Increased Aortic Pulse Wave Velocity Is Associated With Silent Cerebral Small-Vessel Disease in Hypertensive Patients


Abstract—Aortic stiffness predicts an excess risk of stroke, supposedly via cerebral small-vessel disease. White matter hyperintensities, silent lacunar infarcts, and brain microbleeds, manifestations of cerebral small-vessel disease on neuroimaging, may precede overt cerebrovascular disease. Therefore, we assessed whether aortic stiffness is also related to such lesions. In 167 hypertensive patients (85 men) without a history of cardiovascular or cerebrovascular disease, a mean age of 51.8±13.1 years, and untreated office blood pressure levels of 169±25/104±12 mm Hg, we determined aortic pulse wave velocity and office and ambulatory 24-hour pulse pressure (off medication), as well as the volume of white matter hyperintensities and the presence of lacunar infarcts and microbleeds using brain MRI. Linear and logistic regression analyses were performed to assess the relationships between the arterial stiffness measures and brain lesions. Aortic stiffness and pulse pressure were significantly related to each of the brain lesions in univariate analyses (P<0.05). Multivariate analyses, adjusted for age, sex, brain volume, mean arterial pressure, and heart rate, showed that a higher pulse wave velocity was significantly associated with a greater volume of white matter hyperintensities (unstandardized regression coefficient: 0.041; 95% CI: 0.005 to 0.078; P<0.05) and the presence of lacunar infarcts (odds ratio [per SD increase in pulse wave velocity]: 1.78; 95% CI: 1.06 to 2.99; P<0.05) but not with microbleeds. The models for pulse pressure failed to reach statistical significance in multivariate analyses. In conclusion, aortic stiffness is independently associated with manifestations of cerebral small-vessel disease in hypertensive patients, linking systemic large- to cerebral small-artery disease. (Hypertension. 2008;52:1120-1126.)

Key Words: aortic stiffness ■ pulse wave velocity ■ pulse pressure ■ cerebral small-vessel disease ■ brain ■ hypertension

The arterial system gradually stiffens because of the shared effects of ageing, high blood pressure (BP), and other vascular risk factors. Arterial stiffness can be assessed by noninvasive pulse wave velocity (PWV) measurements. In particular, the velocity of the carotid-femoral or aortic pulse wave appears to be of prognostic importance and is considered to be the “gold standard” for arterial stiffness. Several studies, in both population- and patient-based cohorts, have demonstrated a strong association between increased aortic PWV and excess risk of cardiovascular complications, including stroke. Whether the risk of stroke is mediated by large- and/or small-vessel disease is not clear, but the previously reported increased risk of stroke in the presence of preclinical cerebral microvascular disease, ie, white matter hyperintensities (WMHs), silent lacunar infarcts (LACs), and/or brain microbleeds (BMBs), suggests small-vessel disease involvement. O’Rourke and Safar hypothesized that cerebral microvascular disease results from the damaging forces of abnormal flow pulsations extending into small cerebral arteries as a consequence of arterial stiffening. However, the relationship between arterial stiffness and manifestations of cerebral small-vessel disease has not been investigated in great detail, and studies have yielded conflicting results.

The present study was undertaken to assess the associations between aortic PWV and WMHs, LACs, and BMBs as manifestations of silent cerebral small-vessel disease on MRI of the brain in a cohort of hypertensive patients without a history of symptomatic cardiovascular or cerebrovascular disease. We also included the peripheral pulse pressure (PP), because it is a widely accepted surrogate marker for arterial stiffness.

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1120
Methods

Participants
The selection of patients has been described in detail elsewhere. Briefly, patients who were referred for the evaluation of their hypertension to our outpatient department were eligible for inclusion in the present study. As part of the routine workup, which included ambulatory BP monitoring (ABPM) over a 24-hour period, standard 12-lead electrocardiography, aortic PWV measurements, and routine laboratory investigations, patients were asked to discontinue their antihypertensive medication for ≥2 weeks. An experienced internist decided based on the patients’ clinical information provided by the referring physician and independent of the study whether it was possible to stop temporarily the antihypertensive medication. In addition, patients consented to a repeat ABPM (also off medication) and an MRI of the brain. None of the participants, who were aged 20 to 82 years, had any of the following conditions: indication of secondary hypertension or chronic renal failure, documented diabetes, ischemic or valvular heart disease, atrial fibrillation, a history of transient ischemic attacks or stroke, or a diagnosis of obstructive sleep apnea syndrome.

