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Night-time systolic blood pressure and subclinical cerebrovascular disease: the Cardiovascular Abnormalities and Brain Lesions (CABL) study

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Aims Although ambulatory blood pressure (BP) is a better predictor of cardiovascular outcomes than office BP, its association with subclinical cerebrovascular disease is not clarified. We investigated the associations of office and ambulatory BP values with subclinical cerebrovascular disease in a population based, predominantly elderly cohort without prior stroke.

Methods and results Eight hundred and twenty-eight participants underwent 24-h ambulatory BP monitoring (ABPM), 2D echocardiography and brain magnetic resonance imaging in the Cardiac Abnormalities and Brain Lesion (CABL) study. Daytime, night-time, and 24-h BPs, nocturnal dipping pattern, morning surge (MS), and 24-h variability were assessed. Subclinical cerebrovascular disease was defined as silent brain infarcts (SBIs) and white matter hyperintensity volume (WMHV). The association of BP measures with the presence of SBI and upper quartile of log-WMHV (log-WMHV4) was analysed. SBIs were detected in 111 patients (13.4%). Mean log-WMHV was -0.99 ± 0.94. In multivariable analysis, only night-time systolic BP (SBP) was significantly associated with SBI [odds ratio (OR) 1.15 per 10 mmHg, $P = 0.042$], independent of cardiovascular risk factors, and pertinent echocardiographic parameters. Although daytime, night-time, 24-h BPs, and non-dipping pattern were all significantly associated with log-WMHV4 (all $P < 0.05$), night-time SBP showed the strongest association (OR 1.21 per 10 mmHg, $P = 0.003$) and was the sole independent predictor when tested against the other BP parameters. Office BP measures, MS, and BP variability were not associated with subclinical cerebrovascular disease in adjusted analyses.

Conclusion Elevated night-time SBP is strongly associated with subclinical cerebrovascular disease. Night-time SBP by ABPM allows to identify individuals at higher risk of hypertensive brain injury.

Keywords ambulatory blood pressure monitoring • night-time blood pressure • silent brain infarcts • white matter hyperintensity

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Introduction

Hypertension is the most common cardiovascular disorder, and its prevalence increases with age; after age 50 years, it affects over 50% of individuals.[1] Stroke is a major complication in patients with hypertension and a common cause of death and disability worldwide. In addition, hypertension also causes cardiac morphological changes, including left ventricular (LV) hypertrophy and left atrial (LA) dilatation, which are independent risk factors for stroke.[2–4] Ambulatory blood pressure monitoring (ABPM) provides information not obtained from office blood pressure (BP) measurements, such as daytime and night-time BPs, nocturnal BP dipping pattern and 24-h variability, as well as excessive elevation after awakening, known as morning surge (MS).[5–7] Several epidemiological and clinical studies have shown that ambulatory BP, especially nocturnal BP, is a better predictor of future stroke than office BP.[8–12]

In population-based studies, the prevalence of asymptomatic vascular brain lesions is substantially higher than that of clinically overt disease. Silent brain infarcts (SBIs) and white matter hyperintensities (WMHs) are commonly seen on brain magnetic resonance imaging (MRI) of elderly adults and carry an increased risk of stroke, cognitive impairment, dementia, and death.[13–17] However, it is unclear which measures of BP are the strongest predictors of subclinical cerebrovascular disease. The aim of the present study was to compare the relationship of office and ambulatory BP values and circadian variation measures with the presence of subclinical cerebrovascular disease in a sample of the general population without history of stroke, also taking into consideration the presence of hypertension-related cardiac morphological changes.

