

ORIGINAL RESEARCH

Association of Vascular Properties With the Brain White Matter Hyperintensity in Middle-Aged Population

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BACKGROUND: The periventricular white matter is more sensitive to the systemic hemodynamic alterations than the deep white matter because of differences in its vascular structure and systemic circulation relationship. We hypothesize that periventricular white matter hyperintensity (PVWMH) volume shows greater association than deep white matter hyperintensity (DWMH) volume with vascular properties (VPs) reflecting arterial stiffness and cardiovascular remodeling, indicators of the systemic circulation.

METHODS AND RESULTS: A total of 426 participants (age, 59.0±6.1 years; 57.5% women; and 39.7% Black race) in the Genetic Study of Atherosclerosis Risk who were aged ≥50 years and had brain magnetic resonance imaging were studied. VPs included pulse pressure, hypertensive response to exercise, diastolic brachial artery diameter, diastolic common carotid artery diameter, common carotid artery distensibility coefficient, and left ventricular function. The relative associations of VPs with PVWMH and DWMH as multiple measures within the same individual were determined using multilevel linear models. We also determined if age modified the differences in VPs associations with PVWMH and DWMH. Our findings indicated that, within the same subject, PVWMH volume had greater association than DWMH volume with pulse pressure ($P=0.002$), hypertensive response to exercise ($P=0.04$), diastolic brachial artery diameter ($P=0.012$), and diastolic common carotid artery diameter ($P=0.04$), independent of age and cardiovascular risk factors. The differences of PVWMH versus DWMH associations with VPs did not differ at any age threshold.

CONCLUSIONS: We show, for the first time, that PVWMH has greater association than DWMH, independent of age, with vascular measurements of arterial stiffness and cardiovascular remodeling suggesting that changes in the systemic circulation affect the PVWMH and DWMH differently.

Key Words: arterial stiffness ■ brain magnetic resonance imaging ■ vascular properties ■ white matter hyperintensity

White matter hyperintensities (WMHs) are the most prevalent form of cerebral small vessel disease (cSVD) that is seen on brain magnetic resonance imaging (MRI), and their burden is associated with greater risk of vascular cognitive impairment, stroke poor functional outcome, and recurrence.^{1,2}

WMHs can be classified into periventricular WMH (PVWMH) and deep WMH (DWMH) based on their proximity to the ventricles.³ This classification has been associated with distinct clinical phenotypes and different pathophysiological mechanisms favoring stronger association of PVWMH with alterations of systemic

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Presented in part at the International Stroke Conference 2022 in New Orleans, Louisiana, February 9 to 11, 2022, and published in abstract form in *Stroke*. 2022;53:AWP14. https://doi.org/10.1161/str.53.suppl_1.WP14

Supplemental Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024606>

For Sources of Funding and Disclosures, see page 10.

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CLINICAL PERSPECTIVE

What Is New?

- We show, for the first time, that the periventricular white matter hyperintensity shows greater association than deep white matter hyperintensity with vascular property measurements, reflecting the systemic arterial stiffness and cardiovascular remodeling.
- This suggests that alterations in the systemic hemodynamic circulation affect the periventricular white matter more preferentially than the deep white matter.

What Are the Clinical Implications?

- Our study points toward the potential future targeting of arterial stiffness in the treatment of patients with cerebral small-vessel disease as well as inclusion of vascular property measurements as end points in these studies.
- Our study also suggests the potential difference in the cardiovascular risk profile of periventricular and deep white matter hyperintensity that may necessitate different therapeutic approaches.

Nonstandard Abbreviations and Acronyms

AS	arterial stiffness
BA	brachial artery
CCA	common carotid artery
cSVD	cerebral small-vessel disease
DWMH	deep white matter hyperintensity
HRE	hypertensive response to exercise
PER	peak emptying rate
PFR	peak filling rate
PP	pulse pressure
PVWMH	periventricular white matter hyperintensity
SBP	systolic blood pressure
VPs	vascular properties
WMH	white matter hyperintensity

hemodynamics compared with DWMH based on recent genomic analysis and mathematical modeling.^{4–6}

Cardiovascular risk factors, in particular hypertension, are linked to the pathogenesis of WMH.^{7,8} Hypertension is also closely linked to the alteration of the systemic hemodynamics, and its incidence is associated with the development of stiffness of the large arteries.^{9,10} Endothelial dysfunction and structural changes of the vascular wall media are found to be the main pathophysiological events responsible

for development of arterial stiffness (AS), which further worsens the hypertensive disease.^{11,12} As a result, the arterial system wall eventually undergoes remodeling with subsequent changes in its diameter.¹⁰ The longstanding AS and hypertension also result in myocardial remodeling with associated left ventricular hypertrophy and reduced diastolic and/or systolic function.^{13,14} Furthermore, preliminary evidence suggests that the hemodynamic changes associated with AS are transmitted to the intracranial circulation and potentially damage the brain medium and small vessels.^{15,16} Elevated pulsatility in the middle cerebral arteries was seen in direct connection with increased aortic stiffness, whereas clinical studies have found associations among cSVD measures and faster brachial-ankle pulse wave velocity, a direct measure of AS.^{15,17} Finally, experimental mathematical modeling of the cerebral circulation theorizes that these hemodynamic alterations may preferentially damage the periventricular white matter more than the deep white matter.⁶ However, clinical association of this selective PVWMH susceptibility to the systemic hemodynamic alterations remains lacking.

In this work, we aim to expand these prior observations by assessing the association of WMH with several vascular parameters that are direct reflection of the pathophysiological consequences of AS on the cardiovascular system hemodynamics and remodeling. These measurements include pulse pressure (PP), hypertensive response to exercise (HRE), diastolic brachial artery (BA) diameter, diastolic common carotid artery (CCA) diameter, CCA distensibility, and filling and emptying rates of the left ventricle. Our primary hypothesis is that within the same subject, the PVWMH volume will show greater association than DWMH volume with these vascular property (VP) measurements. Subsequently, because age is the main driving factor for the development of AS and WMH, we perform exploratory moderation analysis examining the effect of age on the interaction of PVWMH and DWMH volumes with the VP measurements.

