AJH 2007; 20:154–161

Impact of Blood Pressure Variability on Cardiac and Cerebrovascular Complications in Hypertension

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Background: The independent prognostic value of daytime and night-time blood pressure (BP) variability estimated by noninvasive 24-h BP monitoring is unclear.

Methods: We followed 2649 initially untreated subjects with essential hypertension for up to 16 years (mean, 6). Variability of BP was estimated by the standard deviation of daytime or night-time systolic BP (SBP) and diastolic BP (DBP). A BP variability either less than or equal to the group median or greater than the group median (12.7/10.4 mm Hg for daytime SBP/DBP and 10.8 and 8.9 mm Hg for night-time SBP/DBP) identified subjects at low or high BP variability.

Results: During follow-up there were 167 new cardiac and 122 new cerebrovascular events. The rate of cardiac events (×100 person-years) was higher (all $P < .05$) in the subjects with high than in those with low BP variability (daytime SBP: 1.45 *v* 0.72, daytime DBP: 1.29 *v* 0.91; night-time SBP: 1.58 *v* 0.62; night-time DBP: 1.32 *v* 0.85). The rate of cerebrovascular events was also higher (all $P < .05$) in the subjects with high than in those with low BP variability. In a multivariate analysis, after adjustment for several confounders, a high night-time SBP variability was associated with a 51% ($P = .024$) excess risk of cardiac events. The relation of daytime BP variability to cardiac events and that of daytime and night-time BP variability to cerebrovascular events lost significance in the multivariate analysis.

Conclusions: An enhanced variability in SBP during the night-time is an independent predictor of cardiac events in initially untreated hypertensive subjects. Am J Hypertens 2007;20:154–161 © 2007 American Journal of Hypertension, Ltd.

Key Words: Arterial hypertension, blood pressure variability, pulse pressure, hypertrophy, prognosis, blood pressure monitoring, epidemiology.

Although a precise assessment of blood pressure (BP) variability is only possible with beat-to-beat BP recording, 24-h noninvasive ambulatory BP monitoring allows some estimate of other measures of BP variability including the so-called "random" BP variability, usually triggered by transient stressors.[1,2] Random BP variability is generally estimated by the standard deviation (SD) of several BP measures during day or night. In cross-sectional[1,2] and longitudinal[3] studies, BP variability showed a direct association with target organ damage[1,2] and its progression[3] in hypertensive patients. However, the independent prognostic value of BP variability is poorly supported. In the Ohasama study,[4] the prognostic impact of BP variability on cardiovascular mortality was significant after adjustment for several confounding factors. In another study,[5] BP variability showed a univariate association with subsequent cardiovascular events. In a previous smaller analysis of the *Progetto Ipertensione Umbria Monitoraggio Ambulatoriale* (PIUMA) study,[6] we found a univariate association between elevated BP variability and a composite pool of cardiac, cerebrovascular, and peripheral vascular events, but such a relationship disappeared in a multivariate analysis.

Furthermore, it is unknown whether the prognostic impact of BP variability is similar at cardiac, cerebrovascular and peripheral vascular level. Thus the aim of the present study was to elucidate the prognostic value of BP variability in a large hypertensive population, with separate analysis of the prognostic impact of BP variabilitiy at the cardiac and cerebrovascular levels and a thorough

Received April 4, 2006. First decision July 21, 2006. Accepted July 27, 2006.

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Supported by a grant from the Associazione Umbra Cuore e Ipertensione, Perugia, Italy.

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0895-7061/07/$32.00
doi:10.1016/j.amjhyper.2006.07.017

assessment of the impact of diurnal and nocturnal BP variability.

