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A Combined Measure of Vascular Risk for White Matter Lesions

Amber Watts[a,*], **Robyn A. Honea**[b], **Sandra A. Billinger**[c], **Kathleen T. Rhyner**[a], **Lewis Hutfles**[b], **Eric D. Vidoni**[b], and **Jeffrey M. Burns**[b]

[a]Department of Clinical Psychology, University of Kansas, Lawrence, KS, USA

[b]Alzheimer's Disease Center, University of Kansas, Fairway, KS, USA

[c]Department of Physical Therapy & Rehabilitation Science, University of Kansas Medical Center, Kansas City, KS, USA

Abstract

Background—Though hypertension is a commonly studied risk factor for white matter lesions (WMLs), measures of blood pressure may fluctuate depending on external conditions resulting in measurement error. Indicators of arterial stiffening and reduced elasticity may be more sensitive indicators of risk for WMLs in aging; however the interdependent nature of vascular indicators creates statistical complications.

Objective—The purpose of the study was to determine whether a factor score comprised of multiple vascular indicators would be a stronger predictor of WMLs than traditional measures of blood pressure.

Methods—In a sample of well-characterized nondemented older adults, we used a factor analytic approach to account for variance common across multiple vascular measures while reducing measurement error. The result was a single factor score reflecting arterial stiffness and reduced elasticity. We used this factor score to predict white matter lesion volumes acquired via fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging.

Results—The combined vascular factor score was a stronger predictor of deep WML ($\beta = 0.42$, $p < 0.001$) and periventricular WML volumes ($\beta = 0.49$, $p < 0.001$). After accounting for the vascular factor, systolic and diastolic blood pressure measurements were not significant predictors.

Conclusions—This suggests that a combined measure of arterial elasticity and stiffening may be a stronger predictor of WMLs than systolic and diastolic blood pressure accounting for the multicollinearity associated with a variety of interrelated vascular measures.

Keywords

Arterial stiffness; factor analysis; magnetic resonance imaging; vascular elasticity; white matter lesions

[*]Correspondence to: Amber Watts, PhD, Department of Clinical Psychology, University of Kansas, 1415 Jayhawk Boulevard, Fraser 426, Lawrence, KS 66045, USA. Tel.: +1 785 864 2604; Fax: +1 785 864 5696; amberwatts@ku.edu.

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INTRODUCTION

Typical aging is associated with an accumulation of deleterious effects on brain structure, including degeneration in white matter [1]. White matter is particularly susceptible to age-associated changes, especially cerebrovascular disorders and ischemia [2–4]. White matter lesions (WMLs), detectable through magnetic resonance imaging (MRI), increase with age and are common in older adults including those who are otherwise healthy [5]. Accumulation of WMLs is associated with poor cognitive function [6, 7], risk of dementia and stroke [8, 9], and depressive symptoms [10]. Two major classifications of WMLs are periventricular (PVWMLs), those contiguous with the margins of the lateral ventricles, and subcortical or "deep" (DWMLs), those that are separate from the ventricles. PVWMLs have generally been associated with cognitive changes, whereas those fully bounded by white matter ("deep") have more often been associated with depression and related illnesses [1, 11, 12].

Vascular risk factors are precursors of both types of WMLs. Hypertension is associated with increased rates of both PVWMLs and DWMLs [13] and duration of hypertension is an important factor [13, 14]. Some studies suggest that control of hypertension with medications results in less severe WMLs [13]. However, both increases and decreases in blood pressure are associated with more severe PVWMLs [15]. Though hypertension is a commonly studied vascular risk factor for WMLs, investigation of other vascular indicators such as arterial stiffening may shed light on the causes and consequences of WMLs in aging [16]. Arterial stiffening, thickening, and endothelial dysfunction have been associated with severity of WMLs and cognitive decline independent of blood pressure level [17]. Duprez et al. [18] reported that reduced large and small artery elasticity were associated with greater severity of cerebral WMLs and not significantly associated with blood pressure levels. The ability of the small and large arteries to stretch with increased blood flow (i.e., sheer stress) is an indicator of elasticity. Small and large artery elasticity indices are markers of arteriosclerosis and atherosclerosis respectively and linked to WMLs [19]. Decreased elasticity due to aging is associated with a reduction in blood flow toward the brain [20].