METHODS

Study Sample

The study was approved by the Johns Hopkins Medicine Institutional Review Board (NA_00002856). The data sets included in this analysis are available through application from the GeneSTAR (Genetic Study of Atherosclerosis Risk) Steering Committee. GeneSTAR is an ongoing prospective study of cardiovascular risk factors, occult coronary artery disease and cerebrovascular disease, and incident coronary artery disease and strokes in 3533 initially healthy family members ascertained from probands hospitalized with documented

coronary artery disease and aged <60 years.^{8,18} Participants in the GeneSTAR cohort were approached for 3 different substudies through 3 separate informed consents, including the following: GeneSTAR silent stroke study, which included brain MRI to measure the WMH burden,¹⁹ ARTERY (Arterial Tone and Reactivity Study), which included systemic VP measurements; and ENIGMA (Early Identification of Preclinical Coronary Atherosclerosis in High Risk Families) study, for measuring coronary plaque volumes.²⁰ GeneSTAR involved only healthy family members without any of the following exclusion criteria, including chronic steroid use, life-threatening diseases, neurologic diseases impairing MRI interpretation, implanted metals prohibiting MRI, atrial fibrillation, and symptomatic cardiovascular or cerebrovascular disease. None of the participants had a history of coronary artery disease, stroke, or transient ischemic attack. The GeneSTAR design was previously published in detail.¹⁹ In this current study, we included GeneSTAR participants in both the ARTERY and GeneSTAR silent stroke studies who had the available VP measurements and brain MRI. As our main interest is to understand the differences in association of PVWMH and DWMH volumes with the VP measurements, we selected those participants who were aged >50 years because most of the younger subjects did not have evidence of WMH on their brain MRI. **Figure 1** includes a flow diagram delineating the selection process. All study participants were examined by a physician. Cardiovascular risk factors, medical and social history, and medication use were recorded. Blood pressure, glucose, total cholesterol, and high-density lipoprotein cholesterol were measured after an overnight fast.²¹ Hypertension was defined as average blood pressure $\geq 140/90$ mm Hg, current use of antihypertensive medication, and/or history of physician diagnosis of hypertension. Diabetes was defined as fasting glucose >125 mg/dL, current use of hypoglycemic medication, and/or history of physician diagnosis of diabetes.

Vascular Property Measurements

The following VP measurements were used in the study.

Pulse Pressure

The PP is the difference between systolic and diastolic blood pressures (SBP and DBP, respectively), and it depends on the cardiac output, AS, and pressure wave reflection.²² PP has historically been used as a valuable surrogate of AS. Both SBP and DBP tend to increase with age. However, beyond the age of 50 to 60 years, the PP widens because of increasing SBP without an associated significant increase in DBP.²² Blood pressure was measured by taking an average of 3 repeated measures of the brachial SBP and DBP

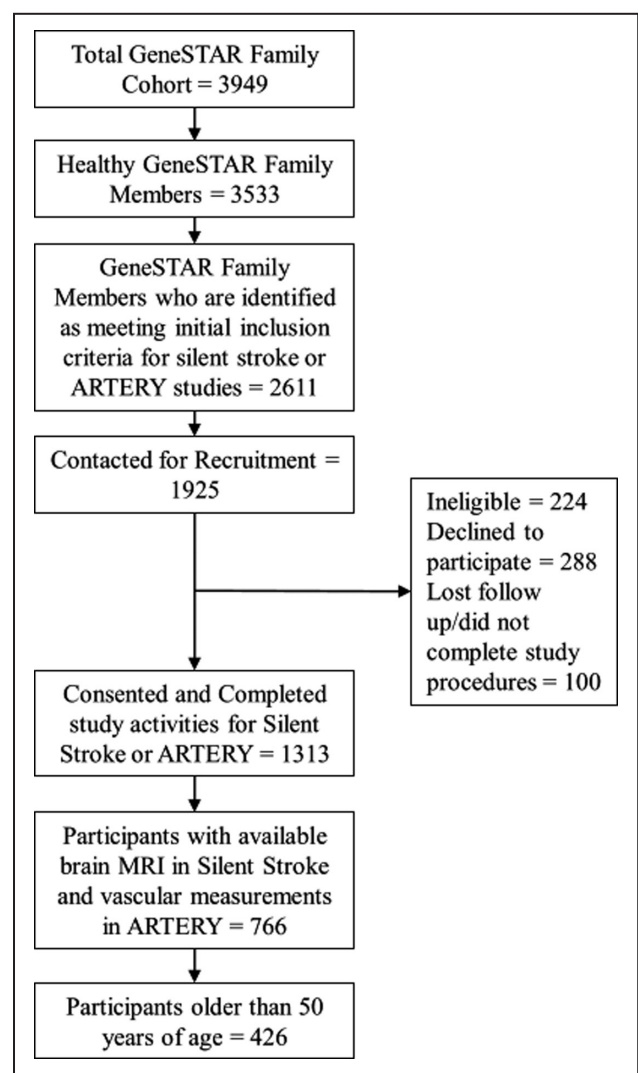


Figure 1. A flow diagram showing the selection process of the current study participants from the original GeneSTAR (Genetic Study of Atherosclerosis Risk) family cohort. ARTERY indicates Arterial Tone and Reactivity Study; and MRI magnetic resonance imaging.

using a sphygmomanometer.²³ PP was subsequently calculated.

