Original Article

Short-Term Blood Pressure Variability Relates to the Presence of Subclinical Brain Small Vessel Disease in Primary Hypertension

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Abstract—Blood pressure (BP) variability is associated with stroke risk, but less is known about subclinical cerebral small vessel disease (CSVD). We aimed to determine whether CSVD relates to short-term BP variability independently of BP levels and also, whether they improve CSVD discrimination beyond clinical variables and office BP levels. This was a cohort study on asymptomatic hypertensives who underwent brain magnetic resonance imaging and 24-hour ambulatory BP monitoring. Office and average 24-hour, daytime and nighttime BP levels, and several metrics of BP variability (SD, weighted SD, coefficient of variation, and average real variability [ARV]) were calculated. Definition of CSVD was based on the presence of lacunar infarcts and white matter hyperintensity grades. Multivariate analysis and integrated discrimination improvement were performed to assess whether BP variability and levels were independently associated with CSVD and improved its discrimination. Four hundred eighty-seven individuals participated (median age, 64; 47% women). CSVD was identified in 18.9%, related to age, male sex, diabetes mellitus, use of treatment, ambulatory BP monitoring–defined BP levels, and ARV of systolic BP at any period. The highest prevalence (33.7%) was found in subjects with both 24-hour BP levels and ARV elevated. BP levels at any period and ARV (24 hours and nocturnal) emerged as independent predictors of CSVD, and discrimination was incrementally improved although not to a clinically significant extent (integrated discrimination improvement, 5.31%, 5.17% to 5.4%). Ambulatory BP monitoring–defined BP levels and ARV of systolic BP relate to subclinical CSVD in hypertensive individuals. **(*Hypertension*. 2015;66:00-00. DOI: 10.1161/HYPERTENSIONAHA.115.05440.)** ● **Online Data Supplement**

Key Words: blood pressure ■ blood pressure monitoring, ambulatory ■ cerebral small vessel diseases ■ stroke ■ stroke, lacunar

Current guidelines recommend the assessment of vascular risk factors, target organ damage, and blood pressure (BP) levels to guide the treatment on primary hypertension.[1] Besides BP levels, other BP-related features, such as the nocturnal dipping[2] or more recently, visit-to-visit or long-term BP variability (BPV), have been independently associated with clinical cardiovascular outcomes in a recent systematic review and meta-analysis.[3]

Also, the prognostic value of BPV measured with ambulatory BP monitoring (ABPM) for 24 hours (also value-to-value or short-term BPV) has been evaluated. Data on short-term BPV from 11 populations[4] suggest a positive association between measures of short-term BPV and cardiovascular death or any (fatal and nonfatal) event. Although the contribution of short-term BPV to the prediction of cardiovascular events was shown to be small (<1%), this is still a matter of debate because results from individual studies support significant contributions.[5,6]

It has been also suggested that the prognostic significance of BPV on stroke risk is weaker for short-term than for long-term BPV in treated hypertension.[7] However, these data need further investigation taking into account not only between subject BPV but also within subject BPV.

Moreover, several indices of short-term BPV have been related to the presence of subclinical damage in one or multiple organs, including the heart, kidney, and vessels, independently of BP levels.[8–10] About the brain, hypertension is a major risk factor for cerebral small vessel disease (CSVD), which is an

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important contributor to stroke and cognitive decline in the elderly. CSVD might be subclinical for long before the first clinical manifestations occur.[11] Therefore, early identification of hypertensive patients with subclinical CSVD might have the potential to prevent future poor outcomes. Although circadian variations have been associated with CSVD before,[12] to our knowledge, the effect of short-term BPV estimated with metrics that avoid the contribution of nocturnal BP fall to BPV, such as weighted SD or average real variability (ARV), has not been established in relation to CSVD. Also, whether these metrics of BPV and BP levels increase the prediction for the diagnosis of CSVD over clinical parameters or office BP levels is not known. In this study, we evaluated the association between short-term BPV and BP levels measured by 24-hour ABPM and the presence of subclinical CSVD in a cohort of Mediterranean hypertensive individuals and investigated its predictive role over office BP levels and clinical information to identify CSVD.

