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ORIGINAL ARTICLE

Association between central systolic blood pressure, white matter lesions in cerebral MRI and carotid atherosclerosis

Isha Shrestha[1], Tetsuya Takahashi[1], Eiichi Nomura[2], Toshiho Ohtsuki[1], Tomohiko Ohshita[1], Hiroki Ueno[1], Tatsuo Kohriyama[1] and Masayasu Matsumoto[1]

White matter hyperintensities (WMHs) observed on cerebral magnetic resonance images (MRIs) are associated with age and hypertension, suggesting a vascular mechanism of pathogenesis. Central systolic blood pressure (cSBP) correlates more closely with measures of cardiovascular disease risk than brachial pressure. We sought to determine whether cSBP correlates with WMHs and if cSBP is predictive of cerebrovascular disease. Radial applanation tonometric measurements for cSBP and augmentation index (AI) were carried out in unselected individuals undergoing carotid ultrasound. WMHs were assessed retrospectively using fluid-attenuated inversion recovery (FLAIR)-MRIs as periventricular (PVH) and deep white matter hyperintensities (DWMH), and they were rated using the Fazekas scale. A total of 179 patients, 94 (53%) men and 85 (47%) women, with a mean age of 66 ± 13 years were included in the study. On MRI, 17, 74, 67 and 21 patients had PVH grades 0, 1, 2 and 3, respectively. Forty-eight, 69, 49 and 13 had DWMH grades 0, 1, 2 and 3, respectively. In our study population, PVH correlated with age, brachial SBP, cSBP and AI (r=0.49, 0.28, 0.23; $P<0.002$ and r=0.13; $P<0.05$, respectively). DWMH also correlated with age, brachial SBP and cSBP (r=0.41, 0.30, 0.22; $P<0.003$, respectively), but not with AI. cSBP values were associated with PVH/DWMH grades 2 and 3, but brachial SBP correlated only with grade 3. Mean carotid intima–media thickness (common carotid arteries (CCA)-IMT) was 0.68 ± 0.13 mm. CCA-IMT and plaque score (PS) correlated with PVH/DWMH. Multivariate regression analysis showed cSBP, age and PS to be independently associated with PVH and DWMH. Correlation of cSBP with PVH and DWMH was independent of PS. Central SBP correlated with PVH and DWMH in FLAIR-MRIs and can better predict WMHs than brachial SBP in earlier stages.
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INTRODUCTION

White matter lesions (WMLs) are frequently observed on cerebral magnetic resonance images (MRIs) of elderly patients without apparent neurological symptoms.[1] These WMLs appear as hyperintense areas in T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRIs and as isointense areas in T1-weighted MRIs. Their presence correlates with gait disturbances,[2] cognitive impairment, dementia[3] and mood disorders.[4] Epidemiological studies have shown that age, hypertension and diabetes, the principal risk factors of cerebrovascular disease (CVD), are associated with white matter hyperintensities (WMHs). This association is suggestive of a vascular mechanism in WMH pathogenesis.[1,5–7] The presence of WMHs is an independent risk factor for stroke.[8] Pathological studies have shown definite structural vascular abnormalities associated with WMHs, strengthening the argument that WMHs have a vascular etiology,[9,10] and thus suggesting that WMHs are associated with atherosclerotic changes in small vessels.

Ultrasonographic findings of increased atherosclerotic plaques and carotid artery intima–media thickness (IMT) are also regarded as the subclinical markers of early atherosclerosis. The presence of these markers is associated with non-modifiable and modifiable risk factors and with the subsequent risk of new or recurrent stroke and myocardial infarction.[11–13] Conversely, studies show that the presence of atherosclerosis is predictive of WMHs.[5,14] The severity of IMT and the presence of plaques in the carotid arteries are also predictive of periventricular WMLs.[15]

Recently, several non-invasive parameters have been introduced to assess vascular stiffness. Central systolic blood pressure (cSBP) and augmentation index (AI) are parameters obtained non-invasively from central arterial waveforms through radial arterial pulse wave analysis