Hypertensive Response to Exercise

An increase in SBP is normally seen in exercise because of increase in cardiac output to match the muscle oxygen demand. However, an exaggerated elevation in SBP beyond the 90th percentile is considered abnormal, and it is referred to as HRE.²⁴ HRE is attributed to endothelial dysfunction leading to lower levels of NO-mediated vasodilatation in young people, whereas it is considered an indirect measure of AS in the older patient population.²⁴ In this study, we defined HRE by measuring the peak SBP using a sphygmomanometer on the BA during treadmill

exercise sestamibi nuclear stress test, according to a published protocol.²⁵

Diastolic BA Diameter

The flow-mediated dilatation response of the BA has been used as a surrogate of endothelial dysfunction associated with AS.²⁶ The baseline resting diastolic diameter of BA is the major determinant of flow-mediated dilatation and correlates with the risk of cardiovascular diseases.^{27,28} The diastolic BA diameter was measured in the right arm using a previously reported method.²⁹ In brief, the right BA diastolic diameter was measured during diastole using a linear-array multifrequency transducer operating at 9 MHz (GE Logiq 700 Device) following 15 minutes of rest at 5 to 9 cm above the antecubital fossa.

CCA Diastolic Diameter

Changes of the arterial diameter occur as part of remodeling from AS and hypertensive disease.¹⁰ Enlargement of the CCA diameter is associated with incident stroke, whereas the CCA intima and media thicknesses are linked to AS and cardiovascular disease.^{30,31} Right CCA diastolic diameter at rest was measured during diastole, similar to the BA diameter measurement technique, before determining CCA distensibility.

CCA Distensibility

Arterial distensibility refers to the relative change in diameter for a given pressure change and is inversely related to AS.²² Right CCA distensibility was measured by a 20-second B-mode ultrasound recording of a longitudinal section of the right distal CCA using a Logiq 700 Device with simultaneous measurement of the right BA blood pressure during the recordings, as was previously described.³²

Cardiac Function

The sustained long-term effect of the systemic AS and hypertensive disease result in myocardial remodeling and development of left ventricular hypertrophy and heart failure.³³ We used the sestamibi exercise stress test to derive metrics representative of cardiac function, including the left ventricle peak emptying rate (PER) as a surrogate of systolic function and peak filling rate (PFR) and PFR/PER index as surrogates of diastolic function.³⁴

Brain MRI Acquisition and Analysis

Brain MRI was acquired on a 3-T Achieva imaging unit (Philips Healthcare, Best, the Netherlands). T1-weighted magnetization-prepared rapid-gradient echo (T1-weighted MPRAGE) and axial turbo spin echo

fluid-attenuated inversion recovery (FLAIR) images were acquired according to the following parameters: (1) T1-weighted MPRAGE: repetition time, 10 ms; echo time, 6 ms; voxel size, 0.75×0.75×1 mm³; contiguous slices; field of view, 240×240 mm; and matrix size, 256×256 mm; and (2) axial turbo spin echo FLAIR image, according to the following parameters: repetition time, 11,000 ms; echo time, 68 ms; inversion time, 2800 ms; voxel size, 0.47×0.47×3 mm³; contiguous slices; field of view, 240×240; and matrix size, 256×256.

White matter hyperintensities (WMHs) volumetric analysis was completed using a semiautomated pipeline that was developed in Medical Image Processing, Analysis, and Visualization (MIPAV).³⁵ The protocol details were published before.¹⁹ Briefly, following skull stripping of MPRAGE sequences and coregistration to FLAIR images, the images were transformed to the Montreal Neurological Institute space. WMHs were manually segmented in the transformed FLAIR image by a trained rater. This was followed by separation of WMHs from the healthy brain tissue and classification with an automated probabilistic method into PVWMH and DWMH (topology-preserving anatomy-driven segmentation).³⁶

Statistical Analysis

Statistical analysis was completed in Stata v15.1 (College Station, TX). Continuous data were presented as means and SDs or medians and interquartile ranges, as appropriate, whereas categorical data were presented as percentages. Before parametric analyses, logarithmic transformations were performed for the volumes of the total WMH, PVWMH, and DWMH, and intracranial volumes to achieve approximate normality in distributions. Because our selected VPs represent the different aspects of AS and its consequences on the cardiovascular system, we tested their levels of association using the Spearman correlation. Subsequently, exploratory analyses to examine the associations of the total WMH volume and each of these VP measurements were performed. These exploratory analyses were completed using linear regression models in which the log-transformed value of the total WMH volume served as the dependent variable, and they were repeated for each of the VP measurements (independent variable). The covariates of interest in these regressions were the log-transformed intracranial volume, sex, race, age, years of education, and the values of glucose, total cholesterol, and high-density lipoprotein. These covariates were sequentially added to the linear regression analyses to form 4 statistical models (models: 0, 1, 2, and 3) that were repeated for each VP measurement of interest. Our covariates did not include hypertension or SBP because the models

tested the association of closely related variables to the SBP (ie, PP and HRE) as the variables of interest.

Subsequently, we tested our primary hypothesis of whether there is a difference in association of PVWMH and DWMH volumes with the VP measurements. As the selected VP measurements are representative of the same underlying biological processes, including AS and its consequences on the cardiovascular system, we chose not to adjust for multiple comparisons in this analysis. To achieve this goal, we modeled the log-transformed volumes of PVWMH and DWMH as 2 measurements of the dependent variable of regional WMH nested within an individual, and individuals were further nested within their families in a multilevel mixed-effects linear regression. This analysis was performed using the combination of covariates of the fully adjusted model (model 3). An indicator variable marking specific region PVWMH versus DWMH was added as a covariate to the model distinguishing the 2 regions. The VP was also added as an independent variable. As this is an entirely within-subject analysis, there is no between-subject variability for the interaction term. Our mixed model allowed the fit of different variances for the dependent variable, depending on the region (ie, heteroskedasticity). For ease of interpretation, we have tabulated the association of PVWMH with VPs, and DWMH with VPs, by linear combination of the main and interaction coefficients. The interaction *P* value is also tabulated.

