Original Article

Association between Arterial Stiffness and Cerebral White Matter Lesions in Community-Dwelling Elderly Subjects

Takahiro OHMINE[1),2)], Yoshikazu MIWA[1),3)], Hiroshi YAO[3),4)], Takefumi YUZURIHA[4)], Yuki TAKASHIMA[4)], Akira UCHINO[5)], Fumi TAKAHASHI-YANAGA[1)], Sachio MORIMOTO[1)], Yoshihiko MAEHARA[2)], and Toshiyuki SASAGURI[1)]

The presence of cerebral white matter lesions (WMLs) on MRI is suggested to be a predictive factor for vascular dementia and stroke. To investigate the relationship between arterial stiffness and WMLs, we performed brain MRI to evaluate the presence of two subtypes of WML—periventricular hyperintensities (PVH) and deep white matter lesions (DWML)—and furthermore, determined the brachial-ankle pulse wave velocity (ba-PWV) as a marker of arterial stiffness in 132 elderly asymptomatic subjects (49 men and 83 women, 70.3±9.0 years). PVH and DWML were observed in 41 (31.0%) and 53 (40.2%) subjects, respectively. The ba-PWV values were significantly greater in subjects with PVH than in those without. DWML also tended to be associated with ba-PWV, but the correlation was not statistically significant. In multiple logistic regression analysis, age and decreased DBP were independently associated with PVH. ba-PWV was also detected as an independent factor for the appearance of PVH (adjusted odds ratio: 2.84, $p=0.015$) but not DWML. These results indicate that the increase in arterial stiffness contributes to the pathogenesis of PVH rather than DWML. Although further study is needed to clarify the difference between WML subtypes, our study suggests that the measurement of ba-PWV is a simple and useful tool for detecting cerebral arterial dysfunction. (*Hypertens Res* 2008; 31: 75–81)

***Key Words*: white matter lesion, magnetic resonance imaging, pulse wave velocity, arterial stiffness, periventricular hyperintensity**

Introduction

Cerebral white matter lesions (WMLs), detected as areas of hyperintensity in T_2-weighted scans and of isointensity in T_1-weighted scans on MRI, are frequently seen in elderly people without apparent neurological symptoms (*1*, *2*). Although the clinical importance of WMLs has not been fully elucidated, the presence of WMLs on MRI was reported to correlate with mental deterioration or cognitive impairment (*3*, *4*), mood disorder (*5*), and gait disturbance (*6*). Previous reports suggested that WMLs are associated with chronic hypoperfusion or ischemia in the white matter (*7*, *8*). It has been shown that WMLs are frequently observed in subjects with traditional cerebrovascular risk factors such as aging, hypertension, or diabetes (*1*, *2*, *9*, *10*) and that the presence of WMLs is an

From the [1)]Department of Clinical Pharmacology and [2)]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [3)]Second Department of Internal Medicine, Kyushu University Hospital, Fukuoka, Japan; [4)]Center for Emotional and Behavioral Disorders, National Hospital Organization Hizen Psychiatric Center, Saga, Japan; and [5)]Department of Radiology, Saga University of Medicine, Saga, Japan.
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Address for Reprints: Yoshikazu Miwa, M.D., Ph.D., Department of Clinical Pharmacology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812–8582, Japan. E-mail: ymiwa@clipharm.med.kyushu-u.ac.jp
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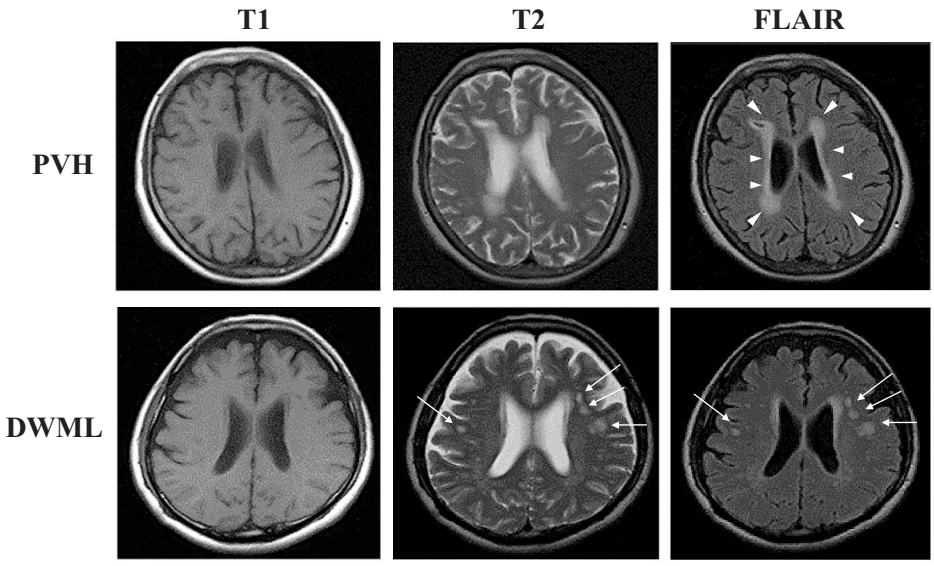

