Average Daily Blood Pressure, Not Office Blood Pressure, Is Associated With Progression of Cerebrovascular Disease and Cognitive Decline in Older People

William B. White, MD; Leslie Wolfson, MD; Dorothy B. Wakefield, MS; Charles B. Hall, PhD; Patrick Campbell, MD; Nicola Moscufo, PhD; Julia Schmidt, BS; Richard F. Kaplan, PhD; Godfrey Pearlson, MD; Charles R.G. Guttmann, MD

Background—High blood pressure (BP) is a risk factor for cerebrovascular disease, including stroke. Little is known about the importance of BP on the progression of microvascular disease of the brain, which has been associated with functional decline in mobility and cognition in older people.

Methods and Results—This was a prospective cohort of subjects 75 to 89 years of age to determine relations among vascular risk factors, white matter hyperintensity volume, and functional status. Ninety-nine subjects were enrolled through the use of a balanced 3×3 matrix stratified by age and mobility performance, and 72 subjects completed all sets of baseline and follow-up studies at 2 years. Subjects were excluded if there were medications or systemic or neurological diseases that could compromise mobility. Ambulatory and clinic BP monitoring, magnetic resonance imaging, gait studies, and neuropsychological testing were performed at baseline and after 24 months. Brain classification into normal white matter and T2-hyperintense white matter hyperintensity volume was performed with semiautomated segmentation. Quantitative measures of mobility and cognitive function were obtained longitudinally. Increased ambulatory systolic BP, but not clinic systolic BP, from baseline to 24 month follow-up was associated with increased white matter hyperintensity volume over that same period, as well as measures of executive function/processing speed. Similar associations were observed for 24-hour BP, awake BP, and sleep BP but not for the surge between the sleep and awake time at the 24-month time point.

Conclusions—These data demonstrate for the first time the importance of 24-hour systolic BP in the progression of brain white matter hyperintensity volume burden associated with impairment of cognitive function in older people. The 24-hour systolic BP may be a potential target for intervention in the elderly to reduce vascular disease of the brain and impairment of function. **(*Circulation*. 2011;124:2312-2319.)**

Key Words: blood pressure ■ blood pressure monitoring, ambulatory ■ cerebrovascular disorders ■ geriatrics ■ hypertension

Small-vessel disease of the brain may present as white matter hyperintensities (WMHs), and are commonly present in the magnetic resonance images (MRIs) of older persons with hypertension and other vascular disease risk factors.[1] These WMHs are clinically relevant in older people because they are associated with functional deterioration of mobility[2] and cognition[2,3] and stroke[4] and have been proposed as an intermediate marker in the research setting.[5] We have previously demonstrated significant relationships between total and regional WMH and measures of mobility, indicating that lesion burden was a key predictor of low mobility performance[6] and that frontal WMH predicted speed of cognitive functioning.[7]

Clinical Perspective on p 2319

An important advantage of ambulatory blood pressure (BP) measurement over clinic values is its enhanced reproducibility, including in older people.[8] Numerous studies have demonstrated that ambulatory BP is a better predictor of cardiac, renal, and cerebral disease in middle-aged and older people with hypertension.[9] However, there are minimal data regarding the impact of 24-hour BP over time on cerebrovascular

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From the Division of Hypertension and Clinical Pharmacology, Calhoun Cardiology Center (W.B.W., P.C.), Department of Neurology (L.W., D.B.W., J.S.), and Department of Psychiatry (R.F.K.), University of Connecticut School of Medicine, Farmington; Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (N.M., C.R.G.G.); Department of Epidemiology and Population Health and Saul B. Korey Department of Neurology, Albert Einstein College of Medicine, Bronx, NY (C.B.H.); and Department of Psychiatry, Yale University School of Medicine, New Haven, CT (G.P.).

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Correspondence to William B. White, MD, Professor and Division Chief, Division of Hypertension and Clinical Pharmacology, Calhoun Cardiology Center, University of Connecticut School of Medicine, 263 Farmington Ave, Farmington, CT 06030-3940. E-mail wwhite@nso1.uchc.edu

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disease and its functional consequences, particularly in the elderly population. We report our findings of a longitudinal prospective cohort study that examined the relationships among ambulatory and clinic BP, progression of WMH, and functional capabilities in older people.

Methods

Patients

Men and women 75 to 89 years of age were recruited for this longitudinal study defining the relationships among BP, WMH accrual, and mobility impairment. From 312 individuals screened, 164 were eligible, consenting individuals, from whom 117 were assessed for possible enrollment. Eighteen patients were excluded because of disorders known to interfere with mobility such as arthritis and Parkinson disease or claustrophobia that disallowed MRI testing; 1 patient was excluded after discovery of a tentorial meningioma. This subject was replaced at baseline. Subjects were enrolled from the community and geriatric practices with the use of a balanced 3×3 matrix that stratified age (75–79, 80–84, and ≥85 years) and mobility performance in terms of Short Physical Performance Battery scores (11–12, 9–10, and <9) as described previously.[10] Patients were excluded if they had underlying neurological diagnoses that would impair mobility or cognitive function. Patients with severe or unstable cardiovascular disorders (eg, myocardial infarction in last 6 months, decompensated heart failure, recent stroke) were excluded. There were 72 patients who had all sets of studies at baseline and after 24 months of observation.