Because age is the main factor in the development of AS and WMH, we subsequently aimed to understand whether age moderates the difference in association of PVWMH/DWMH volumes and VP measurements. To complete this aim, we used maximal likelihood estimation analysis. This analysis was completed as a 3-way interaction between the VP, the indicator variable for brain region, and age as a dichotomous term at different thresholds in a series of models. This moderation analysis explored every possible age threshold within our sample, to see if even with the highest likelihood of the regression fit, the analysis would show a statistically significant association.

RESULTS

Baseline Characteristics

This study included 426 participants (mean age, 59.0±6.1 years; 57.5% women; and 39.7% Black race). The study cohort had a moderate prevalence of cardiovascular risk factors (Table 1). There was evidence of WMH on brain MRI (median total WMH volume, 1707.5 [interquartile range {IQR}, 613–4590] mm³). The median cardiovascular health score for WMH severity in our sample was 1 (IQR, 0–3).³⁷ The cardiovascular health score showed strong correlation with the total

Table 1. Study Sample Baseline Clinical Characteristics

Characteristic	Study sample (N=426)
Age, mean±SD, y	58.97±6.11
Female sex, %	57.51
Black race, %	39.67
Education, mean±SD, y	14.07±2.81
Hypertensive, %	60.33
Current smoking, %	15.26
Diabetic, %	16.51
Current use of lipid-lowering medicine, %	40.38
Systolic blood pressure, mean±SD, mm Hg	128.82±14.05
Diastolic blood pressure, mean±SD, mm Hg	78.1±8.86
Total cholesterol, mean±SD, mg/dL	192.74±40.1
High-density lipoprotein cholesterol, mean±SD, mg/dL	58.7±16.9
Plasma glucose, mean±SD, mg/dL	105.68±34.86
Framingham risk score, mean±SD	9.36±6.9

WMH volume in our sample ($\rho=0.686$; $P<0.0001$). The baseline values of the VP measurements and PVWMH/DWMH volumes are shown in Table 2. Of the 426 subjects, 37 had missing BA diameter and CCA diameter and distensibility coefficient. The baseline

Table 2. Baseline Vascular Property Measurements and WMH Volumes

Vascular properties	Study sample (N=426, except for common carotid artery distensibility and diameter and brachial artery diameter, N=389)
Pulse pressure, mean±SD, mm Hg	50.72±11.76
Hypertensive response during exercise: peak systolic blood pressure on exercise treadmill test, mean±SD, mm Hg	186.64±24.54
Brachial artery resting diastolic diameter, mean±SD, mm	4.55±0.97
Diastolic common carotid artery diameter, mean±SD, mm	7.37±0.79
Common carotid artery distensibility coefficient, mean±SD	0.00178±0.0007
Sestamibi PER, mean±SD, volumes/s	2.77±0.57
Sestamibi PFR, mean±SD, volumes/s	2.28±0.58
Sestamibi PFR/PER index, mean±SD	0.83±0.15
WMH volumes	Study sample (N=426)
Total WMH, median (IQR), mm ³	1707.5 (613–4590)
Periventricular WMH, median (IQR), mm ³	914.5 (181–2690)
Deep WMH, median (IQR), mm ³	399 (163–1036)
Intracranial volume, median (IQR), mm ³	1 565 757 (1 463 001–1 664 394)

IQR indicates interquartile range; PER, peak emptying rate; PFR, peak filling rate; and WMH, white matter hyperintensity.

characteristics, WMH volumes, and VP measurements of these 37 subjects in comparison to the remaining study sample are presented in Table S1. In summary, these characteristics were similar between those 2 groups, except subjects with missing BA diameter and CCA diameter and distensibility were more likely smokers (27.03% versus 14.4%; $P=0.037$) and had smaller PVWMH and DWMH volumes compared with the rest of the cohort (PVWMH volume: missing BA/CCA diameter and distensibility: median, 408 [IQR, 0–1433] mm³ versus remaining sample: median, 992 [IQR, 228–2832] mm³; $P=0.009$; DWMH volume: missing BA/CCA diameter and distensibility: median, 213 [IQR, 0–594] mm³ versus remaining sample: median, 415 [IQR, 174–1102] mm³; $P=0.004$). The correlation matrix of these VP measurements showed variable degrees of correlation among them (Figure 2). In particular, PFR strongly correlated with PER, PFR/PER strongly correlated with PFR, and diastolic CCA diameter moderately correlated with diastolic BA diameter. As expected by the fact that distensibility is conceptually inverse of AS, strong negative correlations were found between CCA distensibility coefficient and PP, diastolic CCA diameter

and CCA distensibility, and PFR with diastolic BA and CCA diameters.

Association of Total WMH Volume With Vascular Property Measurements

Table S2 shows the results of the linear regression exploratory analyses of the associations of total WMH volume with each VP measurements in all 4 statistical models (0, 1, 2, and 3). Total WMH volume was significantly associated with PP, diastolic CCA diameter, and CCA distensibility coefficient (model 0). However, these associations became insignificant when adjusted for age and the rest of the cardiovascular risk factors in model 3, except for the association of total WMH volume with PER ($P=0.029$).