Methods and Subjects

Subjects are included in a large epidemiological ongoing study (Investigating Silent Strokes in Hypertensives [ISSYS]: a magnetic resonance imaging study). The detailed study protocol has been published elsewhere.[13] Briefly, this was a cohort study conducted in randomly selected hypertensives, aged 50 to 70 years, with no previous history of clinical stroke or dementia, and routinely attended by primary care physicians in our health area. The main objectives of this study were to determine the prevalence of several subclinical or silent brain vascular lesions and to study their determinants and relation to further stroke and dementia.

Twenty-Four–Hour ABPM

From 1037 participants included in the ISSYS study, 642 were enrolled in the ABPM substudy. The remaining ones were not included for different reasons, including either refusal of participants, unavailability of the device, or the presence of atrial fibrillation (Figure S1 in the online-only Data Supplement). Those included in the ABPM substudy were significantly older than those who did not participate (median [interquartile range], 64 [60–67] versus 63 [58–67]; P=0.003), but they did not differ on sex or office systolic BP (SBP) or diastolic BP (DBP).

All subjects underwent ABPM with a fully automatic device Spacelabs 90217-5Q (Spacelabs Healthcare, Issaquah, Washington), validated according to the protocol of the British Hypertension Society.[14] ABPM recordings were carried out in work days, and participants were asked to follow their usual activities, although keeping from physical exercise and avoiding excessive movement on their nondominant arm during measurements. Readings were performed every 20 minutes during daytime (06:00–22:59 hours) and every 30 minutes during nighttime (23:00–05:59 hours). Cuffs for obese patients were used when necessary. We required all recordings to have at least 70% valid measurements to be included in this analysis. Also, those with <2 valid measurements per hour during daytime or <1 valid measurement per hour during the sleeping period were also excluded. The recruitment period lasted from November 2010 to May 2012, and ABPM was conducted on the same week of baseline visit. This study was approved by our local institutional review Ethics Committee, and all subjects gave their informed consent to participate.

Metrics of BPV

Several metrics of short-term BPV were calculated in this study: (1) the within-subject SD of all systolic and diastolic readings during 24 hours, daytime, and nighttime; (2) the coefficient of variation defined as the ratio between the variability (SD) and the mean SBP or DBP at the same periods; (3) the weighted SD of SBP and DBP, defined as the mean of day and night SD values corrected for the number of hours included in each of these periods[15]; and finally, (4) the ARV of 24-hour, daytime, and nighttime SBP or DBP, which averages the absolute differences between consecutive measurements and thus accounts for the order in which they were obtained.[16]

We also assessed circadian variation by calculating the nocturnal systolic dip as follows: ([daytime SBP−nighttime SBP]/daytime SBP)×100. Normal dipping was considered in those achieving between 10% and 20% dip.[17]

Other Covariates

Assessment of all covariates included in this study was carried out by interviewing participants and reviewing medical records. These included demographic (age and sex) and clinical variables, such as the history of diabetes mellitus, dyslipidemia, obesity, and alcohol or tobacco consumption. We also collected information about the time since diagnosis of hypertension and treatment with BP-lowering agents (presence, type, and adherence to treatment).

Office BP was measured with an oscillometric device (OMRON M6 Comfort), and the mean of the last 2 of 3 determinations after 5-minute rest was recorded. Detailed description of covariates and definitions of office and ABPM-related BP control is available in the online-only Data Supplement.

Brain Magnetic Resonance Imaging

A brain magnetic resonance imaging with an established data acquisition protocol[13] was carried out within the next month after study entry and ABPM. All examinations were performed with the same 1.5 Tesla MR (Signa HDx 1.5, General Electrics, Waukeska, WI) and included axial and sagittal T1-weighted images and axial propeller T2-weighted, fluid-attenuated inversion recovery, and gradient recalled echo sequences. All magnetic resonance imaging examinations were assessed by trained readers who were blind to participants' characteristics.