The medical ethics committee of the Maastricht University Medical Centre approved the study, and written informed consent was obtained from all of the participants.

Hemodynamic Measurements
Conventional office BP was measured at the hospital by sphygmomanometry (Korotkoff phases I and V). After ≥5 minutes of rest, 3 consecutive measurements were taken at the nondominant arm, with the participant seated, and always by the same trained investigator (L.H.G.H.). We calculated the PP and the mean arterial pressure (MAP) from the corresponding systolic BP (SBP) and diastolic BP (DBP) using the following formulas: PP = SBP – DBP and MAP = DBP + (SBP – DBP)/3. The mean of the second and third measurements was used in the analyses.

Ambulatory BP was monitored noninvasively over a 24-hour period using validated SpaceLabs 90207 or 90217 devices (SpaceLabs Medical, Inc), as described in detail elsewhere. The monitoring sessions were repeated with a median interval of 7 days (interquartile range: 5 to 9 days), because the assessment of the between-MAP, DBP, and PP using the Pressure Import and Export software (interquartile range: 5 to 10 minutes of rest), applying the validated and reproducible foot-to-foot velocity method. An automatic device (after femoral or aortic PWV with the participant in the supine position and an MRI of the brain. None of the participants, who were aged 20 to 82 years, had any of the following conditions: indication of secondary hypertension or chronic renal failure, documented diabetes, ischemic or valvular heart disease, atrial fibrillation, a history of transient ischemic attacks or stroke, or a diagnosis of obstructive sleep apnea syndrome.

The medical ethics committee of the Maastricht University Medical Centre approved the study, and written informed consent was obtained from all of the participants.

Brain MRI
Brain MRI (Intera 1.5-T, Philips Medical Systems) was performed to obtain axial T2-weighted, fluid-attenuated inversion recovery and T2*-weighted gradient echo images, as described recently. WMHs were identified as hyperintense areas in the periventricular and deep white matter on both T2-weighted and fluid-attenuated inversion recovery images (for an example of WMHs, please see Figure S1 in the online supplement at http://hyper.ahajournals.org). Because visual (ie, categorical) WMH rating scales apply arbitrary cutoffs to define lesion severity, display ceiling effects and poor discrimination of absolute lesion volumes, and have limited observer reliability, we semiautomatically quantified the WMH volume (WMHV). Furthermore, volumetric measurements were found to be more sensitive in detecting differences between clinical groups. A detailed description of the quantification of the WMHV, including fully automatic brain volume (BV) measurements, is given in the online supplement (please see the expanded Methods section and Figure S2). A single trained observer (L.H.G.H.), blinded to the participants’ age, sex, and clinical data, performed all of the quantitative WMH assessments after reaching satisfactory agreement with an experienced neuroradiologist (P.A.M.H.). Reliability analyses, carried out on a random sample of 20 scans, yielded excellent interobserver and intraobserver agreement (intraclass correlation coefficients: 0.97 and 0.99, respectively).

Two experienced vascular neurologists (R.J.V.O. and J.L.) assessed all of the scans for the presence of silent LACs and BMBs, independently and blinded to the participants’ age, sex, and clinical data. LACs were defined as small (diameter: 3 to 15 mm), sharply demarcated hyperintense lesions on T2-weighted images with corresponding foci of fluid-attenuated inversion recovery low signal intensity and assessed in the basal ganglia, internal capsule, thalamus (ie, those sites limited to the vascular territories of the lenticulostriate, anterior choroidal, and thalamoperforant arteries) and/or brain stem. We distinguished LACs from perivascular spaces using the fluid-attenuated inversion recovery images, with infarcts characterized by a central cavitation of low signal intensity with a surrounding higher-intensity rim of glotic tissue. BMBs were defined as punctate (diameter: <5 mm), homogeneous foci of low signal intensity on T2*-weighted gradient echo images and assessed throughout the brain, ie, brain stem, cerebellum, basal ganglia, corona radiata, and cortico-subcortical gray and white matter. Symmetrical hypointensities in the globi pallidi, likely to represent calcification or iron deposition, and sulcal flow voids from cortical vessels were disregarded. For examples of LACs and BMBs, please see Figures S3 and S4.