Association of PVWMH and DWMH Volumes With Vascular Property Measurements

Table 3 shows the results of the multilevel mixed-effects linear regression for the association of PVWMH

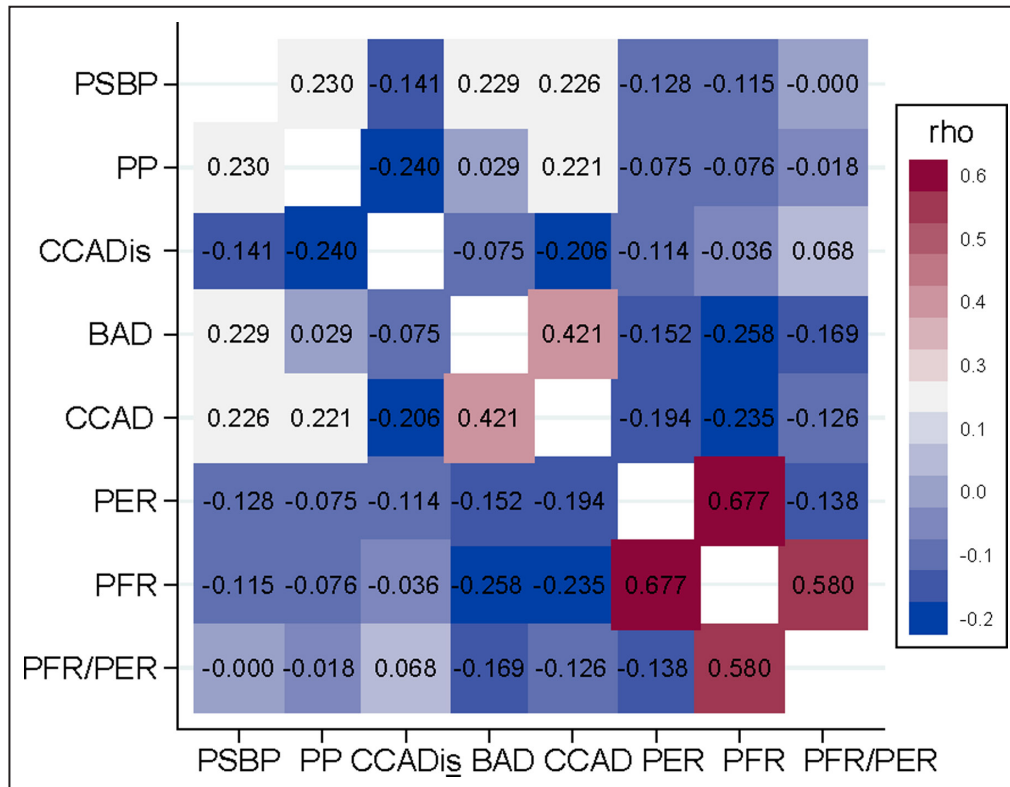


Figure 2. Correlation matrix for the association of vascular property measures. Vascular property measures of stiffness and cardiovascular remodeling showed variable degrees of positive or negative correlations with each other. BAD indicates brachial artery diameter; CCAD, common carotid artery diameter; CCADis, common carotid artery distensibility coefficient; PER, peak emptying rate; PFR, peak filling rate; PP, pulse pressure; and PSBP, peak systolic blood pressure during treadmill stress test.

Table 3. Association of Vascular Property Measurements With WMH Subtypes

Variable	PVWMH volume	DWMH volume	Interaction <i>P</i> value
Peak systolic blood pressure during exercise treadmill test			
Fully adjusted model	0.002 (−0.208 to 0.211)	−0.182 (−0.392 to 0.028)	0.04*
Pulse pressure			
Fully adjusted model	0.131 (−0.085 to 0.348)	−0.145 (−0.362 to 0.071)	0.002*
Diastolic brachial artery diameter			
Fully adjusted model	−0.036 (−0.286 to 0.215)	−0.282 (−0.532 to −0.031)*	0.012*
Diastolic common carotid artery diameter			
Fully adjusted model	0.241 (0.010 to 0.473)*	0.043 (−0.188 to 0.275)	0.04*
Common carotid artery distensibility coefficient			
Fully adjusted model	0.070 (−0.151 to 0.291)	0.109 (−0.112 to 0.330)	0.69
Left ventricular peak emptying rate			
Fully adjusted model	−0.085 (−0.296 to 0.125)	−0.066 (−0.277 to 0.145)	0.83
Left ventricular peak filling rate			
Fully adjusted model	−0.013 (−0.228 to 0.203)	0.106 (−0.109 to 0.322)	0.18
Left ventricular peak emptying rate/systolic peak filling rate			
Fully adjusted model	0.051 (−0.158 to 0.260)	0.186 (−0.023 to 0.395)	0.13

Data are given as β (95% CI). Multilevel mixed linear model for testing the interaction of the log-transformed PVWMH and DWMH volumes with each of the vascular property measurements, including the following covariates: log-transformed intracranial volume, sex, race, age, years of education, and values of glucose, total cholesterol, and high-density lipoprotein cholesterol levels (fully adjusted model). DWMH indicates deep WMH; PVWMH, periventricular WMH; and WMH, white matter hyperintensity.

*Met statistical significance ($P < 0.05$).

and DWMH volumes with each of the VP measurements after adjusting for intracranial volume, age, and cardiovascular risk factors. Within the same subject, we observed statistically significant differences in the relative associations of PVWMH and DWMH volumes with certain VP measurements. These results are represented by significantly larger PVWMH volume than DWMH volume within the same subject in association with higher PP ($P = 0.002$), higher peak systolic blood pressure during exercise stress test ($P = 0.04$), larger diastolic CCA diameter ($P = 0.04$), and lower decrease of diastolic BA diameter ($P = 0.012$). However, there were no statistically significant differences in the relative associations of PVWMH and DWMH volumes with CCA distensibility coefficient or cardiac function within the same subject (Table 3). In between subjects, PVWMH volume was not associated with the VP measurements when adjusted for age and cardiovascular risk factors, except for the association of PVWMH volume with diastolic CCA diameter ($\beta = 0.241$; 95% CI, 0.010–0.473). Similarly, DWMH volume was not associated with the VP measurements in this fully adjusted model, except for the association of diastolic BA diameter with DWMH volume ($\beta = -0.282$; 95% CI, −0.532 to −0.031).

Age Moderation Analysis

We then analyzed whether the observed within-subject associations of larger PVWMH volume than DWMH volume with VP measurements were moderated by age within our cohort using maximal likelihood

estimation. This analysis aimed to identify an age cutoff within our sample where the associations of each of the VP measurements with the interaction of PVWMH/DWMH volumes was maximal. We did not identify through these moderation analyses any age threshold within our sample age distribution where the associations reached statistical significance. Figure 3 shows in detail the results of the age moderation analysis. These findings confirm further the age independence of our results through demonstrating the same observations throughout the age spectrum of our sample.