Fig. 1. *MRI of PVH (upper) and DWML (lower): T_1-weighted (left), T_2-weighted (middle), and FLAIR (right). PVH and DWML were determined as described in the Methods section. Arrowheads and arrows indicate PVH and DWML, respectively.*

independent risk factor for stroke (*11*). WMLs are more frequent in vascular dementia than in other dementias (*12*). Furthermore, several pathological studies reported a thickened intima or atherosclerotic changes of the cerebral arteries in regions containing WMLs (*13*, *14*). These observations suggest that the pathogenesis of WMLs is closely associated with arteriosclerosis or atherosclerosis. However, from the perspectives of time and cost, it is not realistic to use MRI for screening early cerebrovascular damage. Recently, pulse wave velocity (PWV) measurements have been found useful for assessing early atherosclerotic change (especially in vascular stiffness) of the vascular wall. An increase in aortic PWV was reported in patients with end-stage renal disease (*15*) and diabetes (*16*), and as a risk factor for cardiovascular and all-cause mortality (*17*). Aortic PWV is also reportedly elevated in patients with stroke (*18*) and a prognostic factor for vascular dementia or cerebral infarction (*19*). Thus, estimations of PWV can be used for both the screening of atherosclerosis and as a predictor of cardiovascular events. Nevertheless, the relationship between PWV and WMLs has not been examined. In the present study, therefore, to test whether or not PWV values are associated with the prevalence of WMLs, we assessed the presence of two distinct types of cerebral WML—periventricular hyperintensities (PVH) and deep white matter lesions (DWML)—in elderly asymptomatic subjects. We also determined the brachial-ankle PWV (ba-PWV), a noninvasive measure of arterial stiffness using an automatic device, and examined its association with the presence of WMLs on MRI.

Methods

Participants

Between August and November in both 2003 and 2004, we examined 144 elderly asymptomatic subjects (52 men and 92 women) living in the rural community of Sefuri village, population 600, in Saga Prefecture, Japan. We randomly contacted inhabitants through the village office by mail, and only those who agreed to participate were enrolled in the study. The positive response rate was 92.3% (144/156). All participants were living independently at home and had a Mini-Mental Status examination score >24. Subjects with an apparent history of stroke, silent brain infarction on MRI, or arrhythmia including atrial fibrillation, or who were suspected of having peripheral arterial disease (ankle-brachial index [ABI, the ratio of ankle pressure to brachial pressure] <0.9) were excluded. Finally, 132 subjects were analyzed. At the time of physical examination, blood pressure (BP), body mass index (BMI), and hematological and biochemical profiles were determined. Smoking status and medical histories were recorded for all participants at the same time. Blood was drawn in the morning after an overnight fast. Fasting blood glucose, HbA1c, triglyceride, total cholesterol, and high-density lipoprotein (HDL)–cholesterol levels were measured using routine laboratory methods. Low-density lipoprotein (LDL)–cholesterol levels were calculated using Friedewald's formula. Hypertension was defined as either systolic BP (SBP) $\geq$140 mmHg or diastolic BP (DBP) $\geq$90 mmHg, or current use of an antihypertensive agent. Dyslipidemia was defined as LDL-cholesterol $\geq$3.6 mmol/L (140 mg/dL) or

