antagonist nebivolol on central aortic blood pressures, arterial properties, and nitroxidergic activity in individuals with prehypertension.

Background—Preypertension is emerging as a major risk factor for several adverse cardiovascular consequences. Increased pulse wave velocity, aortic augmentation index, and aortic blood pressures have been linked with augmented risk of cardiovascular disease and mortality. While the effects of antihypertensive drugs on these parameters in hypertensive patients have been studied, there are limited data so far in prehypertension.

Methods—50 individuals with prehypertension were randomized to either nebivolol (5 mg daily) or placebo in a double-blind clinical trial. Subjects underwent measurement of pulse wave velocity as well as aortic blood pressure and aortic augmentation index via pulse wave analysis at baseline and 8 weeks. Subjects also had blood and urine biochemistries done at each visit.

Results—Nebivolol achieved significant reductions in central aortic systolic (p=0.011), diastolic (p=0.009), and mean arterial blood pressure (p=0.002). Pulse wave velocity trended toward improvement, but did not achieve significance (p=0.088). Nitric oxide production, measured as urinary nitrite/nitrite excretion, also rose substantially in the nebivolol group (by ~60%, p=0.030).

Conclusions—Central blood pressures can be effectively lowered by beta-blockade while subjects are still in the prehypertension phase, and the effects may be coupled to improved nitric oxide release by the drug.

Keywords

Prehypertension; nebivolol; vascular compliance; pulse wave velocity

INTRODUCTION

Prehypertension, recently defined as a range of SBP 120-139 mmHg or DBP 80-89 mmHg [1], may now afflict up to ~69 million Americans, and has become perhaps the most common risk factor for not only progression to hypertension itself, but also cardiovascular end-organ disease, with consequent increased mortality [2-4]. Optimal treatment of

Address correspondence to: Daniel T. O'Connor, M.D., Department of Medicine (0838), UCSD School of Medicine and VASDHS, 9500 Gilman Drive, La Jolla, CA 92093-0838. Telephone: (858)-5340661. Fax: (858)-5340626. <doconnor@ucsd.edu>. Internet: <http://hypertension.ucsd.edu/>.

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prehypertension, whether pharmacological or non-pharmacological, is still in the early stages of evaluation [5,6] and the physiological changes that occur after such treatment are uncertain. Since increased heart rate (driven by both decreased parasympathetic and increased sympathetic tone) and cardiac index have been noted in prehypertension [4,7], we hypothesized that beta adrenergic blockade would be especially effective at lowering blood pressure in prehypertension.

In addition, increases in large arterial properties such as central blood pressure, pulse wave velocity, and aortic augmentation index have been linked to augmented cardiovascular mortality, and such arterial traits may constitute better predictors of adverse outcomes than brachial blood pressure [8-10]. Such vascular compliance properties may already be altered in prehypertension [11], but it is not certain whether they can be favorably altered by antihypertensive therapy. The novel beta-blocker nebivolol possesses unusual actions, such as vasodilatation via nitric oxide [12]. Since nitric oxide may in turn exert favorable effects on the microvasculature, we performed an investigator-initiated placebo controlled trial to evaluate the effect of nebivolol on arterial properties (including central blood pressure, vascular compliance, pulse wave velocity, aortic wave form) in prehypertensive individuals.

MATERIALS AND METHODS

Subjects

The institutional review board at the University of California, San Diego, approved this study. Subjects were recruited from the San Diego area via internet advertisement and posted flyers. We recruited prehypertensive subjects between the ages of 18-50 years, with a goal of having 50 subjects finish the study. Prehypertension was defined based on JNC-7 as systolic blood pressure 120-139 mmHg or diastolic blood pressure 80-89, or both [1]. On an initial screening visit, subjects' brachial blood pressures and systemic vascular compliance were measured 3 times using a Dynapulse 5200A oscillometric non-invasive blood pressure monitor (Pulse-Metric, Vista, CA <http://www.pulsemetric.com/>), which has been previously validated in measuring BP [13,14]. Measurements were taken in the seated position after at least 5 minutes of rest. The cuff was placed on the right arm with the arm supported at heart level. If a value was obtained that was more than ±10% different from other values, it was discarded at the time of measurement and another reading was obtained. The average of three values was computed. A registered nurse measured height and weight. Subjects then had an EKG in order to confirm that resting pulse was higher than 55 beats/min, with no conduction abnormalities.

Protocol

If subjects qualified they were randomized (in double-blind fashion) by the UCSD investigational pharmacy to receive nebivolol (5 mg daily) versus placebo. Randomization was done using a 4-subject per block method. Subjects had central aortic pressures and aortic augmentation index measured via SphygmoCor CP with radial pulse analysis (SphygmoCor V8.0; AtCor Medical). Pulse wave velocity was also measured using SphygmoCor CP with the patient in a supine position, taking measurements at the carotid and femoral arteries. SBP and DBP measurements taken just prior to testing were used for both pulse wave analysis and for pulse wave velocity. Measures were taken once each visit. Blood and urine samples were obtained at each visit. Investigators and subjects were blinded to drug status throughout the study period.

