Metabolic risks, white matter hyperintensities, and arterial stiffness in high-functioning healthy adults

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Abstract

Background: Arterial stiffness, an age-related feature and measured noninvasively by pulse wave velocity (PWV), is associated with a variety of cardiovascular diseases. Although white matter lesion (WML), representing cerebrovascular micro-angiopathy, is typically considered as a preclinical cardiovascular disease, little is known about the association between PWV and WML. The aim of this study is to examine the association between PWV and WML.

Method: We examined the extent of white matter lesion on cranial magnetic resonance imaging of 93 participants (mean 72.46 years) from the annual Health Examination for the Elderly Program in the National Taiwan University Hospital. Two subtypes of WML including periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) were graded according to Fazekas et al. The brachial-ankle PWV (baPWV) and heart-ankle PWV (haPWV) were measured using an automatic waveform analyzer.

Results: PVH and DWMH were found in 71 (76%) and 58 (62%) participants. Various degree of WML was observed in 80 (86%) participants. Hypertension, use of anti-hypertensive medications, and elevated blood pressure were identified as risk factors of WML. The baPWV and haPWV were correlated with many metabolic risks, including systolic blood pressure, pulse pressure, and serum triglycerides. The baPWV and haPWV were greater in participants with higher grades of WML in the multivariate analyses. The receiver operating characteristics analyses demonstrated that area under curves for haPWV to identify moderate-to-severe PVH and DWMH were 0.78 (95% confidence interval [CI] 0.66–0.91) and 0.72 (95% CI 0.59–0.85), respectively.

Conclusion: Greater PWV is associated with higher grades of WML among high-functioning older adults. Our findings support the notion that measurement of arterial stiffness is useful in clinical practice for detection of preclinical cerebrovascular disease.

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Keywords: Arterial stiffness; Pulse wave velocity; White matter lesions; Leukoaraiosis

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1. Introduction

Magnetic resonance imaging (MRI) of the brain in elderly people commonly shows incidental T2-weighted hyperintensities in the periventricular or subcortical areas, often reported as “white matter lesion” (WML). Recent epidemiological studies have reported a high prevalence of WML in the aging brains. Cardiovascular Health Study, a large population-based cohort study, performed MRIs on community-dwelling older adults from 4 US communities, and found that WML was present in 87% of all participants [1]. The Rotterdam Scan Study of the Netherlands reported a even higher prevalence of WML, with only 5% of community-dwelling older adults had no WML in either periventricular or subcortical white matter [2]. WML, although often overlooked, has important clinical implication because of its close association with multi-system age-related problems, including falls, gait problems, cognitive impairment, depression, and urinary incontinence [3]. It is generally believed that the pathogenesis of WML, although remained largely unknown, involves chronic cerebral hypoperfusion [4], cerebral ischemia [5], as well as atherosclerosis [6]. Advanced age, hypertension [7,8], diabetes mellitus [9], hemodynamic dysregulations [10,11], as well as such genetic factors as Notch3 gene [12] and angiotensin-converting enzyme gene [13] have been identified as important risk factors for WML.

Arterial stiffening is a common feature of aging and is accelerated by cardiovascular risk factors and disorders such as hypertension [14,15], diabetes [15,16] and renal failure [17]. Pulse wave velocity (PWV), a direct measure of arterial stiffness, is an independent predictor of many cardiovascular diseases such as stroke and ischemic heart disease [18]. WML, representing cerebrovascular micro-angiopathy, is typically considered as a “preclinical” cardiovascular disease. Thus, the aim of this study is to test the hypothesis that arterial stiffness—as measured by PWV—is associated with subclinical cerebrovascular microangiopathy, namely, WML. In addition, the usefulness of PWV as a surrogate marker in identifying radiographically evident WML is to be examined. We seek to achieve the study goals by analyzing data in a group of high-functioning older adults who participated in the Health Examination for the Elderly Program (HEEP) in the National Taiwan University Hospital (NTUH), a tertiary medical center in Taipei, Taiwan.

2. Methods

2.1. Source of study participants

The HEEP, a health service funded by Taipei City Government, was opened to senior citizens of Taipei City who are aged 65 or older. The HEEP is provided in 6 tertiary medical centers and 23 community hospitals across Taipei city. The Kong-Kwan campus of the NTUH, located in the Ta-An District, is among one of the field sites for the annual HEEP.