Table 1. Characteristics of the Participants

Age, years	70.3±9.0
Male, %	37.1
Habitual smoking, %	28.0
Hypertension, %	54.5
Dyslipidemia, %	15.9
Diabetes, %	6.8
Body mass index, kg/m^2	23.4±3.6
SBP, mmHg	136.8±18.7
DBP, mmHg	78.9±9.1
MBP, mmHg	97.4±13.8
PP, mmHg	57.4±16.4
HDL-cholesterol, mmol/L	1.5±0.4
LDL-cholesterol, mmol/L	2.9±0.9
Fasting plasma glucose, mmol/L	5.6±1.4
HbA1c, %	5.2±0.7

Data are shown as frequencies or mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

current use of lipid-lowering agents. Diabetes mellitus was diagnosed as fasting blood glucose ≥7.0 mmol/L (126 mg/dL) or current use of oral anti-diabetic agents. Written informed consent was obtained from all participants. The study protocol was approved by the ethical review committee of the National Hospital Organization Hizen Psychiatric Center.

Assessment of WML

A brain MRI examination was performed with a 1.0 Tesla superconducting magnet (MAGNEX XP, Shimadzu, Tokyo, Japan) using the spin echo technique and fluid attenuated inversion recovery (FLAIR) sequences as described previously (*20*). Transverse T_1-weighted (T_R/T_E 510/12 ms), T_2-weighted (T_R/T_E 4,300/22 ms), and FLAIR ($T_R/T_I/T_E$ 6,744/1,588/22 ms) images were obtained with a slice thickness of 6 mm separated by a 1 mm interscan gap. WMLs were specified as areas of high signal intensity in T_2-weighted images and isointense areas of normal brain parenchyma in T_1-weighted images obtained at two slices above the level of the pineal body (Fig. 1). A silent lacunar infarction (SBI) was defined as the presence of high signal intensity on a T_2-weighted image and a corresponding obvious low-intensity area on a T_1-weighted image. *État criblé* was characterized by high signal intensity on the T_2-weighted image and no abnormalities on the T_1-weighted image. The severity of DWML or PVH was classified according to Fazekas *et al*. (*21*) as follows. PVH: Grade 0, absent; Grade 1, caps or pencil-thin lining; Grade 2, smooth halo; Grade 3, irregular and extending into the deep white matter. DWML: Grade 0, absent; Grade 1 punctate; Grade 2, beginning confluent; Grade 3, large confluent. For PVH, we determined the presence and severity using FLAIR images. All scans were reviewed independently by two of the authors (H.Y. and A.U.) blinded to the other clinical data. In the case of disagreement between the raters, a consensus reading was held.

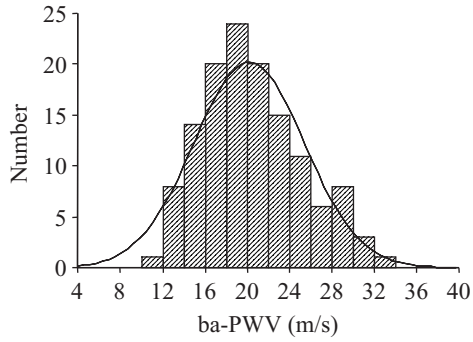

Fig. 2. *The distribution of ba-PWV values. Solid line represents normal distribution.*

PWV Measurement

Oscillometric ba-PWV was automatically measured using AT form (Nihon-Colin AT, Tokyo, Japan) as described previously (*22*). This device records a phonocardiogram, an electrocardiogram, a volume pulse form, and arterial blood pressure at bilateral brachia and ankles. The ba-PWV level was calculated by time-phase analysis of the right brachium and ankle. The intra-observer and inter-observer coefficients of variation obtained using 50 subjects were 2.1% and 2.3%, respectively.