[1]Department of Clinical Neuroscience and Therapeutics, Hiroshima University, Hiroshima, Japan and [2]Department of Neurology, Suiseikai Kajikawa Hospital, Hiroshima, Japan
Correspondence: Dr T Takahashi, Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.
E-mail: tetakaha@mac.com
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(PWA).[16–18] AI and cSBP are closely related to several risk factors for atherosclerosis and future cardiovascular events.[18–21]

In this study, we investigated the relationship between WMHs and enhanced arterial stiffness and sought to determine whether cSBP correlates with WMHs and can serve as a predictor of CVD. We obtained cSBP and AI through PWA and recorded WMHs as detected by FLAIR-MRIs. We also investigated the association of cSBP with carotid atherosclerosis.

METHODS

Study population

Study participants were recruited from unselected consecutive cases attending the carotid ultrasonography clinic for clinically indicated ultrasonographic examination of the extracranial carotid arteries. The study population encompassed a wide range of age groups and underlying diseases including patients with CVD, coronary artery disease, and other neurological and systemic problems. Also included were patients undergoing carotid ultrasonography for preoperative screening. Exclusion criteria included inability to perform the tonometric PWA as in patients with atrial fibrillation, chronic renal failure with patent arteriovenous fistulas in bilateral wrists for hemodialysis, aortitis with impalpable peripheral pulses, inability to obtain MRIs (as patients with pacemakers and other implants), inability to obtain a good carotid sonograph, and inability to obtain informed consent from the patient. Informed consent was obtained from all participants before they were enrolled in the study.

Ultrasound evaluation

The common carotid arteries (CCA) were evaluated using high-resolution B-mode duplex ultrasonography with a 7.5-MHz linear type probe (Aplio, Toshiba Medicals, Tokyo, Japan). Bilateral optimal visualization of the carotid artery was performed with the patients lying in the supine position with their necks slightly hyperextended. We obtained the mean value of maximal IMT measured in the distal CCA far wall (CCA-IMT), the 10-mm section of the artery proximal to the starting point of the carotid bulb. Measurements were taken from the best longitudinal images obtained after multiple visualizations. Plaques in the accessible segments of the CCA as well as the internal carotid artery were described in terms of plaque number and plaque score (PS). Plaques are defined as IMT $\geqslant$ 1.1 mm. Plaque number is the total number of plaques recorded in the CCA-internal carotid artery segments bilaterally. PS is the sum of the heights of all the plaques present bilaterally.[22,23]

Pulse wave analysis

Measurements were taken in a quiet, temperature-controlled room with the patient sitting comfortably on a bed after completing the carotid ultrasonography. Applanation tonometry of the radial artery was performed in the left wrist using the commercially available automated applanation tonometry system (HEM-9000AI, Omron Healthcare, Kyoto, Japan). The built-in software in the Omron system was used to obtain the following measurements: AI, brachial SBP, cSBP, diastolic blood pressure (DBP) and pulse pressure. The validity of the device has already been established.[24]

MRI data acquisition

Participants' MRI findings were obtained retrospectively from the hospital's electronic data bank. We used the most recent images (within the past 6 months, except for three cases where images as old as 10 months were included). The patients were examined on the 1.5 T MRI unit (SIGNA, GE Medical Systems, Fairfield, CT, USA). The WMHs in MRIs were classified into periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH). PVH and DWMH were defined as showing high intensity in FLAIR-MRIs and low intensity in T1-weighted MRIs. PVH includes WMHs in contact with the ventricular wall, and DWMH includes the WMHs situated in the deep white matter and separated from the ventricular wall by a strip of normal-appearing white matter. The severity of PVH and DWMH was rated visually on axial-FLAIR images using the Fazekas scale[25] to assign grades 0–3. A single person performed visual ratings of PVH and DWMH in a blinded manner.