After providing informed consent, subjects underwent neurological and cognitive assessment, as well as BP monitoring, gait laboratory assessment, and MRI of the brain. Assessors were blinded to clinical, mobility, and imaging outcomes. The study was approved by the institutional review boards at the University of Connecticut Health Center (Farmington, CT) and Hartford Hospital (Hartford, CT).

Assessment of BP

Resting clinic BPs were measured in triplicate after the patient had been sitting for 5 minutes by a semiautomated digital device (Omron HealthCare 705CP, Vernon Hills, IL) with an appropriately sized cuff and bladder and averaged. The 24-hour ambulatory BP monitoring was conducted with the Oscar II BP device (Suntech Medical Instruments, Morrisville, NC), which has been validated independently for precision and reliability.[11] BPs were obtained every 15 minutes from 6 AM to 10 PM and every 30 minutes from 10 PM to 6 AM, as previously described.[8] Data were transferred to the Accuwin software program (Suntech Medical Instruments) for analysis. Components of the ambulatory BP monitoring for analysis included the 24-hour mean systolic and diastolic BPs, awake and sleep BPs, and early morning surge BP (2-hour postawakening BP−2-hour preawakening BP=early morning surge) as previously described.[8]

Assessment of Mobility

Mobility was assessed with the Tinetti Gait score[12] and laboratory testing of mobility performance that included timed stair descent, walk time, and self-paced maximum velocity. Gait speed was measured as participants walked at a comfortable pace over an 8-m course with 1 m for acceleration and deceleration. In addition to gait speed, time to descend 3 stairs at a comfortable pace was used as a measure of walking-moving.

Assessment of Cognitive Function

Measures of executive functioning and process speed included the Trail Making Test (Trails Part B), the Stroop Color and Word Test, and the California Computerized Assessment Package simple and sequential reaction times. Trail Making tests the speed of visual search, attention, mental flexibility, and motor function.[13] The Stroop Color and Word Test assesses how well an individual suppresses a habitual response in favor of an unusual one, thus assessing complex processing speed. Slower Stroop performance has been associated with greater WMH.[14] The California Computerized Assessment Package consists of 3 reaction time tests: a simple, a choice, and a serial reaction time. Simple reaction time measures general motor slowing. Choice reaction time is a go–no go paradigm that measures response inhibition and processing speed. Serial reaction time measures divided attention and processing speed.[13]

Brain MRI and Quantitative WMH Volume

MRIs were acquired and white matter lesions quantified with a protocol described elsewhere.[6] Briefly, high-resolution MRIs were acquired with a 3-T Siemens Allegra scanner (Erlangen, Germany). The brain was imaged with 3 sequences: a T1-weighted magnetization prepared rapid gradient echo (MPRAGE), a T2-weighted 3D fast spin-echo (T2), and a fluid-attenuated inversion recovery (FLAIR). Preprocessing included correction of magnetic field–related signal inhomogeneities and linear affine registration of FLAIR and T2 series to the MPRAGE series. A semiautomated segmentation method was used to assign each pixel in the intracranial cavity a value corresponding to gray matter, normal white matter, WMH, or cerebrospinal fluid on the basis of both signal intensity and anatomic location. To account for brain size variability, the total volume of WMH was expressed as a fraction of the intracranial cavity volume: WMH fraction=[total WMH (mL)/intracranial cavity volume (mL)]×100%. All MRI analyses were performed by a researcher blinded to clinical and gait laboratory data.

To validate the WMH segmentation method, we randomly selected 10 subjects in the study and compared WMH results with a gold standard obtained on these subjects by an expert neuroradiologist in our group who manually outlines the WMH from FLAIR images. The WMH volumes obtained from the gold standard and from the study method outputs were 1.46±1.14% and 1.62±1.18% of intracranial cavity volume, respectively. The intraclass correlation coefficient for the 2 methods was 0.99 (95% confidence interval, 0.98–0.99; $P<0.00001$). The reproducibility of the method was assessed on 10 subjects whom participated in a test-retest experiment that consisted of 2 brain MRI acquisitions on the same day but >1 hour apart. For this experiment, the intraclass correlation coefficient was 0.99 (95% confidence interval, 0.97–0.99; $P<0.00001$). The proportion of pixels reproducibly classified as WMH were 77.5±12.3% (95% confidence interval, 68.7–86.3). Mean±SE in the WMH measurement was 0.02±0.20% of the intracranial cavity volume.

Statistical Analysis

SAS version 9.1 (SAS Institute, Inc, Cary, NC) was used for statistical analyses. Data were analyzed cross-sectionally (at 24 months) and longitudinally (change from baseline to 24 months). Change was calculated as (24 months minus baseline) for all variables.