Most subjects who signed up for the annual HEEP in the NTUH are independent community-dwelling elders of Ta-An District of Taipei City. The following assessments are provided in a typical HEEP: questionnaires for chronic disease profile, physical examinations and anthropometric measures, chest X-ray, electrocardiogram, urine/stool examination, and laboratory analyses including complete blood count, liver function, renal function, triglyceride, and cholesterol.

Participants of the current study were randomly selected from those who signed up for the HEEP in the NTUH. Participants of HEEP was excluded from the study if they had a known diagnosis of dementia; were functionally impaired requiring assistance in dressing, personal hygiene, or bathing; were terminally ill; were contra-indicated for MRI examination such as claustrophobia or pacemaker implantation; were unavailable during the study period; had impairment in vision, hearing, or communicative ability, hence making participation in the study impossible; or had histories of myocardial infarction or stroke.

From October 2006 through December 2007, 93 eligible individuals agreed to participate and had complete information in interview data, brain MRI, PWV measurement, and laboratory examinations. The NTUH Institutional Review Board reviewed and approved the study. Informed consents were obtained from all participants.

2.2. Sociodemographic and interview data

Age, gender, educational level, averaged hours of sleep per night, and status of smoking and alcohol drinking were obtained by self-report. Co-morbidities including hypertension, diabetes mellitus, heart disease (defined as a history of coronary heart disease, congestive heart failure, or angina), chronic lung disease, depressive disorder were ascertained by self-report questionnaires. During the interview, we asked participants to bring all medications, including vitamin supplements and over-the-counter medications, that they were actively taking. Cognitive function was ascertained using Mini-Mental State Examination. Center for Epidemiologic Studies Depression Scale (CES-D), ranged from 0 to 60 with a higher score indicating more depressive symptom, was used to ascertain depression symptom.

2.3. Metabolic risks

Two supine blood pressure (BP) determinations were taken by a trained research assistant with a mercury sphygmomanometer. BPs were measured in the right arm unless otherwise specified. Averaged systolic BP (SBP) and diastolic BP (DBP) were obtained. Pulse pressure (PP) was defined as averaged SBP minus averaged DBP. Waist circumference was measured at the iliac crest to the nearest 0.1 cm. Blood specimens were processed in the NTUH central laboratories for analysis. Levels of serum total cholesterol and triglycerides were measured enzymatically, and levels of HDL cholesterol were measured using

precipitation. Serum fasting glucose levels were processed by using the hexokinase enzymatical method. Use of anti-hypertensives, lipid-lowering agents, and anti-diabetic medications, including oral hypoglycemic agents or insulin injection, were ascertained by self-report questionnaires.

2.4. Pulse wave velocity

PWV was measured with the subject in a supine position after 15 min of rest using an automatic waveform analyzer (Colin VP-2000, Omeron Inc., Japan). The instrument simultaneously recorded right and left brachial and tibial arterial pressure wave forms, lead I of the electrocardiogram, and a phonocardiogram. A carotid tonometry sensor incorporating an array of 15 micropiezoresistive transducers was coupled with this device for analysis of common carotid arterial wave. Occlusion cuffs, connected to both plethysmographic and oscillometric sensors, were placed around both arms and ankles for pulse wave analysis and BP measurements. The time difference between the brachial and ankle arterial pressure wave was determined by the wave front velocity theory. The distance between the arm and ankle was automatically calculated based on the patient's height. Finally, the baPWV (brachial-ankle PWV) was calculated by dividing the distance with the time difference. Measurement of right and left baPWV was obtained for an average of 10 s. The averaged left and right baPWVs of each subject were used for subsequent analyses. The haPWV (heart-ankle PWV) was derived by similar method. The time difference was the period between S2 heart sound and the initial point of tibial arterial pressure wave.