Methods

The *Progetto Ipertensione Umbria Monitoraggio Ambulatoriale* (PIUMA) study is an observational registry of morbidity and mortality in initially untreated subjects with essential hypertension.[7–9] Briefly, entry criteria included an office blood pressure (BP) ≥140 mm Hg for systolic BP (SBP) or ≥90 mm Hg for diastolic BP (DBP) on at least three visits, as well as the absence of secondary causes of hypertension, previous cardiovascular disease, and life-threatening conditions. The PIUMA protocol was approved by our institutional Ethical Committee and all subjects gave their informed consent to be included in the registry. The BP was measured by a physician with a mercury sphygmomanometer with subjects sitting and relaxed from at least 10 min. Three measurements were averaged for analysis. Both SBP and DBP were identified by Korotkoff phases I and V. Standard 12-lead electrocardiography (ECG) was recorded at 25 mm/sec and 1 mV/cm calibration. Subjects with complete right or left bundle branch block, previous myocardial infarction, Wolff-Parkinson-White syndrome, and atrial fibrillation were excluded. No subject was being treated with digitalis. Diagnosis of left ventricular (LV) hypertrophy by ECG was made by using the Perugia score,[10,11] which is defined by the presence of at least one of the following: a typical strain pattern, a modified Cornell voltage (sum of S wave in V_3 and R wave in aVL >2.0 mV in women and >2.4 mV in men), or a Romhilt-Estes score ≥5 points.

Ambulatory BP was recorded using an oscillometric device (SpaceLabs 5200, 90202 and 90207, SpaceLabs, Redmond, WA), and measurements were automatically taken every 15 min throughout 24 h. Reproducibility of ambulatory BP readings in our patients has been assessed in a previous study.[12] The BP variability was estimated by the SD of daytime (10 AM to 8 PM) or night-time (0 to 6 AM) SBP and DBP. The use of fixed clock time intervals eliminate the transition periods in the morning and evening, during which a variable proportion of subjects may be actually awake or asleep. The median value of BP variability was used to identify subjects at low or high BP variability. Pulse pressure (PP) was calculated as the difference between systolic and DBP. Mean BP was calculated as DBP + (PP/3). A rough estimate of the quantity of sleep during ambulatory BP monitoring was possible by asking the subjects about whether they slept "as usual," "up to 2 hours less than usual," "2–4 hours less than usual," or "more than 4 hours less than usual" in the night when they wore the monitor.

Follow-Up and End Points

Antihypertensive treatment was tailored individually and based on lifestyle and pharmacologic measures. Follow-up of patients was mostly done by family doctors, with periodic check-up visits referred to the hospital staff. The overall duration of follow-up to the time of an event or censoring was as much as 16 years (median, 6 years). For assessment of end-points, hospital record forms and other source documents of patients who experienced a cardiovascular event or died were reviewed in conference by the authors of this study. Details about the International standard criteria used to diagnose outcome events in the PIUMA study have been reported in prior reports.[8,9]

Data Analysis

Statistical analysis was performed using SPSS (SPSS Inc, Chicago, IL) and SAS-Stat (SAS Institute, Cary, NC). Parametric data are reported as mean ± standard deviation. Comparisons between the groups were made using one-way analysis of variance.

For survival analyses, event-free curves were estimated using Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. For the subjects who experienced multiple events, survival analysis was based on the first event. The independent effect of several prognostic factors on survival was tested by stepwise Cox model.[13] Cardiac and cerebrovascular events were analyzed separately. As a first step, we tested a baseline model using the following variables: age (years), sex (women, men), family history of premature cardiovascular disease (no, yes), diabetes (no, yes), serum cholesterol (mmol/L), serum triglycerides (mmol/L), smoking habits (nonsmokers, current smokers), body mass index (kg/m^2), antihypertensive treatment at follow-up (lifestyle measures alone, diuretics and β-blockers alone or combined, angiotensin-converting enzyme inhibitors and calcium-antagonists alone or combined, other drug combinations), LV hypertrophy at ECG (no, yes). Then subsequent improvements in the model fitting were tested by entering, one at a time, the various BP components (SBP, DBP, mean BP, PP) using both the office and the average 24-h ambulatory values. As a final step, into the best-fitting model we forced, one at a time, the different components of BP variability (ie, the SD of daytime and night-time SBP and DBP). In two-tailed tests, P values $< .05$ were considered statistically significant.

Results

The main characteristics of the population ($N = 2649$) at the baseline visit are shown in Table 1. Mean age was 51 years. Prevalence of women was 47%. Prevalence of diabetes was 6.9%.

