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ORIGINAL ARTICLE

Ambulatory blood pressure, asymptomatic cerebrovascular damage and cognitive function in essential hypertension

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Prolonged exposure to elevated blood pressure (BP) can lead to both structural (white matter lesions (WML) or infarctions) and functional changes in the brain. We studied in previously diagnosed essential hypertensive individuals if diurnal BP variation and ambulatory BP (ABP) profile (daytime, night time and 24-h BP averages) were related to evidence of WML, the presence of 'silent' infarcts, and cognitive performance. A group of 86 patients (mean age 57.4±10 years, range 40–80) were first screened for hypertension-related organ damage and underwent 24-h ABP monitoring, magnetic resonance imaging (MRI) of the brain, and a comprehensive neurocognitive assessment. Age and ABP profile were related to more periventricular, but not subcortical, WML and to presence of lacunar infarctions on MRI. After correction for demographical group differences, no association was found between night time dipping of BP on the one hand and both WML load and cognitive parameters (verbal memory, sensorimotor speed, cognitive flexibility) on the other. The presence of lacunar infarctions, however, predicted lower performance on verbal memory. Furthermore, daytime and 24-h pulse pressure averages were associated with pWML, whereas systolic BP and mean arterial pressure (MAP) for daytime, night-time and 24-h periods were higher in patients with lacunar infarctions. Notwithstanding the large variability of WML in this sample, the evidence of a connection between diurnal BP variation and early target organ damage in the brain was not convincing. However, the ABP profile may be predictive of cerebral lesion type.
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Keywords: ambulatory blood pressure; white matter lesions; cognitive function; memory

Introduction

Hypertensive individuals are at risk for target organ damage, including in the brain. In hypertension, atherosclerotic changes occur in the large and small cerebral arteries, together with a reduced autoregulation of cerebral blood flow.[1,2] Hypertension not only increases the risk for stroke, but it has also been associated with the prevalence of subcortical and periventricular white matter lesions (WML), as observed with magnetic resonance imaging (MRI).[3] The presence of WML is a prognostic factor for the development of stroke[4,5] and, on a functional level, for cognitive impairment,[6] particularly when attentional processes, speed of information processing[7] and frontal lobe function are involved.[8] The aetiology of WML still is poorly understood, but seems to be related to small vessel disease, demyelinisation, and the occurrence of cerebral ischaemia.[9,10] Apart from hypertension,[3] other risk factors for WML are age, diabetes, and a history of stroke or heart disease.[11] WML also appear to be very common in healthy older individuals.[11] In essential hypertension, the presence of WML has been associated with the duration[3,12] and severity of this condition,[13,14] the lack of blood pressure (BP) control in treated patients,[15,16] and an exaggerated decline in nocturnal BP.[17,18] However, recent studies on ambulatory BP (ABP) monitoring and WML did not replicate the latter finding, but rather stressed the severity of elevated BP[19] and a blunted fall in nocturnal heart rate.[14] In addition, steady and pulsatile components of daytime, night time and 24-h BP have gained increased interest in the prediction of WML, lacunar infarctions and stroke.[20,21] So far, studies on hyper-

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tension and WML have been focussing primarily on older patient groups. Moreover, the description of WML in terms of subtype (subcortical or periventricular) and quantity has often been rather crude. This may complicate drawing conclusions from these studies because the etiology of WML subtypes may actually differ.[22] Improved methods to quantify WML subtypes have become available and have been validated and studied in large population samples.[23] For example, based on a strict WML scoring protocol, periventricular WML (pWML) were associated with lower psychomotor speed and general cognitive function in 1077 individuals from the Rotterdam scan study, aged 60 years and older,[24] while subcortical WML (sWML) were related with depressed mood.[25] In addition, pWML were associated with a three-fold greater reduction in general cognitive functioning (Mini-Mental State Examination) after a mean follow-up duration of 7.3 years.[26]

We designed the present study in untreated, asymptomatic, middle-aged to older essential hypertensive individuals, in order to identify possible relationships between ABP, cerebral damage (WML or lacunar infarctions) on MRI, and the cognitive performance in different functional domains. For this purpose, the diurnal BP profile was derived from ABP recordings, the subtype and quantity of WML were determined according to a well-established protocol[27] and a comprehensive battery of cognitive tests was administered to evaluate the potential consequences of diurnal BP variation on cognitive function and cerebral WML load.