Subjects were given 58 nebivolol or placebo tablets, and instructed to take one tablet daily. Follow-up appointments were made approximately 8 (+/-1) weeks after the initial appointment. Subjects then underwent the same evaluation as at the first appointment.

Subjects were asked to bring their pill bottles to the second appointment to ascertain compliance by pill counts.

Assays

Biochemical assays were done using standardized commercial spectrophotometric or ELISA kits. Urinary nitric oxide was measured by monitoring the conversion of the nitric oxide metabolite nitrate to nitrite, by nitrate reductase. Nitrite was then subjected to the Griess reaction, and measured via a colorimetric assay with absorption at a wavelength of 540-570 nm (R&D Systems Inc.); the assay was linear over a range from 3-200 μM, with intra-assay coefficients of variation at 1.6-2.5%, and inter-assay coefficients at 1.5-4.8%. Exogenous nitrate recovery in urine averaged 101% (range: 87-112%) in this system. Urinary H2O2 was measured using an NWLSS™ NWK-HYPO1 colormetric assay with absorption at 560-595 nm (Northwest Life Science Specialties LLC). Urinary isoprostane was analyzed using an NWLSS™ NWK-1S001 ELISA assay for 8-isoprostane (Northwest Life Science Specialties LLC). Plasma IL-6 was measured using an electrochemiluminescence MSD® Cytokine Assay (Meso Scale Discovery).

Statistics

Statistical analysis was done in SPSS (v17.0; Chicago, IL). Physiological and biochemical data were analyzed for repeated (paired) measures (baseline and treatment) using the non-parametric Wilcoxon signed ranked test, since some variables (e.g., biochemical traits) displayed either excessive kurtosis or skewness values >2. Demographic and other baseline trait analysis was done using the Mann-Whitney U-test, except for biogeographic ancestry, which was performed using Chi-Square.

RESULTS

Subjects

We evaluated a total of 68 subjects in order to enable 50 subjects to complete the study (supplemental Figure 1). Two subjects dropped out due to flu-like symptoms, two were lost to follow-up, and one dropped out of the study after the initial visit but never took the medication. Baseline characteristics of subjects are summarized in Table 1. Baseline traits were similar ($p>0.05$) between the two randomized groups (nebivolol and placebo), with the exception of age ($p=0.048$; Table 1).

Arterial properties

Hemodynamic monitoring by SphygmoCor CP detected several changes in central aortic BP values. Aortic SBP decreased in the nebivolol arm, from 112.7±2.5 to 106.2±2.4 mmHg ($p=0.011$), though not after placebo ($p=0.629$). Aortic DBP also decreased after nebivolol, from 79.1±2.1 to 71.3±1.9 mmHg ($p=0.009$), though not after placebo ($p=0.353$). Initial aortic MAP was 94.2±2, decreasing to 86.8±1.9 mmHg in the nebivolol arm ($p=0.002$), while the placebo limb aortic MAP was unchanged ($p=0.244$). Aortic pulse pressure did not change significantly in either group: nebivolol arm ($p=0.710$) or placebo arm ($p=0.647$), consistent with parallel central reductions in both SBP and SBP on nebivolol.

Aortic augmentation analysis was obtained by SphygmoCor radial pulse wave analysis. Aortic augmentation pressure did not significantly change in either the nebivolol ($p=0.939$) or the placebo arms ($p=0.680$). When normalized to a standard heart rate of 75 beats/min, aortic augmentation index still did not change on either the nebivolol ($p=0.415$) or placebo arms ($p=0.988$). Finally, pulse wave velocity did not change significantly after either nebivolol ($p=0.088$) or placebo ($p=0.519$).

As expected during beta-adrenergic blockade, heart rate fell by ~11% (from 72.0±1.9 to 64.4±2.3 beats/min) in the nebivolol arm (p=0.001), though not on placebo (p=0.157).

Biochemical traits

Biochemical analyses probed potential effects of nebivolol on nitric oxide and inflammation in prehypertensive individuals. Urinary nitrate/nitrite excretion (measured as a surrogate for nitric oxide) increased by ~60% in the nebivolol arm, from 40.3±5.1 to 64.4±14.3 μmoles/mg Cr (p=0.030), but did not change during placebo (61.8±11.9 to 65.5±10.5 μmoles/mg Cr p=0.710). Plasma IL-6 levels, which are known to be elevated prehypertension [15], were unchanged in either nebivolol (p=0.353) or placebo arms (p=0.932). We also measured urine H_2O_2 and urine isoprostane monitor oxidative stress, which is increased in prehypertension[16]; urine H_2O_2 did not change significantly in either the nebivolol arm (p=0.363) or the placebo arm (p=0.638). Urine isoprostane excretion, a marker for oxidative injury (or lipid peroxidation), was unchanged in either arm (nebivolol, p=0.192; placebo, p=0.493).