The study population was subdivided (Table 1) into four groups by occurrence of cardiac as well as cerebrovascular events. At entry, subjects with future events differed on several aspects from those who did not experience events. Prevalence of men, diabetes, and cigarettes smoking among patients with future cardiac events were higher than in those without (all $P < .05$). Other variables usually considered for cardiovascular risk stratification (age, total cholesterol, creatinine, uric acid) also differed (all $P < .05$)

Table 1. Main demographic and biochemical characteristics of subjects with and without future cardiac and cerebrovascular events

Variable	Total population (*N* = 2649)	Cardiac events		Cerebrovascular events	
		No event (*N* = 2482)	Event (*N* = 167)	No event (*N* = 2527)	Event (*N* = 122)
Age (y)	51.2 (12)	50.7 (12)	58.5* (11)	50.7 (12)	62.2* (11)
Sex (% men)	53	53	65*	53	65*
Diabetes (%)	6.9	4.9	22.0*	5.8	23.4*
Cigarette smoking (%)	22.8	22.1	32.3*	22.2	32.3*
Glucose (mg/dL)	101 (24)	100 (22)	115* (35)	100 (23)	111* (34)
Creatinine (mg/dL)	0.98 (0.24)	0.97 (0.24)	1.06* (0.32)	0.98 (0.24)	1.06* (0.24)
Total Cholesterol (mg/dL)	216 (42)	216 (42)	223† (46)	216 (43)	217 (38)
HDL-Cholesterol (mg/dL)	49 (12)	49 (12)	43* (10)	49 (12)	47 (12)
LDL-Cholesterol (mg/dL)	139 (37)	139 (37)	151* (39)	139 (37)	141 (37)
Triglycerides (mg/dL)	148 (101)	148 (102)	161 (88)	148 (101)	162 (97)
Uric acid (mg/dL)	4.8 (1.42)	4.7 (1.42)	5.2* (1.43)	4.8 (1.42)	5.1† (1.43)
Na (mmol/L)	141 (5.4)	141 (5.5)	141 (2.4)	141 (5.4)	141 (3)
Potassium (mmol/L)	4.2 (0.39)	4.2 (0.39)	4.3† (0.43)	4.2 (0.39)	4.2 (0.40)
LV hypertrophy at ECG (%)	16.7	15.7	32.0*	15.8	35.1*

ECG = electrocardiography; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LV = left ventricular.
Continuous variables expressed as mean (± standard deviation).
* $P < .01$; † $P < .05$.

between the subjects with cardiovascular events during the follow-up than in those who remained free of events (Table 1).

The main BP characteristics of the population are reported in Table 2. A BP variability less than or equal to the group median, or greater than the group median (12.7/10.4 mm Hg for daytime SBP/DBP and 10.8 and 8.9 mm Hg for night-time SBP/DBP), was used to identify subjects at low or high BP variability. At entry, subjects with future occurrence of cardiac or cerebrovascular events had office and ambulatory BP higher than those with free-event survival (Table 2). Subjects with future events also showed a more elevated standard deviation of daytime and night-time SBP/DBP (all $P < .05$) and a greater prevalence of LV hypertrophy when compared with subjects who remained free of events.

Cardiovascular Events

Months or years after the baseline visit there were 289 first cardiovascular events, 167 of which were cardiac and 122 were cerebrovascular. Specifically, there were three subjects with fatal acute myocardial infarctions (AMI), 55 with nonfatal AMI, 37 with unstable angina, 15 with coronary-aortic bypass graft, 15 with sudden death, 33 with heart failure requiring hospitalization, 9 with other cardiac death, 15 with fatal stroke, 75 with nonfatal stroke, and 32 with transient ischemic attack. The overall event rate was 1.82 per 100 person-years. The crude rates for cardiac and cerebrovascular events in subjects at low and high BP variability are showed in Fig. 1.

Cardiac Events

In the subjects at low and high BP variability, the rate of cardiac events (×100 person-years) was 0.72 *v* 1.45 × 100 person-years, 0.91 *v* 1.29 × 100 person-years, 0.62 *v* 1.58 × 100 person-years and 0.85 *v* 1.32 × 100 person-years for daytime SBP, daytime DBP, night-time SBP, and night-time DBP, respectively (Fig. 1). The univariate relative risks for cardiac events are shown in Fig. 2.