2.5. MRI assessment

Subjects underwent MR examination by a 1.5-T MR unit (Sigma, General Electric Healthcare System, Milwaukee, USA). The examination produced three sets of 5-mm-thick in axial, sagittal, and coronal lanes for localization. Then we obtained the standard axial images parallel to the AC and PC line. They included T1-weighted FLAIR images (TR/TE/TI=2000 ms/minimal full/720 ms, matrix=320×192, FOV=22 cm, slice thickness=3.5 mm), axial proton density and T2-weighted images (TR/TE=3425 ms/minimal full and 103.7 ms, matrix=288×192, FOV=22 cm), and T2-weighted FLAIR images (TR/TE/TI=9000 ms/80 ms/2250 ms, matrix=288×224, FOV=22 cm).

Imaging data, archived electronically, were sent to NTUH Department of Medical Imaging reading center for interpretation by a neuroradiologist (Liu HM) without knowledge of participants' clinical information. Fazekas rating scale was used to describe two different types of white matter hyperintense signal abnormalities, or WML, surrounding the ventricles and in the deep white matter [19]. Periventricular hyperintensity (PVH) was graded as 0=absence, 1 (mild)=“casps” or pencil-thin lining, 2 (moderate)=smooth “halo”, 3 (severe)=irregular PVH extending into the deep white matter. Separate deep white matter hyperintense signals (DWMH) were rated as 0=absence, 1 (mild)=punctuate foci, 2 (moderate)=beginning confluence of foci, 3 (severe)=large confluent areas. Total burden of WML, defined as WML grade, was estimated by summing the PVH grade and the DWMH grade, forming a scale from 0 to 6. The presence of silence infarct, as defined as asymptomatic hyperintense

Table 1
Characteristics of study participants

Characteristics	Women (n=48)	Men (n=45)	P value	Total
Continuous variables ^a				
Age (year)	70.69 (4.39)	74.34 (5.92)	0.001	72.46 (5.47)
Education (year)	12.42 (2.66)	13.89 (2.78)	0.011	13.13 (2.80)
Body mass index (kg/m ²)	23.93 (3.17)	23.80 (2.80)	0.836	23.87 (2.98)
Averaged hours of sleeping per night (h)	5.48 (0.99)	6.46 (0.97)	<0.001	5.95 (1.09)
MMSE score (0–30)	29.27 (0.92)	29.36 (1.19)	0.700	29.31 (1.05)
CES-D score (0–60) ^c	4.54 (6.70)	3.07 (4.94)	0.232	3.83 (5.93)
baPWV (cm/s)	1090 (118)	1134 (133)	0.098	1112 (127)
haPWV (cm/s)	1687 (276)	1712 (328)	0.684	1699 (301)
Categorical variables ^b				
Current smoker	0 (0)	3 (6.67)	0.069	3 (3.23)
Not drinking alcohol	28 (58.33)	13 (28.89)	0.004	41 (44.09)
History of hypertension	24 (50)	23 (51.11)	0.915	47 (50.54)
History of diabetes mellitus	5 (10.42)	5 (11.11)	0.914	10 (10.75)
Heart disease	8 (16.67)	6 (13.33)	0.653	14 (15.05)
Silent infarct	1 (2.08)	4 (8.89)	0.146	5 (5.38)
Moderate-to-severe PVH	3 (6.25)	12 (26.67)	0.007	15 (16.13)
Moderate-to-severe DWMH	7 (14.58)	10 (22.22)	0.341	17 (18.28)
Moderate-to-severe PVH or DWMH	7 (14.58)	15 (33.33)	0.033	22 (23.66)

Abbreviations: baPWV, brachial-ankle pulse wave velocity; CES-D, Center for Epidemiologic Studies Depression Scale; haPWV, heart-ankle pulse wave velocity; MMSE, Mini-Mental State Examination; WML, white matter lesion.

^a Values in the continuous variables were expressed as mean (standard deviation).

^b Values in the categorical variables were expressed as number (percent).

^c A higher score in CES-D indicates more depressive symptoms.