Methods

Study population

The study population was derived from the Cardiovascular Abnormalities and Brain Lesions (CABL) study, a community-based epidemiological study to investigate the cardiovascular predictors of subclinical cerebrovascular disease. CABL based its recruitment on the Northern Manhattan Study (NOMAS), a population-based prospective study that enrolled 3298 participants from the community living in northern Manhattan between 1993 and 2001. The study design and recruitment details of NOMAS have been described previously.[18] Beginning in 2003, NOMAS participants were invited to participate in an MRI substudy if they (i) were at least 55 years of age, (ii) had no contraindications to MRI, and (iii) did not have a previous diagnosis of stroke. From September 2005 to July 2010, NOMAS MRI participants that voluntarily agreed to undergo a more extensive cardiovascular evaluation including transthoracic echocardiography and ABPM were included in CABL. A total of 1004 participants were included in CABL, 828 of whom successfully underwent 24-h ABPM and 2D echocardiography, and are included in the present study. Written informed consent was obtained from all study participants. The study was approved by the Institutional Review Boards of Columbia University Medical Center and the University of Miami.

Risk factor assessment and office BP measurement

Cardiovascular risk factors were ascertained through direct examination and interviews conducted by trained research assistants. Diabetes mellitus was defined by current use of insulin or hypoglycaemic agents, or a fasting glucose of ≥126 mg/dL, tested on ≥2 occasions. Hypercholesterolaemia was defined as total serum cholesterol >240 mg/dL, or the use of lipid-lowering medications. Body mass index was calculated using height and weight (kg/m^2). Office systolic BP (SBP) and diastolic BP (DBP) were measured on the non-dominant arm in a sitting position after 5 min of rest, using a sphygmomanometer calibrated against a reference mercury sphygmomanometer and with arm cuff of appropriate size. BPs were recorded twice with a 5-min interval, and the average of the two recordings was used. Hypertension was defined as office SBP ≥140 mmHg or DBP ≥90 mmHg (mean of two readings), or antihypertensive medication use.

Ambulatory BP measurement

ABPM was performed with an appropriately sized BP cuff on the non-dominant arm, using a BP monitor (SpaceLabs Model 90207, Snoqualmie, WA, USA) previously validated by the British Hypertension Society Protocol[19] and calibrated against a reference mercury sphygmomanometer. The methods of ambulatory BP monitoring have been previously published.[20] Briefly, the participants were asked to follow their usual routine and to note their activities at the time of each BP reading in a diary, as well as their sleep onset and wake-up times. Ambulatory BP readings were automatically taken and recorded every 15 min during waking hours and every 30 min during sleeping hours for 24 h. The mean SBP and DBP were calculated for the 24-h period and separately for daytime (awake) and night-time (sleep) periods, defined by subjects' diary reports of actual asleep and awake times. Elevated ambulatory BPs were defined as follows; elevated 24-h ABP as mean 24-h SBP ≥130 mmHg and/or DBP ≥80 mmHg; elevated daytime ABP as mean daytime SBP ≥135 mmHg and/or DBP ≥85 mmHg; and elevated night-time ABP as mean night-time SBP ≥120 mmHg and/or DBP ≥70 mmHg.[21]

Several additional BP parameters were also derived from ABPM measures. Night-to-day SBP ratio (mean night-time SBP/mean daytime SBP) was calculated and categorized into two patterns: dipping pattern (≤0.90) and non-dipping pattern (>0.90).[12,22] BP variability was calculated based on the coefficient of variation over 24 h. Finally, we assessed three different definitions for the MS.[8,23] MS-1, the average SBP in the first 2-h after awakening minus the average SBP in the last 2-h before awakening; MS-2, the average SBP in the first 2-h after awakening minus the average SBP during all nocturnal sleep period; MS-3, the average SBP of the first 2-h after awakening minus the lowest average of three SBP measurements during the night.

2D echocardiographic examination

The echocardiographic examination was performed using a commercially available system (iE 33, Philips, Andover, MA, USA) by a trained, registered cardiac sonographer blinded to the participant's clinical information according to a standardized protocol. The dimensions of the cardiac chambers were measured in the standard manner.[24] LV ejection fraction was obtained, using the Simpson's method, from apical four- and two-chamber views.[24] LV mass was calculated with a validated method[25] and indexed for the participant's body surface area. LA anteroposterior diameter was measured as recommended[24] and also indexed by body surface area.

