AORTIC PULSE WAVE VELOCITY PREDICTS FOCAL WHITE MATTER HYPERINTENSITIES IN A BIRACIAL COHORT OF OLDER ADULTS

Caterina Rosano, MD, MPH[a], **Nora Watson, PhD**[a,*], **YueFang Chang, PhD**[b,*], **Anne B. Newman, MD, MPH**[a], **Howard J. Aizenstein, MD, PhD**[c], **Yan Du, PhD**, **Vijay Venkatraman, PhD**, **Tamara B. Harris, MD, MS**[f], **Emma Barinas-Mitchell, PhD**[a], and **Kim Sutton-Tyrrell, PhD**[a]

[a]University of Pittsburgh, Department of Epidemiology; Pittsburgh, PA

[b]University of Pittsburgh, Department of Neurological Surgery; Pittsburgh, PA

[c]University of Pittsburgh, Department of Psychiatry; Pittsburgh, PA

[f]National Institute on Aging, Laboratory of Epidemiology, Demography, and Biometry; Bethesda, MD

Abstract

While the cross-sectional relationship of arterial stiffness with cerebral small vessel disease is consistently shown in middle-aged and young-old adults, its less clear if these associations remain significant over time in very old adults. We hypothesize that arterial stiffness is longitudinally associated with white matter characteristics and associations are stronger within watershed areas.

Neuroimaging was obtained in 2006–08 from 303 elderly (mean age 82.9 years, 59% women, 41% black) with pulse wave velocity measures in 1997–98. Multivariable regression models estimated the coefficients for pulse wave velocity (cm/sec) in relationship to presence, severity and spatial distribution of white matter hyperintensities, gray matter volume and fractional anisotropy from diffusion tensor, adjusting for demographic, cardiovascular risk factors and diseases from 1997–98 to 2006–08.

Higher pulse wave velocity in 1997–98 was associated with greater white matter hyperintensities volume in 2006–08 within the left superior longitudinal fasciculus (age and total brain white matter hyperintensities-adjusted p=0.023), but not with white matter hyperintensities in other tracts, or with fractional anisotropy or gray matter volume from total brain (p>0.2). Associations were stronger in blacks than in whites remaining significant in fully adjusted models.

Elderly with white matter hyperintensities in tracts related to processing speed and memory are more likely to have had higher pulse wave velocity values ten years prior, before neuroimaging data being available. Future studies should address whether arterial stiffness can serve as an early biomarker of covert brain structural abnormalities and whether early arterial stiffness control can promote successful brain aging, especially in black elderly.

Corresponding Author: Caterina Rosano, MD, MPH, 130 N. Bellefield Ave, Room 507, Pittsburgh, PA 15213, Phone: 412-383-1294, Fax: 412-383-1308, rosanoc@edc.pitt.edu.
*Contributed equally to preparation of manuscript.

Keywords

pulse wave velocity; small vessel disease; longitudinal; fractional anisotropy; community-dwelling elderly

INTRODUCTION

Stiffness of the central arteries is an important determinant of microvascular injury in aging and hypertension[1,2]. Potential cognitive and renal consequences of arterial stiffness[3,4] may reflect gradual loss of the cushioning capacity of the aorta and subsequent transmission of damaging flow pulsations to the fragile microvasculature of the target organs[2,5]. Moreover, lower cerebral blood flow secondary to stiffening can also contribute to parenchymal damage and white matter hyperintensities[6].

The brain is one of the organs preferentially susceptible to small vessel injury secondary to arterial stiffness because its low-impedance vascular system is exposed to highly pulsatile flow throughout the cardiac cycle[2]. Initial studies suggest that central arterial stiffness may potentially exacerbate age-associated changes in brain connectivity. However, with the exception of one prospective study of incident stroke,[7] most of the evidence to date is correlational. Prior studies have applied lower resolution neuroimaging methods to examine the cross-sectional association with arterial stiffness in exceptionally well-functioning and racially homogeneous cohorts of young elderly[8–17], or of middle-aged patients with overt vascular disease[18–24]. Overall, strongest evidence exists for a cross-sectional association between pulse wave velocity (PWV), a measure of aortic stiffness, and semiquantitive visual ratings of white matter hyperintensities (WMH), a crude marker of small vessel disease (SVD). Studies examining other measures of arterial stiffness, including pulse pressure, also found cross-sectional associations with visual ratings of WMH[25, 26], small brain infarcts[27] and with lower fractional anisotropy (FA), a marker of micro-structural white matter abnormalities[28].

