

Increased Cerebral Arterial Pulsatility in Patients With Leukoaraiosis

Arterial Stiffness Enhances Transmission of Aortic Pulsatility

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Background and Purpose—Arterial stiffening reduces damping of the arterial waveform and hence increases pulsatility of cerebral blood flow, potentially damaging small vessels. In the absence of previous studies in patients with recent transient ischemic attack or stroke, we determined the associations between leukoaraiosis and aortic and middle cerebral artery stiffness and pulsatility.

Methods—Patients were recruited from the Oxford Vascular Study within 6 weeks of a transient ischemic attack or minor stroke. Leukoaraiosis was categorized on MRI by 2 independent observers with the Fazekas and age-related white matter change scales. Middle cerebral artery (MCA) stiffness (transit time) and pulsatility (Gosling's index: MCA-PI) were measured with transcranial ultrasound and aortic pulse wave velocity and aortic systolic, diastolic, and pulse pressure with applanation tonometry (Sphygmocor).

Results—In 100 patients, MCA-PI was significantly greater in patients with leukoaraiosis (0.91 versus 0.73, $P<0.0001$). Severity of leukoaraiosis was associated with MCA-PI and aortic pulse wave velocity (Fazekas: $\chi^2=0.39$, MCA-PI $P=0.01$, aortic pulse wave velocity $P=0.06$; age-related white matter change: $\chi^2=0.38$, MCA-PI $P=0.015$; aortic pulse wave velocity $P=0.026$) for periventricular and deep white matter lesions independent of aortic systolic blood pressure, diastolic blood pressure, and pulse pressure and MCA transit time with MCA-PI independent of age. In a multivariate model ($r^2=0.68$, $P<0.0001$), MCA-PI was independently associated with aortic pulse wave velocity ($P=0.016$) and aortic pulse pressure ($P<0.0001$) and inversely associated with aortic diastolic blood pressure ($P<0.0001$) and MCA transit time ($P=0.001$).

Conclusions—MCA pulsatility was the strongest physiological correlate of leukoaraiosis, independent of age, and was dependent on aortic diastolic blood pressure and pulse pressure and aortic and MCA stiffness, supporting the hypothesis that large artery stiffening results in increased arterial pulsatility with transmission to the cerebral small vessels resulting in leukoaraiosis. (*Stroke*. 2012;43:2631-2636.)

Key Words: arterial stiffness ■ cerebral pulsatility ■ etiology ■ leukoaraiosis ■ white matter disease

Prevention of premature leukoaraiosis by treating the underlying causes in middle age may reduce the risk of stroke¹ and dementia² and other consequences of cerebral small vessel disease,^{3,4} but the etiology is not yet fully understood. The relative importance of hemodynamic factors as opposed to a primary microangiopathy⁵ in the development of leukoaraiosis is unclear and associations with age, hypertension, and diabetes are consistent with both processes.⁶ Previous studies have suggested a relationship between increased middle cerebral artery (MCA) pulsatility measured by transcranial Doppler ultrasound and leukoaraiosis or lacunar infarction in patients with hypertension⁷ and diabetes,⁸ although not necessarily independent of age. However,

increased cerebral pulsatility has often been interpreted as a consequence of small vessel disease due to changes in downstream resistance⁹ rather than as a causal factor related to increased central arterial stiffness and reduced damping of the cerebral arterial waveform,¹⁰ yet the cerebral circulation appears to be specifically adapted to dampen the arterial waveform¹¹ and increased aortic stiffness has been associated with leukoaraiosis,¹² lacunar stroke,¹³ and cerebral pulsatility.¹⁰ However, these relationships all strongly covary with age and are susceptible to residual confounding. Previous studies have not measured leukoaraiosis, aortic pulse wave velocity (PWV), and middle cerebral pulsatility optimally in the same patient group and no study has also measured aortic

Received February 29, 2012; final revision received July 13, 2012; accepted July 18, 2012.

