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

Jason T. Davis, MD; Dalal N. Pasha, BS; Srikrishna Khandrika, PhD; Maple M. Fung, MD; Milos Milic, PhD; Daniel T. O'Connor, MD

From the Department of Medicine, VA San Diego Healthcare System and the University of California, San Diego, CA

The aim of the current study was to characterize the effects of the novel β-adrenergic antagonist nebivolol on central aortic blood pressures, arterial properties, and nitroxidergic activity in individuals with prehypertension. Prehypertension 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. Fifty individuals with prehypertension were randomized to either nebivolol (5 mg per day) or placebo in a double-blind clinical trial. Patients 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. Patients also had blood and urine biochemistries done at each visit. Nebivolol achieved significant reductions in central aortic systolic (*P*=.011), diastolic (*P*=.009), and mean arterial blood pressure (*P*=.002). Pulse wave velocity trended toward improvement but did not achieve significance (*P*=.088). Nitric oxide production, measured as urinary nitrite/nitrite excretion, also rose substantially in the nebivolol group (by approximately 60%, *P*=.030). Central blood pressures can be effectively lowered by β-blockade while patients are still in the prehypertension phase, and the effects may be coupled to improve nitric oxide release by the drug. *J Clin Hypertens (Greenwich)*. 2013; 15:69–74 ©2012 Wiley Periodicals, Inc.

Prehypertension, recently defined as a range of systolic blood pressure (SBP) 120 mm Hg to 139 mm Hg or diastolic blood pressure (DBP) 80 mm Hg to 89 mm Hg,[1] may now effect up to approximately 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 prehypertension, whether pharmacologic or nonpharmacologic, 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 β-adrenergic blockade would be especially effective in lowering blood pressure (BP) in prehypertension.

In addition, increases in large arterial properties such as central BP, pulse wave velocity (PWV), and aortic augmentation index have been linked to augmented cardiovascular mortality, and such arterial traits may constitute better predictors of adverse outcomes than brachial BP.[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 β-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 BP, vascular compliance, PWV, aortic wave form) in prehypertensive individuals.

Address for correspondence: Jason T. Davis, Department of Medicine (0838), UCSD School of Medicine and VASDHS, 9500 Gilman Drive, La Jolla, CA 92093-0838
E-mail: jasontdavis18@gmail.com

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MATERIALS AND METHODS

Patients

The institutional review board at the University of California, San Diego approved this study. Patients were recruited from the San Diego area via internet advertisement and posted flyers. We recruited prehypertensive patients between the ages of 18 and 50 years, with a goal of having 50 patients finish the study. Prehypertension was defined based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) as systolic BP 120 mm Hg to 139 mm Hg or diastolic BP 80 mm Hg to 89 mm Hg, or both.[1] On an initial screening visit, patients' brachial BPs and systemic vascular compliance were measured 3 times using a Dynapulse 5200A oscillometric noninvasive BP 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 3 values was computed. A registered nurse measured height and weight. Patients then underwent electrocardiography in order to confirm that resting pulse was higher than 55 beats per minute, with no conduction abnormalities.

Protocol

If patients qualified, they were randomized (in double-blind fashion) by the University of California San Diego investigational pharmacy to receive nebivolol (5 mg daily) vs placebo. Randomization was done using a 4-patient per block method. Patients had central aortic pressures and aortic augmentation index measured via SphygmoCor CP with radial pulse analysis (SphygmoCor V8.0; AtCor Medical, Sydney, Australia). PWV 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 PWV. Measures were taken once each visit. Blood and urine samples were obtained at each visit. Investigators and patients were blinded to drug status throughout the study period.

Patients were given 58 nebivolol or placebo tablets and instructed to take 1 tablet daily. Follow-up appointments were made approximately 8(±1) weeks after the initial appointment. Patients then underwent the same evaluation as at the first appointment. Patients were asked to bring their pill bottles to the second appointment to ascertain compliance by pill counts.

Assays

Biochemical assays were performed using standardized commercial spectrophotometric or enzyme-linked immunosorbent assay (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 nm to 570 nm (R&D Systems Inc, Minneapolis, MN). The assay was linear over a range from 3 μM to 200 μM, with intra-assay coefficients of variation at 1.6% to 2.5% and inter-assay coefficients at 1.5% to 4.8%. Exogenous nitrate recovery in urine averaged 101% (range, 87% to 112%) in this system. Urinary hydrogen peroxide (H_2O_2) was measured using an NWLSS NWK-HYPO1 colormetric assay (Northwest Life Science Specialties, LLC, Vancouver, WA) with absorption at 560 nm to 595 nm. Urinary isoprostane was analyzed using an NWLSS NWK-1S001 ELISA assay for 8-isoprostane (Northwest Life Science Specialties LLC). Plasma interleukin (IL) 6 was measured using an electrochemiluminescence MSD Cytokine Assay (Meso Scale Discovery, Gaithersburg, MD).