DISCUSSION

Overview and central aortic pressures

While our sample size was not especially large (at n=50), these statistically significant observations indicate that central blood pressures in prehypertensive subjects can improve with pharmacologic therapy. The finding that prehypertensives respond to antihypertensive therapy is not novel [5]; by contrast, the current study extends hemodynamics to examination of large arterial properties in prehypertension during pharmacologic therapy, with beneficial effects upon central aortic systolic, diastolic pressure, and mean arterial pressure, as well as systemic vascular compliance. Central aortic blood pressures are reportedly lowered by nebivolol in hypertension [17], and thus our observations in prehypertension are directionally coordinate. Such reductions in central pressures may be important for several reasons. First, central arterial pressures seem to be better predictors of adverse cardiovascular outcomes (including mortality) than peripheral pressures [10,18-20]. Prehypertensives are at greater risk than normotensives for such outcomes [2-4], and lowering central pressures may help diminish their risk level, though this has not been confirmed longitudinally at this juncture. Second, central BP responses to drug therapy have not been extensively studied in prehypertensives, and the central response to treatment is thus novel. Finally, different antihypertensive drugs (including medications within the same class) can have varying effects on central BP despite similar effects on peripheral pressures [17,19,21], adding our results to the body of literature that may determine which antihypertensives exert the most beneficial effects on outcomes.

Nitric oxide

Since nebivolol exerts documented effects on nitroxidergic vasodilation in certain experimental systems [12], we monitored renal nitric oxide production by excretion of its metabolites nitrate/nitrite [22]. We found a significant (p=0.03) and substantial (by ~60%) increase in production of nitric oxide in the nebivolol arm compared to placebo. This increment in nitric oxide formation may contribute to blood pressure changes, since this endogenous nitrovasodilator has demonstrable effects on vascular resistance and hence blood pressure, and its deficiency has been linked to hypertension both directly and perhaps via the autonomic system, though the role of nitric oxide in prehypertension is less clear [23-25]. A rise in nitric oxide does not explain the decrease in heart rate that we observed, since inhibition of nitric oxide formation may lower heart rate[26], however the beta-1 antagonist effects of nebivolol are likely to be overriding on heart rate.

Since prehypertension has been linked to both metabolic abnormalities and inflammation [15], we hypothesized that antihypertensive treatment might reverse either oxidative stress or its consequent activation of inflammation [27]. Urine H_2O_2 was measured to evaluate oxygen radical formation, which is increased in hypertension, while urinary isoprostane excretion served to probe lipid peroxidation [28], and measurement of the cytokine IL-6 interrogated inflammatory processes; these 3 markers did not change after nebivolol or placebo.

It was not completely clear why the initial/baseline nitric oxide was lower in the nebivolol group than the placebo group (Table 1). However, despite randomization, the nebivolol group was significantly older (p=0.048); greater age is associated with lower nitric oxide levels, providing one possible explanation [29,30].

Arterial elasticity: PWV and aortic augmentation

PWV has been associated with coronary calcification and increased mortality, thus provoking interest in its response to treatment [8,31]. Studies on the effects of antihypertensive agents on PWV in prehypertension are sparse. One other study examined changes in PWV with nutritional (non-drug) intervention in prehypertensives, without change in PWV [32]. One study showed improvements in aortic distensibility and stiffness measurements after metoprolol or perindopril, but did not evaluate PWV specifically [33]. Nebivolol is reported to decrease PWV in hypertension[34,35] though the effect may not persist beyond one year according to a recent study [17]. Our data showed only a non-significant change in PWV. This important as increased PWV has been linked to cardiovascular mortality in multiple studies [17,35]. Increased PWV has been observed in prehypertension, [11], though our population had lower values than those previously reported and were in fact within the normal range for their age (5.1-10.7 meters/sec) [36,37]. This could be due to the fact that our population had a younger average age than those previously reported. The lower baseline values along with our small sample size may have made our power to detect a change in PWV lower than expected and masked any significant changes in PWV (observed power post hoc: 0.256).