Risk factors

Data regarding the patients' risk factors for atherosclerosis, such as hypertension, diabetes mellitus, dyslipidemia, history of stroke or transient ischemic attack, ischemic heart disease or coronary artery disease, and smoking habits were obtained from hospital records. Risk factors were defined as follows: hypertension: SBP $\geqslant$ 140 mm Hg and/or DBP $\geqslant$ 90 mm Hg or using antihypertensive medication; diabetes mellitus: fasting blood glucose $\geqslant$ 7.0 mmol l^{-1} or using oral hypoglycemic agents or insulin; dyslipidemia: low-density lipoprotein-cholesterol $\geqslant$ 3.6 mmol l^{-1} or using lipid-lowering agents; smoking was defined as 'current smokers' or 'nonsmokers.'

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 11.5. for Windows, SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± s.d. or %, unless stated otherwise. Pearson's and Spearman's correlation coefficients were used for continuous and ordinal variables, respectively. Comparison of the variables between groups was carried out using the χ^2-test for categorical variables and analysis of variance and post hoc tests (Tukey HSD) for continuous variables. Univariate correlation analyses were used to assess the relationships between variables of interest. Multivariate

Table 1 Characteristics of patients with different grades of PVH and DWMH

		MRI-PVH grades				*MRI-DWMH grades*			
Characteristics	*Total*	*0*	*1*	*2*	*3*	*0*	*1*	*2*	*3*
N	179	17	74	67	21	48	69	49	13
Male (%)	94 (52.5)	10 (58.8)	39 (52.7)	33 (49.3)	11 (52.4)	30 (62.5)	32 (46.4)	26 (53.1)	5 (38.5)
Age (years)	66 ± 13	43 ± 14	65 ± 11	71 ± 10	71 ± 9	57 ± 16	67 ± 11	72 ± 10	71 ± 11
cSBP (mm Hg)	137 ± 18	123 ± 19	137 ± 24	141 ± 22	152 ± 28	129 ± 20	140 ± 21	141 ± 27	161 ± 30
SBP (mm Hg)	131 ± 12	122 ± 16	131 ± 21	135 ± 21	148 ± 24	125 ± 16	134 ± 20	137 ± 24	153 ± 26
AI (%)	83 ± 17	74 ± 15	82 ± 15	85 ± 18	85 ± 17	78 ± 17	85 ± 16	82 ± 17	91 ± 11
HR (beats min^{-1})	73 ± 13	75 ± 15	72 ± 12	74 ± 14	71 ± 11	75 ± 14	72 ± 11	75 ± 15	67 ± 9
DBP (mm Hg)	78 ± 13	75 ± 14	77 ± 11	79 ± 13	77 ± 14	75 ± 12	78 ± 12	79 ± 12	74 ± 15
PP (mm Hg)	56 ± 18	48 ± 15	54 ± 17	57 ± 17	71 ± 24	50 ± 14	55 ± 16	58 ± 20	78 ± 25
CCA-IMT (mm)	0.68 ± 0.13	0.62 ± 0.14	0.77 ± 0.15	0.83 ± 0.17	0.91 ± 0.35	0.72 ± 0.15	0.79 ± 0.17	0.83 ± 0.15	0.98 ± 0.41
Plaque score	3.37 ± 3.57	1.12 ± 2.50	2.0 ± 2.26	2.93 ± 2.51	3.57 ± 3.52	1.59 ± 2.62	2.51 ± 2.23	2.84 ± 2.57	3.69 ± 3.74

Abbreviations: AI, augmentation index; CCA-IMT, common carotid artery intima–media thickness; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensities; HR, heart rate; *N*, number; PVH, periventricular hyperintensities; SBP, brachial systolic blood pressure; PP, pulse pressure; PS, plaque score.
Data are presented as mean ± s.d. or as the number (%) of patients.

linear regression analysis was carried out to check the independent relationships of cSBP with WMHs. All *P*-values <0.05 were considered statistically significant.