Several vascular indicators may predict WMLs even after accounting for blood pressure. However, due to the interdependent nature of these vascular measures, they are highly overlapping in their contributions to statistical variation, thus creating problems with multicollinearity. A factor analytic approach to this analysis allows us to account for the variance in common between the separate items and eliminate variance due to measurement error or variance due to unique characteristics of each measure [21]. Thus, a factor analytic model will allow us to better investigate a combination of multiple vascular risk factors reflecting arterial stiffness and reduced elasticity. We hypothesize that this combined vascular risk factor will be associated with WMLs even after accounting for traditional measures of blood pressure and other potential covariates.

MATERIALS AND METHODS

Sample and recruitment

Data were collected from participants enrolled in the Brain Aging Project at the University of Kansas. The Brain Aging Project was designed as a longitudinal observational study of older adults, both nondemented individuals and those with early-stage AD, 65 years and older. The Brain Aging Project focused on the assessment of physical health and metabolism. The present study included nondemented participants who had a battery of tests including a clinical assessment, metabolic assessment, vascular compliance, cardiovascular fitness assessment, and structural MRI, among other tests documented in previous publications [22–25]. All study procedures were conducted in accordance with the Helsinki Declaration of 1975 and approved in compliance of the ethical standards of the University of Kansas Medical Center Institutional Review Board. Participants were recruited by self-referral in response to media coverage and word of mouth. Informed consent was obtained for all participants prior to enrollment into the study.

The present study reports findings for healthy older adult control participants (n = 63) who were without evidence of functional cognitive impairment (Clinical Dementia Rating [CDR] 0) [26]. We excluded participants who were missing data for the vascular measures or whose MRI scan was excluded due to movement or artifact based on visual inspection. Study exclusions at baseline include diabetes mellitus (clinical diagnosis, use of an anti-diabetic agent, or 2-h post-load serum glucose >199), unstable ischemic heart disease within the last 2 years as previously described, neurological disease, schizophrenia, clinically significant depression, abnormalities in serum vitamin B12 levels, thyroid disease, use of psychoactive or investigational medications, significant visual or auditory impairment, history of alcohol abuse, and systemic illness that would impair completion of the study [22]. Participants were excluded if they had mobility impairments that would interfere with exercise testing. Twenty-nine percent of our participants reported using blood pressure medications including ACE inhibitors, angiotensin 2 receptor blocker, beta blockers, calcium channel blockers, diuretics, and thiazides.

Vascular measures

A nurse clinician recorded the participants' vital signs, including cardiovascular dynamics (blood pressure, heart rate, estimated cardiac output, arterial elasticity, vascular resistance, body temperature, and estimated stroke volume) which were measured after approximately 20 min supine using the PulseWave CR-2000 (Hypertension Diagnostics, Eagan, MN). A standard sphygmomanometer cuff was placed over the dominant upper arm and an automated tonometer was placed over the radial artery. Blood pressure was assessed using the average of two measurements. Pulse pressure was calculated as systolic blood pressure minus diastolic blood pressure. Measures of vascular compliance were determined (non-invasively) by recording the radial artery pulse contour by tonometry. The measure was obtained by a technician experienced with the technique using the equipment to assess both large (C1) and small (C2) artery elasticity.