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The online-only Data Supplement is available with this article at <http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.112.655837/-/DC1>.

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Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.112.655837

Table 1. Demographic Characteristics of Patients According to Severity of Leukoaraiosis

	Fazekas Scale Score				P Value
	0 (n=30)	1 (n=21)	2 (n=24)	≥3 (n=25)	
Age, y	53 (15)	66.5 (12)	68.5 (11)	74.9 (7.9)	<0.0001
Male	22 (73)	13 (62)	14 (58)	17 (68)	0.58
Event type					
Stroke	11 (37)	9 (43)	9 (38)	9 (36)	0.76
TIA	19 (63)	12 (57)	15 (63)	16 (64)	
Hypertensive	9 (30)	7 (33)	12 (50)	17 (68)	0.03
Diabetes	2 (6.7)	3 (14)	2 (8.3)	6 (24)	0.10
Family history*	5 (17)	5 (24)	5 (21)	10 (40)	0.08
Hyperlipidemia	9 (30)	8 (38)	7 (29)	12 (48)	0.27
Atrial fibrillation	0 (0)	1 (4.8)	3 (13)	3 (12)	0.05
Current smoker	7 (23)	2 (9.5)	4 (17)	5 (20)	0.82
Blood pressure, mm Hg					
Systolic	124.1 (16.4)	132.9 (14.9)	131.6 (18.8)	129.6 (19.9)	0.28
Diastolic	78.7 (11.8)	77.6 (11.1)	74.4 (12.7)	70.7 (12.3)	0.01
Creatinine	79.8 (15.4)	75.3 (16)	77.5 (17.9)	89.6 (25.7)	0.08
BMI, kg/m ²	28.1 (5.9)	27.5 (5.3)	27.5 (5.5)	26.9 (3.8)	0.44

Severity of leukoaraiosis is measured according to the total score on the Fazekas scale. Continuous variables are presented as mean (SD) with *P* values for trend across levels of leukoaraiosis. Frequencies are presented as no. (%) with *P* values for trend.

TIA indicates transient ischemic attack; BMI, body mass index.

*Family history refers to a reported history of stroke in either parent.

pulsatility and middle cerebral artery stiffness, key components of the hypothesized mechanism in which increased aortic pulsatility is transmitted through stiff large vessels to the cerebral microvasculature.

Therefore, we performed the first study assessing the dependence of leukoaraiosis on arterial stiffness and pulsatility in both the aorta and MCA in patients with recent transient ischemic attack or minor stroke to assess the degree to which leukoaraiosis depends independently on each of these measures after adjustment for significant clinical features, particularly age.

Methods

Consecutive consenting and eligible participants within 6 weeks of a transient ischemic attack or minor stroke (National Institutes of Health Stroke Scale <5) were recruited to a physiological substudy of the Oxford Vascular Study (OXVASC)¹⁴ between January and December 2011 from the acute transient ischemic attack and stroke clinic associated with the study. Participants were excluded if they were <18 years, unable to have an MRI scan, cognitively impaired (Mini-Mental State Examination <23), pregnant or had a recent myocardial infarction (<1 month), unstable angina, heart failure (New York Heart Association 3–4 or ejection fraction <40%), or untreated severe bilateral carotid stenosis (>70%) or occlusion. The study was approved by the Oxfordshire Research Ethics Committee.

MRI scans were performed during the acute clinical assessment on a 3-T MRI system (Siemens Magnetom Verio) according to a standardized protocol using vendor-designed sequences. The protocol comprised T2-weighted turbo spin echo and fluid-attenuated inversion recovery sequences, diffusion and susceptibility-weighted images, a T1-weighted spin-echo 2-dimensional sequence postcontrast application as well as a time-of-flight MR angiography of the

intracranial vessels and a contrast-enhanced MR angiography of the large neck arteries.