The interobserver agreement, expressed as Cohen’s k, was 0.51 for LACs and 0.69 for BMBs, signifying moderate-to-substantial agreement. However, in case of disagreement between the 2 observers, lesions were always ascertained by consensus.

Risk Factors
Information on lifestyle habits, past and current morbidity (including current treatment), and hypertension history (including the self-reported age of diagnosis and previous use of antihypertensive medication) were obtained by interview and verified by inspection of recently started medical charts. Smoking was classified as never, past, or current. Alcohol consumption was estimated in units of intake per day. The duration of hypertension was estimated as the time (in months) passed since the self-reported age of diagnosis until inclusion in the study.

Height and weight were measured without shoes and wearing light indoor clothing to determine body mass index (kilograms per meter squared). Venous blood samples, routinely drawn after an overnight fast, were analyzed for serum creatinine, serum total cholesterol, and high-density lipoprotein cholesterol levels, as well as plasma glucose levels, using standard laboratory procedures.
Statistical Analysis
To detect group differences between unpaired data we applied the independent samples t test for normally distributed variables, the Mann-Whitney U test for variables with skewed distributions, and the Pearson χ² statistic or Fisher’s exact test for categorical variables.

We assessed the associations of the arterial stiffness measures with WMHs (both in terms of volume and severity [third tertile versus lower 2 tertiles]), LACs, and BMBs by means of linear or logistic regression analyses, whenever appropriate. Regression models were adjusted for age and sex (and BV in case of WMHs; model 1) and additionally for MAP and heart rate (model 2). Significant models were then further explored with additional adjustments for the use of BP-lowering medication during PWV measurements (n=15), previous antihypertensive treatment, body mass index, smoking status, and the ratio of total:high-density lipoprotein cholesterol. Covariates were forced into the models simultaneously (enter procedure). Because age is an important determinant of arterial stiffness, we repeated the regression analyses with respect to WMHVs for participants younger (n=83) and for those older (n=84) than the median age of 52.7 years.

To illustrate the relationship between PWV and the volume of WMHs, we produced plots of the predicted WMHVs versus the aortic PWV. The predicted WMHVs are the volumes predicted by the regression equation between PWV and the untransformed WMHVs, adjusted for age, sex, and BV. First, we obtained the predicted WMHVs for the total study population. Subsequently, we obtained the predicted WMHVs for participants younger (n=83) and for those older (n=84) than the median age of 52.7 years in separate analyses.

A 2-tailed P<0.05 was considered statistically significant. Analyses were performed using the statistical software packages SPSS (version 11.0.4 for Macintosh, SPSS, Inc) and Prism (version 4.00 for Windows, GraphPad Software, Inc).

Results
Characteristics
Altogether, we included 167 patients in the present study. Based on the untreated office BP levels, we diagnosed 159 participants (95%) with hypertension. Eight participants (5%) had normal BP levels, although the referring diagnosis was hypertension. The characteristics of the study population according to tertiles of aortic PWV are summarized in Table 1. Older age, male sex, long-standing hypertension, higher office and ambulatory BP levels (including PP), and higher serum creatinine and plasma glucose levels were significantly associated with increasing tertiles of aortic PWV (P≤0.049).

Arterial Stiffness and Manifestations of Silent Cerebral Small-Vessel Disease
Brain MRI was performed with a median interval of 10 days (interquartile range: 2 to 17 days) from the hemodynamic measurements. The WMHV and the number of severe WMHs, LACs, and BMBs increased from the first to the third tertile of aortic PWV (Table 1). Linear regression analyses, performed after the WMHV had been logarithmically transformed because of skewed distribution, showed that higher aortic PWV was significantly associated with a greater volume of WMHs, independent of age, sex, BV, MAP, and heart rate (all models P≤0.05; Table 2). Furthermore, the relation between aortic PWV and WMHV remained statistically significant for both participants younger (n=83; unstandardized regression coefficient: 0.074; 95% CI: 0.027 to 0.122) and for participants older (n=84; unstandardized regression coefficient: 0.065; 95% CI: 0.017 to 0.112) than the median age of 52.7 years (both models P<0.01).