It is not clear whether arterial stiffness would be more strongly related with abnormalities affecting specific networks, or whether these associations would remain significant over long period of times in community-dwelling older adults. Understanding the longitudinal relationship of arterial stiffness with neuroimaging markers of brain networks can help identify precise biomarkers of brain abnormalities early in the neurodegenerative process. Early identification of subclinical brain abnormalities, and specifically of WMH, can have public health implications because these markers are important prognostic factors for functional decline, disability, and dementia[29–33] and may be amenable to intervention[34].

The aim of this study is to quantify the contribution of exposure to PWV with presence of covert brain abnormalities in very old adults several years later. We hypothesize that these associations are independent of hypertension and other risk factors and intervening vascular events. We further hypothesize that associations are most evident in frontal-subcortical tracts and specifically in superior longitudinal tracts related to processing speed and memory, because of prior evidence that PWV is longitudinally associated with cognitive impairment in these cognitive domains[2,35]. These tracts may be selectively vulnerable to central arterial stiffening because of their geographic localization within "watershed" areas perfused by arterioles with few interconnections and their selective vulnerability to vascular insults. Lastly, we test the hypothesis that these associations are stronger in black compared to white participants.

METHODS

Study Population

Participants were recruited from the Health, Aging and Body Composition Study, an ongoing study which began in 1997–98[36]. See details at http://hyper.ahajournals.org.

Of the 1,455 participants with arterial PWV measures at study entry in 1997–98 at the Pittsburgh site, 739 returned for an in-person assessment in 2006–08. Of these, 622 completed eligibility interviews to participate in the Healthy Brain Project, a neurological study of mobility control. A total of 322 participants with PWV measurements were included in the Healthy Brain Project. Of these, 303 (mean age 82.9 years, 59% women, 41% blacks) had white matter hyperintensities measured at 3 Tesla and were included in this analyses. Of these 303 elderly, 273 (82.9 years, 56% women, 42% blacks) also had diffusion tensor imaging (DTI) data at 3 Tesla and were included in the analysis of DTI data. The analyses of WMH data were also repeated in the n=273 subsample. The University of Pittsburgh institutional Review Board approved this study. All participants gave informed consent.

Pulse Wave Velocity

Pulse Wave Velocity was measured in cm/sec noninvasively and with high reliability[37] via simultaneous Doppler-recorded carotid and femoral pulse waveforms (model 810A, 9.0- to 10-MHz probes, Parks Medical Electronics, Inc). Details previously published; please see http://hyper.ahajournals.org.

Magnetic Resonance Image Acquisition

Participants were scanned with a Siemens 12-channel head coil on a 3T Siemens Tim Trio MR scanner at the Magnetic Resonance Research Center of the University of Pittsburgh, using a previously published protocol[38–40]. Details on measurements of WMH, gray matter and intracranial volume and diffusion tensor have been previously published and are reported at http://hyper.ahajournals.org.

Tracts included in the analysis (Figure S1) included those known to be associated with executive control and processing speed (superior longitudinal fasciculus)[41], as well as tracts known to be associated with memory (longitudinal fasciculus temporal portion, uncinate fasciculus)[42], and mobility (anterior thalamic radiation, corticospinal tract)[43], in addition to interhemispheric connections (corpus callosum, frontal and occipital portions). The cingulum bundle was examined as a whole and separately for the lower (posterior) and upper (antero-dorsal) portions for the left and right hemisphere.

The diffusion-weighted images were pre-processed using the FMRIB's Diffusion Toolbox to remove unwanted distortions due to eddy current; the tensor were computed, and diagonalized to determine the eigen values from which the FA and MD maps were computed as previously described[40].

Other measures of interest

In addition to demographic variables (age, race, sex and education (years of school, 12 years versus >12 years)), body mass index, systolic and diastolic blood pressure and pulse pressure, stroke, hypertension, cardiovascular disease and diabetes mellitus were obtained from the in-person visit in 1996–97 until time of MRI in 2006–08 at regular intervals (yearly with the exception of years 4 and 7). Current smoking, drinking habit (number of drinks/week in prior 12 months), and physical activity (kcal, Kg/week) were obtained at study entry and time of MRI as previously described[40] and were also considered as potential life-style covariates. Systolic blood pressure was measured twice per visit and results were averaged.

Participants' reports of diagnosis and use of specific medications or procedures were used to identify vascular events. Anti-hypertensive medication use (having taken these medications at least 50% of the time between study entry and time of MRI) was considered a covariate of interest because of potential effects on PWV and brain health. Finally, to evaluate whether cognitive performance concurrent with PWV might explain the association between PWV and brain integrity after ten years of follow-up, scores on the modified minimental state examination and the Digit Symbol Substitution Test were obtained at study entry and at time of MRI. We chose the Digit Symbol Substitution Test (DSST) because it is a test of attention and psychomotor speed that is sensitive to cerebral small vessel disease[44], and because we previously found it was associated with PWV[35].