The primary analyses used the progression model of Diggle et al[15] to simultaneously model the cross-sectional associations of baseline BP with WMH, cognitive, and functional outcomes at baseline and the association of the change in BP between follow-up and baseline with the change in WMH, cognition, and function between follow-up and baseline. Chronological age and low-density lipoprotein (LDL) cholesterol levels were included the models as possible confounders in all analyses. This method avoids the entangling cross-sectional and longitudinal effects. Random intercepts were included in the model to take into account the fact that individuals could contribute >1 observation to the analysis. BP measurements analyzed included clinic systolic, 24-hour mean systolic, awake systolic, sleep systolic, and early morning surge systolic BPs. Outcomes analyzed included WMH, mobility, and cognition. The WMH was corrected for intracranial cavity volume and expressed as a percent. Specific mobility measures included Tinetti Gait Score, time to descend 3 stairs (seconds), and self-paced maximum velocity (m/s). Cognitive measures included Trail Making B, California Computerized Assessment Package sequential reaction time, and Stroop Color and Word. Of note, in this age population, systolic BP has far more clinical

importance than diastolic BP[16]; hence, the focus for the analyses was on systolic BP.

To examine the association of WMH with functional status, we also conducted cross-sectional regression analyses for each of the dependent variables (mobility and cognition). These models were performed for the 24-month data. Final models for the mobility measures controlled for age and LDL cholesterol levels. A 2-tailed level of $\alpha \leq 0.05$ was the threshold for statistical significance in all analyses.

Several different analyses were conducted to study whether there might exist threshold levels of clinic and 24-hour systolic BP that may be associated with the progression of WMH. Locally weighted scatterplot smoother (lowess) curves were constructed to visually depict the relationships. Second, the population was subdivided into 2 groups of ambulatory systolic BP at 24 months (those with mean 24-hour BPs <135 and ≥135 mm Hg at 24 months and those who had a dipper versus nondipper 24-hour profile defined as a ≥10% decline in sleep versus awake BP for dippers and <10% decline in sleep versus awake BP for nondippers). Total WMH, mobility, and cognitive measures at 24 months were compared via the scatterplot smoother curves; relations among the 2 groups of 24-hour systolic BP with the various outcome measures and age and LDL cholesterol were evaluated with Kruskal-Wallis nonparametric tests.

Results

Patient Characteristics

Ninety-nine participants, all white, with a mean age of 82±3.8 years were initially enrolled in the study; 95 completed a baseline ambulatory BP recording. Two years later, a total of 23 patients had died, moved into a convalescent home, had a pacemaker implanted, or declined participation in the 24-hour BP monitoring portion of the study, leaving 72 patients for the final analysis (Table 1). The characteristics of the 23 patients who dropped out of the study before the 24-month analysis time point were similar at baseline to those of the 72 patients who remained in the cohort analysis for age, sex, WMH, and mobility but had a significantly higher 24-hour systolic BP at baseline (≈7 mm Hg higher; $P=0.021$).

Of subjects enrolled, 70% had a history of hypertension, 13% had coronary artery disease, 6% had diabetes mellitus, and 48% had dyslipidemia (LDL cholesterol >130 mg/dL). Over the next 2 years, for the 72 participants, there were no major changes in body weight or clinic or ambulatory BP, and only 3 patients had major interval medical problems: development of stroke, heart failure, or valvular disease. At baseline, 64% of subjects were taking antihypertensive drug therapy; 69% were taking antihypertensive drug therapy at 24 months (2 patients stopped antihypertensive therapy and 6 patients started or had changes in antihypertensive therapy). Clinical decisions related to drug therapies were made by the patients' primary care physicians without input from study staff. Total and LDL cholesterol fell significantly in the cohort; at baseline, 50% of subjects were taking lipid-lowering drugs, and 9 patients started cholesterol-lowering medications, whereas 8 discontinued them over 24 months. The mean volume of WMH increased significantly over the 2-year period. One of the 4 mobility measures, time to descend stairs, increased significantly, as did 1 of the 4 cognitive measures (Trails B).

