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Relation of Blood Pressure Variability to Carotid Atherosclerosis and Carotid Artery and Left Ventricular Hypertrophy

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Abstract—The relationship of blood pressure (BP) variability to cardiovascular target-organ damage is controversial. Studies examining BP variability and left ventricular (LV) hypertrophy have been contradictory, and only limited data on the relation of BP variability to carotid atherosclerosis and carotid artery hypertrophy exist. BP variability was assessed as the standard deviation and coefficient of variation of awake and asleep pressures in 511 normotensive or untreated hypertensive subjects who underwent ambulatory BP monitoring and cardiac and carotid ultrasonography. Although the presence of focal carotid plaque was associated with an increase in ambulatory pressures and pressure variability, the differences in variability were eliminated by adjustment for age and absolute pressures. Similarly, LV mass was significantly related to BP variability, but the significance of this finding was eliminated after adjustment for important covariates. In multivariate analyses, age was the primary determinant of carotid artery cross-sectional area, with a weak but independent contribution from awake systolic and diastolic BP variability in addition to absolute pressure. BP variability was not independently related to either carotid or LV relative wall thickness, both measures of concentric remodeling. In the present study, awake BP variability was weakly but independently associated with carotid artery cross-sectional area, a measure of arterial hypertrophy. However, neither systolic nor diastolic BP variability was independently associated with carotid atherosclerotic plaque or LV mass. (*Arterioscler Thromb Vasc Biol.* 2001;21: 1507-1511.)

Key Words: blood pressure ■ hypertension ■ hypertrophy ■ carotid arteries ■ atherosclerosis

B lood pressure (BP) variability is modulated by both intrinsic cyclic vasomotion and the impact of physical and mental activity[1] and is inversely related to baroreceptor reflex sensitivity, its primary determinant.[2] An increase in BP variability is additionally seen with aging and hypertension.[2,3] Whereas early studies of BP variability were based on intra-arterial recordings in selected subjects, the development of reliable, noninvasive, ambulatory BP monitoring has permitted more widespread study of its determinants and consequences. BP variability is most commonly quantified as the standard deviation (SD) of BP readings assessed during a particular activity or time period or as the coefficient of variation (CV; SD of blood pressure/mean pressure), which adjusts for the tendency of those with a higher average BP to also have a higher SD.[3,4]

Two recent studies, one population based[4] and the other hospital based,[5] have suggested that an increase in BP variability (primarily manifested as an increase in daytime systolic BP variability) is associated with an increase in subsequent cardiovascular events[5] and cardiovascular mortality.[4] The mechanism of this relationship remains speculative but may involve an excess of underlying cardiovascular target-organ damage, including carotid atherosclerosis, as either a cause or a result of increased BP variability, or left ventricular (LV) hypertrophy, both of which are markers of enhanced cardiovascular risk.

Several studies have detected a direct relationship between increased BP variability and the presence of echocardiographic evidence of LV hypertrophy[6] or more widespread target-organ damage by using scoring systems that incorporate electrocardiographic and/or roentgenographic evidence of LV hypertrophy.[7–10] Other studies have not found a relation between BP variability and echocardiographic LV mass,[6,11–15] particularly when the confounding effects of age and mean systolic BP are considered.[15] An inverse relation has been reported between diastolic BP variability and LV systolic function.[14]

Limited data on the influence of BP variability on the development or presence of carotid artery hypertrophy and atherosclerosis exist. Among patients hospitalized for neurological disorders, Sander and Klingelhöfer[16] found that diurnal systolic BP variability was the strongest independent

correlate of carotid artery wall thickness. In addition, exaggerated BP reactivity, which may be viewed as a relatively high-frequency measure of BP variability, has been associated with the presence[17] and progression[18] of carotid atherosclerosis. However, experimental evidence suggests that absolute pressure is a more potent stimulus for atherosclerosis than is variability of pressure.[19] Thus, the present study was designed to examine the relation of BP variability to cardiovascular hypertrophy and carotid atherosclerosis in a large population. Although dampened baroreceptor sensitivity and enhanced BP variability might be associated with cardiovascular hypertrophy and atherosclerosis, the extent to which this relation exists independent of important covariates, including age and absolute BP, is unknown and was a major focus of analyses.