DISCUSSION

In this study, we show, for the first time, that PVWMH volume is more closely associated with several properties of the cardiovascular system representing AS and cardiovascular remodeling than DWMH volume, independent of age and cardiovascular risk factors. Furthermore, these observed associations are not moderated by age in our study sample. Our results add to a growing body of experimental, histological, and genomic evidence suggesting that PVWMH and DWMH are affected differently by the cardiovascular risk factors and changes in systemic hemodynamics.

WMHs are the most prevalent radiographic phenotype of cSVD that are seen on FLAIR imaging.¹ The most distinctive feature between PVWMH and DWMH in the literature has been the proximity to the ventricles, where PVWMHs are considered to be contiguous

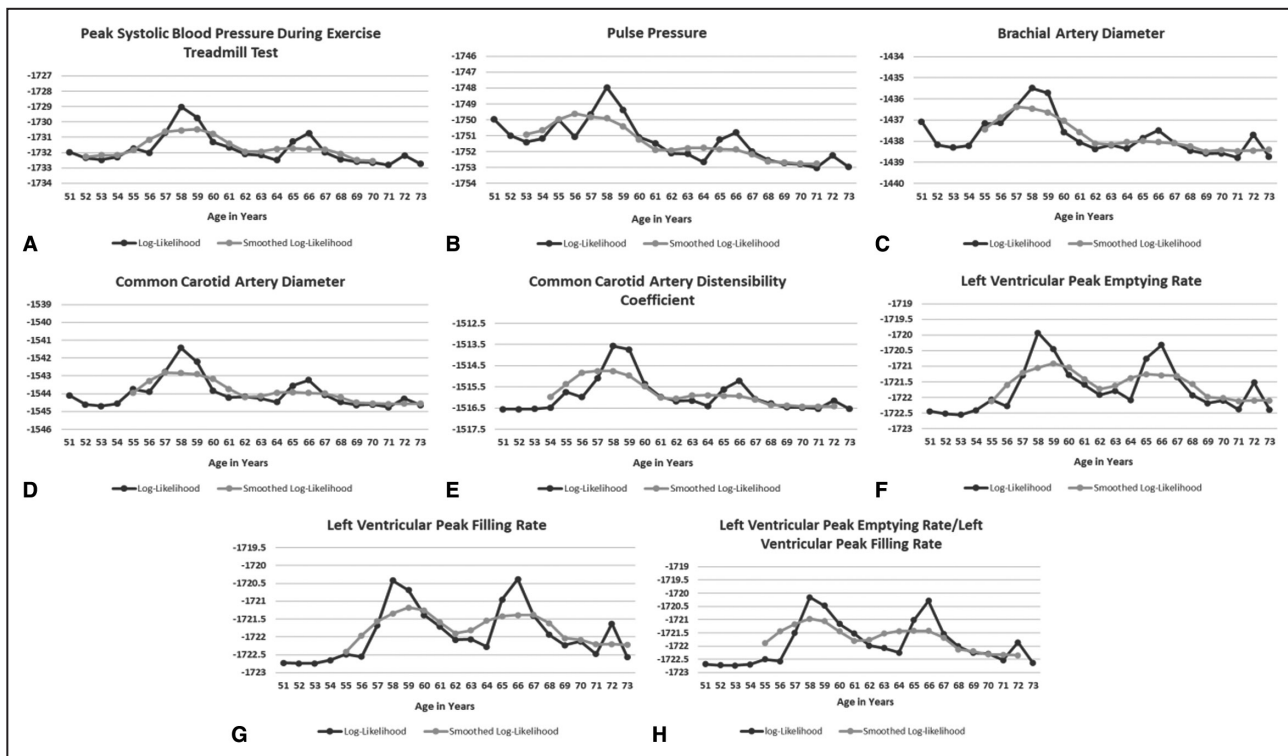


Figure 3. Moderation analysis of age for the difference in association of periventricular white matter hyperintensity (PVWMH)/deep white matter hyperintensity (DWMH) volumes with each of the vascular property measurements, including peak systolic blood pressure during treadmill test (A), pulse pressure (B), brachial artery diameter (C), common carotid artery diameter (D), common carotid distensibility coefficient (E), left ventricular peak emptying rate (F), left ventricular peak filling rate (G), and left ventricular peak emptying rate/left ventricular peak filling rate (H).

The black curve represents the log value of the likelihood to maximize the difference in association of PVWMH/DWMH volume with the vascular property measurement at each age value within our sample. The gray curve represents the smoothed values. The analysis did not reach statistical significance threshold ($P < 0.05$) at any age cutoff within our sample.

with the margins of each lateral ventricle and DWMHs are separate from it.⁴ This radiologic classification has been associated with different histopathological correlates, where PVWMHs are associated with ependymal loss, differing degrees of myelination in adjacent fiber tracts, and cerebral ischemia with associated demyelination.^{4,38} DWMHs are associated with microcytic infarcts and patchy rarefaction of myelin.⁴ In a recent study of large population genomic data, PVWMH and DWMH were found to have shared and distinct genetic architecture.⁵ Genetic analyses indicated PVWMH was more associated with genes that are implicated in pathogenesis of ischemic stroke and loss of structural integrity of the vessel wall and vascular function.⁵ Our group has recently identified an association between PVWMH volume with coronary artery plaque volume, providing additional evidence for the association of PVWMH with changes in the systemic hemodynamic circulation.³⁹ These results are in line with mathematical models showing that the blood vessels at the brain base are prone to the systemic effects of hypertension more than the small vessels in the subcortical areas.⁶ To elucidate the differential associations of PVWMH

and DWMH with the systemic hemodynamic alterations, we chose in this study several VP parameters that are closely linked to AS, a major determinant of the systemic arterial hemodynamics.^{22,24,26,27,30,32,33} Our current findings provide additional evidence that PVWMH is more sensitive to changes in the systemic hemodynamic circulation than the DWMH. In addition, our current and previous findings suggest that differences exist between PVWMH and DWMH clinical, histological, and genomic correlates. Additional studies based on serum biomarkers and advanced vascular and neuroimaging remain needed to independently confirm the exact PVWMH and DWMH correlates and their differences as phenotype of cSVD.