Cerebrovascular Events

A high BP variability was also associated with a higher incidence of cerebrovascular disease in univariate analyses. Cerebrovascular event rates (×100 person-years) for low or high BP variability were 0.45 *v* 1.10 × 100 person-years, 0.66 *v* 0.94 × 100 person-years, 0.54 *v* 1.01 × 100 person-years and 0.67 *v* 0.90 × 100 person-years for daytime SBP, daytime DBP, night-time SBP, and night-time DBP respectively (Fig. 1). The univariate relative risks for cerebrovascular events are shown in Fig. 3.

Multivariate Analysis

As shown in Table 3, the risk of cardiac events was 51% higher ($P = .024$) in the subset with elevated night-time SBP variability as compared with the subset with low BP variability. Such excess risk held after adjustment for the significant influence of several confounders. Overall, 308 subjects were not included in the Cox model because of missing values in one or more covariates. None of the covariates reported in Table 3 showed statistically significant differences between the subjects included and those excluded from the multivariate analysis. The event-free survival in the subsets with low and high variability of night-time SBP are shown in Fig. 4. The other components of BP variability did not achieve independent statistical significance. None of the four components of BP variability showed an independent association with cerebrovascular events.

Table 2. Main blood pressure characteristics of subjects with and without future cardiac and cerebrovascular events

		Cardiac events		Cerebrovascular events	
Variable	Total population	No event (*N* = 2482)	Event (*N* = 167)	No event (*N* = 2527)	Event (*N* = 122)
Office SBP (mm Hg)	157 (19)	157 (19)	163 (21)*	157 (19)	168 (20)*
Office DBP (mm Hg)	97 (10)	97 (10)	96 (11)	97 (10)	97 (11)
Office mean BP (mm Hg)	117 (11)	117 (11)	119 (12)	117 (11)	120 (11)*
Office PP (mm Hg)	60 (17)	59 (17)	67 (20)*	59 (17)	71 (20)*
Office HR (beats/min)	75 (11)	75 (11)	73 (11)†	75 (11)	73 (10)†
24-h SBP (mm Hg)	137 (15)	137 (14)	146 (18)*	137 (15)	147 (18)*
24-h DBP (mm Hg)	87 (10)	87 (10)	88 (11)	87 (10)	89 (11)†
24-h Mean BP (mm Hg)	104 (11)	103 (11)	107 (12)*	103 (11)	108 (12)*
24-h PP (mm Hg)	51 (10)	50 (10)	57 (14)*	50 (10)	58 (14)*
24-h HR (beats/min)	75 (9)	75 (9)	74 (10)	75 (9)	73 (8)*
Daytime SBP (mm Hg)	142 (15)	142 (15)	150 (17)*	142 (15)	150 (18)*
Daytime DBP (mm Hg)	91 (10)	92 (10)	92 (12)	91 (10)	92 (11)
Daytime mean BP (mm Hg)	108 (11)	108 (11)	111 (12)*	108 (11)	112 (12)*
Daytime PP (mm Hg)	51 (11)	51 (10)	58 (14)*	51 (10)	58 (14)*
Daytime HR (beats/min)	79 (10)	79 (10)	77 (11)†	79 (10)	76 (9)*
Night-time SBP (mm Hg)	127 (17)	127 (16)	137 (20)*	127 (16)	140 (21)*
Night-time DBP (mm Hg)	77 (11)	77 (11)	80 (12)*	77 (11)	81 (12)*
Night-time mean BP (mm Hg)	94 (12)	94 (12)	99 (13)*	94 (12)	101 (14)*
Night-time PP (mm Hg)	50 (11)	49 (10)	57 (15)*	49 (10)	58 (16)*
Night-time HR (beats/min)	68 (9)	68 (9)	68 (10)	68 (9)	67 (9)
SD daytime SBP	13.1 (3.4)	13.0 (3.3)	14.4 (3.†*	13.0 (3.4)	14.8 (3.5)*
SD daytime DBP	10.6 (2.5)	10.6 (2.5)	11.2 (2.8)*	10.6 (2.5)	11.2 (2.6)†
SD nighttime SBP	11.5 (3.8)	11.3 (3.7)	13.1 (4.2)*	11.4 (3.7)	13.3 (4.3)*
SD nighttime DBP	9.3 (2.8)	9.3 (2.8)	10.1 (2.9)*	9.3 (2.8)	9.9 (3.0)*