On univariate logistic regression analyses, we found aortic PWV to be significantly related to WMHs (third tertile versus lower 2 tertiles), LACs, and BMBs (all P<0.01 or less). However, in the adjusted models (1 and 2), the associations attenuated, and only the relation with LACs remained statistically significant. Every SD increase in aortic PWV was associated with a 1.78-higher likelihood of LACs (P<0.05; model 2, Table 2). On additional adjustments for the use of BP-lowering medication during PWV measurements (n=15), previous antihypertensive treatment, body mass index, smoking status, and the ratio of total:high-density lipoprotein cholesterol (exploration of significant models), the regression models of both WMHV (unstandardized regression coefficient: 0.043; 95% CI: 0.006 to 0.080) and LACs (odds ratio [per SD increase in PWV]: 1.21; 95% CI: 1.00 to 2.14) remained statistically significant (P<0.05).

The associations of the office and ambulatory 24-hour PPs with manifestations of cerebral small-vessel disease were, in general, weaker than those observed for aortic PWV and failed to reach statistical significance in fully adjusted analyses (model 2, Table 2).

Plots of the predicted WMHVs versus the aortic PWV (Figure 1) illustrate that the volume of WMHs increased with increasing PWV levels. Furthermore, with higher age, the associations were stronger, but the splay of the distribution was greater (Figure 2). Because the regression equations are specific for each group, the models produce group-specific predicted WMHVs. Consequently, the data points of the younger and older age groups do not match those of the total study population.

Discussion
The present study demonstrates that, in hypertensive patients without a history of cardiovascular and cerebrovascular disease, the aortic PWV is positively associated with the extent of WMHs and the presence of silent LACs, independently of age, MAP, and other vascular risk factors. We observed independent associations between aortic PWV and manifestations of silent cerebral small-vessel disease. Every SD increase in aortic PWV was associated with a 1.78-higher likelihood of LACs in adjusted analyses. The relation between aortic stiffness and the volume of WMHs was continuous, without distinct thresholds, and continued down to PWV levels within the normal range. Notably, in participants younger than the median age of 52.7 years, the association between aortic stiffness and WMHV, although weaker, was present as well, which might reflect accelerated vascular ageing in the presence of hypertension.20 Previously, the relationship between arterial stiffness and cerebral microvascular disease has been investigated by assessing brachial-ankle PWV and arterial compliance. The results, however, were conflicting. Although some investigators reported that, in elderly subjects, stiffer arteries were significantly associated with higher grades of WMHs,10,12 others failed to find such an association for silent brain infarcts in a younger and predominantly normotensive population.11 The frequency of microbleeds increased from 9% in the first tertile of aortic
PWV to 25% in the third tertile, and higher levels of PWV and PP were significantly associated with the presence of BMBs on univariate regression analyses. However, the associations lost their significance on multivariate analyses. Although the number of patients with BMBs was small, this trend for more microbleeds with higher PWV levels justifies further evaluation of the PWV-microbleed relationship in larger (and preferably longitudinal) studies.

We found aortic PWV but not peripheral PP to be associated with WMHs and LACs. This difference can be attributed to a number of factors. First, our study population is relatively young, with half of the participants being <52.7 years of age (median). Although peripheral PP increases with age, the steepest rise occurs after the age of 50 years. Furthermore, peripheral PP is a consequence rather than a cause of arterial stiffness and, as such, only an indirect measure of arterial stiffness. In young subjects (age <50 years), PP is considered to reflect central PP and, as such, only an indirect measure of arterial stiffness and, as such, only an indirect measure of arterial stiffening and related cardiovascular disease in elderly only. Aortic PWV, on the other hand, is a direct measure that increases gradually with age and, hence, better reflects central PP in young subjects. In addition, the distensibility of the aorta, an elastic artery, decreases with age, whereas the distensibility of the muscular brachial artery is unrelated to age.24 As such, PP may be a reliable marker of arterial stiffness. In young subjects (age <50 years), PP is considered to reflect central PP and, as such, only an indirect measure of arterial stiffening and related cardiovascular disease in elderly only. Aortic PWV, on the other hand, is a direct measure that increases gradually with age and, hence, better reflects central PP in young subjects. In addition, the distensibility of the aorta, an elastic artery, decreases with age, whereas the distensibility of the muscular brachial artery is unrelated to age.24