For the purpose of this study, we identified several markers of CSVD, specifically the presence and number of lacunar brain infarcts and the presence of white matter hyperintensities (WMH) located either in the periventricular or in the deep subcortical areas. Dilated Virchow–Robin spaces, microbleeds, and brain atrophy were not considered in our study. Briefly, lacunar brain infarcts (or lacune of presumed vascular origin according to the STandards for ReportIng Vascular changes on nEuroimaging [STRIVE] criteria[18]) were defined as lesions with cerebrospinal fluid–like signal characteristics in all pulse sequences and with the presence of a hyperintense rim surrounding the lesion

in fluid-attenuated inversion recovery sequences that were located in the territory of a perforating arteriole and had a maximum diameter comprised between 3 and 20 mm. WMH were rated in fluid-attenuated inversion recovery sequences according to the Fazekas scale. Briefly, these scale grades are for periventricular: 0 (absent lesions); 1 (caps or pencil-thin lining); 2 (smooth halo); 3 (irregular periventricular lesions extending into the deep white matter) and for deep white matter: 0 (absent); 1 (punctuate foci): 2 (beginning of confluent foci); 3 (large confluent areas).[19] We classified subjects as having CSVD when they had at least 1 lacunar infarct or scored ≥2 points in either the periventricular or in the deep white matter in the Fazekas scale (Figure S2).

Statistical Analyses

Normality for BP measurements was assessed by the Kolmogorov–Smirnov test. Correlations between BPV metrics were assessed by nonparametric tests.

Univariate analyses were conducted to assess the association between clinical variables, 24-hour, awake, and asleep BP levels, BPV metrics, and the presence of CSVD. To account for multiple testing, false discovery rate corrections were applied in these analyses. Next, as there are not established cutoffs for BPV, the ARV of SBP was categorized into 3 groups (low, medium, and high) according to tertiles, and we conducted univariate analysis to determine which variables were related to the degree of BPV in our sample.

Then, to study the association between ambulatory BP levels and 24-hour BPV parameters and CSVD, we conducted forward stepwise logistic regression models adjusting for potential confounders, such as age, sex, diabetes mellitus, waist circumference, office DBP levels, and the use of BP-lowering agents. All models were carried out including equal measures (either SBP or DBP) and concerning the same periods (ie, when a 24-hour parameter of SBP variability was tested in the model, 24-hour SBP was also included in the model). Covariates were chosen based on the literature[20–22] or on our univariate analysis.

Finally, we evaluated the potential usefulness of ABPM parameters (both SBP levels and BPV metrics) over clinical factors and office BP levels as predictors of CSVD by comparing the areas under the receiver operating characteristics curves of both models containing or not ABPM information. Comparisons were assessed by means of Delong method using MedCalc 12.4 software.[23] Improvements on the performance of office BP levels and other clinical variables by the addition of ABPM parameters were also measured by the integrated discrimination improvement statistic, which assesses improvement in risk discrimination (ie, how well a model separates subjects with CSVD when compared with those without CSVD) by estimating the change in the difference in the mean predicted probabilities of CSVD between those with and without it, after introducing ABPM parameters to the clinical model. Positive values indicate improved discrimination. Confidence interval (95%) for the integrated discrimination improvement test was calculated by bootstrapping implemented with R software. Statistical significance for all analysis was set at $P<0.05$.

Results

A total of 487 participants were analyzed; median age was 64 (59–67) years; and 46.8% were women. Most of them were treated with BP-lowering drugs (95.1%) and were longstanding hypertensive individuals (median duration, 8.6 years).