Arterial stiffness is the hallmark of vascular aging and is attributed to several pathophysiological processes affecting the composition of the vessel wall, including elastin fragmentation and deposition of collagen, production of matrix metalloproteases, nonenzymatic glycation of protein, leading to cross linkage of collagen, and endothelial dysfunction.^{11,40} These biological changes alter the viscoelastic properties of the arterial system, leading to lower arterial distensibility

and reduced compliance (ie, stiffer vessels) with subsequent elevation of SBP and widening of PP.^{41,42} These pathophysiological processes and associated hemodynamic changes eventually result in the development of clinical hypertension, arterial remodeling with changes in the large arteries' diameter, and left ventricular dysfunction.^{10,13} Associated alterations of the intracranial hemodynamics have also been detected using transcranial doppler ultrasound studies of middle cerebral arteries in patients with evidence of WMH.^{15,16} In addition, a clinical study identified an association of increased AS with radiographic markers of cSVD.¹⁷ Our current results add new observations by demonstrating the selective susceptibility of the periventricular white matter to the hemodynamic alterations in the systemic circulation. Our findings are supported by the association of PVWMH with several VPs, reflecting the different pathophysiological mechanisms of arterial stiffness and remodeling, including the structural changes of the arterial medial layer by measuring PP,⁴² endothelial dysfunction, and decrease in NO by measuring HRE,²⁴ and arterial wall remodeling, by measuring the diastolic diameter of CCA and BA.¹⁰ Indeed, the correlation analysis showed variable degrees of association among these VP measurements. We postulate the reason for the lack of association of PVWMH volume with CCA distensibility coefficient is potentially attributable to the special location of CCA and its bifurcation, which may limit distensibility and its measurement because of the carotid bony canal.⁴³ Finally, PVWMH volume was not associated with cardiac function in our cohort, which is likely a reflection of the healthy status of our middle-aged population without a known cardiac disease.

Aging is the main risk factor for AS and cSVD, and it is difficult to control for as it interacts with several cardiovascular risk factors.^{11,40,44} Mechanisms by which the aging process affects the large systemic arteries and the brain small vessels show considerable overlap, such as endothelial dysfunction.^{7,11} We aimed in this work to comprehensively understand the complex association of age with our VP measurements and WMH and control for it. As anticipated, adding age to the statistical models 2 and 3 in the between-subject analysis reduced the significance of the most statistical associations, particularly in regard to total WMH, PVWMH, and DWMH volumes. To address this, we compared within the subject volumes of PVWMH and DWMH using multilevel mixed-effects linear regression models. Our within-subject analysis allowed us to show that the association of PVWMH volume with vascular properties is independent of age. We also performed age moderation maximal likelihood estimation analysis to further address whether any of these observed associations were significantly different at any age threshold. The negative maximal likelihood estimation analysis

confirms that we did not identify an age threshold where the difference in association of PVWMH and DWMH volumes with vascular properties was statistically significant. In other terms, we observed similar stronger association of PVWMH than DWMH with vascular properties across the age spectrum of our cohort in both young subjects and those who are older and have larger volumes of both PVWMH and DWMH.

There are many pitfalls to our study design. It is a cross-sectional study, and we cannot confirm a causative effect of AS or its associated VP measurements on the emergence of WMH and its subtypes. We did not include a direct measurement of AS, such as pulse wave velocity.⁴⁵ However, we have included several indirect measures of the systemic arterial vasculature that are linked with the different pathophysiological mechanisms or the hemodynamic consequences of AS or its associated arterial remodeling. Hence, we are certain that our measurements are good representation of the status of the arterial system. The inclusion of a healthy middle-aged population in our study is of particular interest because it will capture patients at the early stages of their disease before progression of WMH and development of confluency, allowing for the distinction between PVWMH and DWMH. Our goal is to perform future research studies including follow-up brain MRI scans and repeated vascular measurements to ascertain the magnitude of worsening of WMH in relationship to direct AS measurements. Future mechanistic studies should take into consideration the associations of AS with other emerging mechanisms for cSVD as well as the effect of medications that may alter the systemic vascular properties, such as statin or antihypertensive medications, on both PVWMH and DWMH. Future therapeutic studies should target AS measures as the disease end points. Such approach would form a paradigm shift in treating cSVD and its subsequent vascular cognitive impairment.

CONCLUSIONS

We report, for the first time, that PVWMH shows a stronger association with vascular property measures associated with systemic arterial stiffness and cardiovascular remodeling in comparison to DWMH, independent of age and other cardiovascular risk factors. These findings need to be confirmed in future prospective studies.

ARTICLE INFORMATION

Received November 12, 2021; accepted March 7, 2022.

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Sources of Funding

This work was supported by the National Institute of Neurological Disorders and Stroke (NINDS) grant NS062059, National Heart, Lung, and Blood Institute grants HL092165, HL009747, and K23HL105897, and the National Center for Research Resources and the National Center for Advancing Translational Sciences, to Johns Hopkins Institute for Clinical and Translational Research, grant UL1RR025005. Dr Johansen receives funding from the NINDS grant K23NS112459.

Disclosures

None.