All axial T2 scans were scored according to a modified version of the Fazekas¹⁵ scale by an experienced observer (M.S.) blinded to clinical and physiological data, because this score is the simplest, most commonly used and well-validated semiquantitative score for leukoaraiosis. M.S. also graded scans by the age-related white matter change (ARWMC)¹⁶ score to demonstrate the consistency of the results. Finally, leukoaraiosis was also independently scored by M.S. and a consultant neuroradiologist (W.K.), who was not blinded to the patient's clinical details, on a simple 4-point scale: "none," "mild," "moderate," or "severe" relative to the patient's age (Oxford scale). For comparison, the Fazekas and ARWMC scores were also categorized into 4 approximately equally sized groups (Fazekas: none 0, mild 1, moderate 2, severe ≥3; ARWMC: none 0, mild 1–3, moderate 4–9, severe ≥10).

Physiological tests were performed at rest in a quiet, dimly lit, temperature-controlled room (21–23°C). Applanation tonometry (Sphygmocor; AtCor Medical, Sydney, Australia) was used to measure carotid-femoral PWV, aortic augmentation index, and central aortic systolic, diastolic and pulse pressure (ao-SBP, ao-DBP, ao-PP)¹⁷ calibrated to the average of 3 brachial blood pressures measured supine after at least 10 minutes rest. Transcranial Doppler ultrasound (Doppler Box; Compumedics DWL, Singen, Germany) was performed with a handheld 2-MHz probe at the temporal bone window on the same side as carotid applanation. The waveform envelope was acquired at 100 Hz simultaneously with electrocardiogram and blood pressure at 200 Hz (Finometer; Finapres Medical Systems) through a Powerlab 8/30 with LabChart Pro software (ADInstruments). The MCA was insonated at 50 mm, or if this was not adequate, at the depth giving the optimal waveform. Data were exported to Matlab R2010a for calculation of mean MCA transit time (MCA-TT) measured from the QRS complex to the foot of at least 7 beats as identified by intersecting tangents.¹⁸ All waveforms were visually inspected and beats corrupted by artifact were excluded.