Statistical Analysis

Data are presented as means±SD, means±SEM, or frequencies. In a simple regression analysis, Pearson's correlation coefficients were used for continuous variables, and Spearman's correlation coefficients were used for categorical variables. Differences in variables between the groups were assessed with unpaired Student's *t*-test. Predictive variables, including ba-PWV for the presence of WMLs, were analyzed using a logistic regression analysis. The independent variables were age, sex (men: 1, women: 0), body mass index, habitual smoking (yes: 1, no: 0), antihypertensive therapy (yes: 1, no: 0), DBP, pulse pressure (PP), HDL-cholesterol, LDL-cholesterol, HbA1c, and ba-PWV. $p<0.05$ was considered statistically significant. All statistical analyses were performed with StatView Version 5.0 (SAS Institute, Cary, USA).

Results

The participants' characteristics are summarized in Table 1. Their ages ranged from 55 to 89 years. About 76% of hyper-

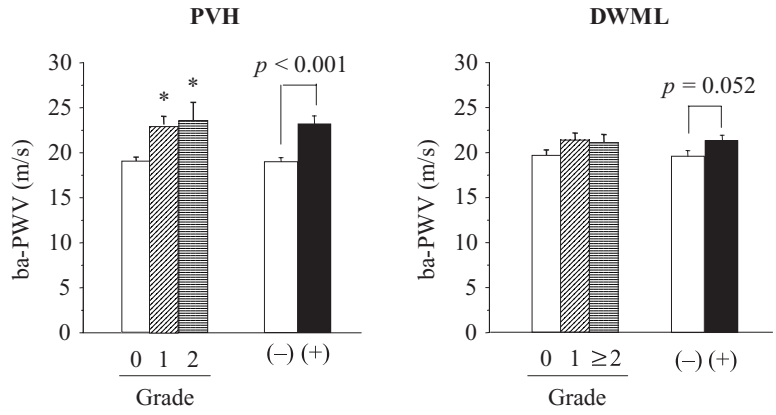

Fig. 3. *The values of ba-PWV in subjects classified by the severity of DWML or PVH according to Fazekas et al. (21). Statistical significance among groups was assessed with ANOVA. Statistical significance between subjects with (+) or without (–) WMLs was assessed with unpaired Student's t-test. Error bars indicate SEM. *p < 0.01 vs. Grade 0.*

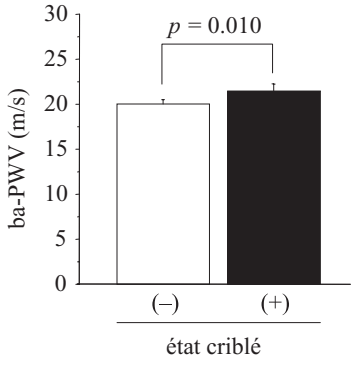

Fig. 4. *The age-adjusted values of ba-PWV in subjects with (+) or without (–) état criblé. Error bars indicate SEM.*

tensive subjects (55 of 72 subjects) were being treated with an antihypertensive agent. PVH and DWML were observed in 41 subjects (Grade 1, 35 subjects; Grade 2, 6 subjects) and 53 subjects (Grade 1, 36 subjects; Grade 2, 16 subjects; Grade 3, 1 subject), respectively. No subjects had Grade 3 PVH.

In a simple correlation analysis, the presence of PVH was positively correlated with age ($r=0.44$, $p<0.001$), and inversely correlated with DBP ($r=-0.27$, $p=0.002$), and MBP ($r=-0.19$, $p=0.026$). DWML was also associated with age ($r=0.28$, $p=0.001$), and DBP ($r=-0.18$, $p=0.044$). Other traditional atherosclerotic risk factors, such as sex, body mass index, SBP, PP, fasting plasma glucose level, and HbA1c showed no significant correlations with WMLs. Age- and sex-adjusted regression analysis also showed no significant correlation between traditional atherosclerotic risk factors and WMLs (data not shown).