Image acquisition and interpretation of brain MRI

A detailed description of the assessment of subclinical cerebrovascular lesions has been published previously.[26,27] In brief, brain imaging was performed on a 1.5-T MRI system (Philips Medical Systems). SBIs were defined as either a cavitation on the fluid-attenuated inversion recovery

Table 1 Characteristics of the study population

N = 828	
Age (years)	70.9 ± 9.0
Male gender	330 (39.9)
Race/ethnicity	
White	103 (12.4)
Black	131 (15.8)
Hispanic	579 (69.9)
Other	15 (1.8)
Hypertension	650 (78.5)
Diabetes	245 (29.6)
Hypercholesterolaemia	569 (68.8)
Atrial fibrillation	53 (6.4)
Body mass index (kg/m^2)	28.3 ± 4.8
BP variables	
Office SBP (mmHg)	135.6 ± 17.7
Office DBP (mmHg)	78.5 ± 9.4
24-h SBP (mmHg)	124.9 ± 14.4
24-h DBP (mmHg)	74.2 ± 9.0
Daytime SBP (mmHg)	128.2 ± 14.5
Daytime DBP (mmHg)	74.2 ± 9.0
Night-time SBP (mmHg)	118.8 ± 16.3
Night-time DBP (mmHg)	66.1 ± 9.4
BP non-dipping pattern	531 (64.1)
Morning surge-1 (mmHg)	6.61 ± 11.3
Morning surge-2 (mmHg)	8.61 ± 10.7
Morning surge-3 (mmHg)	23.7 ± 11.8
24-h SBP variability (CV)	13.7 ± 3.44
Echocardiography	
LV end-diastolic diameter (mm)	44.8 ± 4.7
LV end-systolic diameter (mm)	28.4 ± 4.7
LV ejection fraction (%)	63.6 ± 7.1
LV mass index (g/m^2)	102.5 ± 25.6
LA diameter index (mm/m^2)	22.2 ± 3.0
Brain MRI	
SBI	111 (13.4)
Log-WMHV	-0.99 ± 0.94

Values are presented as mean ± standard deviation or *n* (%).
CV, coefficient of variation; DBP, diastolic blood pressure; LA, left atrium; LV, left ventricle; MRI, magnetic resonance imaging; SBI, silent brain infarcts; SBP, systolic blood pressure; WMHV, white matter hyperintensity volume.

sequence of at least 3 mm in size, distinct from a vessel (owing to the lack of signal void on T2 sequence), and of equal intensity to cerebrospinal fluid in the case of lacunar infarction, or as a wedge shaped cortical or cerebellar area of encephalomalacia with surrounding gliosis consistent with infarction attributable to distal arterial branch occlusion. WMH volume (WMHV) analysis was based on a fluid attenuated inversion recovery image and performed by using the Quantum 6.2 package on a Sun Microsystems Ultra 5 workstation. WMHV was expressed as a proportion of total cranial volume corrected for head size, and log-transformed (log-WMHV) to achieve a normal distribution for analysis as a continuous variable. The upper quartile of log-WMHV (log-WMHV4) was used as the dependent variable in the categorical analyses. The time difference between ABPM and MRI was <90 days in 509 (61.5%) participants. All measurements were performed blinded to participant clinical information.

Statistical analysis

Categorical variables are presented as frequencies and percentages and continuous variables are expressed as mean ± standard deviation. Univariable and multivariable logistic regression analyses were used to evaluate the associations of office and ambulatory BP measures with subclinical cerebrovascular disease. Multivariable models were adjusted for the factors associated with subclinical cerebrovascular disease at the $P < 0.05$ level in the univariable analyses and time interval between ABPM and brain MRI. Odds ratios (ORs) with their 95% confidence interval were reported. A *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

Results

The clinical characteristics of the study population are shown in *Table 1*. Presence of SBI was detected in 111 patients (13.4%). Mean log-WMHV was -0.99 ± 0.94 (median -1.11, min -5.88, max 1.74). *Table 2* shows the univariable associations of clinical and echocardiographic variables with SBI and log-WMHV4. Age, hypertension, atrial fibrillation, LV mass index, and LA diameter index were associated with both SBI and log-WMHV4; gender was associated only with SBI, whereas race was associated only with log-WMHV4.