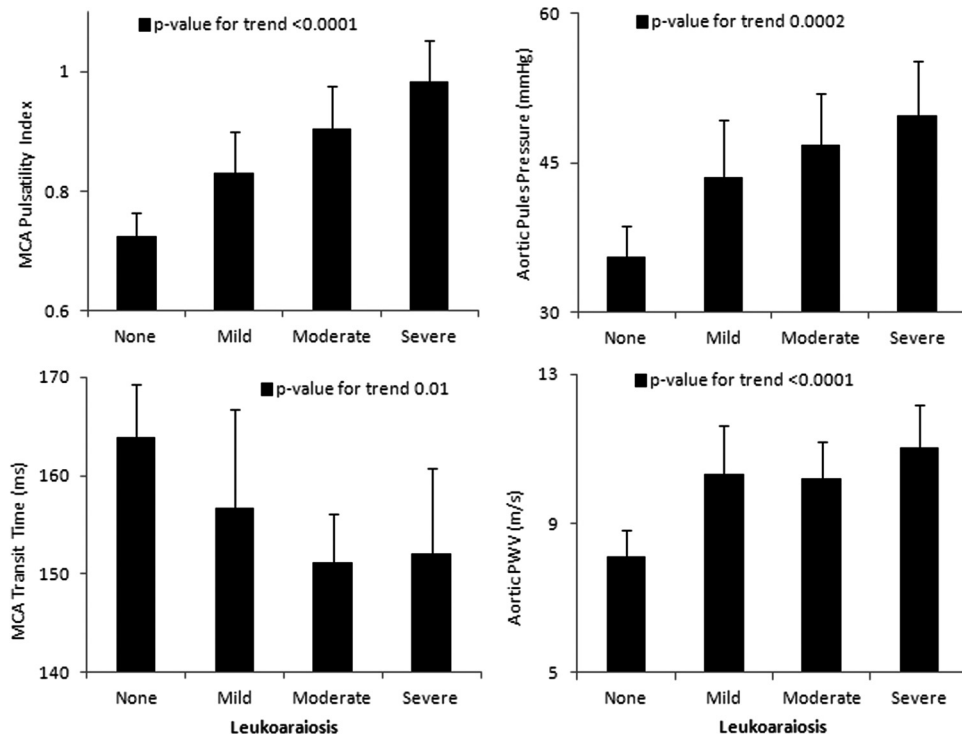


Figure 1. Relationship between severity of leukoaraiosis and stiffness or pulsatility in the aorta and middle cerebral artery. Severity of leukoaraiosis is classified according to the total score on the Fazekas scale (none=0, mild=1, moderate=2, severe ≥ 3). Groups are represented as mean (95% CI) with probability values by a linear test for trend across groups. MCA indicates middle cerebral artery; PWV, pulse wave velocity.

MCA-PWV was calculated as the distance between the sternal notch and the temporal bone window divided by MCA-TT.¹⁹ MCA pulsatility was calculated as Gosling's pulsatility index (MCA-PI=(systolic cerebral blood flow volume–diastolic cerebral blood flow volume)/mean cerebral blood flow volume).

Kappa statistics were derived to assess interrater agreement for assessment of leukoaraiosis with the Oxford score and agreement of severity of leukoaraiosis between the Fazekas and ARWMC scales. Differences between patient groups in continuous variables were assessed by *t* tests or analysis of variance with tests for linear trend for severity of leukoaraiosis, whereas differences in frequencies were compared by χ^2 tests. Univariate relationships between continuous variables were assessed by linear regression. Multivariate predictors of continuous physiological outcome variables were determined by general linear models but due to the nonnormal, positively skewed distribution of the semiquantitative scores for leukoaraiosis, relationships between leukoaraiosis severity and either clinical or physiological measures were assessed with ordinal regression. Relationships were assessed with and without adjustment for age and sex and then adjusted for additional cardiovascular risk factors including: history of hypertension, stroke, hypercholesterolemia, current smoking, family history of stroke, diabetes, height, and brachial SBP and DBP.

All analyses were performed in Matlab R2010a, SPSS 17.0, and Microsoft Excel 2010.

Results

Of 110 patients recruited, 10 (9%) had inadequate temporal bone windows for transcranial Doppler ultrasound. Thirty patients had no leukoaraiosis on the Fazekas scale (38 had no periventricular leukoaraiosis and 42 had no deep white matter lesions) compared with 39 on the ARWMC and Oxford scales. The interrater agreement for leukoaraiosis in 100 consecutive cases imaged by MRI and rated by the Oxford scale was good ($\kappa=0.78$; 95% CI, 0.65–0.90 for presence of

leukoaraiosis and weighted $\kappa=0.66$; 0.56–0.76 for severity of leukoaraiosis). Agreement in assessment of the severity of leukoaraiosis between the ARWMC and Fazekas scales was also good (weighted $\kappa=0.60$; 0.48–0.72).

In univariate comparisons, age, frequency of hypertension, and a lower DBP were associated with increasing severity of leukoaraiosis (Table 1). MCA-PI increased with age, female sex, diabetes, creatinine, and a lower DBP (online-only Data Supplement table I), whereas aortic PP was associated with elevated SBP, age, and female sex. Aortic PWV was similarly associated with age, SBP, hypertension, and creatinine but MCA-TT was only associated with age. There was no relationship between event type (stroke versus transient ischemic attack), etiology or territory, and either leukoaraiosis or physiological measures.