The mean ba-PWV was 20.2±5.2 (m/s). The ba-PWV values were normally distributed (Fig. 2) and did not differ significantly between genders (men: 20.0±5.3 m/s, women: 20.3±5.2 m/s). When subjects were divided into two groups according to the presence of WMLs, ba-PWV was significantly greater in subjects with PVH than in those without (Fig. 3). DWML also tended to be associated with ba-PWV, but this correlation was not statistically significant. We also assessed the presence of *état criblé* (dilatation of perivascular space) as a surrogate marker of stiffening of small arteries and investigated its association with ba-PWV. Subjects with *état criblé* tended to have greater age-adjusted ba-PWV values than those without, but the difference was not significant (Fig. 4). In a multiple logistic regression analysis including age, sex, and other traditional atherosclerotic risk factors (BMI, smoking, antihypertensive agent, DBP, PP, LDL-cholesterol, HDL-cholesterol, and HbA1c), ba-PWV was detected as an independent factor for the appearance of PVH (odds ratio 2.84, $p=0.015$) (Table 2). Aging and decreased DBP were also independently associated with PVH. The association between ba-PWV and PVH did not change when SBP and MBP were forced into the model instead of DBP.

Discussion

In the present study, we showed that ba-PWV is associated with the appearance of WMLs on MRI in elderly asymptomatic subjects. In particular, the increase in ba-PWV is an independent predictor for the prevalence of PVH.

PWV, often used as a marker of arterial stiffness, is useful for detecting early atherosclerotic changes in the vascular wall. Increased aortic PWV was reported as a risk factor for cardiovascular and all-cause mortality (*17*), vascular dementia, and stroke (*18*) independent of other traditional atherosclerotic risk factors. ba-PWV, a noninvasively measurable PWV, was strongly associated with aortic PWV (*23*) and was elevated in subjects with diabetic complications including cerebral infarction (*24*), abdominal aortic calcification (*22*), and coronary artery disease (*25*). Although the pathogenesis

Table 2. Multiple Logistic Regression Analyses Relating to the WMLs

	PVH		DWML	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	2.58 (1.36–4.89)	0.004	1.68 (0.98–2.86)	0.060
Sex	1.12 (0.58–2.16)	0.723	1.34 (0.78–2.29)	0.277
Habitual smoking	1.32 (0.67–2.57)	0.421	1.04 (0.61–1.76)	0.889
Body mass index	1.14 (0.63–1.98)	0.628	1.35 (0.86–2.12)	0.194
Diastolic blood pressure	0.48 (0.26–0.84)	0.010	0.68 (0.44–1.04)	0.080
Pulse pressure	0.90 (0.54–1.51)	0.706	0.92 (0.58–1.45)	0.729
LDL-cholesterol	0.91 (0.50–1.62)	0.729	1.35 (0.85–2.12)	0.212
HDL-cholesterol	1.03 (0.60–1.77)	0.930	0.94 (0.60–1.47)	0.815
HbA1c	1.25 (0.76–2.07)	0.377	1.01 (0.65–1.57)	0.959
Antihypertensive therapy	0.66 (0.38–1.14)	0.141	1.17 (0.75–1.82)	0.495
ba-PWV	2.84 (1.02–7.89)	0.015	1.21 (0.47–3.16)	0.488

WMLs, white matter lesions; PVH, periventricular hyperintensities; DWML, deep white matter lesions; OR, odds ratio; CI, confidence interval; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Adjusted ORs for continuous variables were indicated for 1 SD.

of WMLs remains largely unknown, it is generally believed to involve chronic hypoperfusion or ischemia in cerebral circulation (*7*). A recent report indicated that the severity of WMLs is an independent predictor of symptomatic stroke due to arteriolosclerosis, and that the progression of WMLs is associated with subsequent stroke in patients with initially mild WMLs (*26*).

