Increased Cerebral Arterial Pulsatility in Patients With Leukoaraiosis
Arterial Stiffness Enhances Transmission of Aortic Pulsatility

Alastair J.S. Webb, BMBCh, MSc; Michela Simoni, MD, MRCP; Sara Mazzucco, MD, PhD; Wilhelm Kuker, FRCR; Ursula Schulz, PhD; Peter M. Rothwell, FMedSci

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: χ²=0.39, MCA-PI P=0.01, aortic pulse wave velocity P=0.06; age-related white matter change: χ²=0.38, MCA-PI P=0.015; aortic pulse wave velocity ρ=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 (r²=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 microangiopathy6 in the development of leukoaraiosis is unclear and associations with age, hypertension, and diabetes are consistent with both processes.8 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 hypertension2 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 resistance5 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...
Table 1. Demographic Characteristics of Patients According to Severity of Leukoaraiosis

<table>
<thead>
<tr>
<th>Fazekas Scale Score</th>
<th>0 (n=30)</th>
<th>1 (n=21)</th>
<th>2 (n=24)</th>
<th>≥3 (n=25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53 (15)</td>
<td>66.5 (12)</td>
<td>68.5 (11)</td>
<td>74.9 (7.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>22 (73)</td>
<td>13 (62)</td>
<td>14 (58)</td>
<td>17 (88)</td>
<td>0.58</td>
</tr>
<tr>
<td>Event type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>11 (37)</td>
<td>9 (43)</td>
<td>9 (38)</td>
<td>9 (36)</td>
<td>0.76</td>
</tr>
<tr>
<td>TIA</td>
<td>19 (63)</td>
<td>12 (57)</td>
<td>15 (63)</td>
<td>16 (64)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>9 (30)</td>
<td>7 (33)</td>
<td>12 (50)</td>
<td>17 (68)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (6.7)</td>
<td>3 (14)</td>
<td>2 (8.3)</td>
<td>6 (24)</td>
<td>0.10</td>
</tr>
<tr>
<td>Family history*</td>
<td>5 (17)</td>
<td>5 (24)</td>
<td>5 (21)</td>
<td>10 (40)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>9 (30)</td>
<td>8 (38)</td>
<td>7 (29)</td>
<td>12 (48)</td>
<td>0.27</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0 (0)</td>
<td>1 (4.8)</td>
<td>3 (13)</td>
<td>3 (12)</td>
<td>0.05</td>
</tr>
<tr>
<td>Current smoker</td>
<td>7 (23)</td>
<td>2 (9.5)</td>
<td>4 (17)</td>
<td>5 (20)</td>
<td>0.82</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>124.1 (16.4)</td>
<td>132.9 (14.9)</td>
<td>131.6 (18.8)</td>
<td>129.6 (19.9)</td>
<td>0.28</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78.7 (11.8)</td>
<td>77.6 (11.1)</td>
<td>74.4 (12.7)</td>
<td>70.7 (12.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Creatinine</td>
<td>79.8 (15.4)</td>
<td>75.3 (16)</td>
<td>77.5 (17.9)</td>
<td>89.6 (25.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.1 (5.9)</td>
<td>27.5 (5.3)</td>
<td>27.5 (5.5)</td>
<td>26.9 (3.8)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

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) 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 Fazekas 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) 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) 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. All waveforms were visually inspected and beats corrupted by artifact were excluded.
MCA-PWV was calculated as the distance between the sternal notch and the temporal bone window divided by MCA-TT. 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 (κ=0.78; 95% CI, 0.65–0.90 for presence of leukoaraiosis and weighted κ=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 κ=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 *χ*²=0.39, MCA-PI *P*=0.01, ao-PWV *P*=0.06; ARWMC *χ*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
Leukoaraiosis is strongly associated with cognitive impairment, an increased risk of stroke, increased morbidity as a result of stroke, and increased mortality. However, it is unclear whether leukoaraiosis has a predominantly ischemic etiology due to either chronic ischemia or incomplete episodic infarction or whether it represents a primary microangiopathy that directly causes both leukoaraiosis and the associated physiological changes. 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 flow or cerebrovascular reactivity, whereas...
the physiological associations with leukoaraiosis are con-
sectional, observational study and therefore it is possible that
leukoaraiosis are only independent markers of age.

We assessed the association of leukoaraiosis and cerebral pulsatility due to increased endothelial shear stress, or due to impaired cerebral autoregulation of fluctuations in blood pressure. Previous studies demonstrating a relationship between leukoaraiosis and either cerebral pulsatility or aortic stiffness have only assessed one component of this mechanism and could not determine whether increased cerebral pulsatility results from leukoaraiosis or whether arterial stiffening and leukoaraiosis 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 leukoaraiosis 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 leukoaraiosis, 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 leukoaraiosis 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. 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 leukoaraiosis 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 stroke and cognitive impairment. 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 leukoaraiosis. Further research needs to assess the longitudinal relationship between cerebral pulsatility and the development of leukoaraiosis and ideally test whether interventions which reduce cerebral pulsatility or aortic stiffness also prevented development of leukoaraiosis.