Multivariable analyses were performed with each BP parameter tested separately as possibly associated with SBI and WMH, adjusting for the effect of clinical and echocardiographic variables identified by univariable analyses. Multivariable analyses showed that, among all BP parameters considered, only night-time SBP was significantly associated with SBI (adjusted OR 1.15 per 10 mmHg, $P = 0.042$; *Table 3*). As for WMHs, all ambulatory SBP and DBP variables, as well as non-dipping pattern, were associated with log-WMHV4, independent of the clinical and echocardiographic parameters (all $P < 0.05$; also *Table 3*). On the other hand, office BP measures, the various definitions of MS and BP variability were not associated with either SBI or WMHV.

To identify the most important ABPM predictor of WMHV, we first entered SBP and DBP values obtained at the same time period of the day into the multivariable model (*Table 4*). SBP was more strongly associated with log-WMHV4 than DBP in both the daytime and night-time periods. When daytime and night-time SBP were entered in the same model, night-time SBP, but not daytime SBP, remained an independent predictor for log-WMHV4 (*Table 5*, Model 1). Finally, when we included night-time SBP and non-dipping pattern in the same model, only night-time SBP remained independently associated with log-WMHV4 (adjusted OR 1.21 per 10 mmHg, $P = 0.003$; *Table 5*, Model 2). When night-time SBP was examined as a categorical variable, elevated night-time SBP (night-time SBP ≥120 mmHg) was independently associated with log-WMHV4 (adjusted OR 1.53, $P = 0.031$). The association of categorized night-time SBP groups (<120 mmHg, 120–129 mmHg, 130–139 mmHg, and ≥140 mmHg) with log-WMHV4 is shown in *Figure 1*. The risk of log-WMHV4 increased progressively with increasing night-time SBP values, although the top two categories appeared to have very similar risk after adjusting for clinical and echocardiographic covariates. When a sensitivity analysis was performed in participants with ABPM and MRI

Table 2 Variables associated with SBI and upper quartile of log-WMHV

	SBI		Log-WMHV-4	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age >70 years	2.18 (1.42–3.34)	<0.001	4.78 (3.31–6.92)	<0.001
Male gender	1.58 (1.06–2.36)	0.026	0.91 (0.66–1.26)	0.566
Race				
White	1 (reference)		1 (reference)	
Black	1.22 (0.61–2.44)	0.574	2.65 (1.45–4.83)	0.002
Hispanic	0.75 (0.42–1.35)	0.333	1.24 (0.73–2.09)	0.426
Other	0.39 (0.05–3.16)	0.377	1.04 (0.27–4.03)	0.958
Hypertension	2.76 (1.45–5.27)	0.002	4.21 (2.45–7.24)	<0.001
Diabetes mellitus	1.22 (0.80–1.87)	0.354	1.19 (0.85–1.67)	0.312
Hypercholesterolaemia	0.90 (0.59–1.37)	0.616	1.12 (0.80–1.58)	0.516
Atrial fibrillation	2.51 (1.31–4.79)	0.005	2.08 (1.17–3.69)	0.013
Body mass index (kg/m^2)	0.98 (0.93–1.02)	0.252	0.98 (0.94–1.01)	0.162
Office SBP (per 10 mmHg)	1.16 (1.04–1.29)	0.008	1.24 (1.13–1.36)	<0.001
Office DBP (per 10 mmHg)	1.05 (0.85–1.30)	0.651	1.21 (1.02–1.43)	0.027
Office BP ≥140/90 mmHg	1.75 (1.17–2.62)	0.006	1.64 (1.19–2.25)	0.002
Office BP ≥130/80 mmHg	1.38 (0.86–2.21)	0.186	1.91 (1.30–2.82)	0.001
24-h SBP (per 10 mmHg)	1.34 (1.17–1.53)	<0.001	1.48 (1.32–1.66)	<0.001
24-h DBP (per 10 mmHg)	1.24 (0.99–1.56)	0.060	1.26 (1.06–1.51)	0.011
Elevated 24-h BP (≥130/80)	2.00 (1.34–2.99)	<0.001	2.28 (1.66–3.15)	<0.001
Daytime SBP (per 10 mmHg)	1.30 (1.14–1.48)	<0.001	1.41 (1.26–1.58)	<0.001
Daytime DBP (per 10 mmHg)	1.19 (0.96–1.48)	0.118	1.17 (0.98–1.39)	0.080
Elevated daytime BP (≥135/85)	2.05 (1.37–3.08)	<0.001	1.86 (1.34–2.58)	<0.001
Night-time SBP (per 10 mmHg)	1.32 (1.17–1.48)	<0.001	1.46 (1.32–1.62)	<0.001
Night-time DBP (per 10 mmHg)	1.27 (1.03–1.55)	0.024	1.36 (1.15–1.60)	<0.001
Elevated night-time BP (≥120/70)	1.70 (1.13–2.55)	0.011	2.50 (1.80–3.48)	<0.001
BP non-dipping pattern	1.52 (0.98–2.37)	0.062	2.01 (1.41–2.86)	<0.001
Morning surge-1 (mmHg)	0.99 (0.97–1.01)	0.282	0.98 (0.96–0.99)	0.004
Morning surge-2 (mmHg)	0.99 (0.97–1.01)	0.416	0.98 (0.97–0.998)	0.026
Morning surge-3 (mmHg)	0.999 (0.98–1.02)	0.907	0.995 (0.98–1.01)	0.513
24-h SBP variability (CV)	1.04 (0.98–1.10)	0.170	1.05 (1.01–1.10)	0.022
LV ejection fraction (%)	0.98 (0.95–1.004)	0.101	0.99 (0.97–1.01)	0.335
LV mass index (g/m^2)	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.02)	<0.001
LA diameter index (mm/m^2)	1.11 (1.04–1.18)	0.002	1.11 (1.05–1.17)	<0.001