Table 1. Characteristics of the Patient Population at Baseline and 24 Months

Parameter	Baseline Mean (SD)	24-Month Mean (SD)	*P*
Age, y	82.1 (3.9)	84.2 (3.9)	NA
Sex, M:F	31:46	31:46	NA
Body mass index, kg/m^2	26.7 (4.7)	26.3 (4.5)	0.02
Blood pressure (mean±SD), mm Hg			
Clinic	136/71 (16/9)	136/68 (15/10)	0.90/0.01*
24-h	129/66 (12/6)	131/67 (14/7)	0.77/0.77
Awake	132/68 (12/7)	132/68 (14/7)	0.89/0.69
Sleep	122/60 (15/8)	125/60 (17/10)	0.11/0.37
Early morning surge	9/10 (16/11)	9/8 (16/10)	0.91/0.37
Biochemical studies			
Total cholesterol, mg/dL	198 (39)	180 (41)	<0.0001*
Low-density lipoprotein cholesterol, mg/dL	126 (36)	102 (33)	<0.0001*
High-density lipoprotein cholesterol, mg/dL	56 (15)	55 (16)	0.06
Triglycerides, mg/dL	100 (41)	95 (41)	0.25
Serum glucose, mg/dL	99 (14)	101 (17)	0.09
Insulin, μIU/mL	7.64 (7.92)	8.02 (10.63)	0.47
High-sensitivity C-reactive protein, mg/L	3.32 (3.99)	3.49 (5.48)	0.79
Plasminogen activator inhibitor, mg/mL	21.9 (13.5)	24.6 (19.3)	0.08
Magnetic resonance imaging			
Total brain volume, mL	1402.2 (143.1)	1401.6 (144.1)	0.43
White matter hyperintensity volume, mL	13.9 (12.8)	20.5 (16.2)	<0.0001*
White matter hyperintensity/ total brain volume (%)	1.00 (0.90)	1.47 (1.20)	<0.0001*
Functional assessments			
Mobility parameters			
Tinetti Gait	11.24 (1.19)	11.24 (1.31)	0.92
8-ft walk time, s	3.1 (0.7)	3.2 (0.8)	0.40
Maximum velocity, m/s	0.70 (0.15)	0.70 (0.18)	0.84
Time to descend 3 stairs, ms	5019 (1121)	6400 (2521)	<0.0001*
Cognitive studies			
Trails B, s	114 (68)	130 (76.)	0.05*
Stroop Color and Word Reaction time, ms	27 (9.0)	26 (9)	0.23
Sequential process time, ms	589 (149)	545 (194)	0.07
Simple reaction time, ms	414 (132)	417 (164)	0.72

*Significant.

Impact of Therapy and Outcomes

Regression analyses that included the use of antiplatelet therapy, antihypertensive drugs, and lipid-lowering therapy to predict ambulatory BP and functional outcomes were evaluated. No therapy was a significant predictor in any of the models.

Table 2. Relations Among Clinic and Ambulatory Blood Pressure Components With White Matter Hyperintensity and Functional Parameters at 24 Months

	24-h Systolic BP		Clinic Systolic BP		Awake Systolic BP		Sleep Systolic BP		Morning Surge in Systolic BP	
At 24 mo	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
Total WMH, %	0.026 (0.004–0.048)	0.02*	0.006 (−0.013 to 0.025)	0.5	0.021 (−0.002 to 0.043)	0.07	0.02 (0.002–0.038)	0.03*	−0.001 (−0.02 to 0.017)	0.88
Change in WMH, %	0.011 (0.001–0.020)	0.02*	0.004 (−0.004 to 0.012)	0.33	0.01 (0.001–0.02)	0.03*	0.007 (0–0.015)	0.05*	0.001 (−0.007 to 0.008)	0.88
Tinetti Gait	−0.013 (−0.038 to 0.012)	0.32	−0.008 (−0.029 to 0.013)	0.44	−0.013 (−0.037 to 0.012)	0.32	−0.004 (−0.024 to 0.016)	0.69	−0.01 (−0.03 to 0.011)	0.35
Stair descent time, ms	17.016 (−30.04 to 64.07)	0.47	−5.145 (−46.71 to 36.42)	0.81	0.006 (−0.041 to 0.052)	0.80	0.019 (−0.019 to 0.056)	0.32	0.004 (−0.033 to 0.041)	0.82
Maximal gait velocity, m/s	−0.003 (−0.014 to 0.008)	0.57	−0.001 (−0.01 to 0.008)	0.82	0 (−0.003 to 0.003)	0.97	−0.002 (−0.004 to 0.001)	0.25	0.001 (−0.002 to 0.003)	0.58
Walk time, s	0.011 (−0.005 to 0.027)	0.17	−0.005 (−0.018 to 0.008)	0.42	0.006 (−0.009 to 0.022)	0.41	0.012 (−0.001 to 0.024)	0.07	−0.001 (−0.014 to 0.012)	0.91
Trails B, s	0.596 (−0.60 to 1.791)	0.32	1.246 (0.071–2.421)	0.04*	0.44 (−0.741 to 1.622)	0.46	0.916 (−0.031 to 1.863)	0.06	−0.887 (−1.833 to 0.058)	0.07
Stroop Color and Word, ms	−0.105 (−0.247 to 0.038)	0.15	−0.114 (−0.24 to 0.011)	0.07	−0.082 (−0.224 to 0.06)	0.25	−0.099 (−0.213 to 0.015)	0.09	0.085 (−0.028 to 0.198)	0.14
Sequential process time, ms	2.600 (−1.124 to 6.323)	0.17	0.47 (−2.615 to 3.554)	0.76	1.636 (−2.097 to 5.37)	0.39	2.611 (−0.375 to 5.596)	0.09	−0.822 (−3.882 to 2.239)	0.59
Simple reaction time, ms	1.887 (−1.287 to 5.061)	0.24	0.47 (−2.152 to 3.093)	0.72	2.106 (−1.024 to 5.236)	0.18	0.917 (−1.644 to 3.479)	0.48	−1.297 (−3.845 to 1.251)	0.31