Statistical Analysis

PWV was highly skewed and was used as log transformed in all main analyses. However, results are reported using quartiled PWV (with cut-offs from this study population and also form the parent population) or standardized untransformed PWV to ease interpretability of results. WMH volumes were also highly skewed and were dichotomized using the median as a cut off. The ratio of total gray matter volume by intracranial volume was computed and interpreted as a marker of brain atrophy.

Associations between neuroimaging marker and PWV that were significant above the Sidak correction factor for multiple comparisons (p=0.0028 for n=18 comparisons) were retained in further analyses. Logistic models with WMH median in each tract as dependent variable and PWV (as continuous or quartiles), age, and WMH from total brain as main independent variables were used. Age- and total WMH-adjusted partial correlation coefficients were used to evaluate the associations of PWV with fractional anisotropy, gray matter volume and brain atrophy. Adjustment for WMH from total brain was applied to examine whether associations of WMH or FA from a given tract were specific for that tract or were explained by overall WMH burden. MRI measures that were associated with PWV at p<0.05 after adjustment for age and for total WMH entered multivariable regression models further adjusted for selected covariates. Covariates were selected if they were associated with the outcome in univariate analyses. Models were also adjusted for hypertension, incident stroke, incident vascular events, and slope of systolic blood pressure, diastolic blood pressure, pulse pressure and of body mass index, computed using the values of the risk factors measured at the in person visits between study entry and time of MRI. Additionally, a stepwise model predicting the brain MRI measure of interest (p-entry = 0.1; p-out = 0.5) was run to identify the most parsimonious model. Analyses were repeated for men and women and for blacks and whites separately. All analyses were performed with SAS 9.1 and SPSS 19.0.

RESULTS

The analysis cohort (n=303) ranged in age from 79–89 years at time of the MRI (mean age 82.9 years, 59% women, 41% blacks), walked at a gait speed close to 1.0 m/sec, and had cognitive scores in the higher range for adults of similar age, both for the DSST[45] and 3MSE score[45] (Table S1). The average number of antihypertensive medication used was 2.34 (1.92).

Compared to the parent cohort (Table S2), these participants had lower PWV, similar BMI, blood pressure, and lifestyle habits (not shown) and they were also less likely to have cardiovascular diseases, stroke, hypertension or diabetes. Higher PWV at study entry was significantly associated with higher DSST score measured at time of brain MRI (p=0.04). Cross-sectional associations of PWV with demographics, cognitive test scores and health-related measures were overall similar to those previously published in the larger Health ABC cohort[46]. Of note, higher PWV was not associated with older age in this cohort. WMH

volume was similar in the right and left hemisphere for each of the tracts (Table S3) except for the anterior thalamic radiation and uncinate fasciculus (right> left) and the inferior longitudinal fasciculus (left> right).

Higher PWV was correlated above the Sidak threshold with greater WMH volume from total brain and less strongly with lower FA from total brain (age-adjusted p<0.0001 and p=0.047). After adjustment for WMH volume from total brain, the association of PWV with fractional anisotropy from total brain was no longer significant (p=0.2). Age-adjusted correlations with total brain atrophy and with total gray matter volume were p= 0.5 and p=0.7, respectively.

Differences in PWV between those with WMH> median as compared to those without were in the expected direction for all tracts bilaterally. However, age-adjusted between-group differences in PWV were significant above the Sidak threshold only for the left superior longitudinal fasciculus (total fasciculus: p=0.001; temporal portion: p=0.0003) and not for the other tracts (p>0.2). Associations of PWV with WMH>median in the left longitudinal fasciculus were similar after adjustment for age and in men and women (not shown), although they were larger in blacks as compared to whites (Table 1). Of note, associations were no longer statistically significantly different after stratifying the sample by race.

To better appreciate the size of the association of PWV with presence of WMH >median, unadjusted logistic models were obtained after stratifying by PWV quartiles (Table 2). The probability of having WMH>median followed the expected trend across increasing PWV quartiles, with a steep increase in odds ratios for the 4th quartile. Compared to those with PWV<575.30 cm/sec, the probability of having WMH>median was almost 3 times as high for those with PWV> 966.00 cm/sec. Results were similar when using quartiles from the parent population and in the subsample of n=273.