Supplemental Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of subjects with missing brachial artery diameter, common carotid artery diameter and distensibility data referred to in the table as “missing vascular property measurements” and those with available all vascular property measurements

Characteristic	Vascular Properties Missing (N=37)	Vascular Properties Available (N= 389)	P value
Age (years, mean \pm SD)	59.24 \pm 5.95	58.95 \pm 6.13	0.78
Female sex (%)	67.57%	56.56%	0.2
Black race (%)	54.05%	38.3%	0.16
Education (years, mean \pm SD)	14.04 \pm 2.52	14.07 \pm 2.84	0.95
Hypertensive (%)	54.05%	57.33%	0.7
Current smoking (%)	27.03%	14.4%	0.037*
Diabetic (%)	18.92%	16.2%	0.76
Current use of lipid lowering medicine (%)	32.43%	41.13%	0.3
Systolic blood pressure (mmHg, mean \pm SD)	132.04 \pm 14.57	128.51 \pm 13.98	0.15
Diastolic blood pressure (mmHg, mean \pm SD)	78.1 \pm 9.07	78.1 \pm 8.85	0.99
Total cholesterol (mg/dl, mean \pm SD)	195.92 \pm 44.32	192.44 \pm 39.69	0.62
High density lipoprotein cholesterol (mg/dl, mean \pm SD)	55.64 \pm 14.54	58.98 \pm 17.09	0.26
Plasma glucose (mg/dl, mean \pm SD)	104.92 \pm 34.6	105.75 \pm 34.93	0.74
Framingham Risk Score (mean \pm SD)	11.56 \pm 9.52	9.15 \pm 6.54	0.2
Peak Systolic Blood Pressure During treadmill testing (mmHg, mean \pm SD)	191.28 \pm 29.3	186.21 \pm 24.05	0.24
Pulse Pressure (mmHg, mean \pm SD)	53.94 \pm 12.61	50.41 \pm 11.65	0.08
Sestamibi PER (volumes/sec, mean \pm SD)	2.67 \pm 0.62	2.78 \pm 0.57	0.27
Sestamibi PFR (volumes/sec, mean \pm SD)	2.26 \pm 0.69	2.28 \pm 0.57	0.81
Sestamibi PFR/PER	0.84 \pm 0.15	0.83 \pm 0.15	0.51
WMH volume (mm ³ , median [IQR])	2019 [690-4400]	1669 [605-4626]	0.72
Periventricular WMH volume (mm ³ , median [IQR])	408 [0-1433]	992 [228-2832]	0.009*
Deep WMH volume (mm ³ , median [IQR])	213 [0-594]	415 [174-1102]	0.004*

IQR: Interquartile range; mm³: millimeter cubic; mmHg: millimeter mercury; mg/dl: milligram per deciliter; PER: peak emptying rate; PFR: peak filling rate; SD: standard deviation; WMH: white matter hyperintensity; (%): percentage; *statistically significant (P<0.05)

Table S2. Association of the total white matter hyperintensity volume (dependent variable) with each of the vascular property measurements in the study cohort

	HRE		PP		Diastolic BA diameter		Diastolic CCA diameter	
	Beta (95% CI)	P Val	Beta (95% CI)	P Val	Beta (95% CI)	P Val	Beta (95% CI)	P Val
Model 0	0.123 [-0.023 - 0.269]	0.099	0.220 [0.074 - 0.366]	0.003 *	-0.034 [-0.204 - 0.136]	0.69	0.178 [0.008 - 0.348]	0.04*
Model 1	0.112 [-0.035 - 0.258]	0.13	0.224 [0.081 - 0.367]	0.002 *	-0.013 [-0.204 - 0.178]	0.89	0.209 [0.034 - 0.385]	0.02*
Model 2	0.092 [-0.047 - 0.230]	0.19	0.062 [-0.084 - 0.208]	0.4	-0.148 [-0.332 - 0.036]	0.11	0.039 [-0.135 - 0.214]	0.66
Model 3	0.084 [-0.058 - 0.226]	0.25	0.053 [-0.097 - 0.202]	0.49	-0.152 [-0.337 - 0.033]	0.11	0.041 [-0.135 - 0.217]	0.66
	CCA Distensibility Coefficient		PER		PFR		PER/PFR	
	Beta (95% CI)	P Val	Beta (95% CI)	P Val	Beta (95% CI)	P Val	Beta (95% CI)	P Val
Model 0	-0.182 [-0.339 - -0.025]	0.02*	-0.136 [-0.283 - 0.010]	0.07	-0.085 [-0.233 - 0.063]	0.26	0.028 [-0.118 - 0.174]	0.71
Model 1	-0.125 [-0.283 - 0.034]	0.12	-0.158 [-0.307 - -0.009]	0.04*	-0.129 [-0.282 - 0.024]	0.1	-0.002 [-0.148 - 0.144]	0.98
Model 2	0.093 [-0.067 - 0.253]	0.25	-0.186 [-0.327 - -0.046]	0.009 *	-0.081 [-0.227 - 0.065]	0.28	0.103 [-0.038 - 0.244]	0.15
Model 3	0.091 [-0.070 - 0.253]	0.27	-0.158 [-0.300 - -0.016]	0.029 *	-0.059 [-0.206 - 0.088]	0.43	0.100 [-0.042 - 0.242]	0.17

Separate linear regression analysis was performed for each of the vascular property measurements (independent variable) with the log-transformed total white matter hyperintensity volume (dependent variable). In each regression analysis, covariates were added sequentially in model 0, 1, 2 and 3. Model 0 covariates: log-transformed intracranial volume; model 1 covariates: log-transformed intracranial volume, sex and race; model 2 covariates: log-transformed intracranial volume, sex, race and age; model 3 covariates: log-transformed intracranial volume, sex, race, age, years of education, and values of blood sugar, total cholesterol and high density lipoprotein levels. BA: brachial artery; CCA: common carotid artery; CI: confidence interval; HRE: hypertensive response to exercise; PER: peak emptying rate; PFR: peak filling rate; PP: pulse pressure; Val: value; * statistically significant (P<0.05).