RESULTS

A total of 179 patients were included in the study. Of the total participants, 94 (52.5%) were males. The mean ± s.d. age of the participants was 66 ± 13 years (median, 68 years). Clinical characteristics for each grade of PVH and DWMH are shown in Table 1. Of the total patients, 88 had a history of stroke and 14 had a history of coronary artery disease or ischemic heart disease. Among the stroke patients, 12.1% had transient ischemic attacks, 4.0% had hemorrhagic strokes and 83.9% had ischemic strokes. With respect to subtypes of ischemic stroke, 34.3% had large artery atherosclerosis, 12.1% had cardioembolic events, 29.3% had small artery occlusion, 2.0% had strokes of other determined cause, and 6.1% had strokes of undetermined cause according to the TOAST classification.

Table 2 shows the diagnosis and risk factors of the study participants. The number of patients with PVH grades 0, 1, 2 and 3 was 17, 74, 67 and 21, respectively. Similarly, the number of patients with DWMH grades 0, 1, 2 and 3 was 48, 69, 49 and 13, respectively. Of the total patients, 41 (22.9%) were taking antihypertensive medications. PVH and DWMH correlated with the diagnosis of hypertension ($r=-0.36$, $P<0.0001$ and $r=-0.36$, $P<0.0001$, respectively) and past history of CVD ($r=-0.22$, $P<0.003$ and $r=-0.16$, $P<0.036$), but they did not show any association with diabetes mellitus, dyslipidemia, past coronary artery disease or smoking habits. Investigation of the association between the MRI findings and cSBP in men and women separately showed that women had a stronger association than men.

Univariate analysis revealed that cSBP is correlated with brachial SBP and also moderately with AI (Figure 1). CCA-IMT showed a significant positive correlation with cSBP, as well as AI, but the association was weaker with AI compared with cSBP (Figure 1).

Table 2 Clinical characteristics of the study participants

	Men (n=*94*)	*Women* (n=*85*)	P-*value*
Age (years)	66	65	<0.001
Hypertension (%)	56.4	45.9	NS
Antihypertension therapy	22.3	24.7	NS
Calcium channel blocker	5.6	8.9	
Angiotensin receptor blocker	6.7	3.9	
ACE inhibitor	2.2	5.0	
Diuretics/β-blockers/others	6.1	3.4	
Diabetes mellitus (%)	34.5	24.7	<0.002
Dyslipidemia (%)	29.8	44.7	<0.0001
Smoking habits (%)	55.3	14.1	0.0002
History of CVD (%)	50.0	47.1	NS
History of CAD (%)	4.3	9.4	<0.001
Parkinsonism (%)	10.6	14.1	NS
Dementias (%)	3.2	9.4	0.042
Other neurological diseases (%)[a]	18.1	23.5	NS
Other systemic diseases (%)[b]	16.0	11.8	NS

Abbreviations: ACE, angiotensin-converting enzyme; CAD, coronary artery disease; CVD, cerebrovascular disease; IHD, ischemic heart disease; NS, not significant; *n*, number; TIA, transient ischemic attack.
Values are the mean or frequency. *P*-values refer to un-paired *t*-test for continuous variables and χ^2-analysis for categorical variables.
[a]Includes cases with vertigo, neuropathies, seizure disorders, migraine and so on.
[b]Includes patients with renal and hepatic disorders, various cancers, those undergoing carotid ultrasonography for preoperative screening.