BP = blood pressure; DBP = diastolic BP; HR = heart rate; PP = pulse pressure; SBP = systolic BP.
Continuous variables expressed as mean (± standard deviation).
* $P < .01$; † $P < .05$.

Other potential determinants of outcome (see data analysis), including drug treatment at follow-up, did not achieve significance.

Effects of Sleep

Variability of night-time SBP/DBP did not differ (all P = NS) among the subjects whose reported duration of sleep during ABP monitoring was as long as usual (11/9 mm Hg), up to 2 h less than usual (12/9 mm Hg), 2 to 4 h less than usual (12/9 mm Hg), or more than 4 h less than usual (11/9 mm Hg).

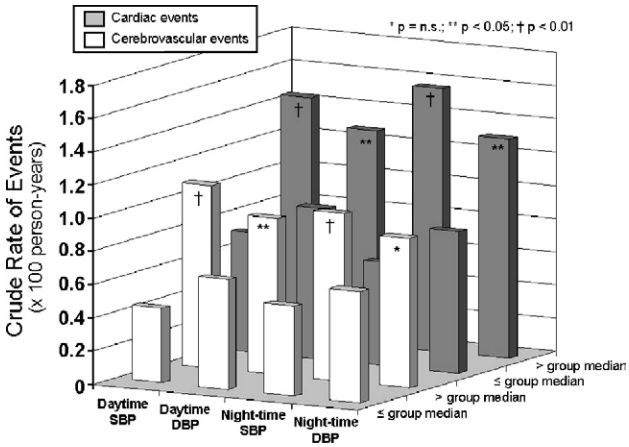

FIG. 1. Rate of cardiac events (black columns) and cerebrovascular (white columns) events according to high or low blood pressure variability.

Discussion

An increased variability of SBP during the night, defined by a SD above the group median (10.8 mm Hg), identified hypertensive subjects at increased risk of cardiac events over a mean follow-up of 6 years. These data have been obtained in a large sample of initially untreated subjects with predominantly systolic and diastolic hypertension whose age spanned more than eight decades. The 51% higher risk of cardiac events associated with high BP variability remained significant in a robust model of several covariates including age, sex, diabetes, cholesterol, cigarette smoking, 24-h ambulatory PP, and LV hypertrophy. No independent relation was detected between BP variability and cerebrovascular events.

Mechanism of BP Variability

Several mechanisms may play a role in the regulation of BP variability. Briefly, high BP variability may result from