Table 2

Age and sex-adjusted association between potential risk factors for white matter hyperintensity and arterial stiffness^a

Potential risk factors	WML grade		baPWV		haPWV	
	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>
Demographics						
Years of education (year)	−0.055 (0.05)	0.273	−13.25 (11.20)	0.240	−1.16 (4.50)	0.798
Live alone	0.542 (0.523)	0.303	159.74 (117.31)	0.177	62.62 (46.79)	0.184
Income > 60,000 NTD per month	−0.288 (0.285)	0.314	−50.96 (64.39)	0.431	−20.75 (25.67)	0.421
Disease/medication history						
Hypertension	0.714 (0.256)	0.007	101.57 (59.25)	0.090	53.05 (23.34)	0.025
Diabetes mellitus	−0.292 (0.43)	0.499	191.25 (95.08)	0.047	76.62 (37.90)	0.046
Heart diseases	−0.17 (0.38)	0.656	−118.57 (84.9)	0.166	−42.41 (33.92)	0.214
Chronic lung disease	−0.479 (0.429)	0.267	10.33 (97.38)	0.916	−18.02 (38.78)	0.643
Depressive disorder	−1.154 (0.746)	0.125	−47.89 (170.41)	0.779	−56.47 (67.71)	0.407
Use of anti-hypertensive	0.708 (0.257)	0.007	78.49 (59.69)	0.192	34.31 (23.75)	0.152
Use of lipid-lowering agents	0.012 (0.452)	0.980	51.34 (101.71)	0.615	25.69 (40.52)	0.528
Health-related behaviors						
Current smoker	0.401 (0.794)	0.615	−136.6 (178.68)	0.447	−11.22 (71.47)	0.876
Not drinking alcohol at all	0.164 (0.281)	0.561	−62.86 (63.17)	0.322	−19.20 (25.25)	0.449
Averaged hours of sleep per night (hour)	0.184 (0.139)	0.187	1.14 (31.56)	0.971	6.37 (12.57)	0.613
Metabolic risks						
Systolic blood pressure (mmHg)	0.016 (0.008)	0.035	6.83 (1.62)	<0.001	3.16 (0.62)	<0.001
Diastolic blood pressure (mmHg)	0.028 (0.011)	0.017	3.23 (2.63)	0.224	1.63 (1.04)	0.122
Pulse pressure (mmHg)	0.005 (0.009)	0.574	6.51 (1.82)	0.001	2.94 (0.71)	<0.001
Fasting glucose (mg/dL)	−0.013 (0.009)	0.161	2.27 (2.02)	0.265	1.07 (0.80)	0.188
Waist circumference (cm)	0.012 (0.017)	0.474	4.68 (3.84)	0.226	0.81 (1.54)	0.600
Triglyceride (mg/dL)	0.003 (0.002)	0.185	1.55 (0.52)	0.004	0.79 (0.20)	<0.001
HDL cholesterol (mg/dL)	−0.001 (0.012)	0.965	−6.07 (2.65)	0.024	−1.71 (1.07)	0.114
Total cholesterol (mg/dL)	0.006 (0.004)	0.176	0.54 (0.99)	0.589	0.39 (0.39)	0.327
Metabolic Z score	0.051 (0.049)	0.298	39.15 (10.20)	<0.001	15.86 (4.06)	<0.001

Abbreviations: baPWV, brachial-ankle pulse wave velocity; haPWV, heart-ankle pulse wave velocity; WML, white matter lesion.

^a Separate multiple linear regression was performed with WMH grade, baPWV, and haPWV as dependent variables and with age, sex, and each potential risk factor as independent variables. Parameter estimates (β) can be interpreted as differences in WMH grade, haPWV, and haPWV with 1-unit change in the potential risk factor.

on T2-weighted images while hypointense on T1-weighted images, was also recorded.

2.6. Statistical analysis

Differences in baseline characteristics between men and women were compared by Student's *t*-test, Wilcoxon Rank Sum test, or chi-squared test. To examine the association of potential risk factors with WML and PWV, we performed multiple linear regression, with WML and PWV as the dependent variables and with age, sex, and the potential risk factors as independent variables. To consider various metabolic risk factors as a whole, we also calculated the metabolic Z score. The score was derived by converting each component of the metabolic risk factors, namely blood pressure, waist circumference, fasting glucose level, serum triglyceride level, and serum HDL level, into a Z score based on means of the study population.[20] The metabolic Z score was calculated by summation of the former four Z scores minus the HDL Z score. The relations of metabolic risk, by utilizing the composite metabolic Z score, to PWV and WML were assessed by using multiple linear regression.