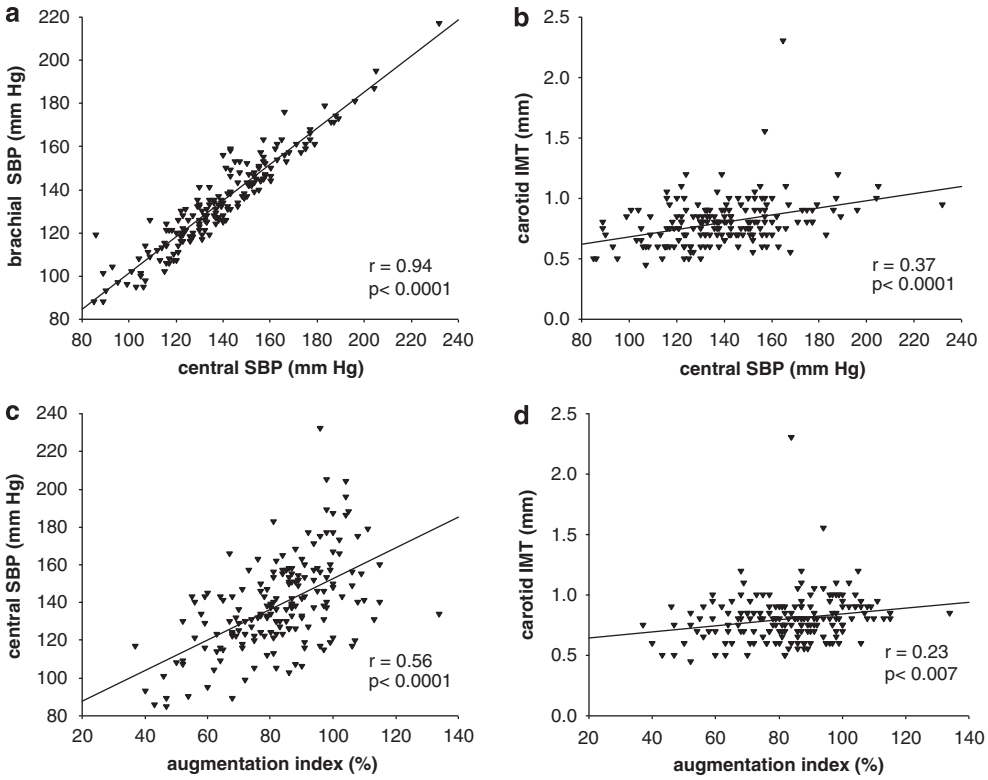

Figure 1 Univariate analyses among the parameters: scatter plots showing the relationships between brachial systolic blood pressure (SBP) and central SBP (y=17.64+0.89x) (**a**); carotid intima–media thickness (IMT) and central SBP (y=0.38+0.00x) (**b**); central SBP and augmentation index (AI) (y=71.76+0.81x) (**c**); and carotid IMT and AI (y=0.59+0.00x) (**d**).