	Change in 24-h Systolic BP		Change in Clinic Systolic BP		Change in Awake Systolic BP		Change in Sleep Systolic BP		Change in Morning Surge in Systolic BP	
	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
Total WMH, %	0.02 (0.01–0.029)	0.000*	0.003 (−0.004 to 0.009)	0.42	0.016 (0.007–0.026)	0.001*	0.013 (0.005–0.022)	0.004*	−0.002 (−0.009 to 0.005)	0.641
Tinetti Gait	−0.015 (−0.057 to 0.028)	0.503	0.004 (−0.022 to 0.029)	0.776	−0.013 (−0.053 to 0.027)	0.521	−0.021 (−0.057 to 0.015)	0.262	0.005 (−0.023 to 0.033)	0.73
Stair descent time, ms	6.973 (−23.35 to 37.29)	0.654	−4.693 (−24.53 to 15.15)	0.645	−7.905 (−35.41 to 19.60)	0.576	16.281 (−9.135 to 41.70)	0.215	−3.8 (−22.91 to 15.31)	0.698
Maximal gait velocity, m/s	−0.001 (−0.008 to 0.005)	0.694	−0.002 (−0.006 to 0.001)	0.219	0.001 (−0.005 to 0.008)	0.649	−0.002 (−0.008 to 0.003)	0.436	0.002 (−0.002 to 0.007)	0.303
Walk time, s	0.01 (−0.001 to 0.022)	0.076	0 (−0.007 to 0.007)	0.945	0.007 (−0.004 to 0.017)	0.23	0.007 (−0.003 to 0.017)	0.161	0.003 (−0.004 to 0.01)	0.423
Trails B, s	1.081 (0.128–2.035)	0.030*	0.153 (−0.58 to 0.887)	0.684	0.937 (0.027–1.847)	0.048*	0.898 (0.086–1.709)	0.034*	−0.121 (−0.804 to 0.561)	0.729
Stroop Color and Word, ms	−0.106 (−0.228 to 0.016)	0.093	−0.016 (−0.094 to 0.061)	0.678	−0.088 (−0.204 to 0.028)	0.142	−0.092 (−0.195 to 0.011)	0.086	0.078 (0.007–0.149)	0.036*
Sequential process time, ms	0.874 (−2.561 to 4.31)	0.620	−1.876 (−4.07 to 0.319)	0.099	−0.662 (−3.95 to 2.626)	0.695	1.618 (−1.305 to 4.54)	0.282	−0.453 (−2.767 to 1.862)	0.703
Simple reaction time, ms	3.913 (1.13–6.696)	0.008*	0.508 (−1.364 to 2.38)	0.596	2.223 (−0.378 to 4.824)	0.099	2.608 (0.233–4.982)	0.035*	−0.488 (−2.374 to 1.398)	0.614

BP indicates blood pressure; CI, confidence interval; and WMH, white matter hyperintensity.
*Significant.

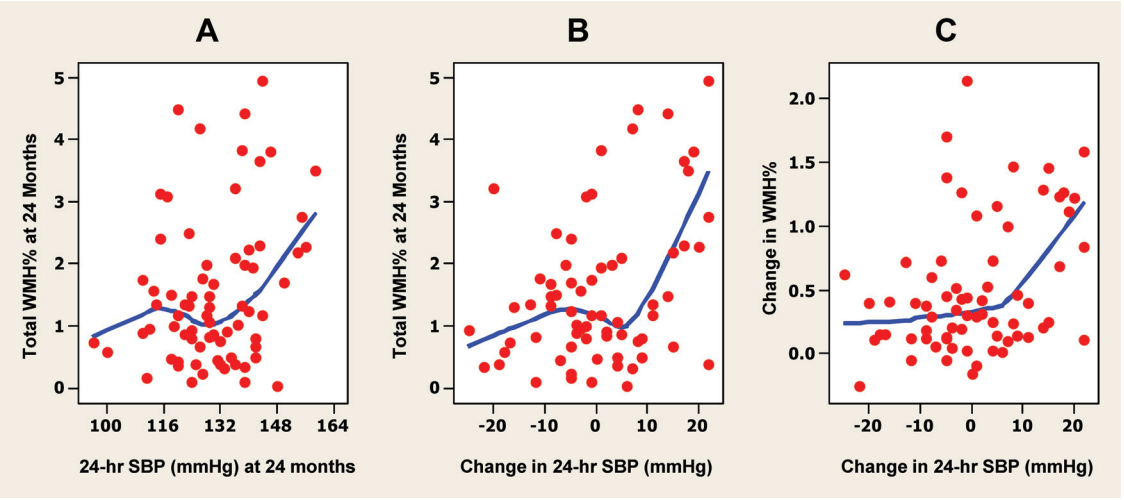

Figure 1. White matter hyperintensity (WMH) and ambulatory blood pressure (BP). Locally weighted scatterplot smoother plots of 24-hour average systolic BP (SBP) and WMH lesions (as percent of total intracranial volume; **A**), change in 24-hour SBP and WMH (%; **B**), and change in 24-hour SBP and change in WMH (%) at 24 months (**C**).