Methods

Study Population

The study population consisted of 511 subjects (197 hypertensive and 314 normotensive, based on clinical and ambulatory pressure readings) who underwent a standard protocol (see below) as part of studies of cardiovascular structure and function that has previously been reported in part.[20,21] Three hundred fifty-six subjects were normotensive or hypertensive participants in a worksite-based study of job strain and cardiovascular disease, and 155 subjects were normotensive or hypertensive individuals evaluated at The New York Hospital and invited to participate in the study protocol. Fifty-six percent of subjects were men; the average age of all subjects was 50 ± 12 years (mean$\pm$SD; range, 18 to 88 years; 6% >70years). Hypertensive subjects were otherwise healthy, and the presence of secondary forms of hypertension was excluded on the basis of clinical and laboratory data; 57% of hypertensive subjects had received pharmacological antihypertensive therapy, which had been discontinued from 3 weeks to several years before the study. All subjects were studied under protocols approved by the Institutional Review Board of Cornell University Medical College.

Ambulatory BP Recording and Variability

All subjects underwent 24-hour ambulatory BP monitoring with a SpaceLabs 90207 monitor. Monitoring was performed on a workday or a day of usual activity. As previously described,[22] readings were obtained every 15 minutes during the day and every 30 minutes during the night. Subjects noted their activity and time of retiring in a diary, and BP recordings were classified as awake or asleep determinations based on diary entries rather than on arbitrary time periods. Mean 24-hour BP was calculated after taking into account the frequency of pressure determination and by weighting awake and asleep readings for the proportion of the ambulatory recording that they occupied. BP variability was calculated as the SDs of mean awake and asleep systolic and diastolic pressures and as their CVs (SD/mean BP$\times$100).

Echocardiography and Carotid Ultrasonography

Echocardiography and carotid ultrasonography were performed in all subjects by a highly experienced research technician, according to a standard protocol and using previously described methods.[23] M-mode strip-chart recordings of the LV were coded and read blindly on as many as 6 high-quality cycles by a single investigator using a digitizing tablet. Penn convention measurements were used to calculate LV mass.[24,25] American Society of Echocardiography measurements[26] were used for LV chamber diameter, wall thicknesses, and relative wall thickness (RWT). When the M-mode beam could not be oriented along the LV minor axis from available chest wall acoustic windows, measurements made according to the American Society of Echocardiography recommendations for 2-dimensional echocardiography[27] were substituted.

As previously described,[20,21] a 7.0- to 7.5-MHz duplex transducer was used to scan the common, internal, and external carotid arteries for discrete atherosclerotic plaques,[28] defined as the presence of a focal protrusion into the lumen at least 50% greater than the surrounding wall. Two-dimensionally guided M-mode recordings of the distal common carotid artery were recorded on videotape and subsequently digitized with a frame grabber and customized software (ARTSS©, Cornell Research Foundation, New York, NY). Electronic calipers were used to measure the internal diameter (D_d) and far-wall intimal-medial thickness (IMT_d)[29] at end diastole, recognized from the minimal arterial diameter, as well as the diameter at peak systole (D_s). Internal diameter measurements were made by continuous tracing of the intima-lumen interfaces of the near and far walls. Arterial geometry was further characterized by calculation of arterial relative wall thickness (RWT_{art}) as $RWT_{art}=2\times IMT_d/D_d$ and of arterial cross-sectional area (CSA), a measure of arterial wall mass, as $CSA=\{\pi\times[IMT_d+(D_d/2)]^2\}-[\pi\times(D_d/2)^2]$. Both LV mass and carotid CSA were indexed for body surface area to adjust for differences in body size.

Brachial BP was taken in triplicate, averaged at the termination of the ultrasound examination, and designated as basal BP, ie, BP after supine rest for 30 to 60 minutes in a darkened room.