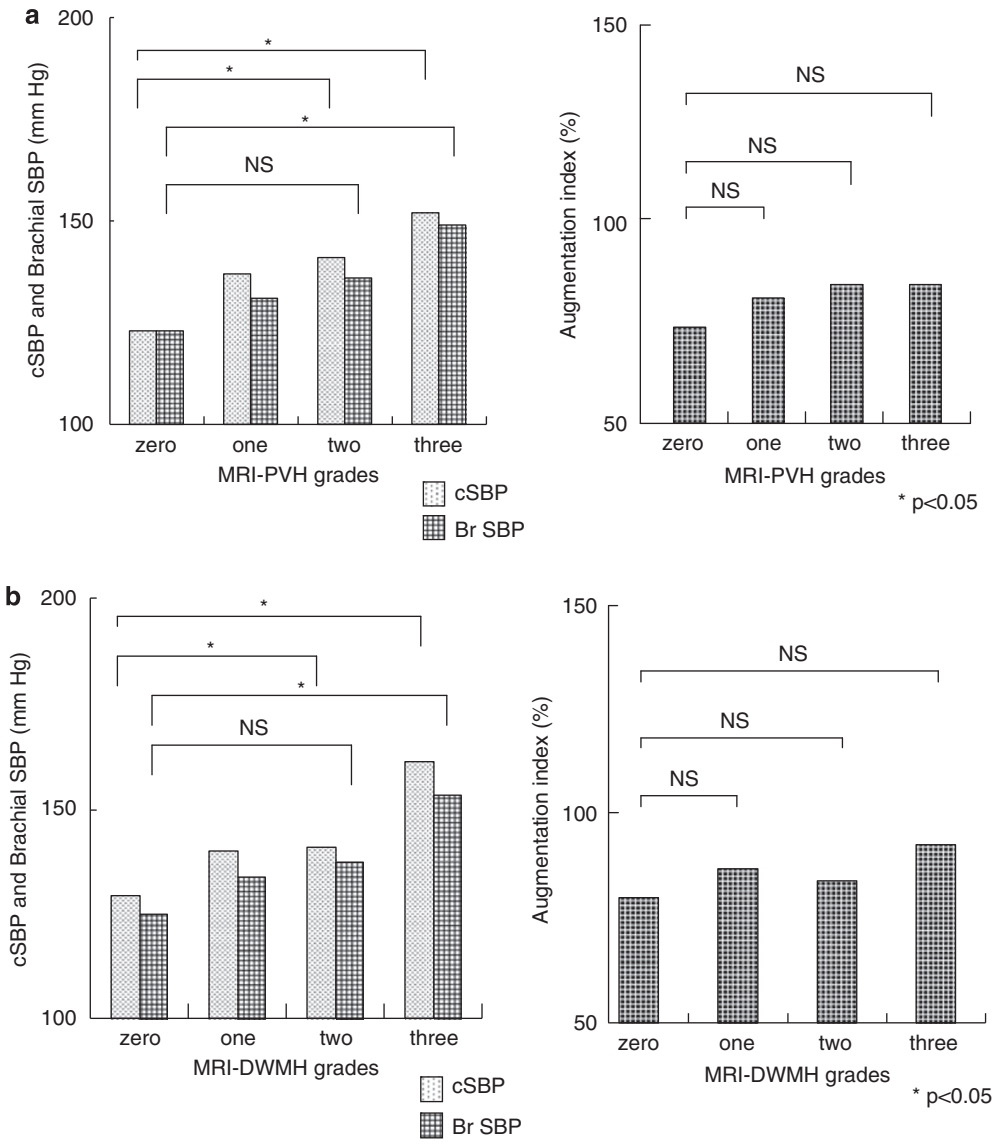

Figure 2 Central systolic blood pressure (cSBP) values showed a significant association with the periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH) grades 2 and 3, but brachial SBP had a significant association with only the extreme grades (grade 3) of both PVH and DWMH (panels **a** and **b**). The grades of both PVH and DWMH did not correlate with the augmentation index (AI). Analysis of variance, *post hoc* test (Tukey HSD). *$P<0.05$; NS, not significant.

In the correlation analysis, the presence of PVH showed positive correlations with age (r=0.49, $P<0.0001$), SBP (r=0.28, $P<0.0001$) and cSBP (r=0.23, $P<0.002$). DWMH also showed associations with age (r=0.41, $P<0.0001$), SBP (r=0.30, $P<0.001$) and cSBP (r=0.22, $P<0.003$). PVH was correlated with AI (r=0.13, $P<0.05$), but DWMH was not. The presence of PVH was positively correlated with CCA-IMT, PS and plaque number but not with DBP or pulse pressure. Positive correlation was also seen between DWMH and CCA-IMT, PS, plaque number and pulse pressure but not with DBP.

The cSBP values in the PVH grades 0, 1, 2 and 3 were 123 ± 19, 137 ± 24, 141 ± 22 and 152 ± 28 mm Hg, respectively. The cSBP values in the DWMH grades 0, 1, 2 and 3 were 129 ± 20, 140 ± 21, 141 ± 24 and 161 ± 30 mm Hg, respectively. When the relationships between the increasing PVH grades and parameters of PWA were investigated, cSBP showed a significant positive correlation with PVH grades, whereas AI was not correlated (Figure 2a). DWMH grades also showed significant correlations with cSBP but not with AI (Figure 2b). The differences in the cSBP values in PVH and DWMH grades 0 and 3 as well as 0 and 2 were significant, but for the brachial SBP, the differences were significant only for grades 0 and 3 (Figures 2a and b).

The mean CCA-IMT in the total study sample was 0.68 ± 0.13 mm. CCA-IMT increased along with increases in PVH and DWMH grades. Similarly, PS also increased with the increase in PVH and DWMH grades (Table 1).

The results of multivariate linear regression analysis in stepwise manner, with PVH and DWMH grades as dependent variables, are shown in Table 3. In model 1, we adjusted for age, male sex, AI, CCA-IMT and PS. In model 2, we also adjusted for cSBP. We found that cSBP, but not AI, was independently related to PVH and DWMH. Age and PS also showed independent relationships with PVH and DWMH.