Univariable logistic regression analysis.
CI, confidence interval; CV, coefficient of variation; DBP, diastolic blood pressure; LA, left atrium; LV, left ventricle; OR, odds ratio; SBI, silent brain infarcts; SBP, systolic blood pressure; WMHV, white matter hyperintensity volume.

performed within 3 months of each other ($N = 509$), the results of the fully adjusted models were concordant with those of the general analysis, with night-time SBP being the strongest predictor of log-WMHV4 (adjusted OR 1.19 per 10 mmHg, $P = 0.043$).

Discussion

Our study demonstrates that night-time SBP, obtained averaging several measurements from ABPM, is the strongest predictor of the presence of subclinical cerebrovascular disease in a predominantly elderly sample of the general population without history of stroke. The association between night-time SBP and subclinical brain disease was independent of traditional cardiovascular risk factors and of echocardiographic abnormalities related to hypertension and stroke.

In healthy adults, BP is characterized by a circadian pattern, with values that are normally higher during the day and decrease during sleep. ABPM can be used for a more complete assessment of an individual's BP status than that afforded by office BP. It has been demonstrated that ABPM measures are better predictors of cardiovascular events and mortality than office BP.[5–7] In 1988, O'Brien *et al.*[22] reported for the first time that hypertensive patients with a blunted nocturnal BP fall had a greater prevalence of strokes and named these patients 'non-dippers'. Since then, several studies investigated the association between nocturnal BP non-dipping and cerebrovascular disease. However, the studies on BP non-dipping and stroke risk have provided conflicting results.[9,10,12] Night-to-day SBP ratio was not associated with stroke in 7458 individuals during median follow-up of 9.6 years.[9] On the other hand, another study showed that