Materials and methods

Subjects

Participants for this study were recruited from the hypertension outpatient clinic at the Department Of Internal Medicine of the University Hospital Maastricht. A group of 105 patients, aged between 40 and 80 years and who were previously diagnosed with essential hypertension, were selected for this study. Exclusion criteria were clinically documented ischaemic or valvular heart disease, congestive heart failure, cerebrovascular accidents, or transient ischaemic attacks, chronic renal failure (serum creatinine $>150\,\mu$mol/l), secondary hypertension, or claustrophobia (MRI investigation). In all patients, antihypertensive medication was discontinued 3 weeks prior to the clinical assessments. None of the participants developed adverse events during the drug-free episode. The study was approved by the local Medical Ethics Committee and all gave their informed consent in writing.

BP measurement

Noninvasive ambulatory BP measurements (Spacelabs 90217; Spacelabs Inc., Redmond, WA, USA) were obtained on weekdays, starting early in the morning. Measurements were taken at the nondominant arm, every 15 min during the day and every 30 min at night. Patients were instructed to adhere to their normal daily activities and regular sleeping hours. For analysis, daytime episodes were defined from 09 00 until 21 00, and night time episodes from 01 00 until 06 00, according to the guidelines of the European Society of Hypertension (ESH[28]). BP and heart rate averages, and diurnal BP rhythm were determined for these episodes. Recordings were not edited.

MRI investigation and WML scoring

MRI scans were made on a 1.5 T Philips Intera NT. The scan protocol included axial proton density (PD), T2-weighted fast spin-echo (FSE), and T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences. All scans were analysed off-line in order to obtain estimates of the total volume of sWML, the extent of pWML and the presence of 'silent' lacunar infarctions. WML were scored according to the criteria of Achten *et al*.[27] For this purpose, the axial PD, T2-weighted, and FLAIR image stacks were aligned side by side in synchrony, on a computer screen, using custom software (Brain Image Analysis System[29]) on a Macintosh G3 computer. This program allowed systematic inspection of the synchronised image stacks and manual demarcation of regions of interest (ROIs). At each level, sWML were scored using predefined ROI masks, that is, circles with a diameter of 2, 6, and 12 mm, respectively. Lesions were first identified on the FLAIR image. then confirmed and traced on both other images at the same axial level. If a lesion was present on all three images, the mask that matched the ROI best was fitted over the lesion. After inspection and delineation of all sWML in a stack the program generated an output file containing the number and size of all lesions at each level of the scan. These data were transferred to a standard spreadsheet to yield a total sWML volume score for each patient. In this procedure, ROIs were inflated to spheres with the same diameter, with corresponding volumes of 4.2, 113 and 905 mm^3, respectively. sWML were processed by one medical investigator (MvB) after satisfactory intra-class correlations (ICC) between 0.81 and 0.98 had been reached.[30] These were based on the independent assessments of subsequent series of 10 random stacks by this investigator and an experienced neuroradiologist (PH). Next, the overall sWML volume was calculated. pWML severity, ranging between 0 and 3, was scored separately for frontal and occipital regions ('caps') and the medial periventricular lining ('bands'), which were then summed to an overall pWML score.[27] Finally, the presence of other cerebrovascular lesions (lacunar infarctions) was identified in a separate session by the neuroradiologist (PH).