Conclusions

Leukoaraiosis 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 leukoaraiosis 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.

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Disclosures

None.

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Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility

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Cover Title: Leukoaraiosis: aortic and MCA stiffness and pulsatility

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Supplement figure S1. Relationship between severity of leukoaraiosis on the ARWMC scale and stiffness or pulsatility in the aorta and middle cerebral artery. Severity of leukoaraiosis is classified according to the total score on the ARWMC scale (None=0, mild =1-3, moderate=4-9, severe ≥10). Groups are represented a mean (95%CI), with p-values by a linear test for trend across groups.
Supplemental figure S2. Relationship between severity of leukoaraiosis on the Oxford scale and stiffness or pulsatility in the aorta and middle cerebral artery. Severity of leukoaraiosis is classified according to the Oxford scale as none, mild, moderate or severe. Groups are represented a mean (95%CI), with p-values by a linear test for trend across groups.
### Supplemental Table S1. Relationships between physiological measures and demographic characteristics.

Group differences are presented as mean (SD) and compared by t-tests. For comparisons of continuous variables, \( r^2 \) and p-values are derived from univariate linear regression. *p<0.05 **p<0.01 ***p<0.001.

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<thead>
<tr>
<th>Pulsatility</th>
<th>Arterial Stiffness</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA Pulsatility Index</td>
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</tr>
<tr>
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<table>
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<th>p-value</th>
<th>( r^2 )</th>
<th>p-value</th>
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<th>p-value</th>
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<th>p-value</th>
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<td>&lt;0.001</td>
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<td>0.001</td>
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<td>&lt;0.001</td>
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<td>Diastolic BP</td>
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<td>0.051</td>
<td>0.02</td>
<td>0</td>
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<td>BMI</td>
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<td>0</td>
<td>0.33</td>
<td>0</td>
<td>0.84</td>
<td>0.029</td>
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Supplemental table S2. Demographic and physiological characteristics of patients according to severity of leukoaraiosis by the periventricular subscore of the Fazekas scale. Severity of leukoaraiosis is measured according to the periventricular score on the Fazekas scale. Continuous variables are presented as mean (sd) with p-values derived from ANOVA tests. Frequencies are presented as number (%), with p-values derived from chi-squared tests.

<table>
<thead>
<tr>
<th></th>
<th>Fazekas Periventricular Score</th>
<th></th>
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<th>p-value</th>
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<tr>
<td></td>
<td>0 (n=38)</td>
<td>1 (n=47)</td>
<td>2 (n=15)</td>
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<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age</td>
<td>57 (15)</td>
<td>68 (12)</td>
<td>78 (5.6)</td>
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<td>28 (74)</td>
<td>28 (60)</td>
<td>10 (67)</td>
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<td>Event type:</td>
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<td>Stroke</td>
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<td>16 (34)</td>
<td>5 (33)</td>
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<tr>
<td>TIA</td>
<td>23 (60)</td>
<td>31 (66)</td>
<td>10 (67)</td>
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<td>Hypertensive</td>
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<td>19 (40)</td>
<td>11 (73)</td>
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<td>5 (11)</td>
<td>5 (33)</td>
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<td>9 (20)</td>
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<td>130.6 (18.1)</td>
<td>131.3 (20.3)</td>
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<tr>
<td>Diastolic</td>
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<td>75.3 (11.9)</td>
<td>69.1 (13.1)</td>
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<tr>
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<td>78.9 (21)</td>
<td>93.3 (21.5)</td>
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<td>27.5 (5.1)</td>
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<td><strong>Physiology</strong></td>
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<tr>
<td>MCA PI</td>
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<td>0.89 (0.18)</td>
<td>1.01 (0.17)</td>
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<td>Aortic PP</td>
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<td>45.5 (13.9)</td>
<td>51.2 (12.9)</td>
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<tr>
<td>Aortic PWV</td>
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<td>9.8 (12.1)</td>
<td>12.1 (3.1)</td>
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</table>
Supplemental table S3. Demographic and physiological characteristics of patients according to severity of leukoaraiosis by the deep white matter subscore of the Fazekas scale. Severity of leukoaraiosis is measured according to the deep white matter score on the Fazekas scale. Continuous variables are presented as mean (sd) with p-values derived from ANOVA tests. Frequencies are presented as number (%), with p-values derived from chi-squared tests.