Table 3 Association of BP variables, one at a time, with SBI and WMHV

	SBI		Log-WMHV4	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Office SBP (per 10 mmHg)	1.03 (0.91–1.18)	0.615	1.05 (0.94–1.17)	0.382
Office DBP (per 10 mmHg)	0.96 (0.77–1.21)	0.743	1.12 (0.93–1.36)	0.235
Office BP ≥140/90 mmHg	1.32 (0.85–2.06)	0.219	0.97 (0.67–1.39)	0.863
Office BP ≥130/80 mmHg	0.94 (0.56–1.57)	0.805	1.16 (0.75–1.80)	0.510
24-h SBP (per 10 mmHg)	1.14 (0.98–1.32)	0.090	1.24 (1.09–1.41)	0.001
24-h DBP (per 10 mmHg)	1.10 (0.86–1.40)	0.446	1.28 (1.05–1.56)	0.017
Uncontrolled 24-h BP (≥130/80)	1.33 (0.86–2.06)	0.202	1.50 (1.05–2.15)	0.027
Daytime SBP (per 10 mmHg)	1.11 (0.96–1.29)	0.156	1.20 (1.06–1.36)	0.004
Daytime DBP (per 10 mmHg)	1.09 (0.86–1.37)	0.485	1.23 (1.01–1.49)	0.035
Uncontrolled daytime BP (≥135/85)	1.42 (0.92–2.21)	0.114	1.28 (0.89–1.85)	0.183
Night-time SBP (per 10 mmHg)	1.15 (1.01–1.31)	0.042	1.24 (1.11–1.39)	<0.001
Night-time DBP (per 10 mmHg)	1.10 (0.89–1.36)	0.389	1.28 (1.07–1.53)	0.008
Uncontrolled night-time BP (120/70)	1.14 (0.74–1.78)	0.548	1.70 (1.19–2.45)	0.004
BP non-dipping pattern	1.31 (0.82–2.08)	0.260	1.62 (1.10–2.38)	0.015
Morning surge-1 (mmHg)	0.99 (0.98–1.01)	0.524	0.99 (0.97–1.002)	0.087
Morning surge-2 (mmHg)	0.99 (0.98–1.02)	0.587	0.99 (0.97–1.004)	0.134
Morning surge-3 (mmHg)	0.996 (0.98–1.02)	0.690	0.99 (0.98–1.01)	0.372
24-h SBP variability (CV)	1.00 (0.94–1.06)	0.943	1.01 (0.96–1.06)	0.827

Adjusted by age, gender, hypertension, AF, LV mass index, LA diameter index, and interval between ABPM and brain MRI for SBI, and adjusted by age, race, hypertension, AF, LV mass index, LA diameter index, and interval between ABPM and brain MRI for upper quartile of log-WMHV. Multivariable logistic regression analyses controlling for clinical and echocardiographic covariates.

ABPM, ambulatory blood pressure monitoring; AF, atrial fibrillation; CI, confidence interval; CV, coefficient of variation; DBP, diastolic blood pressure; LA, left atrium; LV, left ventricle; MRI, magnetic resonance imaging; OR, odds ratio; SBI, silent brain infarcts; SBP, systolic blood pressure; WMHV, white matter hyperintensity volume.