Cognitive assessment
All participants underwent a 1.5 h cognitive assessment by an experienced neuropsychological assistant. Different tests were used to probe several aspects of cognitive function, including memory, attention, sensorimotor speed and cognitive processing speed, according to procedures outlined briefly below and described in more detail elsewhere.[31] The same battery of tests has been employed in the Rotterdam scan study.[24]

The word learning task (WLT) is based on the Auditory Verbal Learning Test[32] and evaluates the ability to acquire and retain new verbal information (15 monosyllabic words). The total number of correctly reproduced words in five repeated learning trials is recorded, in addition to the maximum score in five trials and the number of correctly reproduced words after 20 min. The concept shifting task (CST) evaluates behavioural planning and evaluation.[33] A person's ability to alternate two psychological concepts during task performance is measured, in this case cancellation of 16 empty circles arranged in a larger circle (task 0), and circles that contain numbers (A), letters (B), or both (C), in correct order. Task C is considered the more complex 'switch' task. The outcome is the time required to complete each task. Susceptibility to language interference was measured in the Stroop colour word test (SCWT), consisting of three subtasks: (I) colour word naming, (II) colour naming and (III) naming of colour words printed in a different colour ('interference task'). SCWT-III is often used as a test of attentional capacity, which shows robust effects of chronological age.[34]

Other assessments
Other variables related to cardiovascular risk were assessed during the first study visit. Blood samples were drawn in the morning from fasting patients for assessment of total cholesterol and glucose levels. Hypercholesterolemia was defined as a total cholesterol level exceeding 6.5 mmol/l and/or the use of lipid-lowering drugs. Diabetes mellitus (DM) was considered to be present in case of fasting plasma glucose levels above 6.9 mmol/l and/or the reported use of oral antidiabetic drugs, or insulin. The height and weight of patients as measured and body mass index (BMI) was calculated. Physical activity was defined as the total hours spent on physical exercise during 1 week and actual smoking status (yes/no) was recorded. Furthermore, we collected *post hoc* the duration of hypertension history and antihypertensive medication use from the medical records of all participants in order to assess possible confounding of these variables on the results of the study.

Data reduction and analysis
Average levels of systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), pulse pressure (PP) and heart rate (HR) were computed for daytime, night time and 24-h episodes, using a custom computer program available at the Department of Internal Medicine. According to the Verdecchia criterion, participants were classified as *nondippers* when the reduction in both their systolic and diastolic night time BP was $<10\%$ of the average daytime levels,[35] while others were classified as *dippers*. In addition, dipping quantity was expressed as the relative decrease in MAP from daytime to night time episode (*relative dipping*).

Three domains of cognitive performance were defined: memory, sensorimotor speed and cognitive flexibility.[36–38] Compound domain scores were computed for each individual, based on the *Z*-transformed raw scores in the total sample. In this way, a reduction in performance outcome parameters can be achieved while the robustness of the underlying cognitive construct is improved.[39,40] Next, the average *Z*-score was obtained from tests included in the compound performance index. The memory score was derived from the total and delayed-recall scores of the WLT, the cognitive flexibility score was calculated as the average of the C-version of the CST and subtask III of the SCWT, and sensorimotor speed thus combined scores on the 0, A and B versions of the CST and subtask I of the SCWT.[41] In data presentation, plus or minus signs were inverted to make positive values reflect a better than average and negative values a worse than average performance.

First, comparisons were made between both dipper categories, including the cardiovascular risk factor variables and all variables that were used in the analyses (Table 1). Appropriate tests were used to detect group differences (groupwise *t* tests for normally distributed continuous variables, Mann–Whitney U-tests for variables with skewed distributions, or χ^2-tests for variables with a restricted number of classes). Using general linear model (GLM) analysis, dipper groups were compared on cognitive test scores, with control for significant pre-existent group differences (*only* educational level; no cardiovascular risk factors were used). Owing to the skewed distribution of WML data, sWML and pWML scores were broken down into tertile groups,[12] with cutoff values at 33.5 and 402.1 mm^3, and 0.5 and 1.5, for sWML and pWML scores, respectively. pWML were also analysed as a dichotomous feature (present/absent). Next, sWML (tertiles), pWML (tertiles, present/absent) and lacunar infarction (present/absent) groups were compared using GLM on cognitive test performance and BP variables (mean daytime, night time and 24-h, and relative dipping of MAP), with control for age as covariate. As some authors have suggested that the relationship between nocturnal dipping and organ damage is U-shaped,[19,42] we also trichotomised *post hoc* the day/night MAP difference to test differences in WML load and cognitive outcome in these groups.