About brain lesions, 92 (18.9%) participants were classified as having CSVD (55 and 32 participants had periventricular and deep WMH scoring ≥2 points respectively, 48 had at least 1 lacunar infarct, and in 35, ≥2 of these lesions were present). In the univariate analysis (Table 1), CSVD was associated with increasing age, male sex, diabetes mellitus, and with higher ABPM-defined BP levels at any period evaluated (24-hour, daytime, or nighttime). As for office BP levels, only DBP was slightly higher in those with CSVD ($P=0.14$). Treatment was associated with CSVD (93% were treated in the group without CSVD versus 100% in those with CSVD; $P=0.01$), although no differences were observed on the amount of antihypertensive agents ($P=0.19$) or the type of treatment (all $P>0.05$). Moreover, patients receiving treatment at night were not different in terms of the presence of CSVD than those who were not (24.2% versus 16%; $P=0.11$).

Then, we calculated BPV metrics in all periods and found that they were all significantly correlated with each other (Table S1). On BPV metrics and CSVD (Table 2), after taking into account multiple testing, we found that 24-hour, daytime, or nighttime ARV of SBP significantly increased in those with CSVD.

Also, as these imaging markers of CSVD might have different pathophysiology, we analyzed the relationship between BPV metrics and lacunar infarcts and periventricular and deep WMH grades separately and found similar results that the ARV of SBP was the only metric significantly associated with all these lesions (Tables S2–S4). On the contrary, no associations were found between any DBP measurement of variability and CSVD.

Furthermore, to understand the factors influencing BPV, we divided 24-hour ARV of SBP into tertiles and found that increasing ARV was related to male sex, diabetes mellitus, larger waist circumference, and poor office or ABPM-defined control (all $P<0.05$; Table S5). In contrast, increasing BPV was not associated with the presence or type of BP-lowering agents used in our cohort.

Figure S3 represents the contribution (in percentages) of SBP control and ARV of SBP to the prevalence of CSVD. Remarkably, the highest CSVD prevalence (33.7%) was found when 24-hour SBP control was poor and ARV the highest. Moreover, both SBP control and ARV of SBP were also significantly associated with the number of different imaging markers that were present in each participant, as it is shown for 24-hour values in Figure S4.

We performed multivariate analysis to assess whether SBP levels and ARV of SBP were independently associated with CSVD after adjustment by clinical variables, use of BP-lowering treatment, and office BP. As it is shown in Table 3, higher SBP levels and ARV of SBP were independent predictors of CSVD during 24 hours and nighttime, whereas

Table 1. Baseline Factors Associated With the Presence of CSVD

Characteristics	All Subjects, n=487	CSVD=No, n=395	CSVD=Yes, n=92	*P* Value
Age	64 (59–67)	64 (58–67)	65 (62–68)	0.006*
Sex, male	53.2%	50.4%	65.2%	0.010*
Diabetes mellitus	24.8%	22.8%	33.7%	0.029*
Dyslipidemia	71%	71.4%	69.2%	0.69
Smoking habit	14.4%	15.2%	11%	0.29
Central obesity	71.2%	71.1%	71.4%	0.95
Body mass index	29.8±4.3	29.8±4.2	29.7±4.7	0.55
Duration of hypertension, y	8.6 (5.2–12.7)	8.2 (5.1–12.6)	9.3 (5.9–12.9)	0.21
Dipper status	57.1%	62.4%	54.8%	0.20
Established cardiovascular disease	14.4%	13.2%	19.6%	0.11
Office BP control, poor	57.2%	56.2%	61.5%	0.35
Office SBP, mm Hg	142 (132–152.5)	142 (133–152)	141.5 (130–155)	0.89
Office DBP, mm Hg	77.7±9.1	77.4±8.7	79±10.3	0.14
24-h poor control	47.6%	43.8%	64.1%	<0.001*
24-h SBP, mm Hg	125.4 (117.8–133.8)	125 (116.3–132.2)	130.3 (121.3–140)	<0.001*
24-h DBP, mm Hg	76.2±7.4	75.8±7.4	77.8±7.3	0.018*
Daytime hypertension	48.7%	45.5%	62%	0.005*
Daytime SBP, mm Hg	131.6 (123.7–139.6)	131 (122.8–138.3)	135 (126.4–145.7)	0.001*
Daytime DBP, mm Hg	80.8±7.9	80.5±7.9	82±7.7	0.084
Nocturnal hypertension	52.9%	50.5%	63%	0.03*
Nocturnal SBP, mm Hg	116 (106.6–124.5)	115(106–123)	119 (112–130)	0.001*
Nocturnal DBP, mm Hg	69.1±8.0	68.6±7.8	71±8.6	0.011*
BP-lowering treatment	95.1%	93.9%	100%	0.01*
BP-lowering treatment at night	17.6%	16%	24.2%	0.11
No. of BP-lowering agents				
No treatment	4.9%	6.1%	0%	0.19
1 BP-lowering agent	41.7%	41.3%	43.5%	
2 BP-lowering agent	35.7%	35.4%	37%	
≥3 BP-lowering agents	17.7%	17.2%	19.6%	
Adherence to treatment	54%	54.5%	51.7%	0.64
Class of BP-lowering drugs				
ACEIs	48.8%	49.3%	46.7%	0.66
ARB	26.7%	25.2%	32.6%	0.15
β-Blockers	20.5%	19.6%	23.9%	0.36
Nonloop diuretics	46.5%	48%	40.2%	0.18
Dihydropyridinic CCB	17.7%	17%	20.7%	0.41