Patients with leukoaraiosis had significantly greater MCA pulsatility (0.91 versus 0.73, $P<0.0001$), ao-PWV (10.5 versus 8.1 m/s, $P<0.0001$), ao-PP (47.3 versus 35.8 mm Hg, $P<0.0001$), and MCA stiffness, whether measured as mean TT (153 versus 164 ms, $P<0.0001$) or MCA-PWV (1.38 versus 1.31 m/s, $P=0.016$) on all scales. Furthermore, these relationships showed a dose-response relationship with increasing severity of leukoaraiosis (see Figure 1; online-only Data Supplement Figures II and III). MCA-PI and ao-PWV were independent predictors of total score on the Fazekas and ARWMC scales (ordinal regression: Fazekas $\chi^2=0.39$, MCA-PI $P=0.01$, ao-PWV $P=0.06$; ARWMC $\chi^2=0.38$, MCA-PI $P=0.015$; ao-PWV $P=0.026$) in models including MCA-PI, MCA-TT, ao-PWV, ao-PP, ao-SBP, and ao-DBP. In models adjusting for age, sex, and major cardiovascular risk factors, only MCA-PI and age remained as

Table 2. Associations of Severity of Leukoaraiosis and Middle Cerebral Artery Pulsatility in Multivariate Models Including Demographic and Physiological Variables

Outcome	Global Model			Independent Associations		
	Model Design	r^2/χ^2	P Value	Variable	Beta	P Value
Fazekas scale (adjusted for physiology)	Ordinal regression*	39.44	<0.001	MCA-PI	4.79	0.01
				Aortic PWV	0.15	0.06
Fazekas scale (adjusted for age+sex)	Ordinal regression†	48.07	<0.001	MCA-PI	4.75	0.011
				Age	0.074	0.003
Fazekas scale (adjusted for all variables)	Ordinal regression‡	48.98	<0.001	MCA-PI	4.33	0.037
				Age	0.089	0.002
MCA-PI (adjusted for physiology)	GLM*	0.680	<0.001	Aortic PP	0.006	<0.0001
				Aortic DBP	−0.009	<0.0001
				Aortic PWV	0.011	0.016
				MCA-TT	−0.002	0.001
MCA-PI (adjusted for age+sex)	GLM†	0.686	<0.001	Aortic PP	0.005	<0.001
				Aortic DBP	−0.008	<0.001
				Aortic PWV	0.009	0.079
				MCA-TT	−0.002	0.004
MCA-PI (adjusted for all variables)	GLM‡	0.744	<0.001	Aortic PP	0.006	0.004
				Aortic DBP	−0.006	0.007
				MCA-TT	−0.002	0.006
				Diabetes	0.101	0.005

Severity of leukoaraiosis is measured according to the total score on the Fazekas scale. Ordinal regressions are presented for severity of leukoaraiosis due to the nonnormal distribution of leukoaraiosis severity, whereas physiological determinants of MCA-PI are assessed by general linear models (GLM) with and without adjustment for clinical features.

MCA indicates middle cerebral artery; DBP, diastolic blood pressure; SBP, systolic blood pressure; TT, transit time; PP, pulse pressure.

*Physiological variables include aortic SBP and DBP and pulse pressure, aortic stiffness (PWV), MCA stiffness (transit time), and MCA pulsatility (MCA-PI).

†Additionally adjusted for age and sex.

‡Additionally adjusted for history of hypertension, stroke, hypercholesterolemia, current smoking, family history of stroke, diabetes, height, and brachial systolic and diastolic BP.

independent predictors (Table 2). The same associations with total Fazekas score were also found for periventricular ($\chi^2=0.31$, MCA-PI $P=0.029$, ao-PWV $P=0.044$) and deep white matter scores ($\chi^2=0.34$, MCA-PI $P=0.03$, ao-PWV $P=0.08$) except that ao-PWV was not independently associated with deep lesions. Models including ao-PI instead of aortic PP and MCA-PWV instead of MCA-TT were not significantly different, and the same results were found with adjusted logistic regression comparing patients with leukoaraiosis versus no leukoaraiosis.