Table 1 Descriptive statistics (mean (s.d.), or count (%), in case of categorical variables) by dipping status, according to Verdecchia *et al.* ($N=86$); univariate group differences were tested with groupwise *t* tests (two-tailed), unless indicated otherwise

	Dipper status		*All*
	Nondipper	*Dipper*	
n	13	73	86
Age (years)	55.4±8.5	57.7±10.3	57.4±10.0
Sex (male/female)	10/3	42/31[a]	52/34
Education (1–8)	2.5±1.3	3.9±2.1**	3.7±2.0
Smoking (%)	31	31[a]	31
Physical activity (h)	6.2±5.0	7.8±6.4[b]	7.6±6.2
BMI (kg/m^2)	28.5±4.7	28.9±5.5	28.9±5.4
DM (%)	15	14[a]	14
HC (%)	15	23[a]	22
Daytime BP			
SBP day (mmHg)	159±17	155±19	156±18
DBP day (mmHg)	101±15	97±12	97±12
MAP day (mmHg)	121±14	117±13	117±14
PP day (mmHg)	58±11	59±13	59±12
HR day (bpm)	83±16	80±12	80±13
Night time BP			
SBP night (mmHg)	157±21	132±17***	136±20
DBP night (mmHg)	98±16	78±11***	81±14
MAP night (mmHg)	118±16	97±13***	100±15
PP night (mmHg)	59±14	54±11	54±12
HR night (bpm)	69±11	67±11	67±11
24-h BP			
SBP 24 (mmHg)	159±17	148±18*	150±18
DBP 24 (mmHg)	100±14	91±11**	92±12
MAP 24 (mmHg)	120±14	111±13*	112±13
PP 24 (mmHg)	59±12	57±12	58±12
HR 24 (bpm)	78±14	75±11	75±11
MAP dipping (%)	2.2±5.7	16.6±5.8***	14.4±7.8
Subcortical WML (mm^3)	1158±2702	1029±2235[b]	1048±2294
Periventricular WML (score)	1.85±2.13	1.36±1.70[b]	1.43±1.77
Lacunar infarction (present/absent)	3/10	14/59[a]	17/69
Sensorimotor speed (*Z*-score)	−0.34±1.17	0.06±0.60	0.00±0.91
Cognitive flexibility (*Z*-score)	−0.53±1.27	0.09±0.80* (NS)	0.00±0.72
Memory (*Z*-score)	−0.23±0.86	0.04±0.96	0.00±0.95

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; bpm, beats per minute; WML, white matter lesion; NS, not significant.
*$P\leqslant0.05$; **$P\leqslant0.01$; ***$P\leqslant0.001$; *P*-values of GLM with control for education as covariate are given in parentheses.
[a]χ^2 test.
[b]Mann–Whitney U-test.

Analyses were performed with SPSS 11.5 for Windows (SPSS Inc., Chicago, IL, USA), using an alpha level of 0.05.

Results

Of 105 persons included for this study, MRI data of nine persons were unavailable or considered inadequate due to claustrophobia (one), premature withdrawal from the study (four), or movement artefacts (four). Four patients under 40 years were not included in the analysis. Of the remaining 92 patients, another six patients were excluded because ABPM data were insufficient (<70% successful readings), leaving 86 patients with complete data for analysis. Table 1 presents descriptive statistics of the study sample. Mean age of the group was 57 years (range 40–80) and 60% was male.

Nondipping

In all, 13 (15%) participants were classified as *nondipper*. As may be expected, when dipping status categories were compared, all night time and 24-h BP levels, with the exception of PP, were higher ($P<0.001$ and $P<0.05$, respectively) and the relative night time dipping of the MAP lower ($P<0.001$) in the *nondipper* group. *Dippers* received higher education ($t=3.200$, $P<0.01$) and performed better on cognitive flexibility ($t=2.338$, $P<0.05$). The latter difference disappeared, however, when dipper groups were compared with control for educational level ($F(1,84)=1.957$, NS). Age, sex, presence of

cardiovascular risk factors, average HR, WML lesion scores, presence of lacunar infarctions, and both other cognitive measures did not differ between *dipper* groups.