The vascular compliance test uses two compliance elements, C1 and C2, and inertance and resistance elements to estimate the elasticity of the radial artery. With the use of a computer algorithm the morphology of the arterial pulse contour can be separated into an exponential diastolic decay generated by the release of blood from the large arteries and a sinusoidal wave arising from peripheral wave reflections. The diastolic decay is a function of large artery compliance (C1), while reflections or oscillations represent the compliance characteristics of the resistance vessels and branch points (C2). A comparison of direct brachial artery cannulation with combined radial artery tonometry and oscillometric measurement of brachial artery blood pressure shows a close correlation of systolic, diastolic, and mean arterial blood pressure, cardiac output, with C2 in subjects with well-maintained cardiac output. Arterial elasticity is the measurement of the ability of the artery to stretch in response to each pulse, arterial compliance is the change in volume divided by the change in pressure, and the systemic vascular resistance is calculated from mean arterial blood pressure and estimated cardiac output [27].

Neuroimaging

Structural MRI data were obtained using a Siemens 3.0 Tesla Allegra MRI Scanner. Fluid attenuated inversion recovery (FLAIR) images were used for white matter lesion assessments (Ti = 2500, TR = 10,000, TE = 81.0, flip angle = 180°, slice thickness = 4 mm with 0 gap). WMLs (PVWMLs (contiguous with the ventricle) and DWMLs) were manually traced on FLAIR images as a measure of vascular related brain injury using Medical Image Processing, Analysis, and Visualization (MIPAV, Johns Hopkins University) expressed as volume in mm^3. A single rater (LH) was trained to a threshold of <10% error and reliability of white matter assessments were assessed with 10 blinded repeat assessments inserted randomly into the rater's workflow. The training set used to learn this method was randomly sampled drawn from a larger pool of 191 images, given a random identifier at each rating during training, and provided in batches of 20 (including 10 previously rated images) until repeat absolute error was below 10%. Intra-rater reliability was excellent, absolute-agreement ICC(3,2) = 0.88 (F = 9.9, df = 51, $p < 0.001$).

Statistical analysis

As several of the vascular variables were non-normally distributed, we followed standard practice for correction of skewed distributions that violate assumptions of normality by using logarithmic transformation for small and large artery elasticity, and systemic vascular resistance. To convert all variables into a comparable metric we used percent of maximum scoring (observed score − minimum score/maximum score − minimum score)× 100). This approach is less problematic than using Z-scores [28]. For those variables requiring log transformation, percent of maximum scoring was conducted on the log transformed scores.

We conducted confirmatory factor analysis (CFA) using Mplus version 5 [29] to evaluate the inter-correlations among independent vascular measures including stroke volume, large and small artery elasticity, and vascular resistance. This approach offers improved measurement accuracy by aggregating common variance across multiple subtests and attenuating error idiosyncratic to the individual measures. In accordance with guidelines for proper execution of CFA techniques, we applied theoretical reasoning and well-established

clinical observation to the practice of selecting variables to include, testing models, and interpreting the results [30].

Goodness-of-fit was evaluated based on root mean square error of approximation (RMSEA), which is a measure of discrepancy between predicted and observed model values; values closer to 0 indicate better fit (preferred values <0.09). We also report the comparative fit index which estimates the relative fit of a model compared to an alternative model (CFI >0.90 indicates good fit). We used full information maximum likelihood algorithm to account for missing data.

We hypothesized that a single common factor would best describe the relationship among the vascular measures. Factor analysis was used to evaluate what individual tests had in common, rather than what they did not share. The factor weights estimated from the factor analysis were converted to factor scores that were used in subsequent analyses. Rather than assuming that each vascular measure contributes equally, factor analysis was used to estimate the relative importance and measurement error associated with each individual measure. These estimates (factor weights) were used to create a weighted factor score combining individual measures together into a single score. Thus, the vascular factor score contains the scores for each individual measure weighted by its relative contribution to the whole and adjusted for the measurement error associated with each measure.

To estimate the effect of the combined vascular factor, after accounting for the effects of systolic and diastolic blood pressure, on WMLs we used stepwise multiple regression models in which the vascular factor predicted neuroimaging measures accounting for age, gender, education, body mass index (BMI), use of anti-hypertensive medication, and apolipoprotein (APOE) $\varepsilon 4$ carrier status. We include education as a covariate because there is evidence that education is important in estimating the impact of WMLs on cognitive function [31]. These analyses were conducted both including and excluding individuals with no evidence of WMLs to ensure that the results were not driven by those cases. The effect of the vascular factor on presence or absence of WMLs may be separate from the extent of WML damage in those with evidence of WMLs.