MCA-PI was dependent on both pulsatility and arterial stiffness in both the aorta and the MCA with strong associations with ao-PP, ao-PWV, and MCA-TT and, although there was no association with SBP, there was a strong negative association with DBP (Figure 2). In addition, there was a relationship between aortic and MCA stiffness but only when the analysis was limited to patients with less variable ao-PWV (SD for repeated measures <2): ao-PWV versus MCA-TT $r^2=0.075$, $P=0.013$; ao-PWV versus MCA-PWV $r^2=0.063$, $P=0.023$. In multivariate comparisons, MCA-PI was independently associated with ao-DBP, ao-PP, ao-PWV, and MCA-TT ($r^2=0.680$, ao-PP $P<0.0001$; ao-DBP $P<0.0001$, MCA-TT $P=0.001$; ao-PWV $P=0.016$), all of which were independent of age and cardiovascular risk factors except for ao-PWV (Table 2).

Discussion

This study demonstrates a significant relationship between MCA pulsatility and the presence and severity of leukoaraiosis in a cohort of patients with recent transient ischemic attack and minor stroke with similar results for both periventricular and deep white matter disease. This relationship was independent of age and other physiological measures and was significantly stronger than the association between leukoaraiosis and aortic stiffness or aortic pulsatility. The very strong association ($r^2>0.6$) of MCA-PI with aortic pulsatility, DBP, aortic stiffness, and MCA stiffness further suggests that MCA-PI is mainly dependent on these measures rather than on distal small vessel resistance.

Leukoaraiosis is strongly associated with cognitive impairment,^{1,2} an increased risk of stroke,¹ increased morbidity as a result of stroke,^{20,21} and increased mortality.¹ However, it is unclear whether leukoaraiosis has a predominantly ischemic etiology due to either chronic ischemia^{22,23} or incomplete episodic infarction or whether it represents a primary microangiopathy that directly causes both leukoaraiosis and the associated physiological changes.^{5,24} Although both hypotheses could explain the clinical associations, the former hypothesis is supported by studies showing a relationship between the anatomic distribution of leukoaraiosis and lower cerebral blood flow²² or cerebrovascular reactivity,²⁵ whereas

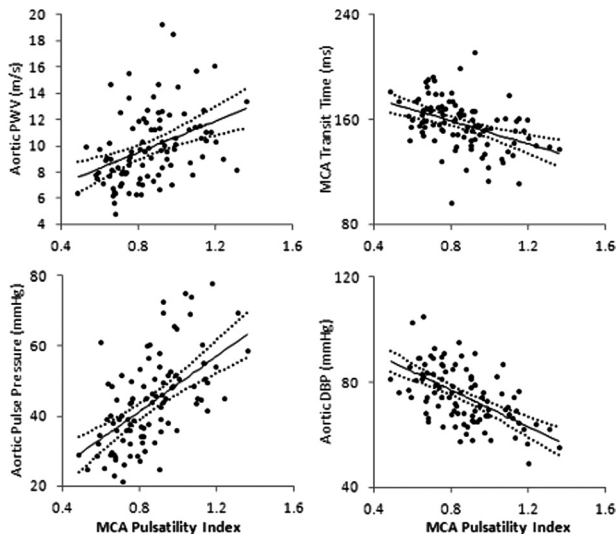


Figure 2. Associations between middle cerebral artery pulsatility index (MCA-PI) and aortic pulse wave velocity, MCA transit time, aortic pulse pressure, and aortic diastolic blood pressure. All relationships depicted are derived from univariate linear regression with 95% CIs, but these relationships are independent in multivariate general linear models (see Table 2).

the latter hypothesis is supported by independent genetic associations with leukoaraiaosis,²⁶ superficially similar white matter disease in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)²⁷ and COL4A1 mutations,²⁸ and the demonstration of increased blood–brain barrier permeability in patients with leukoaraiaosis both in lesions and in normal-appearing white matter.^{5,24} However, ultimately it is likely that these 2 mechanisms are not mutually exclusive.