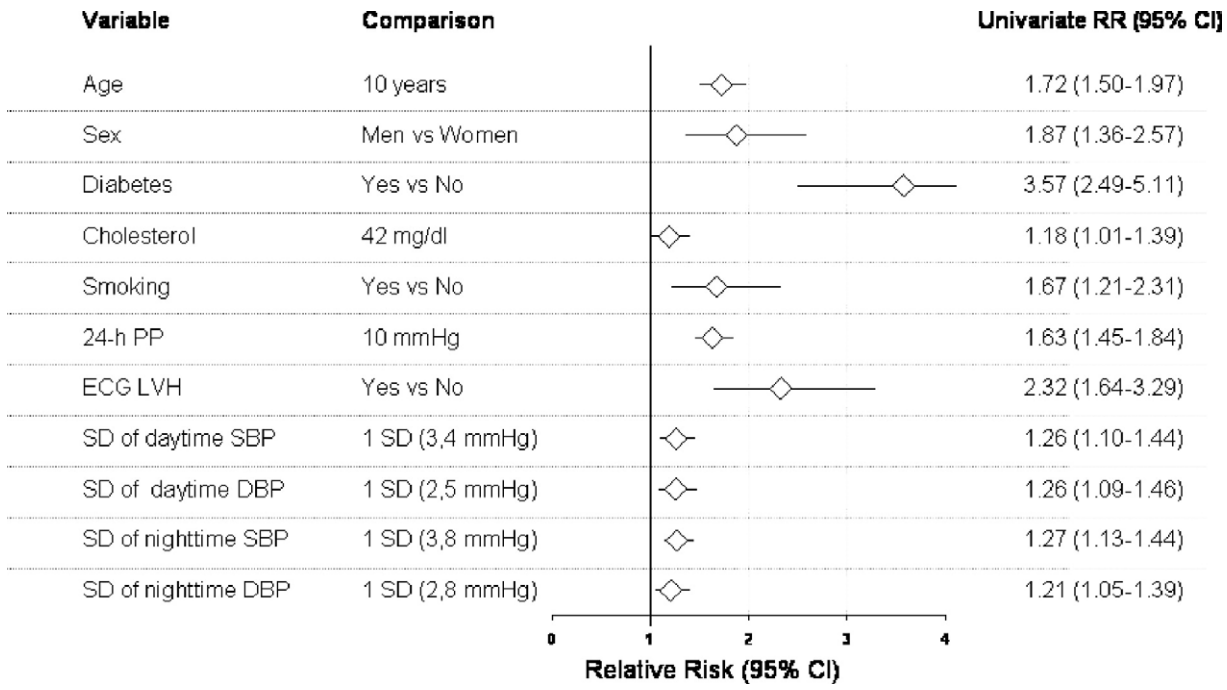

FIG. 2. Univariate predictors of cardiac events.

a depressed baroreflex function, potentially associated with increased stiffness and decreased compliance of the large elastic arteries induced by atherosclerosis, aging, and hypertension.[14,15] A blunted baroreflex function may lead to excessive BP fluctuations in either direction in response to physical and mental stimuli.[14,15]