In multivariable-adjusted logistic regression models, each standard deviation of PWV was associated with a 40% greater probability of having WMH>median in the left superior longitudinal fasciculus independent of demographics (age, race, gender, education) (Table 3, model 1). This effect was minimally attenuated after adjustment for demographics and for systolic blood pressure, BMI, smoking and prevalence of diabetes and cardiovascular disease measured at study entry (Table 3, Model 2). Results were similar after adjustment for these variables measured at time of MRI (Table 3, Model 3) and also after adjustment for changes in vascular markers between study entry and time of MRI, including: incident stroke, incident myocardial infarction, incident cardiovascular events, and slope of change in systolic blood pressure, diastolic blood pressure, pulse pressure and body mass index (not shown). Models adjusted for hypertension, anti-hypertensive medication use, smoking, physical activity or drinking yield similar results (not shown). In stepwise models with all covariates (Table 3, Model 4), PWV was the only variable, among those measured at study entry, to be associated with presence of focal WMH> median. Systolic blood pressure and stroke prevalence (OR, 95% CI: 1.495 [1.088, 2.054] and 5.207 [1.626, 16.674], respectively) at time of MRI were the only other variables retained in the model. Of note, the cross-sectional association of one standard deviation of SBP with presence of WMH was similar to that estimated between PWV measured ten years prior.

DISCUSSION

In this cohort of community-dwelling older adults, greater arterial stiffness was associated with greater volume of white matter hyperintensities localized within the left superior longitudinal fasciculus as measured ten years later. Our results suggest selective spatial

vulnerability of the white matter to long term cerebrovascular consequences of central arterial stiffness in aging.

Our study extends prior cross-sectional findings in racially homogeneous cohorts of adults ranging in age from late 50s to mid-70s in two ways[13–17]. First, we examined longitudinal associations in a racially diverse cohort of older adults living in the community and secondly, we examined the spatial distribution of objective measures of white matter abnormalities, including hyperintensities and fractional anisotropy. Most neuroimaging studies have relied on semiquantitative ratings of hyperintensities combined across two large brain areas: periventricular and deep. Among the reports of a spatial distribution of brain abnormalities in relationship with arterial stiffness[12, 13], results have been discordant. While Shresta et al[12] found a cross-sectional association between higher pulse wave velocity and hyperintensities in periventricular and deep white matter, Ohmine et al[13] found a cross-sectional association only in the periventricular areas. Another cross-sectional investigation applied FA to study the spatial distribution of white matter abnormalities in relationship to pulse pressure, in a small sample of 52 healthy normotensive adults[28]. Similar to our longitudinal findings, this work[28] found a cross-sectional association of pulse pressure with FA in the total brain. However, associations with individual tracts were not significant. Of note, in our study, the association of PWV with FA was no longer significant after adjustment for total WMH. Although it has been shown[28] that WMH can impact the spatial distribution of FA, ours is the first report to indicate that the total burden of WMH can affect the association of pulse pressure with fractional anisotropy. More longitudinal work is needed to examine the interaction of arterial stiffness on macro- as compared to micro-structural characteristics of brain connectivity.

Although we found larger PWV differences in blacks as compared to whites, this analysis did not have adequate power to further investigate these relationships stratified by race.

Our results also extend our knowledge of the relationship between arterial stiffness and brain abnormalities observed in the context of overt vascular disease[18–24]. We found that the longitudinal association of PWV with white matter hyperintensities remained statistically significant after adjustment for blood pressure (including pulse and diastolic blood pressure), diabetes, incident vascular events, and other markers of vascular conditions. Thus, our data implicate underlying central arterial stiffness as a potential novel predictor of focal small vessel disease, beyond these other well-established risk factors for white matter abnormalities in older adults[47].

The association of PWV with WMH was stronger for the left than the right hemisphere. We did not find significant differences in the volume of WMH in the left as compared to the right superior longitudinal fasciculus (p=0.3). Future studies relating small vessel disease burden with vascular architectural differences between hemispheres are needed to explain these observed differences in relationship with risk factors.

The results of our study support previous findings that higher PWV in community-dwelling older adults is associated with selected cognitive domains, namely processing speed[46] and memory[14]. The superior longitudinal tract, containing two bundles critical for processing speed (parietal portion) and memory (temporal portion), might be particularly vulnerable to arterial stiffening and to microvascular alterations in aging and hypertension because it travels across fronto-parietal "watershed" regions. These regions are perfused by arterioles with few interconnections available to preserve the blood supply in the presence of ischemic injury[32]. It is biologically plausible that the structural characteristics of the prefronto-parietal connecting tracts in adults with higher PWV could explain the association of higher PWV with accelerated decline in processing speed. A recent cross-sectional study found

neuroimaging data attenuate the association of PWV with cognitive tests[14]. Future studies with follow-up measures of cognitive function are needed to explore this potential mechanism. We could not test this hypothesis because, at the present time, cognitive measurements for the time following the brain MRI acquisition are unavailable.