Statistical Methods

Statistical analyses were performed with SPSS, release 9.0. Differences between continuous variables were compared with the independent samples *t* test. Adjustment for significant covariates was made by ANCOVA. Proportions were compared by the χ^2 statistic. The associations among continuous variables were evaluated with the Pearson correlation. Independence of association was assessed by linear regression analysis. The nonlinearity of the effect of age was taken into account by adding age^2, in addition to age, in multivariate analyses. The null hypothesis was rejected when 2-tailed $P<0.05$.

Results

Carotid Atherosclerosis and BP Variability

The 121 subjects with carotid atherosclerosis (focal plaque) were significantly older (57 ± 11 vs 47 ± 11 years, $P<0.001$) and more likely to be hypertensive (54% vs 34%, $P<0.001$), current or former smokers (54% vs 43%, $P=0.033$), and male (63% vs 53%, $P=0.067$) than the 390 subjects without atherosclerosis. Although subjects with atherosclerosis had higher fasting cholesterol levels (224 ± 42 vs 214 ± 43 mg/dL, $P=0.027$), there were no differences in fasting glucose (86 ± 20 vs 84 ± 24 mg/dL, $P=$NS). Subjects with atherosclerosis had higher mean basal and ambulatory pressures as well as greater BP variability, as assessed by all SDs of ambulatory BPs and by all CVs other than those for asleep BPs, which were of marginal significance (Table 1). The SDs of awake and asleep BPs were significantly related to age and basal systolic or diastolic pressure (Table 2). The CVs, despite the adjustment for mean BP, remained significantly positively related to basal BP as well as to age. On average, systolic pressure variability was more strongly related to age and basal pressure than was diastolic pressure variability, and awake values were more strongly related to age and basal pressure than were asleep values. When the measures of BP variability were adjusted for age, basal pressure, sex, cholesterol level, and previous antihypertensive treatment, differences between individuals with and without atherosclerosis became minimal and statistically insignificant (Table 3).

Relation of BP Variability to Carotid CSA and LV Mass

All measures of BP variability were significantly related to common carotid artery CSA in bivariate analyses, with correlation coefficients being higher for systolic than for diastolic pressures and correlations with awake pressures

TABLE 1.   Comparison of BP and BP Variability in Subjects With and Without Carotid Atherosclerosis

	Carotid Atherosclerosis		
	Absent (n=390)	P	Present (n=121)
Age, y*	47±11	<0.001	57±11
Basal systolic BP	126±21	<0.001	141±26
Basal diastolic BP	78±12	<0.001	83±12
24-hour systolic BP	126±16	<0.001	138±20
24-hour diastolic BP	80±11	0.001	84±12
Awake systolic BP	131±16	<0.001	141±20
Awake diastolic BP	84±10	0.007	87±11
Asleep systolic BP	114±16	<0.001	126±19
Asleep diastolic BP	69±11	<0.001	74±11
SD awake systolic BP	9.9±3.0	<0.001	11.6±3.5
SD awake diastolic BP	8.1±2.2	0.002	9.0±2.6
SD asleep systolic BP	8.3±3.5	<0.001	9.9±4.2
SD asleep diastolic BP	7.2±2.5	0.006	8.0±3.1
CV awake systolic BP	7.6±1.9	0.001	8.2±2.1
CV awake diastolic BP	9.8±2.6	0.019	10.4±3.2
CV asleep systolic BP	7.3±2.7	0.05	7.9±2.9
CV asleep diastolic BP	10.5±3.5	NS	10.9±4.0

Values are expressed as mean±SD. CVs are values shown $\times 10^2$.

being higher than with asleep values (Table 4). In multivariate analyses, age was the most important independent determinant of carotid CSA; however, awake (especially diastolic), but not asleep, BP variability remained independently related to this measure of vascular mass, in addition to basal pressure and smoking habit. Sex, serum cholesterol, and previous use of antihypertensive treatment did not enter the models. Although BP variability, especially as assessed by SDs rather than by CVs, did relate to LV mass, the correlation coefficients were generally lower than those for carotid CSA. Multivariate analyses adjusting for age, basal pressure, sex, cholesterol level, smoking habit, and prior antihypertensive drug use eliminated systolic and diastolic BP variability as independent correlates of LV mass.