Statistics

Statistical analysis was performed with SPSS version 17.0 (SPSS Inc, Chicago, IL). Physiological and biochemical data were analyzed for repeated (paired) measures (baseline and treatment) using the nonparametric Wilcoxon signed ranked test since some variables (eg, biochemical traits) displayed either excessive kurtosis or skewness values >2. Demographic and other baseline trait analysis was performed using the Mann-Whitney *U*-test, except for biogeographic ancestry, which was performed using chi-square test.

RESULTS

Patients

We evaluated a total of 68 patients in order to enable 50 patients to complete the study (Figure S1). Two participants dropped out because of flu-like symptoms, 2 were lost to follow-up, and 1 dropped out of the study after the initial visit but never took the medication. Baseline characteristics of patients are summarized in Table I. Baseline traits were similar ($P>.05$) between the two randomized groups (nebivolol and placebo), with the exception of age ($P=.048$; Table I and Table S1).

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 mm Hg to 106.2±2.4 mm Hg ($P=.011$), although not after placebo ($P=.629$). Aortic DBP also decreased after nebivolol from 79.1±2.1 mm Hg to 71.3±1.9 mm Hg ($P=.009$), although not after placebo ($P=.353$). Initial aortic mean arterial pressure (MAP) was 94.2±2 mm Hg, decreasing to 86.8±1.9 mm Hg in the nebivolol arm ($P=.002$), while in the placebo arm, aortic MAP was unchanged ($P=.244$). Aortic pulse pressure did not change significantly in either group: nebivolol arm ($P=.710$) or placebo arm ($P=.647$), consistent with parallel central reductions in both SBP and SBP with nebivolol (Table II).

Aortic augmentation analysis was obtained by SphygmoCor radial pulse wave analysis. Aortic augmentation pressure did not significantly change in either the nebivolol ($P=.939$) or the placebo arms ($P=.680$). When normalized to a standard heart rate of 75 beats per minute, aortic augmentation index still did not change in either the nebivolol ($P=.415$) or placebo arms ($P=.988$). Finally, PWV did not change significantly after either nebivolol ($P=.088$) or placebo ($P=.519$).

As expected during β-adrenergic blockade, heart rate fell by approximately 11% (from 72.0±1.9 beats per minute to 64.4±2.3 beats per minute) in the nebivolol arm ($P=.001$) but not in the placebo arm ($P=.157$).

TABLE I. Demographic Characteristics of Study Participants Who Completed the Protocol

Characteristic	Group		Total	*P* Value
	Placebo	Nebivolol		
Patients, No.	25	25	50	
Age, y	30.4±1.6	37.1±1.8	33.7±1.3	**.048**
Men/women	12/13	18/7	30/20	.083
Body mass index, kg/m^2	31.03±1.14	28.55±0.92	29.79±0.86	.473
Starting systolic blood pressure, mm Hg	126.2±1.5	127.4±1.6	126.8±1.1	.485
Starting diastolic blood pressure, mm Hg	84.4±1.0	84.7±1.5	84.5±0.9	.148
Biogeographic ancestry				
African American	3	6	9	.893
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	

Significance of the drug effect (nebivolol or placebo); bold if $P<.05$.

TABLE II. Baseline (Visit 1) and Treatment (Visit 2) Vital Signs, Pulse Wave Analysis, and Biochemical Values