RESULTS

Table 1 summarizes the participant characteristics. For calculation of the vascular factor scores, the hypothesized one factor model fit the data ($X^2(df) = 2.8(2)$; CFI = 0.97; RMSEA = 0.06). All the measures loaded significantly on the factor (Table 2). Vascular factor scores used in subsequent regression analysis were based on the weights (standardized loadings) and error terms specified in this analysis (see Table 2 for the loadings and error terms combined to create the factor scores). Higher vascular scores were positively correlated with older age ($R = 0.43$, $p < 0.001$).

Deep white matter lesions

Stepwise regression indicated that higher scores on the combined vascular factor ($\beta = 0.42$, $p = 0.001$) and years of education ($\beta = 0.26$, $p = 0.03$) significantly predicted greater deep WML volume adjusting for age, gender, systolic and diastolic blood pressure, BMI,

antihypertensive medication use, and APOE ε4 carrier status (adjusted $R^2 = 0.18$). In analyses including only patients with evidence of DWMLs ($n = 44$), the combined vascular factor ($\beta = 0.48$, $p = 0.001$) and years of education ($\beta = 0.28$, $p = 0.049$) significantly predicted greater deep WML volume adjusting for age, gender, systolic and diastolic blood pressure, BMI, antihypertensive medication use, and APOE ε4 carrier status (adjusted $R^2 = 0.23$).

Periventricular white matter lesions

Age ($\beta = 0.43$, $p < 0.001$), gender ($\beta = -0.31$, $p = 0.007$), and education ($\beta = 0.23$, $p = 0.04$) significantly predicted periventricular WMLs adjusting for the same covariates (adjusted $R^2 = 0.26$). The vascular factor did not predict PVWMLs when all participants were included. However, in analyses including only patients with evidence of PVWMLs ($n = 58$), higher scores on the combined vascular factor ($\beta = 0.50$, $p < 0.001$) and years of education (= 0.29, $p < 0.014$) predicted greater lesion volume adjusting for age, gender, systolic and diastolic blood pressure, BMI, antihypertensive medication use, and APOE ε4 carrier status (adjusted $R^2 = 0.27$).

DISCUSSION

Our data suggest that combining related vascular measures into a single factor score allows us to better examine the relationships between arterial stiffness, reduced elasticity, and WMLs, instead of relying on blood pressure measures that fluctuate depending on external conditions and create measurement error. Our vascular factor was a stronger predictor than blood pressure in regression analyses. In fact, systolic and diastolic blood pressure did not contribute significant variance to explaining WMLs when the vascular factor was included the model. Using CFA improves measurement accuracy by combining common variance across vascular measures and minimizing error that is unique to the individual measures. Using a more robust measure of vascular health may be more informative than using a measure such as blood pressure when investigating brain health during aging. While some studies have reported associations between blood pressure and WMLs [33], several others report no association or associations that are inconsistent. For example, the relationship depended on age of individuals measured or time of day when measured [33–35]. These inconsistencies may be due to the variability in blood pressure measures, or the likelihood of individuals on medications for hypertension having lowered blood pressure values, which might otherwise have been associated with WML. In our study, use of anti-hypertensive medications did not predict WMLs after accounting for the other predictors and covariates in the models.

Since white matter is particularly susceptible to age-associated changes [2–4], using a stable measure of vascular health with reduced measurement error allows us greater confidence in understanding the role of vascular disease on the brain. In our study we used vascular measures such as arterial stiffness, arterial elasticity, and estimated stroke volume that are better reflections of overall vascular health than simple blood pressure, which is more subject to fluctuations due to correct size of blood pressure cuff, time of day, body and arm position, and medication use. White coat hypertension, persistently elevated blood pressure

in the presence of health care providers in individuals not taking medication, also makes accurate detection of hypertension difficult [36], and studies suggest that management of white coat hypertension should include cardiovascular risk factors, not blood pressure alone [37].