BP, WMH Percent, and Function

The relationships between change in both clinic and ambulatory BP over the 24-month follow-up period and change in WMH, mobility, and cognitive measures at 24 months are shown by the results of the regression analyses in Table 2. Analyses were adjusted for age and LDL cholesterol at 24 months because the values of these 2 measures changed significantly over the 2 years and were correlated with total WMH at 24 months. The accrual of WMH from baseline was significantly associated with change from baseline in 24-hour systolic BP but not for changes in clinic systolic BP (Table 2). For mobility measures, walk time had a nonsignificant association with 24-hour systolic BP ($P=0.076$). Changes in Trail Making B and simple reaction time were associated with changes in 24-hour systolic BP and sleep systolic BP; change in Trail Making B was also associated with change in awake systolic BP. Stroop Color and Word was the only functional parameter associated with change in surge systolic BP (Table 2). There were no significant associations of any of the cognitive or physical measures or of WMH with any of the BP measures at baseline.

To study the possibility of thresholds in 24-hour systolic BP defining WMH and mobility parameters, smoothed (lowess) scatterplots of BP with WMH (Figure 1) were constructed. At higher levels of 24-hour systolic BP and larger changes in 24-hour systolic BP over time, WMH at 24 months was also higher (Figure 1A and 1B). Larger increases in WMH were also observed with large changes in 24-hour systolic BP (Figure 1C). In contrast, no relationship between clinic systolic and WMH (Figure 2A) or change in clinic systolic BP and WMH at 24 months was evident (Figure 2B).

Using a threshold cut point for 24-hour systolic BP of 135 mm Hg (clinical cut point as defined by the American Society of Hypertension[17]), we also observed a significant difference in total WMH at 24 months but not for change in WMH (Table 3). In addition, several of the functional

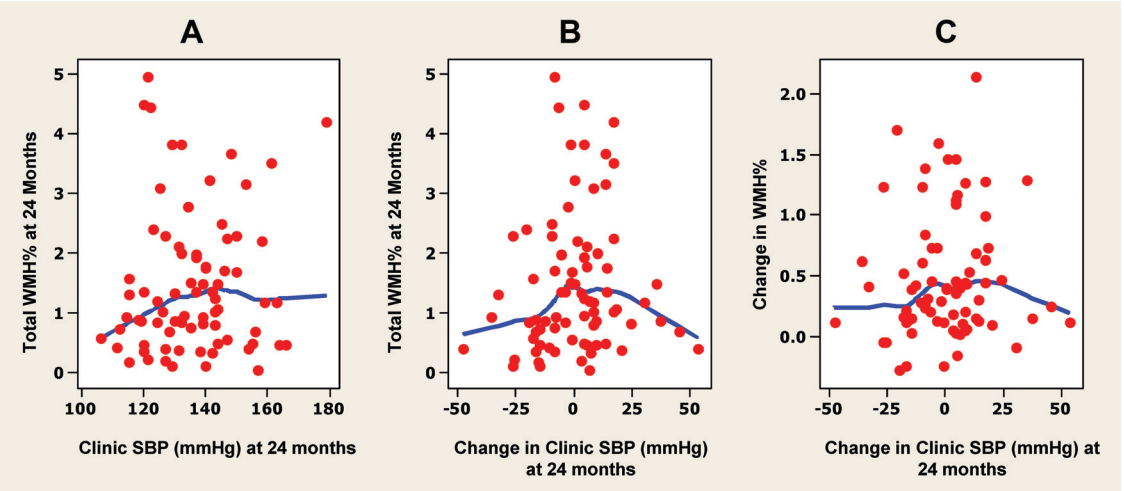

Figure 2. White matter hyperintensity (WMH) and clinic blood pressure (BP). Locally weighted scatterplot smoother plots of clinic systolic BP (SBP) and WMH lesions (as percent of total intracranial volume; **A**), change in clinic SBP and WMH (%; (**B**), and change in clinic SBP and change in WMH (%) at 24 months (**C**).

Table 3. White Matter Lesion Volume and Functional Parameters at 24 Months According to 24-Hour Blood Pressure Cut Points Above and Below 135 mm Hg

	24-h Ambulatory BP		
	<135 mm Hg (n=28)	≥135 mm Hg (n=45)	*P*
24-h Systolic BP, mm Hg	122.0±1.3	142.9±1.2	<0.001†
Total WMH, %	1.26±0.15	1.96±0.26	0.03†
Change in WMH, %*	0.43±0.07	0.62±0.10	0.100
Mobility assessments			
Tinetti Gait	11.5±0.2	11.0±0.3	0.184
Stair descent time, s	5.8±0.4	6.8±0.4	0.023†
Maximal gait velocity, m/s	2.5±0.1	2.2±0.1	0.051†
Walk time, s	2.9±0.1	3.5±0.2	0.003†
Cognitive assessments			
Trails B, s	117.1±8.2	136.5±15.4	0.489
Stroop Color and Word, ms	27.5±1.3	24.7±1.9	0.122
Sequential process time, ms	501.6±30.8	613.8±33.4	0.033†
Simple reaction time, ms	389.0±21.1	461.8±37.2	0.025†

BP indicates blood pressure; WMH, white matter hyperintensity. Data are mean±SEM. *P* values were derived from Kruskal-Wallis testing.

*Change in WML over 24 months.