The associations of baPWV and haPWV (dependent variables) with WML (independent variables), including PVH, DWMH, and WML grade, respectively, were then

examined using multiple linear regression while adjusting for age, sex, metabolic Z score, presence of silence infarct, and the use of anti-hypertensives, lipid lowering agents, and anti-diabetic agents. Participants without any hyperintense abnormalities, i.e. those who had grade 0 PVH, grade 0 DWMH, or grade 0 WMH, were regarded as the reference groups respectively. Adjusted means of baPWV and haPWV

Fig. 1. Adjusted means of pulse wave velocity across quartiles of metabolic Z score.

in different categories of white matter hyperintense abnormalities were obtained by multiple linear regression.

We estimated potential cutoff values of baPWV and haPWV to predict the presence of moderate to severe white matter hyperintense abnormalities, namely, grades 2 to 3 PVH and grades 2 to 3 DWMH, via the receiver operating characteristics (ROC) analyses. The ROC analyses gave an estimate of the overall discriminative ability of PWV by the area under the curve (AUC) statistic. We calculated sensitivity and specificity across the range of possible cutoff PWV values. The ROC curve was plotted with sensitivity on the *y*-axis and (1-specificity) on the *x*-axis. AUC and associated 95% confidence intervals (CIs) were calculated.

3. Results

3.1. Characteristics of study population

A total of 93 participants successfully completed the assessments of MRI and PWV, as well as clinical and laboratory examinations. Selected baseline characteristics of the study population as a whole ($N=93$, mean age 72.46 years) and by gender were summarized in Table 1. Forty-eight female participants represented 52% of the study population. Eighty participants (86%) had various degree of WML. Nearly half (47%) of the study participants had hypertension, 10% diabetes mellitus, and 14% heart diseases. Men tended to be older, to have higher education, greater hand grip strength, higher grades of PVH, and more hours of night sleep than women did. There was no difference in terms of chronic co-morbidities (hypertension, diabetes mellitus, heart disease), PWV, BMI, MMSE scores, depressive symptom, and habitual gait speed between men and women.

3.2. Potential correlates of arterial stiffness and WML

After adjusting for age and sex, WML grade was significantly associated with a history of hypertension, systolic and diastolic blood pressures, and use of anti-hypertensives, but not with educational level, living status (whether to live alone or to live with family members), income, smoking status, alcohol drinking, averaged hours of sleep per night, or the presence of diabetes mellitus, heart diseases, chronic lung disease, or depressive disorder (Table 2).

Age-, and sex-adjusted regression analysis showed that PWV was related to the presence of diabetes mellitus and several metabolic risks. Both baPWV and haPWV were positively associated with systolic blood pressure, pulse pressure, and triglyceride. Additionally, baPWV was significantly associated with HDL cholesterol ($\beta = -6.07$, $p=0.024$) while haPWV with the presence of hypertension ($\beta = 53.05$, $p=0.025$). The metabolic *Z* score, representing the metabolic risks as a whole, was positively associated with both baPWV and haPWV ($p<0.001$, respectively). The adjusted means of baPWV and haPWV (controlling for age,

sex, smoking status, alcohol drinking, use of anti-hypertensives and lipid-lowering agents) based on different metabolic *Z* score quartiles were illustrated in Fig. 1. The trends for the relations of metabolic *Z* score quartiles to both baPWV and haPWV were statistically significant ($p=0.005$ and 0.004 , respectively).

3.3. Association between WML and arterial stiffness

PWV was associated with white matter hyperintensity. After controlling for age, sex, metabolic *Z* score, presence of silent infarct, and use of anti-hypertensives, lipid-lowering, and anti-diabetic agents, participants in the highest grade of PVH had significantly higher baPWV compared to those without PVH (β coefficient=357.42, p value=0.035) (Table 3). Moreover, participants with the highest grade of DWMH tended to have higher baPWV and haPWV compared to those without DWMH (β coefficient for baPWV=385.24, p value=0.018; β coefficient for haPWV=183.82, p value=0.005). Total burden of WML, i.e. WML grade, was also correlated with baPWV and haPWV. Participant who had grades 5 to 6 WML had higher baPWV and haPWV compared to those without any WML (β coefficient for baPWV=366.68, p value=0.035; β coefficient for haPWV=171.81, p value=0.012). Adjusted means of baPWV and haPWV in different grades of white matter signal abnormalities were illustrated in Fig. 2.