The association of PWV with WMH and not with gray matter volume supports the notion that the white matter is a brain tissue particularly sensitive to vascular-related insults[48]. Gradual decline in cerebral volume observed throughout adulthood[49] is consistent with relative sparing of gray matter from vascular insult in aging[28]. Another study in patients with type 1 diabetes also did not find association with gray matter volume[21].

Several limitations should be considered. PWV data were not available at follow-up or concurrent with neuroimaging measurement to demonstrate a temporal association of aortic stiffness with incident brain structural abnormalities. However, associations of baseline PWV with subsequent neuroimaging indices were not explained by slope of change in vascular risk factors or interim events, suggesting a potential prognostic value of PWV in assessment of cerebrovascular risk after extended follow-up. Furthermore, neuroimaging measures were not available at time of the PWV measurement, thus we cannot infer the predictive value of PWV independently of baseline values of WMH. However, adjustment for DSST measured at study entry, a correlate of volume of WMH, did not modify these relationships. Our results indicate that very old adults with WMH are more likely to have had higher PWV values ten years prior, at a point in time when MRI data were not available. Although this study cannot address temporality or mechanistic relationships linking PWV and WMH due to the lack of concurrent PWV and MRI data, these risk estimates warrant future studies to examine such mechanisms.

Strengths of this study include the large, community-dwelling population of very old adults, detailed brain MRI assessment, and evaluation of central arterial stiffness by PWV, which is a valid and noninvasive measure of central arterial stiffness[7, 50]. Although these adults appeared to have overall stable values of subclinical vascular risk factors and function, the prevalence of overt vascular events is comparable to that of elderly of similar age, thus indicating that this is not an exceptionally healthy or selected sample.

Perspectives

While more work is needed to evaluate the hypothesized association of greater aortic stiffness with accelerated worsening in brain connectivity, the current implication of modifiable, vascular contributors to brain abnormalities in aging highlights an important potential to delay associated cognitive and functional declines in late life. Longitudinal studies relating central arterial stiffness with subsequent measures of white matter integrity in older adults living in the community could inform future preventative strategies targeting central stiffness and help maintain function in late life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: Cause and logic of therapy. Hypertension. 2005; 46:200–204. [PubMed: 15911742]

2. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: Implications for end-organ damage. J Appl Physiol. 2008; 105:1652–1660. [PubMed: 18772322]

3. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB. Pulse pressure and pulse wave velocity are related to cognitive decline in the baltimore longitudinal study of aging. Hypertension. 2008; 51:99–104. [PubMed: 18025297]

4. Madero M, Wassel CL, Peralta CA, Najjar SS, Sutton-Tyrrell K, Fried L, Canada R, Newman A, Shlipak MG, Sarnak MJ. Cystatin c associates with arterial stiffness in older adults. J Am Soc Nephrol. 2009; 20(5):1086–93. [PubMed: 19357259]

5. Safar ME, Lacolley P. Disturbance of macro- and microcirculation: Relations with pulse pressure and cardiac organ damage. Am J Physiol Heart Circ Physiol. 2007; 293:H1–7. [PubMed: 17369469]

6. Tarumi T, Shah F, Tanaka H, Haley AP. Association between central elastic artery stiffness and cerebral perfusion in deep subcortical gray and white matter. Am J Hypertens. 2011; 24:1108–1113. [PubMed: 21654859]

7. Laurent S, Katsahian S, Fassot C, Tropeano AI, Gautier I, Laloux B, Boutouyrie P. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke. 2003; 34:1203–1206. [PubMed: 12677025]

8. Matsumoto M, Inoue K, Moriki A. Associations of brachial-ankle pulse wave velocity and carotid atherosclerotic lesions with silent cerebral lesions. Hypertens Res. 2007; 30:767–773. [PubMed: 18037768]

9. Ochi N, Kohara K, Tabara Y, Nagai T, Kido T, Uetani E, Ochi M, Igase M, Miki T. Association of central systolic blood pressure with intracerebral small vessel disease in japanese. Am J Hypertens. 2010; 23:889–894. [PubMed: 20339355]

10. Ochi N, Tabara Y, Igase M, Nagai T, Kido T, Miki T, Kohara K. Silent cerebral microbleeds associated with arterial stiffness in an apparently healthy subject. Hypertens Res. 2009; 32:255–260. [PubMed: 19262493]