Data are provided as mean±SD or median (interquartile range) as appropriate. ACEIs indicate angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; BP, blood pressure; CCB, calcium-channel blockers; CSVD, cerebral small vessel disease; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*Remained significant after correction for false discovery rate.

during daytime, only BP levels but not ARV of SBP predicted this outcome. No significant interactions between SBP control and ARV of SBP were found in the analysis.

Overall predictive capacity of the models containing or not ABPM parameters (BP levels and ARV of SBP) were compared by means of the areas under the receiver operating characteristics curves, which showed a mild and not significant improvement by the addition of ABPM data (area under the curve changed from 0.62 to 0.68, P=0.06 for 24-hour data, other periods not shown). Likewise, integrated discrimination improvement (which assesses how well ABPM parameters improve the sensitivity for the detection of CSVD after being added to the clinical model without sacrificing specificity) was increased incrementally, although this was not clinically relevant (integrated discrimination improvement for 24-hour data=5.3%, between 5.17 and 5.40%, other periods not shown; Figure S5).

Finally, we estimated the individual contribution of the ARV of SBP to the prediction of CSVD beyond clinical variables and also ABPM-defined BP levels, and it was small (0.9% for 24 hours and 1.3% for nocturnal ARV of SBP).

Table 2. Association Between BPV Measurements and CSVD

BPV Measures	CSVD=No, n=395	CSVD=Yes, n=92	*P* Value
Systolic BP			
24-h ARV	9.4 (8.3–10.7)	10.3 (9.3–11.4)	<0.001*
Awake ARV	10 (8.6–11.4)	10.7 (9.3–12.1)	0.005*
Asleep ARV	8.7 (7.2–10.5)	9.9 (7.8–11.8)	0.001*
24-h SD	14.9 (12.7–17.2)	15.4 (12.8–17.4)	0.48
Awake SD	13 (11–15.2)	13.3 (11.4–15.3)	0.32
Asleep SD	10 (8.2–12)	11.1 (8.6–13)	0.04
24-h weighted SD	12.9 (10.9–15.1)	13.2 (11.4–15.3)	0.42
24-h CV	0.12 (0.10–0.14)	0.12 (0.10–0.14)	0.47
Awake CV	0.10 (0.08–0.12)	0.10 (0.08–0.11)	0.94
Asleep CV	0.09 (0.07–0.10)	0.09 (0.07–0.11)	0.67
Diastolic BP			
24-h ARV	6.7 (5.9–7.7)	6.9 (6.1–8.1)	0.13
Awake ARV	6.9 (5.8–8.3)	7.0 (6.1–8.4)	0.12
Asleep ARV	6.5 (5.3–7.7)	6.7 (5.2–8)	0.49
24-h SD	10.6±2.3	10.5±2.5	0.76
Awake SD	8.7 (7.4–10.3)	8.4 (7.6–10.2)	0.87
Asleep SD	7.6±2.2	7.6±2.1	0.99
24-h weighted SD	8.6 (7.4–10.3)	8.3 (7.5–10.2)	0.85
24-h CV	0.14±0.03	0.14±0.03	0.18
Awake CV	0.11 (0.09–0.13)	0.10 (0.09–0.12)	0.52
Asleep CV	0.11±0.03	0.11±0.03	0.38