Patients with PVH and DWMH grades 0 or 1 (PVH I and DWMH I) and grades 2 and 3 (PVH II and DWMH II) were stratified into two groups on the basis of their PS grades (Figure 3). PS grades were

divided into PS I (no or mild PS that is, PS<5) and PS II (moderate-to-severe PS that is, PS⩾5) groups. *T*-test analysis of the differences in the mean cSBP values between the two groups of PVH and DWMH against PS I and II groups showed significant differences in the PS I groups.

DISCUSSION

The main finding of this study is that cSBP is positively correlated with the presence of PVH and DWMH in FLAIR-MRIs in an unselected sample. Our results show that the cSBP values are more closely associated than the brachial SBP with PVH and DWMH grades. Although we found that cSBP also tended to correlate with the atherosclerotic changes in the carotid arteries, the association between cSBP and WMHs was independent of the atherosclerotic changes.

The cSBP values showed significant association not only with high-grade (grade three) lesions but also with the lower grade PVH and DWMH lesions. By contrast, brachial SBP is only significantly associated with these lesions for the extreme grades but not for the lower grades. Though brachial SBP has been and still is an important risk factor, we can suggest from our data that cSBP might be a better predictive indicator, especially to predict the PVH/DWMH lesions in their earlier stages. Further studies with much larger sample sizes are needed to validate the results. To the best of our knowledge, our study is the first to examine the relationships of cSBP with PVH and DWMH.

Table 3 Stepwise linear regression analysis of white matter hyperintensities with other parameters

	PVH presence				*DWMH presence*			
	Model 1		*Model 2*		*Model 1*		*Model 2*	
Correlate	*β*	P	*β*	P	*β*	P	*β*	P
Age	0.49	<0.001	0.42	<0.001	0.40	<0.001	0.31	<0.001
Gender (male sex)	0.07	NS	0.09	NS	0.11	NS	0.15	NS
AI	0.02	NS	0.03	NS	0.03	NS	0.05	NS
CCA-IMT	0.15	NS	0.12	NS	0.16	NS	0.10	NS
Plaque score	0.17	0.02	0.17	0.02	0.22	0.004	0.21	0.006
cSBP			0.14	0.03			0.19	0.008

Abbreviations: AI, augmentation index; cSBP, central systolic blood pressure; CCA-IMT, common carotid artery intima–media thickness; DWMH, deep white matter hyperintensities; NS, not significant; PVH, periventricular hyperintensities.
Results of correlation analysis of PVH presence and DWMH presence to parameters of radial wave analysis; cSBP and AI; and carotid atherosclerosis. Model 1 adjusted for age, gender (male sex), AI, CCA-IMT or plaque score. Model 2 adjusted for variables in Model 1, cSBP. The strength of correlation is expressed by the regression coefficients β.

White matter lesions are frequently observed on cerebral MRIs of elderly patients without apparent neurological symptoms.[1] These WMLs appear as hyperintense areas in T2-weighted and FLAIR-MRIs and as isointense areas in T1-weighted MRIs. They reportedly correlate with gait disturbances,[2] cognitive impairment, dementia[3] and mood disorders.[4] These WMLs are likely to result from ischemic injury to the brain.[26] Exposure of vessels to high pressure results in impairment of cerebral autoregulation[27] or microvascular structural damage,[28] and these are potential mechanisms that may lead to cerebral WMHs. This would represent the cerebral manifestation of hypertensive target organ damage. In a population-based study, Roman *et al.*[29] showed that central pressures more accurately reflect the loading conditions on the cerebral vasculature than brachial pressures do. There are also data suggesting that central pressure and indices correlate more closely with the measures of cardiovascular risk than brachial pressure and that they can independently predict future cardiovascular events.[17,30–32] Furthermore, the results of a large-scale ASCOT-CAFÉ study show that brachial blood pressure is not always a good surrogate for the effects of blood pressure-lowering drugs on arterial hemodynamics, emphasizing the importance of central blood pressure measurements over traditional peripheral blood pressure measurements.[33]

Differing from most of the other studies[20,34,35] that focus on the association between WMHs and arterial stiffness with brachial artery pulse wave velocity parameters, this study examined the relationships of WMHs with cSBP and AI. Increased brachial artery pulse wave velocity is reported to be closely associated with the appearance of PVH in elderly populations[35] and also with the risk of small vessel disease in hypertensive elderly persons.[34] Although the measurement techniques are different, our results support similar findings that stiffness of arteries, in our case cSBP, is associated with WMLs.