11. Saji N, Shimizu H, Kawarai T, Tadano M, Kita Y, Yokono K. Increased brachial-ankle pulse wave velocity is independently associated with white matter hyperintensities. Neuroepidemiology. 2011; 36:252–257. [PubMed: 21677450]

12. Shrestha I, Takahashi T, Nomura E, Ohtsuki T, Ohshita T, Ueno H, Kohriyama T, Matsumoto M. Association between central systolic blood pressure, white matter lesions in cerebral mri and carotid atherosclerosis. Hypertens Res. 2009; 32:869–874. [PubMed: 19644503]

13. Ohmine T, Miwa Y, Yao H, Yuzuriha T, Takashima Y, Uchino A, Takahashi-Yanaga F, Morimoto S, Maehara Y, Sasaguri T. Association between arterial stiffness and cerebral white matter lesions in community-dwelling elderly subjects. Hypertens Res. 2008; 31:75–81. [PubMed: 18360021]

14. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and function: The age, gene/environment susceptibility--reykjavik study. Brain. 2011; 134:3398–3407. [PubMed: 22075523]

15. Coutinho T, Turner ST, Kullo IJ. Aortic pulse wave velocity is associated with measures of subclinical target organ damage. JACC Cardiovasc Imaging. 2011; 4:754–761. [PubMed: 21757166]

16. Hatanaka R, Obara T, Watabe D, Ishikawa T, Kondo T, Ishikura K, Aikawa T, Aono Y, Hara A, Metoki H, Asayama K, Kikuya M, Mano N, Ohkubo T, Izumi S, Imai Y. Association of arterial stiffness with silent cerebrovascular lesions: The Ohasama study. Cerebrovasc Dis. 2011; 31:329–337. [PubMed: 21212664]

17. Kuo HK, Chen CY, Liu HM, Yen CJ, Chang KJ, Chang CC, Yu YH, Lin LY, Hwang JJ. Metabolic risks, white matter hyperintensities, and arterial stiffness in high-functioning healthy adults. Int J Cardiol. 2010; 143:184–191. [PubMed: 19261342]

18. Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, Lodder J, de Leeuw PW. Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. Hypertension. 2008; 52:1120–1126. [PubMed: 18852384]

19. Kearney-Schwartz A, Rossignol P, Bracard S, Felblinger J, Fay R, Boivin JM, Lecompte T, Lacolley P, Benetos A, Zannad F. Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. Stroke. 2009; 40:1229–1236. [PubMed: 19246701]

20. Kim DH, Choi JH, Moon JS, Kim HJ, Cha JK. Association between the severity of cerebral small vessel disease, pulsatility of cerebral arteries, and brachial ankle pulse wave velocity in patients with lacunar infarction. Eur Neurol. 2010; 64:247–252. [PubMed: 20838053]

21. van Elderen SG, Brandts A, van der Grond J, Westenberg JJ, Kroft LJ, van Buchem MA, Smit JW, de Roos A. Cerebral perfusion and aortic stiffness are independent predictors of white matter brain atrophy in type 1 diabetic patients assessed with magnetic resonance imaging. Diabetes Care. 2011; 34:459–463. [PubMed: 21216862]

22. van Elderen SG, Brandts A, Westenberg JJ, van der Grond J, Tamsma JT, van Buchem MA, Romijn JA, Kroft LJ, Smit JW, de Roos A. Aortic stiffness is associated with cardiac function and cerebral small vessel disease in patients with type 1 diabetes mellitus: Assessment by magnetic resonance imaging. Eur Radiol. 2010; 20:1132–1138. [PubMed: 19915847]

23. Washida N, Wakino S, Hayashi K, Kuwahara T, Itoh H. Brachial-ankle pulse wave velocity predicts silent cerebrovascular diseases in patients with end-stage renal diseases. J Atheroscler Thromb. 17:165–172. [PubMed: 20124736]

24. Brandts A, van Elderen SG, Westenberg JJ, van der Grond J, van Buchem MA, Huisman MV, Kroft LJ, Tamsma JT, de Roos A. Association of aortic arch pulse wave velocity with left ventricular mass and lacunar brain infarcts in hypertensive patients: Assessment with mr imaging. Radiology. 2009; 253:681–688. [PubMed: 19864506]

25. Kim CK, Lee SH, Kim BJ, Ryu WS, Yoon BW. Age-independent association of pulse pressure with cerebral white matter lesions in asymptomatic elderly individuals. J Hypertens. 2011; 29:325–329. [PubMed: 21063204]