In view of the potential impact of the duration of hypertension and use of antihypertensive medications on the development and regression of hypertensive hypertrophy,

TABLE 2.   Relation of Measures of BP Variability to Age and Systolic or Diastolic BP

	Age		Blood Pressure*	
	r	P	r	P
SD awake systolic BP	0.52	<0.001	0.66	<0.001
SD awake diastolic BP	0.30	<0.001	0.46	<0.001
SD asleep systolic BP	0.41	<0.001	0.49	<0.001
SD asleep diastolic BP	0.28	<0.001	0.38	<0.001
CV awake systolic BP	0.41	<0.001	0.38	<0.001
CV awake diastolic BP	0.25	<0.001	0.22	<0.001
CV asleep systolic BP	0.28	<0.001	0.22	<0.001
CV asleep diastolic BP	0.17	<0.001	0.11	0.022

*Systolic and diastolic variabilities are correlated with basal systolic and diastolic pressures, respectively.

TABLE 3.   Relation of Carotid Atherosclerosis to BP Variability, Adjusted for Age, Sex, Cholesterol, Prior Antihypertensive Treatment, and Systolic or Diastolic Pressure

	Carotid Atherosclerosis		
	Absent (n=390)	P	Present (n=121)
SD awake systolic BP	10.2±0.1	NS	10.3±0.2
SD awake diastolic BP	8.2±0.1	NS	8.4±0.2
SD asleep systolic BP	8.6±0.2	NS	8.6±0.3
SD asleep diastolic BP	7.3±0.1	NS	7.3±0.3
CV awake systolic BP	7.7±0.1	NS	7.7±0.2
CV awake diastolic BP	9.8±0.1	NS	10.0±0.3
CV asleep systolic BP	7.4±0.1	NS	7.2±0.3
CV asleep diastolic BP	10.6±0.2	NS	10.3±0.4

Values are expressed as adjusted mean±SEM obtained by ANCOVA. CVs are values shown $\times 10^2$.

particularly of the LV, the analyses described in Tables 3 and 4 were repeated in the 136 subjects over the age of 50 who had never received antihypertensive medications. There were no differences in BP variability between the 82 subjects with and the 54 subjects without carotid atherosclerosis. In multivariate analyses, no measure of BP variability was independently related to carotid artery CSA rea or LV mass.

Relation of BP Variability to Cardiovascular Remodeling

To determine whether BP variability might be more strongly related to cardiovascular remodeling than to hypertrophy, relations between common carotid artery and LV RWTs, measures of concentric geometry, were examined. RWT_{art} was weakly, albeit significantly, related to all measures of BP variability (r from 0.13 to 0.27, P from 0.005 to <0.001). However, in multivariate analyses including age, basal pressure, prior antihypertensive medication use, and variability measures, only age was independently related to RWT_{art}. Similar results were obtained for LV RWT and BP variability in bivariate analyses, whereas in multivariate analyses, both age and basal pressure, but not BP variability, were independent determinants of concentric LV geometry.

Discussion

The major finding of the present study is that although carotid atherosclerosis (focal plaque) is associated with an increase in BP variability, this relation is not independent of age and absolute pressure, both well-established influences on BP variability. In contrast, a weak but independent association was identified between BP variability and carotid artery hypertrophy, as manifested by higher carotid CSA. Awake BP variability was related to arterial CSA independent of age and absolute values of awake pressure. In contrast, LV mass was unrelated to systolic or diastolic BP variability.