Both deep and periventricular WMLs were associated with the vascular factor in nondemented elderly. Lower elasticity and higher vascular resistance were associated with greater white matter lesion volumes. The two classes of WMLs have been associated with different etiologies and outcomes. For example, some evidence suggests that PVWMLs may predict the rate of cognitive decline [38] and poorer executive function in nondemented patients [39], and are associated with hypometabolism in frontal regions [39]. PVWMLs are preferentially associated with atherosclerosis, changes in hemodynamics, and hypoperfusion [5]. DWMLs, by contrast, have more often been related to depression and related illnesses [1, 11, 12] and are more likely attributed to hypertension and homocysteine levels, both risk factors for small vessel disease [5]. Individuals with cardiovascular disease typically have a compromised peripheral vascular system including hypertension and poor arterial compliance [27]. Using a computerized device that generates information about cardiovascular health such as the one used in this study and using the combined vascular factor could be beneficial for determining the incidence of and risk for small vessel disease. The unique information provided by the vascular factor score may provide clinicians with useful information for those at risk for small vessel disease. Previous studies suggest that small vessel disease burden is an independent predictor of measures of memory, language, and executive function [40]. Using indicators of arterial stiffness instead of blood pressure could be used to more accurately evaluate these individuals and deliver a lifestyle or pharmaceutical intervention before cerebrovascular damage such as WML occurs.

Limitations of the study include limited generalizability due to our highly educated, mostly Caucasian, Midwestern American sample. Many clinical studies of older adults suffer from a difficulty in recruiting diverse samples and our center is engaged in ongoing efforts to expand the sample to be more diverse and representative. Our findings are consistent with a previous study of small artery elasticity in a multi-ethnic cohort demonstrating that small artery elasticity is a risk factor for cerebrovascular events beyond the effects of blood pressure [18]. A further limitation of the study was that we were unable to estimate reliability for the pulse wave, tonometry, and white matter lesion measures, as each was performed by a single trained rater.

Aging and chronic hypertension facilitate arterial stiffening across the lifespan and ultimately affect cerebrovascular health including WMLs [41]. Our research suggests that a vascular factor including measures of arterial stiffening and reduced elasticity may be more sensitive for predicting WMLs than traditional measures of blood pressure after accounting for the multicollinearity associated with the variety of interrelated vascular measures.

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Table 1

Participant characteristics (n = 63)

	***n* (%)**
Gender (Female)	36 (57%)
Race (Caucasian)	63 (100%)
APOE ε4 Carrier	18 (29%)
Use of Antihypertensive Medications	18 (29%)
	M (SD)
Age (years)	73.3 (6.8)
Education (years)	16.4 (2.6)
Systolic Blood Pressure (mm/Hg)	130.0 (15.7)
Diastolic Blood Pressure (mm/Hg)	72.2 (9.9)
Body Mass Index (kg/m^2)	26.30 (3.7)
Stroke Volume (mL/beat)	68.2 (13.4)
Large Artery Elasticity (mL/mmHg ×10)	13.7 (5.4)
Small Artery Elasticity (mL/mmHg ×100)	4.3 (2.5)
Systemic Vascular Resistance (dynes cm^5)	1641.6 (332.6)
Deep WML Volume (cm^3)	308.37 (649.25)
Periventricular WML Volume (cm^3)	881.67 (1262.60)
Total white matter lesion volume (cm^3)	1190.04 (1850.98)

Table 2

Factor loadings for vascular measures

	Std Loading (λ)	Std Residual (Error) Variances
Stroke Volume	0.75*	0.44*
Large Artery Elasticity	0.71*	0.49*
Small Artery Elasticity	0.79*	0.38*
Vascular Resistance	0.94*	0.13

* $p < 0.001$. Note: Standardized loadings (λ) reflect the strength of the relationship of each item with the shared vascular factor. Similar to a correlation coefficient (range 0.00 to 1.00), a higher number indicates a stronger association.