Data are provided as mean±SD or median (interquartile range) as appropriate. ARV indicates average real variability; BPV, blood pressure variability; CSVD, cerebral small vessel disease; and CV, coefficient of variation.

*Remained significant after correction for false discovery rate.

Discussion

Our main finding in this study is that short-term ARV of SBP, as a measure of BPV, is independently related to the presence of CSVD even after accounting for ambulatory BP levels and other clinical covariates. In addition, we showed that both ambulatory BP levels and ARV of SBP might improve, although not to a clinically significant extent, CSVD discrimination. To that purpose, 24-hour or nighttime assessments are superior to ambulatory daytime or office measurements.

The use of ABPM over office BP levels in treated hypertensives is well established for risk stratification of clinical cardiovascular events[24]; also our results support a stronger association of CSVD with ABPM parameters than with office BP levels, in hypertensive subjects when symptoms are not fully established.

In our study, among several metrics of BPV, only the ARV of SBP was independently associated with the presence and accumulation of neuroimaging markers of CSVD. Other metrics of BPV (such as the SD or coefficient of variation, which are mainly centered in the dispersion around the mean value) were only mildly correlated with ARV and did not relate to CSVD. Possibly, not all metrics of BPV collect the same aspects of this BP component and they might relate differentially with prognosis in hypertension. ARV has some advantages over other metrics, as it focuses on short-term variations between consecutive readings, it avoids the low frequency discontinuous sampling of ABPM for 24 hours, and it does not include the BP changes between the night and day in its estimation. To date, however, there are no accepted standards on how to calculate and report BPV or which cutoffs better discriminate subjects at high or low BPV.

Other studies investigated the relationship between BPV and imaging markers of CSVD in hypertensive cohorts. Sierra et al[25] described no association between 24-hour SD and the presence of WMH, whereas Goldstein et al[26] found awake SD of SBP related to the presence of severe WMH. Other studies including demented subjects[27] found association of WMH with higher SD of SBP at any period, higher asleep coefficient of variation of SBP, and higher maximal variation. Also, BP variation distinguished between those with subcortical vascular ischemic dementia (Binswanger disease) from controls in untreated subjects and was related to the amount of cerebrovascular lesions in treated patients.[28] To our knowledge, no previous study has evaluated the relationship between metrics of BPV, such as ARV or weighted SD and several markers of CSVD before.

In contrast to this short-term BPV, most studies in the past were focused on circadian BP changes occurring between night and day and WMH load. However, results are not consistent among studies. Abnormal BP fall in nondippers and extreme dippers was linked to the presence of WMH[20,21] in hypertensive cohorts and in healthy controls.[22] In contrast and similar to our findings, others[25,27,29] failed to find such associations. Instead, our results would underscore the role of nocturnal hypertension as a main contributor to CSVD. Higher nocturnal BP levels and ARV of SBP were independently related to CSVD, rather than the nocturnal BP fall. In the same direction, it has been recently suggested that the nondipping status could be related to a more advanced disease (with reduced kidney function and overt cardiovascular disease), whereas nocturnal hypertension is also associated with earlier or subclinical organ damage.[30] In our study, the majority (97%) of hours during the night were evaluated with at least 2 measures, providing enough consecutive measurements

Table 3. Associations of 24-hour, Daytime, and Nighttime Blood Pressure Levels and Average Real Variability of SBP With Cerebral Small Vessel Disease