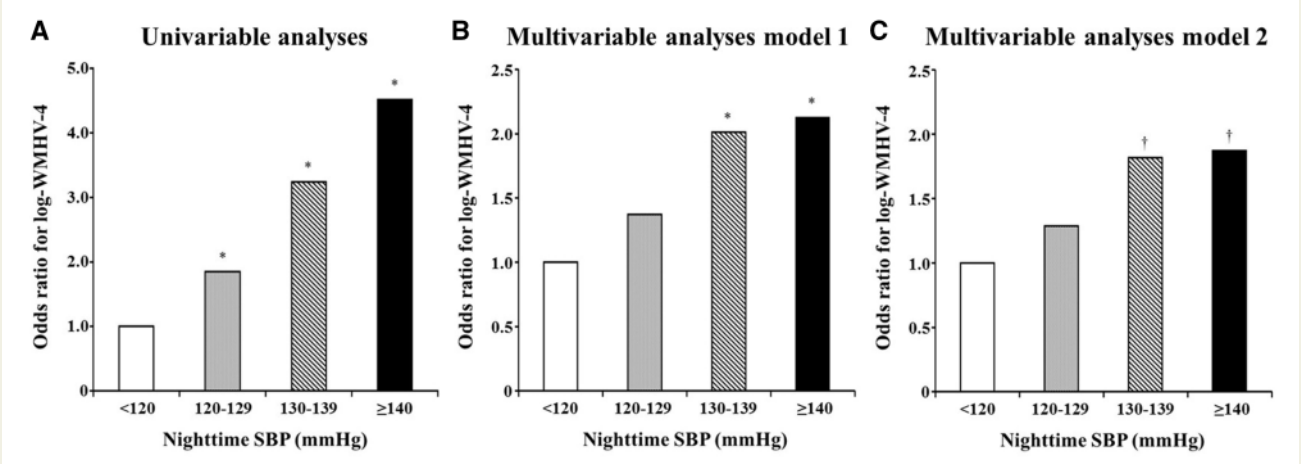

Figure 1 Association of night-time SBP subgroups with log-WMHV4. Reference: night-time SBP <120 mmHg. (*A*) Univariable analyses. (*B*) Multivariable Model 1: adjusted for age, race, hypertension, atrial fibrillation, left ventricular mass index, left atrial diameter index, and interval between ABPM and brain MRI. (*C*) Multivariable Model 2: Model 1 plus BP dipping pattern. ABPM, ambulatory blood pressure monitoring; CI, confidence interval; MRI, magnetic resonance imaging; OR, odds ratio; SBP, systolic blood pressure; WMHV, white matter hyperintensity volume. $^{*}P<0.01$ and $^{\dagger}P<0.05$ vs. night-time SBP <120 mmHg.

night-to-day SBP ratio predicted the occurrence of stroke in a meta-analysis of 17 312 hypertensive patients.[12] Evidence is mounting that the mean nocturnal BP level, rather than nocturnal BP non-dipping pattern, may be the stronger predictor of stroke risk in subjects with or without hypertension.[9,10] Specifically, Fagard *et al.*[10] demonstrated that a 17.6 mmHg difference in nocturnal SBP was associated with an increased risk of stroke in 3468 hypertensive patients, whereas night-to-day SBP ratio was not associated with stroke after adjustment for

Table 4 Comparison of the predictive value of SBP and DBP for upper quartile of log-WMHV

	OR (95% CI)	*P*-value
Daytime		
SBP (per 10 mmHg)	1.18 (1.01–1.39)	0.040
DBP (per 10 mmHg)	1.04 (0.81–1.34)	0.773
Night-time		
SBP (per 10 mmHg)	1.23 (1.05–1.44)	0.009
DBP (per 10 mmHg)	1.01 (0.79–1.30)	0.937

Adjusted by age, race, hypertension, AF, LV mass index, LA diameter index, and interval between ABPM and brain MRI.
ABPM, ambulatory blood pressure monitoring; AF, atrial fibrillation; CI, confidence interval; DBP, diastolic blood pressure; LA, left atrium; LV, left ventricle; MRI, magnetic resonance imaging; OR, odds ratio; SBP, systolic blood pressure; WMHV, white matter hyperintensity volume.

Table 5 Association between night-time SBP and upper quartile of log-WMHV

	OR (95% CI)	*P*-value
Model 1		
Daytime SBP (per 10 mmHg)	1.00 (0.82–1.22)	0.979
Night-time SBP (per 10 mmHg)	1.24 (1.03–1.48)	0.021
Model 2		
BP non-dipping pattern	1.26 (0.82–1.92)	0.288
Night-time SBP (per 10 mmHg)	1.21 (1.07–1.36)	0.003

Adjusted by age, race, hypertension, AF, LV mass index, LA diameter index, and interval between ABPM and brain MRI.
ABPM, ambulatory blood pressure monitoring; AF, atrial fibrillation; CI, confidence interval; LA, left atrium; LV, left ventricle; MRI, magnetic resonance imaging; OR, odds ratio; SBP, systolic blood pressure; WMHV, white matter hyperintensity volume.

24-h SBP. Our results extend these observations to the domain of subclinical cerebrovascular disease, in itself a strong risk factor for clinical stroke.