The relation between BP variability and arterial structure and function has not been extensively examined in humans. Rizzoni et al[12] found significant relations between minimum forearm vascular resistance, an indirect measure of arteriolar structural changes, and BP variability as assessed by the SDs of 24-hour, daytime and nighttime systolic and diastolic pressures in 91 subjects. Absolute, but not relative (pulsatility), diameter changes of the common carotid artery were

TABLE 4.   Relation of BP Variability to Carotid CSA and LVM

BP, mm Hg	Carotid CSA Index			LV Mass Index		
	Bivariate		Multivariate*	Bivariate		Multivariate*
	r	P	P	r	P	P
SD awake SBP	0.45	<0.001	0.028	0.29	<0.001	NS
SD awake DBP	0.30	<0.001	0.011	0.19	<0.001	NS
SD asleep SBP	0.36	<0.001	NS	0.29	<0.001	NS
SD asleep DBP	0.26	<0.001	NS	0.26	<0.001	NS
CV awake SBP	0.31	<0.001	NS	0.08	NS	NS
CV awake DBP	0.24	<0.001	0.016	0.00	NS	NS
CV asleep SBP	0.23	<0.001	NS	0.13	0.022	NS
CV asleep DBP	0.16	0.001	NS	0.06	NS	NS

SBP and DBP indicate systolic and diastolic BP, respectively.

*Multivariate linear regression analysis controlled for age, age^2, sex, basal SBP or DBP, serum cholesterol, smoking habit, and previous use of antihypertensive medication.

significantly related to 24-hour diastolic BP variability in both bivariate and multivariate analyses in a study of 51 hypertensive subjects.[30] Among patients hospitalized for neurological conditions, Sander and Klingelhöfer[16] found diurnal systolic BP variability to be the strongest independent correlate of common carotid artery wall thickness. Although the results of the present study are complementary, significant differences exist between the study of Sander and Klingelhöfer and the present study, including the study population (hospital based vs population based), definition of BP variability (absolute threshold value vs SD), and measurement technique (incorporation of plaque into wall thickness measurement vs separate measurement of plaque and wall thickness). Recent bivariate analyses from the ELSA study have shown a relation between common carotid intimal-medial thickness and the SDs of both 24-hour systolic ($r=0.11$, $P<0.0001$) and pulse ($r=0.23$, $P<0.0001$) pressures[31]; however, it is unclear whether these findings are independent of age and absolute pressure. Our finding that the association between increased BP variability and carotid atherosclerosis was eliminated by consideration of differences in age and absolute BP is consistent with earlier experimental findings in Wistar rats, wherein the induction of hypertension was a much more potent stimulus to the development of aortic atherosclerosis (detected by pathological examination) than was the induced increase in BP variability.[19]

The directional nature of cause-and-effect relations between BP variability and carotid hypertrophy (increase in CSA or mass) is unclear. Although increased BP variability might magnify vascular deformational stress and result in compensatory hypertrophy, RWT$_{art}$ was related only to age in multivariate analyses. Alternatively, age- and BP-related carotid artery hypertrophy (due to increases in both vessel lumen diameter and wall thicknesses[32]) may blunt deformational stress and baroreceptor sensitivity, regardless of associated discrete atherosclerosis, and cause an increase in BP variability. The stronger independent relation of diastolic than systolic BP variability to carotid hypertrophy may reflect the greater strength of the relation between absolute systolic pressure and carotid hypertrophy ($r=0.55$ for systolic and 0.27 for diastolic pressure vs arterial CSA, both $P<0.001$),

thereby minimizing the importance of systolic pressure variability.

The present study's finding of a lack of an independent relation between systolic or diastolic BP variability and LV mass confirms several previous studies despite methodological differences. In some studies, only 24-hour but not daytime or nighttime BP variability was examined.[6,12] Although the study of Schillaci et al[15] additionally evaluated daytime and nighttime pressures, BP variability was examined in a dichotomous fashion, ie, comparing age-adjusted LV mass in groups with low vs high BP variability further subdivided according to quartile of 24-hour systolic BP. The present study indirectly confirms the findings of Devereux et al,[13] wherein BP variability did not differ according to LV geometric pattern.

In conclusion, the present study demonstrates significant but relatively weak residual relations between BP variability and carotid hypertrophy (carotid CSA), independent of the primary impact of aging on arterial hypertrophy. An independent association between carotid atherosclerosis and an increase in BP variability was not detected in this large population of relatively healthy normotensive and hypertensive subjects.

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