Ours is the first study to assess the association of leukoaraiaosis with stiffness and pulsatility in both the aorta and cerebral arteries in one cohort. We demonstrated a significantly stronger association of leukoaraiaosis with MCA-PI than with any other physiological measure despite similar associations with age, suggesting a more direct pathophysiological relationship. In addition, this means that it is unlikely that differences in leukoaraiaosis and cerebral pulsatility are solely due to independent effects of age on the brain. The very strong correlation of MCA-PI with aortic pulsatility and large artery stiffness also suggests a causative pathophysiological relationship. Together these findings imply that increased arterial stiffening causes increased transmission of enhanced aortic pulsatility to the cerebral circulation, causing leukoaraiaosis due to alterations in perfusion during diastole, due to increased endothelial shear stress, or due to impaired cerebral autoregulation of fluctuations in blood pressure. Previous studies demonstrating a relationship between leukoaraiaosis and either cerebral pulsatility⁷ or aortic stiffness¹² have only assessed one component of this mechanism and could not determine whether increased cerebral pulsatility results from leukoaraiaosis or whether arterial stiffening and leukoaraiaosis are only independent markers of age.

Our study has some limitations. First, it was a cross-sectional, observational study and therefore it is possible that the physiological associations with leukoaraiaosis are con-

founded by a systemic primary microangiopathy, but this is unlikely given the strength of the relationship between the physiological variables and MCA-PI. Nonetheless, larger longitudinal studies will be required to confirm these findings. Second, the patients were heterogeneous in both age and stroke etiology. This resulted in an increased range of leukoaraiaosis, increasing the sensitivity of the study, but there were insufficient patients to identify whether these associations differed by specific subgroups, particularly whether the same associations applied to patients with lacunar and non-lacunar stroke. Third, we did not assess whether the relationships between leukoaraiaosis and the vascular indices were confounded by other hemodynamic measures such as longer-term blood pressure variability over beat-to-beat, 24-hour or day-to-day timeframes.²⁹ Finally, we did not address whether there were coexistent changes in blood–brain barrier permeability in this patient group.

Assessing the potential contribution of hemodynamic factors to the etiology of leukoaraiaosis is important for guiding the development of interventions, especially because no direct interventions exist to treat a primary microangiopathy. Current antihypertensive medications may reduce cerebral arterial pulsatility, and this could potentially be part of the explanation for differences between antihypertensive medications in the resultant risk of stroke³⁰ and cognitive impairment,³¹ possibly by effects on blood pressure variability or associated mechanisms. In addition, therapies directed at reducing aortic stiffness in middle-aged patients could delay the development of leukoaraiaosis. Further research needs to assess the longitudinal relationship between cerebral pulsatility and the development of leukoaraiaosis and ideally test whether interventions which reduce cerebral pulsatility or aortic stiffness also prevented development of leukoaraiaosis.

Conclusions

Leukoaraiaosis is closely associated with cerebral arterial pulsatility, which is strongly dependent on aortic pulsatility and large artery stiffness. This is consistent with the hypothesis that arterial stiffening results in increased aortic pulsatility and its transmission to the cerebral circulation and may play a pathophysiological role in the development of leukoaraiaosis and its clinical sequelae. Ultimately, treatment aimed at reducing arterial stiffness in middle age might be most effective in preventing stroke, dementia, and other consequences of cerebral small vessel disease.

Acknowledgments

We gratefully acknowledge the support from the staff and facilities of the Oxford Cardiovascular Clinical Research Facility, specifically the support provided by Jonathan Diesch.

Sources of Funding

One of the authors (Dr Rothwell) is in receipt of a National Institute for Health Research Senior Investigator Award and a Wellcome Trust Senior Investigator Award. One of the authors (Dr Webb) is in receipt of a Medical Research Council (UK) Clinical Training Research Fellowship. One of the authors (Dr Schulz) is funded by a National Institute for Health Research Clinician Scientist Fellowship. The Oxford Vascular Study is funded by the UK Medical Research Council, the National Institute of Health Research, the Stroke Association, the Dunhill Medical Trust, and the Oxford

Partnership Comprehensive Biomedical Research Centre, Thames Valley Primary Care Research Partnership, British United Provident Association Foundation.

Disclosures

None.

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