Blood pressure

Of patients in the lowest sWML volume tertile, 17 (20%) patients had none, or only one small sWML on their MRI scan. pWML and lacunar infarctions were present in 56 (65%) and 17 (20%) patients, respectively (Table 2a and b). Age was associated with higher sWML volume, the presence as well as the severity of pWML and more evidence of lacunar infarction on MRI ($F(2,83) = 9.090$, $P < 0.001$; $F(1,84) = 9.116$, $P < 0.01$; $F(2,83) = 10.532$, $P < 0.001$; and $F(1,84) = 4.645$, $P < 0.05$, respectively). Higher daytime and 24-h SBP and daytime, night time and 24-h PP were related to both the presence and the severity of pWML. Furthermore, daytime, night time and 24-h averages of SBP, MAP and PP were associated with presence of lacunar infarctions. After controlling for age in the analysis, these relationships remained significant for daytime and 24-h PP with respect to the presence of pWML, whereas differences between severity groups (tertiles) disappeared (Table 2a and b). SBP and MAP for daytime, night time and 24-h periods remained significantly associated with lacunar infarctions (Table 2b). Again, evidence of cerebral damage was unrelated to relative dipping of the MAP at night. Higher sWML load was related to lower scores on sensorimotor speed, whereas cognitive flexibility and verbal memory scores decreased with the presence or the severity of pWML and lacunar infarction (all at $P < 0.05$). However, none of these associations remained significant after correction for age in the model, except for verbal memory. In persons with evidence of lacunar infarction this score remained significantly lower after adjustment for age, when compared with controls ($F(1,84) = 6.693$, $P < 0.05$).

Table 2a Descriptive statistics (mean (s.d.), or count (%), in case of categorical variables) by pWML and sWML tertiles; univariate group differences were tested with general linear model (GLM) statistics, unless indicated otherwise

	sWML volume			*pWML score*		
	3	33.5–402.1 mm^3	⩾402.1 mm^3	0	0.5–1.5	>1.5
n	30	28	28	30	26	30
Age (years)	52.5±9.3	57.1±7.4	62.8±10.5***	53.1±8.5	55.4±9.3	63.3±9.3***
Sex (male/female)	18/12	17/11	17/11[a]	17/13	16/10	19/11[a]
Education (1–8)	4.3±1.8	3.4±2.2	3.2±2.0	4.1±1.9	3.4±2.0	3.5±2.1
Smoking (%)	40	30	21[a]	38	23	30[a]
Physical activity (h)	7.6±6.9	7.0±5.3	8.2±6.5[b]	7.2±7.1	6.9±5.8	8.7±5.7[b]
BMI (kg/m^2)	29.0±5.1	27.9±5.6	29.7±5.4	29.8±5.9	28.1±4.8	28.7±5.3
DM (%)	3	21	18[a]	10	27	7[a]
HC (%)	27	14	25[a]	13	35	20[a]
Day-time BP						
SBP day (mmHg)	157±19	151±19	160±17	150±20	156±14	161±19
DBP day (mmHg)	99±14	96±12	97±12	97±14	98±9	97±13
MAP day (mmHg)	118±14	115±14	118±13	115±16	117±10	119±14
PP day (mmHg)	58±14	55±10	63±12	53±10	58±9	65±14*** (NS)
HR day (bpm)	80±14	83±13	78±11	82±12	81±10	77±15
Night time BP						
SBP night (mmHg)	135±19	132±22	140±19	130±20	136±19	141±20
DBP night (mmHg)	82±15	80±14	82±12	81±15	81±12	82±13
MAP night (mmHg)	100±15	98±16	102±14	98±17	100±13	103±15
PP night (mmHg)	53±11	52±11	59±13	49±9	55±11	59±14** (NS)
HR night (bpm)	66±11	71±12	64±8*	68±10	68±9	65±13
24-h BP						
SBP 24 (mmHg)	150±18	146±20	155±15	144±20	150±15	156±17* (NS)
DBP 24 (mmHg)	93±13	91±12	93±11	92±14	93±9	92±12
MAP 24 (mmHg)	113±13	110±14	114±12	110±16	112±10	115±13
PP 24 (mmHg)	56±13	55±10	62±12	52±10	58±10	64±14*** (NS)
HR 24 (bpm)	74±12	79±12	73±9	77±10	76±9	73±13
MAP dipping (%)	15.2±7.8	14.5±7.3	13.6±8.3	14.9±6.5	14.9±7.9	13.6±8.9
Sensorimotor speed (*Z*-score)	0.23±0.47	0±0.6	−0.24±0.95* (NS)	0.17±0.53	0.09±0.53	−0.24±0.95
Cognitive flexibility (*Z*-score)	0.28±0.7	−0.02±0.72	−0.28±1.17	0.33±0.66	0.04±0.59	−0.37±1.19** (NS)
Memory (*Z*-score)	0.11±0.99	−0.07±0.91	−0.04±0.96	0.29±0.83	−0.16±1.07	−0.14±0.92