### Table 1. Characteristics of the Study Population According to Tertiles of Arterial PWV

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n=167)</th>
<th>&lt;10.4 m/s (n=55)</th>
<th>10.4–12.5 m/s (n=56)</th>
<th>&gt;12.5 m/s (n=56)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometrics</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age, y</td>
<td>51.8±13.1</td>
<td>43.9±12.7</td>
<td>51.5±11.9</td>
<td>59.8±9.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>85/82</td>
<td>24/31</td>
<td>25/31</td>
<td>36/20</td>
<td>0.048</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79.9±16.0</td>
<td>77.7±15.1</td>
<td>79.5±15.8</td>
<td>82.4±16.8</td>
<td>0.299</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.5±4.1</td>
<td>27.0±4.2</td>
<td>27.7±4.5</td>
<td>27.8±3.8</td>
<td>0.519</td>
</tr>
<tr>
<td><strong>Lifestyle factors</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>33 (20)</td>
<td>10 (18)</td>
<td>14 (25)</td>
<td>9 (16)</td>
<td>0.464</td>
</tr>
<tr>
<td>&gt;2 alcoholic units per day</td>
<td>26 (16)</td>
<td>6 (11)</td>
<td>6 (11)</td>
<td>14 (25)</td>
<td>0.058</td>
</tr>
<tr>
<td><strong>Hypertension history</strong></td>
<td></td>
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</tr>
<tr>
<td>Duration, months</td>
<td>39 (13 to 120)</td>
<td>19 (10 to 59)</td>
<td>53 (19 to 164)</td>
<td>58 (12 to 139)</td>
<td>0.005</td>
</tr>
<tr>
<td>Previous antihypertensive treatment</td>
<td>131 (78)</td>
<td>39 (71)</td>
<td>44 (79)</td>
<td>48 (86)</td>
<td>0.165</td>
</tr>
<tr>
<td><strong>Hemodynamic measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>169±25</td>
<td>156±19</td>
<td>171±24</td>
<td>181±24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office MAP, mm Hg</td>
<td>126±15</td>
<td>118±13</td>
<td>127±14</td>
<td>131±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>104±12</td>
<td>100±12</td>
<td>106±11</td>
<td>106±12</td>
<td>0.008</td>
</tr>
<tr>
<td>Office PP, mm Hg</td>
<td>66±20</td>
<td>57±13</td>
<td>65±20</td>
<td>75±20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office heart rate, bpm</td>
<td>75±12</td>
<td>74±10</td>
<td>74±11</td>
<td>78±13</td>
<td>0.106</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>150±18</td>
<td>141±16</td>
<td>152±15</td>
<td>159±19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h MAP, mm Hg</td>
<td>112±13</td>
<td>107±12</td>
<td>113±10</td>
<td>117±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>93±12</td>
<td>90±11</td>
<td>94±10</td>
<td>96±13</td>
<td>0.015</td>
</tr>
<tr>
<td>24-h PP, mm Hg</td>
<td>57±12</td>
<td>51±9</td>
<td>58±12</td>
<td>62±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h heart rate, bpm</td>
<td>76±9</td>
<td>75±9</td>
<td>75±9</td>
<td>77±10</td>
<td>0.262</td>
</tr>
<tr>
<td>Aortic PWV, m/s</td>
<td>12.0±2.9</td>
<td>9.2±0.8</td>
<td>11.4±0.6</td>
<td>15.3±2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Biochemical measurements (fasting)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>82 (71 to 94)</td>
<td>80 (68 to 91)</td>
<td>79 (71 to 91)</td>
<td>88 (74 to 102)</td>
<td>0.049</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.3±0.6</td>
<td>5.2±0.5</td>
<td>5.3±0.6</td>
<td>5.5±0.6</td>
<td>0.007</td>
</tr>
<tr>
<td>Total:HDL cholesterol ratio</td>
<td>4.4 (3.4 to 6.5)</td>
<td>4.0 (3.4 to 4.8)</td>
<td>4.7 (3.4 to 5.6)</td>
<td>4.6 (3.5 to 5.7)</td>
<td>0.077</td>
</tr>
<tr>
<td><strong>Brain MRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BV, cm³</td>
<td>1268±125</td>
<td>1290±130</td>
<td>1249±124</td>
<td>1264±119</td>
<td>0.238</td>
</tr>
<tr>
<td>WMHVs, cm³</td>
<td>0.81 (0.36 to 2.93)</td>
<td>0.46 (0.22 to 1.15)</td>
<td>0.74 (0.34 to 1.80)</td>
<td>2.06 (0.69 to 8.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WMHs (third tertile)</td>
<td>56 (33)</td>
<td>10 (18)</td>
<td>15 (27)</td>
<td>31 (55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LACs</td>
<td>36 (22)</td>
<td>8 (15)</td>
<td>8 (14)</td>
<td>20 (36)</td>
<td>0.007</td>
</tr>
<tr>
<td>BMBs</td>
<td>28 (17)</td>
<td>5 (9)</td>
<td>9 (16)</td>
<td>14 (25)</td>
<td>0.080</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD, No. (%), or median (interquartile range). BMI indicates body mass index; HDL, high-density lipoprotein. *P values are for overall differences across tertiles (P for trend).
reflects central arterial stiffening. Accordingly, we found PWV to be associated with WMHs in our younger participants as well. Second, it has been suggested that an increased PP is a predictor of cardiac rather than cerebrovascular disease. Verdecchia et al demonstrated that MAP but not PP predicts the risk of future stroke. In the present study, the associations between PP and cerebral microvascular damage disappeared on adjustments for the MAP. MAP is determined mainly by peripheral microvascular resistance and, thus,