26. Duprez DA, De Buyzere ML, Van den Noortgate N, Simoens J, Achten E, Clement DL, Afschrift M, Cohn JN. Relationship between periventricular or deep white matter lesions and arterial elasticity indices in very old people. Age Ageing. 2001; 30:325–330. [PubMed: 11509311]

27. Saji N, Kimura K, Shimizu H, Kita Y. Silent brain infarct is independently associated with arterial stiffness indicated by cardio-ankle vascular index (CAVI). Hypertens Res. 2012; 35:756–760. [PubMed: 22378472]

28. Kennedy KM, Raz N. Pattern of normal age-related regional differences in white matter microstructure is modified by vascular risk. Brain Res. 2009; 1297:41–56. [PubMed: 19712671]

29. Dufouil C, Godin O, Chalmers J, Coskun O, MacMahon S, Tzourio-Mazoyer N, Bousser MG, Anderson C, Mazoyer B, Tzourio C. Severe cerebral white matter hyperintensities predict severe cognitive decline in patients with cerebrovascular disease history. Stroke. 2009; 40:2219–2221. [PubMed: 19390070]

30. Rosano C, Kuller LH, Chung H, Arnold AM, Longstreth WT Jr, Newman AB. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. J Am Geriatr Soc. 2005; 53:649–654. [PubMed: 15817012]

31. Sachdev PS, Wen W, Christensen H, Jorm AF. White matter hyperintensities are related to physical disability and poor motor function. J Neurol Neurosurg Psychiatry. 2005; 76:362–367. [PubMed: 15716527]

32. Pantoni L. Pathophysiology of age-related cerebral white matter changes. Cerebrovasc Dis. 2002; 13 (Suppl 2):7–10. [PubMed: 11901236]

33. Pantoni L, Poggesi A, Inzitari D. The relation between white-matter lesions and cognition. Curr Opin Neurol. 2007; 20:390–397. [PubMed: 17620872]

34. Firbank MJ, Wiseman RM, Burton EJ, Saxby BK, O'Brien JT, Ford GA. Brain atrophy and white matter hyperintensity change in older adults and relationship to blood pressure. Brain atrophy, wmh change and blood pressure. J Neurol. 2007; 254:713–721. [PubMed: 17446997]

35. Watson NL, Sutton-Tyrrell K, Rosano C, Boudreau RM, Hardy SE, Simonsick EM, Najjar SS, Launer LJ, Yaffe K, Atkinson HH, Satterfield S, Newman AB. Arterial stiffness and cognitive decline in well-functioning older adults. J Gerontol A Biol Sci Med Sci. 2011; 66:1336–1342. [PubMed: 21768503]

36. Simonsick EM, Newman AB, Nevitt MC, Kritchevsky SB, Ferrucci L, Guralnik JM, Harris T. Measuring higher level physical function in well-functioning older adults: Expanding familiar approaches in the health abc study. J Gerontol A Biol Sci Med Sci. 2001; 56:M644–649. [PubMed: 11584038]

37. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, Havlik R, Lakatta EG, Spurgeon H, Kritchevsky S, Pahor M, Bauer D, Newman A. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation. 2005; 111:3384–3390. [PubMed: 15967850]

38. Rosano C, Bennett DA, ABN, Venkatraman V, Yaffe K, Harris T, Kritchevsky S, HJA. Patterns of focal gray matter atrophy are associated with bradykinesia and gait disturbances in older adults. J Gerontol A Biol Sci Med Sci. 2012; 67:957–962. [PubMed: 22367436]

39. Venkatraman VK, Aizenstein HJ, Newman AB, Yaffe K, Harris T, Kritchevsky S, Ayonayon HN, Rosano C. Lower digit symbol substitution score in the oldest old is related to magnetization transfer and diffusion tensor imaging of the white matter [published online ahead of print September 27 2011]. Front Ag Neurosci. 2011; 3 http://www.frontiersin.org/Aging_Neuroscience/10.3389/fnagi.2011.00011/full.