See Table 1 footnote for abbreviations.
*$P \leqslant 0.05$; **$P \leqslant 0.01$; ***$P \leqslant 0.001$; *P*-values of GLM with control for education as covariate are given between parentheses.
[a]χ^2 test.
[b]Mann–Whitney U-test.

Table 2b Descriptive statistics (mean (s.d.), or count (%), in case of categorical variables) by pWML status and lacunar infarction status; univariate group differences were tested with GLM, unless indicated otherwise

	pWML		*Lacunar infarction*	
	Absent	*Present*	*Absent*	*Present*
n	30	56	69	17
Age (years)	53.1±8.5	59.6±10.1**	56.2±9.7	61.9±10.3*
Sex (male/female)	17/13	35/21[a]	39/30	13/4[a]
Education (1–8)	4.1±1.9	3.4±2.1	3.8±2.0	3.2±2.1
Smoking (%)	38	27[a]	34	18[a]
Physical activity (h)	7.2±7.1	7.8±5.8[b]	8.0±6.6	6.0±4.3[b]
BMI (kg/m^2)	29.8±5.9	28.4±5.1	29.40±5.6	26.9±3.8
DM (%)	10	16[a]	9	35[a] **
HC (%)	13	27[a]	23	18[a]
Daytime BP				
SBP day (mmHg)	150±20	159±17* (NS)	153±18	166±18* (*)
DBP day (mmHg)	97±14	97±11	96±11	101±17
MAP day (mmHg)	115±16	118±12	116±13	124±16* (*)
PP day (mmHg)	53±10	62±13*** (*)	57±12	64±14* (NS)
HR day (bpm)	82±12	79±13	80±12	79±15
Night time BP				
SBP night (mmHg)	130±20	138±19	133±19	146±20* (*)
DBP night (mmHg)	81±15	81±13	80±11	86±20
MAP night (mmHg)	98±17	101±14	98±13	108±19* (*)
PP night (mmHg)	49±9	57±12** (NS)	53±12	60±11* (NS)
HR night (bpm)	68±10	67±11	68±11	65±11
24-h BP				
SBP 24 (mmHg)	44±20	153±16* (NS)	147±17	161±17** (**)
DBP 24 (mmHg)	92±14	93±11	91±10	97±17
MAP 24 (mmHg)	110±16	113±12	110±12	119±16* (**)
PP 24 (mmHg)	52±10	61±12*** (*)	56±11	64±13* (NS)
HR 24 (bpm)	77±10	74±12	75±11	74±13
MAP dipping (%)	14.9±6.5	14.2±8.4	14.8±7.7	13.2±8.0
Sensorimotor speed (*Z*-score)	0.17±0.53	−0.09±0.79	0.08±0.68	−0.30±0.80
Cognitive flexibility (*Z*-score)	0.33±0.66	−0.18±0.97* (NS)	0.10±0.82	−0.43±1.13* (NS)
Memory (*Z*-score)	0.29±0.83	−0.15±0.98* (NS)	0.14±0.92	−0.58±0.88** (*)

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; bpm, beats per minute; sWML, subcortical white matter lesion score; pWML, periventricular white matter lesion score; NS, not significant.
*$P\leqslant0.05$; **$P\leqslant0.01$; ***$P\leqslant0.001$; *P*-values of GLM with control for age as covariate are given in parentheses.
[a]χ^2 test.
[b]Mann–Whitney U-test.