†Significant.

parameters showed more substantial decline in patients with 24-hour systolic BPs ≥135 mm Hg versus those who had a 24-hour systolic BP <135 mm Hg.

WMH volume and functional parameters were evaluated according to "dipping status" at 24 months (Table 4). For the purposes of this analysis, subjects who had a decline in sleep systolic BP relative to awake systolic BP of >10% were considered dippers or extreme dippers if >20% (n=26), and those who had a lack of decline in sleep systolic BP relative to awake systolic BP were considered nondippers (<10% for a nondipper and <0% for a riser; n=46). Mobility function was better in dippers compared with nondippers (Table 4), whereas there were no differences in WMH or cognitive function according to dipper status. Of note, various systolic BP variability measures (the SD of the 24-hour mean systolic BP, awake systolic BP, or sleep systolic BP) were not associated with WMH or functional parameters.

Table 4. White Matter Lesion Volume and Functional Parameters at 24 Months According to Dipping Status

Parameter	Risers/ Nondippers (n=46)	Dippers/Extreme Dippers (n=26)	*P*
Clinic systolic BP, mm Hg	135.8±2.2	135.6±2.8	0.82
24-h Systolic BP, mm Hg	130.7±2.0	128.7±2.3	0.62
Total WMH, %	1.6±0.2	1.3±0.2	0.57
Change in WMH, %	0.53±0.08	0.46±0.08	0.78
Mobility assessments			
Tinetti Gait	11.1±0.2	11.5±0.2	0.22
Stair descent time, s	6.5±0.3	5.7±0.6	0.02*
Maximal gait velocity, m/s	0.7±0.02	0.8±0.04	0.04*
Walk time, s	3.3±0.1	2.9±0.1	0.02*
Cognitive assessments			
Trails B, s	135.6±10.9	104.5±8.3	0.12
Stroop Color and Word, ms	26.1±1.4	26.9±1.5	0.39
Sequential process time, ms	551.7±31.1	523.1±35.8	0.78
Simple reaction time, ms	434.3±27.7	385.5±22.3	0.3

BP indicates blood pressure; WMH, white matter hyperintensity.

*Significant.

Total WMH Volume and Function at 24 Months

Regression analyses were also conducted to examine the relationships between the mobility and cognitive measures with WMH at 24 months. After adjustment for age and LDL cholesterol levels, 3 of the 4 mobility measures and all of the cognitive measures were significantly related to WMH volume at 24 months.

Discussion

Principal Findings

Prior studies have shown that cumulative clinic BP and out-of-office BP measurements are linked to WMH and its progression[18,19] and that progression of white matter grade is associated with cognitive decline.[20] In the present study, we demonstrate that ambulatory systolic BP but not clinic systolic BP is associated with volumetric WMH progression and its effect on the function of older persons evaluated in a longitudinal fashion. In our cohort of subjects 75 to 90 years of age, we evaluated progression of WMH over 2 years in those who had office and ambulatory BP and volumetric MRI. Regression analyses were performed to assess the relations among changes in BP, WMH, mobility, and cognitive function. Our data demonstrate that the 24-hour average systolic BP is associated with microvascular brain disease, characterized by volumetric MRI–derived white matter lesions on volume, and is significantly associated with impairment of several measures of mobility and cognition. Most notably, worsening ambulatory BP was associated with accrual of WMH and impaired executive function, even after controlling for baseline BP in a longitudinal progression model.[15] In contrast, the clinic systolic BP was not related to progression of WMH or functional measures.

Clinical threshold analyses subdividing the data into groups of normal (<135 mm Hg) versus abnormal (≥135 mm Hg) ambulatory systolic BP at 2 years demonstrated significant differences for WMH and the functional indexes. In the higher 24-hour systolic BP group, WMH was increased and stair descent times and walk times were slower compared with the normal 24-hour BP group, whereas gait velocity was less. Gait speed in the higher ambulatory systolic BP group decreased 0.3 m/s more than in the normal ambulatory systolic BP group; stair descent time also was 1 second slower in this group. Although these differences may appear small, they represent changes at 2 years. Mobility limitations linked to WMH occur gradually, so this decrement is part of a long-term process that may compromise gait velocity over ≥10 years.[21] Finally, there were also significant relationships among the 24-hour systolic BP values and WMH values at 2 years with some measures of executive functioning processing speed. Thus, our results are novel and

demonstrate for the first time that 24-hour ambulatory BP, not clinic BP, predicts progression of WMH volume within 2 years and is linked to significant and clinically important functional decline in older people.

BP Reproducibility

One likely reason for our findings that 24-hour BP and changes in sleep systolic BP predict cerebrovascular disease and functional outcomes in the elderly but clinic BP does not is the markedly enhanced reproducibility of ambulatory and sleep BP over that of static clinic BP measurements.[8,22] In fact, in the population studied here, although there were only small changes in office, 24-hour, awake, and sleep mean BP values between baseline and 2 years later, the variability (SD of the differences between visits) was much lower for 24-hour BP compared with the office BP (11.7/5.9 versus 17.8/9.0 mm Hg; $P<0.01$).[8] However, the reproducibility of the 24-hour BP was also substantially better than that of the early morning BP. These findings may also explain in part why 24-hour and awake systolic BPs have stronger relationships with WMH and mobility than with the morning surge in BP.