3.4. ROC curves, sensitivity, and specificity

Fig. 3 displayed the ROC curves for the discriminative ability of haPWV and baPWV to identify the presence of

Table 3

Multivariate-adjusted regression analyses for the associations between white matter hyperintense signal abnormalities and pulse wave velocity (PWV)

MRI finding	baPWV		haPWV	
	β (SE)	<i>P</i> value	β (SE)	<i>P</i> value
Periventricular hyperintensities (PVH)				
Grade=0 (reference)	Reference		Reference	
Grade=1	-12.24 (74.46)	0.870	-19.62 (29.63)	0.510
Grade=2	124.32 (116.97)	0.291	66.73 (46.56)	0.156
Grade=3	357.42 (166.14)	0.035	117.99 (66.12)	0.079
Deep white matter hyperintensities (DWMH)				
Grade=0 (reference)	Reference		Reference	
Grade=1	-63.27 (65.41)	0.341	-21.29 (26.09)	0.417
Grade=2	8.12 (97.85)	0.935	17.05 (38.98)	0.663
Grade=3	385.24 (154.47)	0.018	183.82 (62.81)	0.005
White matter lesion (WML)				
Grade=0 (reference)	Reference		Reference	
Grade=1–2	-74.17 (89.36)	0.409	-36.24 (34.94)	0.303
Grade=3–4	8.70 (107.60)	0.936	19.13 (42.07)	0.651
Grade=5–6	366.68 (170.20)	0.035	171.81 (66.55)	0.012

Separate multiple linear regression was performed with baPWV and haPWV as dependent variables and with white matter hyperintense signal abnormalities as independent variable while adjusted for age, sex, metabolic *Z* score silent infarct, and use of anti-hypertensives, lipid-lowering, and anti-diabetic agents.

Fig. 2. Adjusted means of pulse wave velocity in different grades of white matter hyperintense abnormalities. Solid line refers to brachial-ankle pulse wave velocity. Dashed line refers to heart-ankle pulse wave velocity. The adjusted covariates include age, sex, metabolic Z score, presence of silent infarct, and use of anti-hypertensives, lipid-lowering, and anti-diabetic agents.

moderate-to-severe PVH and DWMH. We demonstrated that, compared to baPWV, haPWV was a better measurement in identifying the presence of moderate-to-severe WMLs. AUCs for haPWV and baPWV to identify moderate-to-severe PVH were 0.78 (95% confidence interval [CI]=0.66–0.91) and 0.68 (95% CI=0.54–0.82), respectively. AUCs for haPWV and baPWV to identify moderate-to-severe DWMH were 0.72 (95% CI=0.59–0.85) and 0.66 (95% CI=0.53–0.80), respectively.

The optimal cutoffs to identify moderate-to-severe PVH and DWMH were determined by calibrating the haPWV values to find a best balance between sensitivity and specificity. A range of possible cutoff values were provided in the Table 4. Using a haPWV cutoff of 1177 cm/sec, the sensitivity and specificity in identifying grades 2–3 PVH

Table 4

Sensitivity and specificity of pulse wave velocity in identifying moderate-to-severe white matter hyperintense abnormalities

haPWV cutoff (cm/sec)	PVH ($\geq$ grade 2)		DWMH ($\geq$ grade 2)	
	Sensitivity	Specificity	Sensitivity	Specificity
1043	0.93	0.40	0.88	0.39
1053	0.87	0.41	0.82	0.41
1071	0.80	0.46	0.82	0.47
1085	0.80	0.50	0.76	0.50
1092	0.73	0.54	0.71	0.54
1160	0.73	0.71	0.71	0.71
1177	0.73	0.76	0.65	0.75
1190	0.60	0.77	0.53	0.76
1195	0.53	0.79	0.47	0.79
1208	0.53	0.82	0.47	0.82
1253	0.47	0.91	0.29	0.88
1273	0.40	0.94	0.24	0.91