We did additional analyses on historical data in both dipper categories about hypertension duration (8.8 vs 9.2 years in dippers/nondippers, respectively), the number of antihypertensive medications taken prior to ABPM (1.9 vs 1.8) and duration of past antihypertensive medication usage (4.7 vs 3.6 years): no significant differences were apparent in these data. Finally, a *post hoc* comparison of WML load and cognitive variables based on tertiles of day/night MAP dipping did not reveal evidence for a nonlinear relationship between nondipping and WML load or cognitive function.

Discussion

To the best of our knowledge, this study is the first to investigate the relationship between ABP and a combination of both morphological and functional characteristics of brain structures that are engaged in cognitive performance, using ABPM, MRI and a comprehensive battery of cognitive tests. We linked the evidence of early cerebral damage (sWML and pWML, or presence of lacunar infarction) to diurnal BP variation, ABP profile and indicators of neurocognitive functioning in previously diagnosed essential hypertensive individuals. Nondipping during the night was unrelated to both cognitive variables and imaging parameters, after appropriate control for possible confounders (i.e., difference in educational level). Age was a strong indicator of sWML, pWML and lacunar infarction prevalence on MRI. When age differences were accounted for, differences in either daytime and 24-h PP on the one hand, and daytime, night time and 24-h SBP and MAP on the other, remained statistically significant between pWML and lacunar infarction groups, respectively. However, the associations between cognitive function and imaging measures disappeared, except for a significant difference in memory function between individuals with and without lacunar infarctions.

The results of previous studies concerning the prevalence of WML in patients with hypertension are equivocal, which may be related, at least in part, to differences in patient selection and MRI scoring systems.[43] As pointed out by Sierra and others, most studies have been performed in older individuals, or populations with a wide age range.[14] When these investigators studied a group of 66 never-treated hypertensive patients between 50 and 60 years of age they did find higher levels of ABP in a group characterised by WML presence, compared to non-WML controls, but no between-group differences were apparent in the nocturnal BP fall.

In agreement with the latter findings, both dipping status and relative MAP dipping were unrelated to cerebral pathology in the present study. In the Japanese population, nondipping but also extreme dipping have repeatedly been associated with silent cerebrovascular disease, such as WML and lacunar infarctions.[44] Studies in Caucasian populations though are limited and their results are not beyond dispute.[14,45–47] Most of these were limited in size[14,47] or lesions were described in terms of presence or absence only.[14,45] Furthermore, with respect to the classification of dipping, there is no consensus on what BP variable to use (SBP, DBP or MAP), which cutoff values are optimal and how data should be presented (relative dipping or dipping status). Studies, and patient groups within studies, may also differ with respect to the duration of hypertension and treatment history of which reliable information can be difficult to obtain. Hypertension history or the duration of antihypertensive medication did not affect our results. Still, methodological differences such as described here can complicate the comparison of our findings with those of aforementioned studies. On a final note, some authors suggested that repeated ABPM may yield more accurate assessment of dipper status and thus improve the use of diurnal BP variation in risk assessment.[48,49] Therefore, the consequences of diurnal BP variations on the brain remain to be elucidated further, at least in Caucasians.