We did not observe changes in aortic augmentation pressure or index after nebivolol. Non-vasodilating beta blockers as a class can raise aortic augmentation index, since heart rate and AIx tend to vary inversely [38]. However, the aortic augmentation index (AIx) was unchanged even after normalization to a heart rate of 75 beats/min. AIx decreases in hypertensives treated with nebivolol, though this effect may diminish over time [17,35]. Earlier studies hypothesized that AIx may increase while vessels stiffen over long time intervals as a consequence of strain from long-standing hypertension, [39] or simply increase in parallel with age up to about middle age, after which AIx tends to decline.[40] However, AIx is not simply a function of vessel stiffness but also other factors such as heart rate, vascular tone, and even height, and therefore not a pure marker vascular compliance [4142]. Our subjects had relatively normal baseline values of Aix; this coupled with our relatively small sample size could render drug-induced changes in AIx difficult to detect. The current literature is lacking in this aspect, since the only previous study of AIx in prehypertension dealt with large doses of intravenous medication, certainly a less clinically useful therapeutic approach [43].

Conclusions and perspectives

While our study is limited by relatively small sample size and should be interpreted as such, the results do raise the possibility that the treatment of prehypertensive individuals with beta-adrenergic antagonists such as nebivolol may influence central aortic pressures, traits linked epidemiologically to mortality risk. While it is premature to suggest that prehypertension should be treated pharmacologically, it may be important to note that potentially beneficial changes in central arterial pressure as well vascular compliance and

endothelial function can be brought about by intervention even while patients are still in the prehypertension phase.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary of abbreviations

BP	blood pressure
DBP	diastolic blood pressure
SBP	systolic blood pressure
PWV	pulse wave velocity
HR	heart rate
IL-6	interleukin 6
Cr	creatinine
AIx	aortic augmentation index
JNC 7	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

Table 1

Demographic characteristics of study participants who completed the protocol.

	Group			
Characteristic	**Placebo**	**Nebivolol**	**Total**	**Sig (p-value)**
N	25	25	50	
Age (years)	30.4±1.6	37.1±1.8	33.7±1.3	**0.048**
Gender (M/F)	12/13	18/7	30/20	0.083
BMI (kg/mˆ2)	31.03±1.14	28.55±0.92	29.79±0.86	0.473
Starting systolic BP (mmHg)	126.2±1.5	127.4±1.6	126.8±1.1	0.485
Starting diastolic BP (mmHg)	84.4±1.0	84.7±1.5	84.5±0.9	0.148
Biogeographic ancestry				0.893
African American	3	6	9	
Asian Indian	2	1	3	
Caucasian	13	12	25	
Hispanic	3	3	5	
Filipino	1	1	2	
Japanese	1	0	1	
Korean	1	1	2	
Native Hawaiian	0	1	1	
Other	1	0	1	

Table 2

Baseline (visit 1) and treatment (visit 2) vital signs, pulse wave analysis, and biochemical values.

	Nebivolol visit 1	Nebivolol visit 2	Sig (nebivolol)	Placebo visit 1	Placebo visit 2	Sig (placebo)
Hemodynamic traits						
Aortic SBP (mmHg)	112.7±2.5	106.2±2.4	**0.011**	107.7±1.9	106.6±2.0	0.629
Aortic DBP (mmHg)	79.1±2.3	71.3±1.9	**0.009**	75.9±1.7	74.0±1.8	0.312
Aortic MAP (mmHg)	94.2±2.1	86.8±1.9	**0.002**	90.4±1.6	88.6±1.9	0.314
Aortic pulse pressure (mmHg)	33.6±2.3	34.9±1.8	0.710	31.8±1.4	32.6±1.2	0.647
Aortic augmentation pressure (mmHg)	7.4±2.0	6.8±1.6	0.939	5.5±1.0	5.3±1.1	0.862
Aortic augmentation index for HR 75 (%)	14.7±3.4	11.9±3.8	0.415	14.5±2.4	12.8±2.9	0.534
Pulse wave velocity (meters/sec)	6.73±0.28	6.00±0.18	0.088	5.95±0.19	5.78±0.19	0.441
Heart rate (beats/min)	72.0±1.9	64.4±2.3	**0.001**	75.6±1.9	72.1±2.0	0.157
Biochemical traits						
Urine NO excretion (micromoles/mg Cr)	40.31±5.05	64.38±14.25	**0.030**	61.77±11.86	65.54±10.54	0.710
Plasma IL-6 (pg/mL)	1.626±0.598	1.647±0.689	0.353	1.351±0.258	1.351±0.285	0.932
Urine isoprostane excretion (pg/mg Cr)	1.80±14	213±20	0.192	165±17	185±22	0.493
Urine H2O2 excretion (micromoles/mg Cr)	0.652±0.274	2.79±1.83	0.363	0.500±0.281	0.578±0.194	0.638

NO: Nitric oxide metabolites
IL-6: lnterleukin-6
Sig: Significance of the drug effect (nebivolol or placebo); **bold** if $p<0.05$.