Fig. 3. Receiver operating characteristic (ROC) curves for haPWV and baPWV to identify the presence of moderate-to-severe white matter hyperintense abnormalities, including PVH (Fig. 2-a) and DWMH (Fig. 2-b). AUCs for haPWV and baPWV to identify moderate-to-severe PVH were 0.78 (95% confidence interval=0.66–0.91) and 0.68 (95% confidence interval=0.54–0.82), respectively. AUCs for haPWV and baPWV to identify moderate-to-severe DWMH were 0.72 (95% confidence interval=0.59–0.85) and 0.66 (95% confidence interval=0.53–0.80), respectively.

were 0.73 and 0.76, respectively. The sensitivity and specificity in identifying DWMH were both 0.71 if the haPWV cutoff was 1160 cm/s.

4. Discussion

Our study demonstrated that arterial stiffness was a risk factor for WML independent of age, sex, metabolic composite score including blood pressure, waist circumference, fasting glucose level, serum triglyceride level, and serum HDL level, as well as the use of anti-hypertensives, lipid-lowering, and anti-diabetic agents. Our findings supported and extended previous studies examining the relationship between cerebral small vessel disease and arterial stiffness. Ohmine and colleagues investigated the association between arterial stiffness and MR white matter hyperintensities in 132 community-dwelling older Japanese and showed that baPWV was independently associated with the appearance of WML on MRI, in particular PVH [21]. In patients of hypertension, researchers demonstrated that increased arterial stiffness was associated with silent cerebral small-vessel disease shown in MRI [22,23]. We consolidated these findings by further demonstrating that PWV was a fairly good marker in identifying the presence of radiographically evident WML. The AUCs, representing the discriminative power, for haPWV to identify the presence of moderate-to-severe PVH and DWMH were 0.78 and 0.72, respectively.

Our study has the following implication. PWV has recently attracted significant research interest in that measurements of PWV have been found useful in assessing cardiovascular risk. Compelling evidence has supported the notion that increased arterial stiffness is a risk factor for cardiovascular events [24–26]. In fact, the associations between arterial stiffness and adverse cardiovascular outcomes have been documented in a wide range of populations, including hypertensive individuals [24], persons with end-stage renal disease [27], as well as general population [25,26]. In addition to being a predictor of adverse

cardiovascular outcomes, PWV, a simple and noninvasive measurement of arterial stiffness using an automatic device, appears to be a significant indicator for preclinical cerebrovascular disease as well. Even after adjusting for the composite metabolic risk score, PWV, significantly refining the risk stratification above and beyond classic metabolic risk factors, still remains its significant association with WML. Taken together, measurement of PWV could be considered as a useful tool in identifying susceptible individuals for the development of potential sequelae of WML, namely cognitive impairment, gait/balance problems, or falls—collectively called geriatric syndromes. Identification of PWV as an important correlate of WML can thus facilitate appropriate interventions, including lifestyle alterations, pharmaceutical management, or physical rehabilitation, in persons with such preclinical, asymptomatic endophenotypes.

Our study has potential limitations that deserve comment. Because of the cross-sectional design, causal relationship between arterial stiffness and WML cannot be established. Atherosclerotic change of cerebrovascular circulation is generally considered to have a crucial role in the pathogenesis of WML. The relationship between arterial stiffness and WML should be explored prospectively. Second, although we have demonstrated the optimal cutoff values of haPWV to identify moderate-to-severe PVH and DWMH, the sensitivity and specificity were not high. Therefore, utilizing PWV as a surrogate marker for high grade WML needs to be further studied. Lastly, our study has weakness in terms of generalizability because the study population was composed of high-functioning older adults who voluntarily participated the health evaluation. The participants were free of dementia and physical limitation, with a mean MMSE score of 29.3 and none of the participants requiring assistance in activities of daily living. Although we provided important insights regarding potential preventive strategies in totally asymptomatic, otherwise healthy older adults, the association between arterial stiffness and WML among general population needs further investigation.

In conclusion, greater PWV is associated with higher grades of WML among high-functioning older adults. Efforts to prevent arterial stiffening through reduction of cardiovascular risks will likely ameliorate the progression of WML, thus improving the health outcomes of older adults. Our findings support the notion that measurement of arterial stiffness is useful in clinical practice for risk stratification.

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