Prior Investigations

Prior cross-sectional studies have demonstrated a relationship between ambulatory BP and WMH in middle-aged or older people.[23–27] In contrast to the present study, however, the majority of these cross-sectional studies used more qualitative assessments of white matter lesions (present or absent),[26,27] total brain volume measurements,[25] or a semiquantitative scoring system of WMH.[24] The present study obtained segmentation maps and total WMH volume in milliliters (quantified by multiplying voxel volume [mm^3] by the number of WMH pixels [divided by 1000]).[6] This methodology allows quantification of white matter lesion burden in brain regions with pathways supporting mobility.[2,6] Hence, it is possible that a combination of improved reproducibility of BP assessment over time using ambulatory monitoring[8] and more precise measures of WMH played a role in our ability to demonstrate a meaningful impact on function despite the relatively small number of patients in our cohort.

The results of the present study add to a large body of data demonstrating the superiority of 24-hour BP over that of clinic (or doctor's office) BP in predicting hypertensive target organ disease, particularly cardiac size and structure,[28,29] and renal impairment with proteinuria.[30] In addition, ambulatory BP monitoring has been shown to be predictive of renal abnormalities in individuals with no history of hypertension.[31]

Study Limitations

The number of subjects from this cohort of subjects with a mean age of 82 years at baseline who were available for assessment at year 2 declined substantially as a result of death and disability. Of the 23 unavailable subjects, only 5 were unwilling to wear the ambulatory BP recorder. Of the 72 patients who wore the monitor twice, 71 had complete data (nocturnal BP was missing in 1 subject). However, despite the reduction in available study patients at 24 months, there were highly significant findings relating changes in 24-hour systolic BP with changes in WMH and significant findings relating 24-hour systolic BP at 24 months with mobility assessments.

The methodology used in our study was not specifically designed to identify and separate leukoaraiosis and lacunae. Leukoaraiosis is a combination of white matter pallor, demyelination, and microvascular ischemia and appears as hyperintense (WMH) signal in T2-weighted MRI scans. Lacunes are discrete microvascular infarcts caused by occlusion (usually atherosclerosis) of a small penetrating vessel and appear as small cavities 3 to 15 mm in diameter with signal intensity comparable to that of cerebrospinal fluid. In our study, it is not likely that large lacunes were included in the final mapping of WMH. However, we cannot exclude the presence of very small lacunae; hence, areas identified as WMH may be a combination of both leukoaraiosis and possibly small silent lacunae. However, because of the expert overreads for the segmentation mapping to remove potential artifacts, we expect that the impact of the potential inclusion of small lacunae in the final total WMH volumes to be minimal. Finally, many statistical tests are being reported, so it is possible that some of the significant associations are due to chance; however, it should be noted that the association of 24-hour BP with WMH, mobility, and cognition were a priori hypotheses.

Implications of the Findings

The data suggest that an intervention targeting mean 24-hour systolic BP might reduce progression of microvascular disease and thus favorably affect function. Of interest is that the mean values in the highest tertile of clinic and 24-hour systolic BP are 153 and 144 mm Hg, respectively. Only the Hypertension in the Very Elderly Trial (HYVET)[32] has studied the benefits of therapy in an age group similar to that in the present study. Because clinic systolic BP, not ambulatory BP, was targeted, it is not known what the goal of therapy for ambulatory BP should be in patients >80 years of age. In HYVET, differences in clinic systolic BP of 15 mm Hg translated into reductions in stroke mortality within 2 years. In our longitudinal study, a 14-mm Hg difference in 24-hour systolic BP was associated with 40% less WMH and correspondingly improved function within a range that would be considered normal for this age group by many clinicians. From these findings, a clinical trial comparing WMH volume and functional measures of mobility and cognition in groups whose ambulatory BP is maintained at the higher versus lower ends of the normal systolic BP spectrum seems warranted.

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Disclosures

None.

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CLINICAL PERSPECTIVE

High blood pressure (BP) is a risk factor for cerebrovascular disease, including stroke. Little is known about the importance of BP on the progression of microvascular disease of the brain, which has been associated with functional decline in mobility and cognition in older people. In this prospective cohort study of older people averaging 82 years of age, relations among clinic and ambulatory BP, white matter hyperintensity volume, and functional status were determined over 2 years. Changes in the 24-hour ambulatory systolic BP, but not clinic systolic BP, were associated with the amount of white matter hyperintensity volume accrued at the 24-month follow-up and the progression of white matter hyperintensity volume from baseline, as well as measures of executive function/processing speed. Higher levels of 24-hour systolic BP were associated with white matter hyperintensity volume and mobility measures at 2 years; no such relation was seen with clinic systolic BP. Hence, these data demonstrate the importance of 24-hour systolic BP in the progression of brain white matter hyperintensity volume burden associated with impairment of function in older people. The 24-hour systolic BP may be a potential target for intervention in the elderly to reduce vascular disease of the brain and impairment of function.