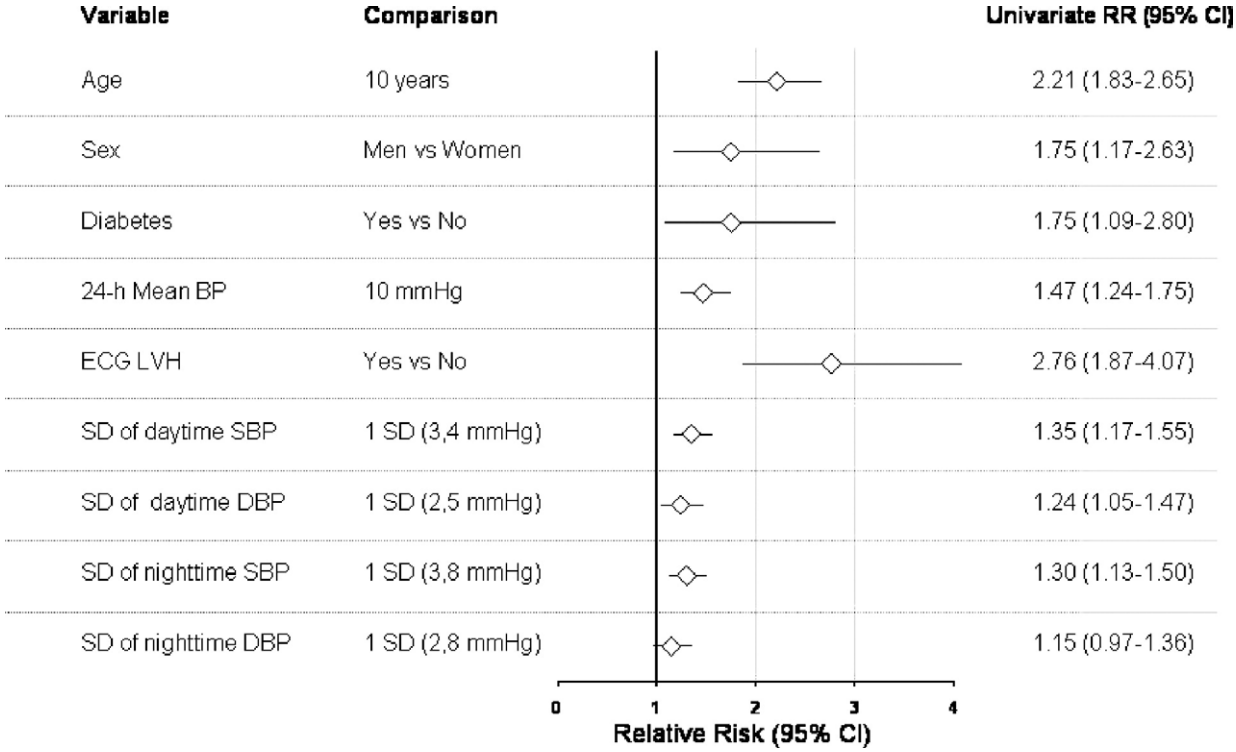

FIG. 3. Univariate predictors of cerebrovascular events.

Table 3. Results of multivariate analysis for cardiac events

Variable	Comparison	Relative risk (95% CI)	*P* value
Age	10 years	1.48 (1.26–1.73)	.0001
Sex	Men *v* women	1.95 (1.37–2.79)	.0001
Diabetes	Yes *v* no	2.55 (1.71–3.80)	.0001
Cholesterol	42 mg/dL	1.23 (1.05–1.45)	.005
Smoking	Yes *v* no	1.75 (1.21–2.52)	.003
ECG LVH	Yes *v* no	1.78 (1.23–2.58)	.002
SD of night-time SBP	≤ vs >10.8 mm Hg	1.51 (1.06–2.16)	.024
Night-time SBP	1 SD (17 mm Hg)	1.27 (1.17–1.50)	.005

ECG LVH = electrocardiographic left ventricular hypertrophy; SBP = systolic blood pressure; SD = standard deviation.

Variability of BP and Prognosis

Variability of BP might be considered as a prognostic marker that reflects diffuse atherosclerotic processes leading to an increased arterial stiffness, but it could also represent a direct and independent stimulus for progression of organ damage. In sinoaortic-denervated rats with increased BP variability and normal 24-h BP, myocardial damage, renal lesions, and vascular remodeling were found at necropsy just 4 weeks after denervation.[16] Some clinical studies showed a direct association between BP fluctuations and target organ damage.[1,2] However, the relation between BP variability and target organ damage was not clearly independent of the average levels of BP. For example, in the PIUMA study untreated subjects with essential hypertension were subdivided into groups with progressively higher 24-h SBP. In each group, subjects were classified into subgroups at low or high BP variability according to their standard deviation of daytime and night-time SBP either less than or greater than the group median. Within each group, LV mass at echocardiography did not differ between the subgroups at low *v* high SBP variability.[17]

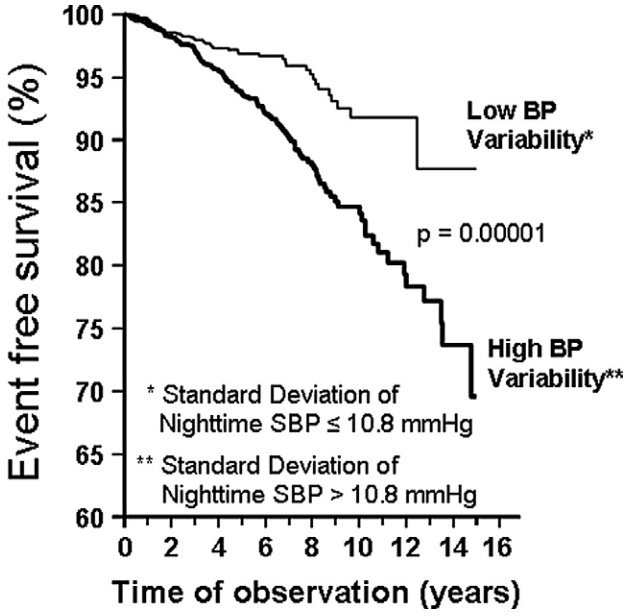

FIG. 4. Cardiac events during follow-up in hypertensive subjects with low and high variability of night-time systolic blood pressure at entry.