	OR (95% CI), *P* Value		
Characteristics	24-h	Daytime	Nighttime
Mean SBP, mm Hg	1.03 (1.01–1.05), 0.005	1.03 (1.01–1.05), 0.001	1.02 (1.01–1.04), 0.004
Average real variability, mm Hg	1.16 (1.02–1.33), 0.024	1.07 (0.97–1.19), 0.17	1.11 (1.02–1.22), 0.020

Models are adjusted by age, sex, diabetes mellitus, waist circumference, office DBP, use of antihypertensive treatment, and the corresponding mean SBP and average real variability of SBP of each period. CI indicates confidence interval; DBP, diastolic blood pressure; OR, odds ratio; and SBP, systolic blood pressure.

to calculate ARV. This should be taken into account for the design of future studies aimed to assess the role of BP variation at night.

Several factors are different in this study and other previous studies. We only excluded subjects with the presence of previous stroke and dementia, whereas other studies did not include those with cardiac, renal, or systemic diseases. Also almost all our participants were treated with BP-lowering drugs at the time of the ABPM and most of them long before that too. In fact, we found that treatment itself was associated with the presence of CSVD (possibly related to longer duration of hypertension), although its effect was not independent after adjusting by other confounders.

Our study has both strengths and limitations. This study has been performed in a large sample of hypertensive subjects who were randomly collected in a community setting, avoiding selection biases. Also, we analyzed at once various metrics of BPV, including some that can avoid the contribution of nocturnal BP fall in their estimation and performed fully adjusted models to correct for the presence of vascular risk factors that might have an effect in cerebral lesions or BPV. Also, we not only described an association between ARV of SBP and CSVD but also provided a measure of discrimination of this metric and BP levels to diagnose CSVD.

Several considerations need to be taken into account for the interpretation of our results. Our prevalence of CSVD was lower than in previous studies, and because we only found 1 metric of BPV (ARV of SBP) associated with CSVD, a replication study in an independent cohort would reinforce our findings. Probably, reducing the time between measurements (considering intervals of ≤15 minutes between readings) or evaluating BP continuously would provide a more accurate assessment of BPV, although this latter approach cannot be easily reached in large epidemiological studies. Also, to determine the real contribution of BPV to CSVD, future studies would need to investigate the reproducibility of short-term BPV measurements over time and design prospective studies with progression of CSVD and clinical end points (lacunar stroke and subcortical vascular dementia) as outcomes. These studies would need to control for a possible effect of cognitive performance on ABPM because CSVD is strongly associated with cognitive impairment and also to address the potential effect of different levels of physical activity during ABPM on short-term BPV and CSVD.

So far, it is thought that increased BPV would lead to more mechanical stress on the wall vessel, endothelial injury,[31] and arterial stiffness,[32] which may favor CSVD[33]; however causal relationships cannot be established. Finally, it is important to keep in mind that not all antihypertensive drugs have the same effect in BPV and indeed, those drugs able to reduce both BP levels and BPV have major effects on the reduction of stroke risk.[34] The potential benefit of treating patients with subclinical CSVD with the selection of treatment based on BPV too, to prevent stroke and dementia, deserves to be explored in further studies.

Perspectives

This study has identified ABPM-defined BP levels and ARV of SBP as independent predictors of CSVD in asymptomatic hypertensives. Both ABPM parameters improved discrimination of CSVD compared with clinical variables and office BP levels, although to a little extent.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Average real variability of systolic blood pressure (BP) as a measure of short-term BP variability relates to the presence of cerebral small vessel disease (CSVD) independently of BP levels.
- Both BP levels and average real variability improve discrimination of CSVD compared with office BP levels and clinical parameters, although to a small extent.

What Is Relevant?

- Still, the usefulness of these ambulatory BP monitoring parameters to discriminate CSVD in a clinical context might be limited.
- Our results emphasize the role of nocturnal hypertension and BP variability in relation to the presence of CSVD.

Summary

BP variability is related to the presence of CSVD, independently of BP levels. Both ambulatory BP monitoring–defined BP levels and variability improve discrimination of CSVD, compared with clinical variables and office BP, in long-treated and asymptomatic hypertensive subjects. However, this small increase in discrimination might be not clinically significant.