MRI-defined SBIs and WMHs are commonly present in elderly adults and are important markers of cerebral small vessel disease. Although SBIs and WMHs are not typically associated with overt, clinical stroke symptoms, they are not entirely silent or benign, as they are often associated with subtle neurological symptoms, and increased risk of stroke, cognitive impairment, dementia, and death.[13–17] The present manuscript reports a comprehensive assessment of different BP measures as they relate to the presence of subclinical cerebrovascular disease in the largest study with ABPM on the general population reported thus far. Furthermore, we show that the described associations were independent of echocardiographic indicators of hypertensive heart disease, such as LV hypertrophy and LA dilatation, which are known to be associated with stroke risk.[2–4] The underlying mechanisms of our main finding are not entirely clear, but we hypothesize several potential explanations. Elevated night-time BP may represents a persistent sympathetic overactivity, and therefore, be a better reflection of the mechanical stress on the arterial wall than daytime BP.[28] Impaired endothelial function,[29] platelet activation and enhanced inflammatory response,[30] and increased salt sensitivity[31] might be responsible for the association between elevated night-time SBP and subclinical cerebrovascular disease, because these factors are reported to be associated with nocturnal hypertension. Finally, the presence of a sleep disorder may also be involved in the observed association. In fact, sleep apnoea syndrome is associated with elevated night-time BP[32] as well as subclinical cerebrovascular disease.[33]

Although an increase in BP after awakening is a physiologic phenomenon, a marked and rapid elevation is associated with increased risk of cerebrovascular disease. Accumulating evidence suggests the existence of a significant association between MS and stroke, although the definitions of MS were not uniform across studies.[8,11] Pierdomenico *et al.*[11] showed that high MS predicted the incident stroke in treated hypertensive patients. Kario *et al.*[8] demonstrated a higher incidence of multiple SBIs in patients with MS (≥55 mmHg) than in those without it (57% vs. 33%). In our study, MS was not significantly associated with subclinical brain disease. This discrepancy may be explained by the different populations and comorbidities. Indeed, Asians appear to have greater morning BP elevation compared with Westerners.[34]

The clinical significance of ambulatory BP variability has also been examined in previous studies, showing conflicting results.[35,36] No BP variability parameter predicted stroke in 2649 hypertensive patients during mean follow-up of 6 years.[35] However, a recent study showed a positive relationship between ambulatory BP variability and incidence of stroke in 8938 individuals.[36] In our study, BP variability showed no independent association with subclinical cerebrovascular disease, suggesting that elevated mean BP values, especially at night, may be more important determinants of silent brain disease than BP fluctuations in the 24 h.

Because SBIs and WMHs carry an increased stroke risk, closer follow-up may be needed in individuals with elevated night-time SBP. Antihypertensive therapy focusing on the night-time period, for example, through the administration of antihypertensive drugs at bedtime, and/or more intensive risk factor control may have beneficial effects on subclinical cerebrovascular disease.[37] Furthermore, treatment of underlying conditions, such as continuous positive airway pressure therapy for sleep apnoea, may be useful for lowering night-time SBP.[38] However, these hypotheses require testing in prospective controlled trials. Our study also encourages further investigations of the underlying pathophysiological mechanisms that link night-time SBP and subclinical cerebrovascular disease.

Study limitations

The study cohort included predominantly elderly participants, with high prevalence of cardiovascular risk factors; therefore, the results may not directly apply to cohorts with different demographic composition and risk profiles. Because of the cross-sectional design of our study, we cannot establish a cause-effect relationship between night-time SBP and subclinical cerebrovascular disease. Although we accounted for several potential confounders, especially echocardiographic measures, and performed multivariate analyses adjusted for the main variables associated with subclinical cerebrovascular disease, we cannot exclude the possibility of unmeasured confounders playing a role in the observed associations. Finally, we did not

evaluate the prognostic value for subsequent clinical stroke of the presence of subclinical cerebrovascular disease as well as ABPM measures, as both of them are established stroke risk factors.[8–13,15]

Conclusions

In a predominantly elderly sample of the general population without history of stroke, night-time SBP measured by ABPM was associated with an increased risk of subclinical cerebrovascular disease, independent of traditional risk factors and echocardiographic changes related to hypertension and stroke. The assessment of night-time SBP by ABPM may identify individuals at higher risk of silent hypertensive-related brain target organ damage.

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