In a previous analysis of the PIUMA study,[6] the relationship between BP variability and subsequent incidence of cardiovascular morbid events was assessed in 1372 hypertensive subjects who experienced 106 major cardiovascular events over a mean follow-up of 2.9 years. The rate of a composite pool of cardiovascular events increased with variability of SBP during both the daytime and night-time. However, BP variability failed to be entered into a multivariate model after correction for age, diabetes mellitus, and average night-time SBP.[6] Based on these findings we suggest that the adverse impact of increased BP variability on a composite pool of cardiovascular events was largely spurious and resulted from the confounding effect of factors such as age, BP, and diabetes.[6] In the Ohasama study,[4] the prognostic impact of BP variability on cardiovascular mortality was significant after adjustment for several covariates including age, sex, use of antihypertensive drugs, smoking, obesity, diabetes, hyperlipidemia, and 24-h SBP and DBP. In a study by Sander et al,[5] a daytime variability in SBP >15 mm Hg was associated with a greater risk of cardiovascular events when compared with a lesser variability (≤15 mm Hg), but the independent prognostic impact of such finding was not assessed.

Comparison With Previous Studies

To elucidate the prognostic value of BP variability in subjects with essential hypertension, we analyzed separately the prognostic impacts of BP variability on cardiac and cerebrovascular events. The smaller sample size in our prior analysis[6] did not allow an outcome-specific analysis. Whereas both daytime and night-time BP variability showed significant univariate associations with cardiac and cerebrovascular events, the sole independent association between BP variability and outcome occurred between night-time SBP and cardiac events. Notably, 24-h PP and 24-h mean BP emerged as the ambulatory BP components that were more closely associated with cardiac and cerebrovascular events, respectively, as noted in

a previous analysis of the PIUMA study.[18] These findings deserve some comment. There is evidence that a wide PP, potentially associated with enhanced stiffening of elastic large arteries,[19,20] predicts coronary artery stenosis,[21] carotid artery lesions,[22] and LV hypertrophy.[23] An elevated PP is a strong predictor of cardiac events.[24] Our study is the first to demonstrate that an excessive BP variability, estimated by an increased SD of night-time SBP, adds prognostic information to that provided by a wide ambulatory PP. The better prognostic impact of night-time over daytime BP variability is difficult to explain. Our findings are consistent with previous outcome-based studies which showed the superiority of night-time over daytime ambulatory BP averages for prediction of a composite pool of cardiovascular events.[25,26]

The failure of BP variability to predict cerebrovascular events independently of mean ambulatory BP and other traditional risk factors also deserves mention. It is well known that BP and its changes induced by treatment parallel the risk of stroke more closely than that of myocardial infarction.[27] Although an independent association has been noted in some studies between BP variability and intima-media thickness in the carotid arteries,[28] it could be speculated that the prognostic information provided by mean BP includes most of the information incorporated in the BP variability.

Study Limitations

Because our study was conducted in subjects of white ethnicity, caution should be used in applying the results to different ethnic groups. Furthermore, because ambulatory BP monitoring was done only at study entry, results can be applied to untreated subjects with clinical diagnosis of hypertension, not to subjects under treatment. Two other limitations inherent to intermittent BP recording to estimate BP variability was the lack of beat-to-beat assessment and the uncertainty regarding its short-term and long-term reproducibility. Indeed the reproducibility of the SD of ambulatory BP has not been established in previous prognostic studies of BP variability.[4–6]

In conclusion, our study indicates that a high BP variability, defined by a standard deviation of SBP >10.8 mm Hg during the night-time in untreated hypertensive subjects undergoing 24-h noninvasive BP monitoring, refines risk stratification by identifying subjects at increased risk for cardiac events. Because the prognostic impact of a high BP variability was independent of several important risk markers including LV hypertrophy and 24-h ambulatory PP, our findings suggest that the standard deviation of night-time SBP, as an index of BP variability, may be added to the list of "new" prognostic markers in hypertensive patients.

Acknowledgment

The authors are grateful to Francesca Saveri for secretarial assistance.

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