In our study, we established a good association between the MRI-WMHs and cSBP, but no such association existed with AI. The different relationships of AI and cSBP with WMHs in our study could be explained by assuming that these two measurements provide different information about arterial structure and function. As age, height, DBP[36] and heart rate[37] are known determinants of AI, AI does not reflect arterial stiffness alone. We suppose, for this very reason, that the association between AI and WMHs was weaker in this study.

In this study, we uniquely investigated the MRI-WMHs in unselected patients, unlike earlier studies in which within risk-factor groups were included. Similar to earlier studies,[1,2] our study also showed that age is independently associated with both PVH and DWMH. Females had a stronger association between the MRI findings and cSBP. In addition, cerebral WMHs are associated with carotid

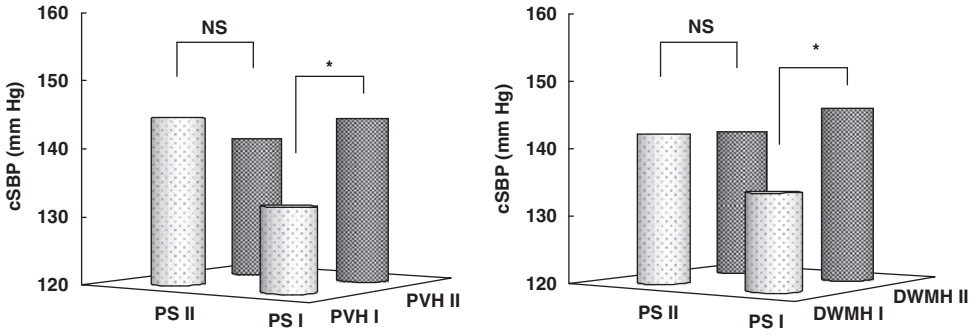

Figure 3 Central systolic blood pressure (cSBP) in patients with periventricular hyperintensities (PVH) grades 0 or 1 (PVH I) and PVH grades 2 or 3 (PVH II) and in patients with deep white matter hyperintensities (DWMH) grades 0 or 1 (DWMH I) and DWMH grades 2 or 3 (DWMH II), stratified into two groups according to the plaque score (PS) grades, PS I (PS<5) and PS II (PS⩾5). *P*-values refer to *t*-tests. **P*<0.05; NS, not significant.

IMT and PS, as suggested by this study, and also supported by earlier studies.[5,13,15] The presence of aortic atherosclerosis at middle age is predictive for the development of WMLs later in life.[14] But, with further analysis, only PS was independently associated with both PVH and DWMH. The results show that differences in cSBP values between the higher and lower grades of PVH/DWMH were significantly independent of PSs.

In summary, we found that cSBP and brachial SBP show varying degrees of association with PVH and DWMH detected in MRIs. cSBP is more strongly correlated with both PVH and DWMH. We believe that cSBP shows a stronger association with different grades of MRI lesions and systemic atherosclerotic changes. For economical and technical reasons, the measurement of cSBP using radial applanation tonometry could serve as a practical and reliable tool to predict cerebral WMLs and assess atherosclerotic changes.

This study had some limitations. First, the relatively small sample size limits our statistical power. In addition, we cannot establish a causal relationship between the parameters because of the cross-sectional study design. Larger longitudinal studies capable of supporting the relationship between cSBP and the increased risk of CVD found in this study are needed.

In conclusion, this study shows that increased cSBP is closely related to cerebral WMHs in unselected patients. Thus, cSBP might not only serve as a better predictor of CVD but also be used in the regular clinical setting.

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