Supposing that the presence of WMLs reflects early atherosclerotic changes in the cerebral arteries, our result showing an association between ba-PWV and PVH is reasonable. However, the ba-PWV association differed between PVH and DWML. Although we cannot well explain this difference, it may be that PWV is transported *via* the CSF in subependymal regions and therefore affects PVH even more. Pathohistological features may also be distinct between these two types of WMLs. Fazekas *et al*. (*13*) reported intimal thickening of the arterial wall in the region of DWML. With regard to PVH, severe, but not mild or moderate, PVH showed arteriosclerotic changes in the cerebral arteries. Since this series did not include subjects with a high grade of PVH according to their MRI classification (*21*), our subjects may not have had severe arteriosclerosis in the cerebral arteries. However, the important issue is that Fazekas *et al*. (*21*) assessed morphological change (*i.e.*, vascular wall thickening) as a marker of arteriosclerosis. Atherosclerosis consists of morphological change (atherosis) and functional change (sclerosis) of the vessel wall. PWV may finally reflect both changes, because it is associated with the consequence of advanced arteriosclerosis, such as end-stage renal disease (*15*), cardiovascular mortality (*17*), and stroke (*18*) although, in the early phase of atherosclerosis, it mainly reflects functional rather than morphological change in the vascular wall. The correlation between ba-PWV and mild to moderate PVH in the present study may show the functional disturbance of the cerebral arteries. Indeed, a white matter edema that induces demyelination and reactive gliosis is frequently seen in the region of PVH. The increase in ba-PWV may be associated with a functional disturbance, such as an increase in endothelial permeability in irrigated vessels of PVH. In addition, a previous study showed that aortic calcification in middle age predicted PVH but not DWML in the elderly (*27*). Since aortic calcification is closely correlated with aortic PWV (*20*) and pulse pressure (*28*), the increased stiffness in the conduit large artery may contribute to the pathogenesis of PVH.

To our knowledge, only one group has reported a relationship between aortic PWV and PVH grades rated according to Shimada *et al*. (*29*), although there was no significant correlation between them (*30*). However, this WML grading scale did not distinguish between PVH and DWML. Furthermore, the subjects analyzed were over 80 years old and had severe PVH (average grade $=2.2\pm0.9$ in normotensive subjects). Therefore, the possibility that DWMLs were involved in severe PVH cannot be excluded. These factors might have led to their negative results. Conversely, we accurately distinguished between PVH and DWML because our population had modest WMLs and we used the Fazekas classification. Consequently, we found a significant association between ba-PWV and PVH.

One limitation in the present study would be the frequent use of antihypertensive agents among hypertensive subjects. Hypertension is one of the most important risk factors for WMLs; moreover, a recent study reported that optimal blood pressure control suppressed the progression of both PVH and DWML (*9*). Especially in the elderly, peripheral amplification of the arterial wall is gradually reduced with structural arterial stiffening. These changes lead to higher SBP, lower DBP, and wider PP, *i.e.*, isolated systolic hypertension. Indeed, several groups reported that SBP and PP were positively correlated, and DBP inversely correlated, with cardiovascular risk in the elderly (*31*, *32*). We did not find any apparent contribution of SBP or PP to WMLs in our population, whereas decreased DBP was an independent risk factor

for PVH and also tended to be associated with DWML (Table 2). About 80% of hypertensive subjects were treated with antihypertensive agents and were relatively well controlled in the present study. Therefore, the effects of SBP and PP may be diminished. On the other hand, DBP may remain as an independent risk factor, since antihypertensive therapy is less effective for DBP than SBP.

In conclusion, we reported for the first time that increased ba-PWV is closely associated with the appearance of PVH in an elderly asymptomatic population. Although it is difficult to use MRI for health screening, our results suggest that ba-PWV measurement is a simple and useful tool for predicting early cerebrovascular dysfunction.

Acknowledgements

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