	Nebivolol Visit 1	Nebivolol Visit 2	*P* Value (Nebivolol)	Placebo Visit 1	Placebo Visit 2	*P* Value (Placebo)
Hemodynamic traits						
Aortic SBP, mm Hg	112.7±2.5	106.2±2.4	**.011**	107.7±1.9	106.6±2.0	.629
Aortic DBP, mm Hg	79.1±2.3	71.3±1.9	**.009**	75.9±1.7	74.0±1.8	.312
Aortic MAP, mm Hg	94.2±2.1	86.8±1.9	**.002**	90.4±1.6	88.6±1.9	.314
Aortic pulse pressure, mm Hg	33.6±2.3	34.9±1.8	.710	31.8±1.4	32.6±1.2	.647
Aortic augmentation pressure, mm Hg	7.4±2.0	6.8±1.6	.939	5.5±1.0	5.3±1.1	.862
Aortic augmentation index for heart rate 75, %	14.7±3.4	11.9±3.8	.415	14.5±2.4	12.8±2.9	.534
Pulse wave velocity, m/s	6.73±0.28	6.00±0.18	.088	5.95±0.19	5.78±0.19	.441
Heart rate, beats per min	72.0±1.9	64.4±2.3	**.001**	75.6±1.9	72.1±2.0	.157
Biochemical traits						
Urine NO excretion, μmol/mg Cr	40.31±5.05	64.38±14.25	**.030**	61.77±11.86	65.54±10.54	.710
Plasma IL-6, pg/mL	1.626±0.598	1.647±0.689	.353	1.351±0.258	1.351±0.285	.932
Urine isoprostane excretion, pg/mg Cr	1.80±14	213±20	.192	165±17	185±22	.493
Urine H_2O_2 excretion, μmol/mg Cr	0.652±0.274	2.79±1.83	.363	0.500±0.281	0.578±0.194	.638

Abbreviations: Cr, creatinine; DBP, diastolic blood pressure; H_2O_2, hydrogen peroxide; IL, interleukin; MAP, mean arterial pressure; NO, nitric oxide metabolites; SBP, systolic blood pressure.
Significance of the drug effect (nebivolol or placebo); bold if $P<.05$.

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 approximately 60% in the nebivolol arm from 40.3±5.1 to 64.4±14.3 μmol/mg Cr (P=.030), but did not change during placebo (61.8±11.9 to 65.5± 10.5 μmoles/mg Cr P=.710). Plasma IL-6 levels, which are known to be elevated in prehypertension,[15] were unchanged in both the nebivolol (P=.353) or placebo arms (P=.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=.363) or the placebo arm (P=.638). Urine isoprostane excretion, a marker for oxidative injury (or lipid peroxidation), was unchanged in both arms (nebivolol, P=.192; placebo, P=.493).

DISCUSSION

Overview and Central Aortic Pressures

While our sample size was not especially large (N=50), these statistically significant observations indicate that central BPs in prehypertensive patients can improve

with pharmacologic therapy. The finding that prehypertensive patients 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 on central aortic systolic, diastolic pressure, and MAP, as well as systemic vascular compliance. Central aortic BPs 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] Prehypertensive patients are at greater risk than normotensive patients for such outcomes,[2–4] and lowering central pressures may help diminish their risk level, although 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 antihypertensive agents 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=.03) and substantial (by approximately 60%) increase in production of nitric oxide in the nebivolol arm compared with placebo. This increment in nitric oxide formation may contribute to BP changes, since this endogenous nitrovasodilator has demonstrable effects on vascular resistance and hence BP and its deficiency has been linked to hypertension both directly and perhaps via the autonomic system. The role of nitric oxide in prehypertension, however, 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] β_1-Antagonist effects of nebivolol, however, 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 three markers did not change after nebivolol or placebo administration.

It was not completely clear why the initial/baseline nitric oxide was lower in the nebivolol group than the placebo group (Table I); however, despite randomization, patients in the nebivolol group were significantly older (P=.048), and 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] although the effect may not persist beyond 1 year according to a recent study.[17] Our data showed only a nonsignificant change in PWV. This is important because increased PWV has been linked to cardiovascular mortality in multiple studies.[17,35] Increased PWV has been observed in prehypertension,[11] although our population had lower values than those previously reported and were in fact within the normal range for their age (5.1 m/sec to 10.7 m/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. Nonvasodilating β-blockers as a class can raise aortic augmentation index, since heart rate and aortic augmentation index tend to vary inversely.[38] However, the augmentation index was unchanged even after normalization to a heart rate of 75 beats/min. Augmentation index decreases in hypertensive patients treated with nebivolol, although this effect may diminish over time.[17,35] Earlier studies hypothesized that augmentation index 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 augmentation index tends to decline.[40] However, augmentation index 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 of vascular compliance.[41,42] Our patients had relatively normal baseline values of augmentation index. This coupled with our relatively small sample size could render drug-induced changes in augmentation index difficult to detect. The current literature is lacking in this aspect, and the only previous study of augmentation

index in prehypertension has 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 prehypertension with β-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.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Comparison of baseline values for nebivolol and placebo arms.

Figure S1. Recruitment flow diagram for the study. Sixty-eight patients were initially evaluated in order to achieve targeted enrollment and completion of 50 patients.

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