40. Rosano C, Aizenstein HJ, Newman AB, Venkatraman V, Harris T, Ding J, Satterfield S, Yaffe K. Study ftHA. Neuroimaging differences between older adults with maintained versus declining cognition over a 10-year period. Neuroimage. 2012; 62:307–313. [PubMed: 22542701]

41. Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y. Structural correlates of cognitive domains in normal aging with diffusion tensor imaging. Brain Struct Funct. 2012; 217(2):503–515. [PubMed: 21909706]

42. Squire LR, Zola-Morgan S. The medial temporal lobe memory system. Science. 1991; 253:1380–1386. [PubMed: 1896849]

43. Newton JM, Ward NS, Parker GJ, Deichmann R, Alexander DC, Friston KJ, Frackowiak RS. Non-invasive mapping of corticofugal fibres from multiple motor areas--relevance to stroke recovery. Brain. 2006; 129:1844–1858. [PubMed: 16702192]

44. O'Sullivan M, Morris RG, Markus HS. Brief cognitive assessment for patients with cerebral small vessel disease. J Neurol Neurosurg Psychiatry. 2005; 76:1140–1145. [PubMed: 16024894]

45. Rosano C, Newman AB, Katz R, Hirsch CH, Kuller LH. Association between lower digit symbol substitution test score and slower gait and greater risk of mortality and of developing incident disability in well-functioning older adults. J Am Geriatr Soc. 2008; 56:1618–1625. [PubMed: 18691275]

46. Watson NL, Sutton-Tyrrell K, Youk AO, Boudreau RM, Mackey RH, Simonsick EM, Rosano C, Hardy SE, Windham BG, Harris TB, Najjar SS, Lakatta EG, Atkinson HH, Johnson KC, Bauer DC, Newman AB. Arterial stiffness and gait speed in older adults with and without peripheral arterial disease. Am J Hypertens. 2011; 24:90–95. [PubMed: 20940711]

47. Launer LJ. Epidemiology of white matter lesions. Top Magn Reson Imaging. 2004; 15:365–367. [PubMed: 16041288]

48. Peters A. The effects of normal aging on myelin and nerve fibers: A review. Journal of neurocytology. 2002; 31:581–593. [PubMed: 14501200]

49. Ge Y, Grossman RI, Babb JS, Rabin ML, Mannon LJ, Kolson DL. Age-related total gray matter and white matter changes in normal adult brain. Part ii: Quantitative magnetization transfer ratio histogram analysis. AJNR Am J Neuroradiol. 2002; 23:1334–1341. [PubMed: 12223374]

50. Hirata K, Kawakami M, O'Rourke MF. Pulse wave analysis and pulse wave velocity: A review of blood pressure interpretation 100 years after korotkov. Circ J. 2006; 70:1231–1239. [PubMed: 16998252]

Novelty and Significance

1) What is new?

- Hyperintensities in tracts important for memory and processing speed are related to exposure to higher arterial pulse wave velocity 10 years prior.

- These associations were significant in very old adults living in the community.

- This association appears stronger in blacks as compared to white.

2) What Is Relevant?

Arterial pulse wave velocity may be used to estimate the future probability of having brain small vessel disease many years later.

3) Summary

The association between arterial pulse wave velocity and focal white matter hyperintensities persist over a long period of time, it is independent of intervening cardiovascular events and appears stronger in blacks than in white.

Table 1

Mean PWV for those with as compared to those without WMH in the left superior longitudinal

Race		WMH=0				WMH>0			Between- group mean percent difference in PWV	Adjusted p-value[*]
	n	mean	SD	median	n	mean	SD	median		
All	139	759.54	349.4	683.3	164	908.76	449.33	793.5	19.6	0.023
White	88	747.96	361.01	682.5	92	865.38	422.97	760.5	15.7	0.099
Black	51	779.52	330.93	683.3	72	964.2	478.19	843.5	23.7	0.12

PWV: pulse wave velocity;

[*]
p from age and WMH-adjusted models of PWV predicting WMH > 0 / =0

Table 2

Results of univariate logistic regression models according to quartiles of PWV for WMH > median in the left Superior Longitudinal Fasciculus.

Quartiles	Odds Ratio (95% CI) of having WMH median	
	Left	Right
1st, PWV <575.30 cm/sec	Referent	
2nd, 575.30 PWV< 713.80	1.08 (.56,2.06)	.75 (.39,1.41)
3rd, 713.80 PWV< 966.00	1.41 (.74,2.68)	.92 (.49,1.75)
4th, PWV 966.00	2.84 (1.48,5.48)	1.86 (.97,3.56)

PWV: Pulse Wave Velocity; WHM: White Matter Hyperintensities

Table 3

Standardized Odds Ratio and 95% Confidence Interval of having Small Vessel Disease in the left superior longitudinal fasciculus, temporal portion

Outcome	Model 1	Model 2	Model 3	Model 4
PWV	1.56 (1.20, 2.02)	1.51 (1.16, 1.98)	1.47 (1.10, 1.95)	1.41 (1.04, 1.92)
Overall p	0.005	0.002	0.001	<.0001