Previously, others reported ABPM to be superior to casual BP measurements in predicting hypertension-induced cerebrovascular disease.[13] In addition, ambulatory MAP and PP recently gained increased interest in the prediction of silent and symptomatic stroke.[14,20,21] Driven by this line of evidence, we assessed the effects of the ABP profile on WML and lacunar infarctions. When age differences were accounted for, presence of pWML was associated with daytime and 24-h PP, whereas SBP and MAP for daytime, night time and 24-h periods were highest in patients with lacunar infarctions. Otherwise, ABP profile did not predict severity of both pWML and sWML. Intriguingly, these findings suggest that the steady (MAP) and pulsatile (PP) components of BP predispose to different forms of small vessel disease-related white matter abnormalities. Others have hypothesised that small penetrating cerebral arteries are particularly vulnerable to the adverse effects of a steady BP overload (MAP), causing small lacunar infarctions.[20,21] According to this hypothesis and in line with our findings, some authors recently suggested that daytime, night time and 24-h MAP were major determinants for the formation of silent cerebral infarctions, mostly lacunar infarctions.[20] The blood supply of the periventricular white matter is dependent on end arteries which lack appropriate anastomoses.[50] This arterial watershed zone is highly vulnerable to ischaemia during hypotensive periods, especially in hypertensive patients with impaired cerebral autoregulation.[51] Since a high PP reflects an increased arterial stiffness,[52] we speculate that the penetrating cerebral arteries of hypertensive patients with high PP are less potent in their response to hypotension, increasing the risk of developing pWML. Recent findings of Sierra *et al*.[14] are compatible with this notion. They reported higher values of PP, including office, daytime, night time and 24-h averages, among hypertensive patients with pWML, compared to those without. The present results, however, remain to be confirmed in a well-defined, larger population. On multivariate analysis, ABP profile remained significantly associated with the presence, but not with the severity of pWML. To our knowledge, there is no consensus with respect to lesion definition. It is likely that differences in lesion definition may account for this inconsistency, because when continuous data are dichotomised the remaining variance becomes less informative.

The absence of an association between nondipping and cognitive performance does not comply with earlier observations that we made in a study on 115, community dwelling, largely normotensive individuals of approximately the same age range (29–81 years).[53] In that study, nondippers were characterised by lower scores on both memory and sensorimotor speed measures. This inconsistency could indicate that the diurnal BP rhythm of our patients depends for some part on hypertension-induced cerebral abnormalities, which we assume to be not, or less, present in community residents.[54] However, it remains elusive why we failed to replicate earlier findings. Our results also disagree with a recent study in patients with a blunted decline in night time BP, who showed poorer cognitive performance.[55] However, patients in this study had long-standing hypertension (17.3 ± 4.9 years, range 10–26), cognitive performance was assessed using the standard Mini-Mental State Examination, and only 26 patients were included.

WML extent was unrelated to cognitive performance parameters, which is in contrast to the findings from the Rotterdam study where pWML load was associated with lower information processing speed and general cognitive functioning.[24] Results, however, are in line with a smaller population study in 123 older (64–74) individuals that failed to find a linear association between WML load

(measured according to a comparable protocol) and cognitive performance measures[12] and with recent work by Sierra *et al.*,[56] who reported no differences in memory between patients with and without pWML. On the other hand, the present study confirmed recent findings from the Rotterdam study where silent brain infarctions (202 out of 217 were lacunar infarctions) were associated with a greater decline in memory performance, in particular when these were located in the thalamus.[57]

In conclusion, there was no relationship between diurnal BP rhythm and evidence of structural or functional cerebral damage in this population of newly diagnosed hypertensive individuals. Our study was relatively small, but given the substantial variability in WML in this hypertensive population (over 62% having overt white matter changes), we cautiously conclude that an association between WML and cognition will in no case be very robust. Still, our data suggest that the ABP profile may predict lesion type in early asymptomatic cerebral abnormalities.

What is known on this topic
- Ambulatory BP measurement is superior to casual BP measurements in predicting target organ damage due to hypertension.
- Nondipping of diurnal BP has been associated with target organ damage of the brain.
- The relationship between ABP profile, evidence of cerebral damage and cognitive function remains elusive.

What this study adds
- In patients with uncomplicated essential hypertension no evidence was found for a relation between diurnal BP variation on the one hand and cerebral damage or cognitive function on the other.
- Lacunar infarctions may have implications for verbal memory function.
- The ABP profile may shed light on the type of cerebral lesion associated with essential hypertension.

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