Table 2. Relationship Between Arterial Stiffness Measures and WMHs, LACs, and BMBs

<table>
<thead>
<tr>
<th>Brain MRI</th>
<th>Aortic PWV</th>
<th>Office PP</th>
<th>24-h PP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstandardized Regression Coefficient or Odds Ratio (95% CI)</td>
<td>Unstandardized Regression Coefficient or Odds Ratio (95% CI)</td>
<td>Unstandardized Regression Coefficient or Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>WMHV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.126 (0.095 to 0.157)‡</td>
<td>0.016 (0.012 to 0.021)‡</td>
<td>0.021 (0.013 to 0.029)‡</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.071 (0.037 to 0.104)‡</td>
<td>0.008 (0.003 to 0.013)*</td>
<td>0.009 (0.001 to 0.017)*</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.041 (0.005 to 0.078)*</td>
<td>0.003 (−0.003 to 0.009)</td>
<td>−0.001 (−0.010 to 0.008)</td>
</tr>
<tr>
<td>WMHs, third tertile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.98 (1.96 to 4.54)‡</td>
<td>2.89 (1.95 to 4.27)‡</td>
<td>2.58 (1.77 to 3.76)‡</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.79 (1.10 to 2.91)*</td>
<td>1.52 (0.95 to 2.44)</td>
<td>1.72 (1.10 to 2.68)*</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.53 (0.88 to 2.66)</td>
<td>0.94 (0.48 to 1.83)</td>
<td>0.90 (0.50 to 1.62)</td>
</tr>
<tr>
<td>LACs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.16 (1.48 to 3.17)‡</td>
<td>1.65 (1.16 to 2.34)*</td>
<td>1.49 (1.04 to 2.11)*</td>
</tr>
<tr>
<td>Model 1</td>
<td>2.22 (1.40 to 3.52)†</td>
<td>1.49 (0.97 to 2.30)</td>
<td>1.33 (0.89 to 1.99)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.78 (1.06 to 2.99)*</td>
<td>1.38 (0.80 to 2.38)</td>
<td>0.93 (0.55 to 1.56)</td>
</tr>
<tr>
<td>BMBs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.77 (1.21 to 2.61)†</td>
<td>2.10 (1.42 to 3.10)‡</td>
<td>1.76 (1.18 to 2.62)†</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.31 (0.83 to 2.08)</td>
<td>1.72 (1.07 to 2.75)*</td>
<td>1.47 (0.92 to 2.35)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.13 (0.67 to 1.91)</td>
<td>0.85 (0.44 to 1.66)</td>
<td>0.93 (0.52 to 1.68)</td>
</tr>
</tbody>
</table>

Data are presented as unstandardized regression coefficients (for WMHV) and odds ratios (per SD increase in PWV [SD = 2.9 m/s], office PP [SD = 20 mm Hg], or 24-hour PP [SD = 12 mm Hg]) with corresponding 95% CIs. Model 1 is adjusted for age and sex (and BV in case of WMHs). Model 2 is additionally adjusted for office MAP and office heart rate (aortic PWV and office PP) or 24-h MAP and 24-h heart rate (24-h PP).
*P<0.05.
†P<0.01.
‡P<0.001.

Figure 1. Plot illustrating the relationship between aortic PWV and WMHV for the total study population (n=167). The data points illustrate the predicted WMHV vs the aortic PWV, adjusted for age, sex, and BV. The P value indicates the significance level for the corresponding linear regression analysis (using log-transformed WMHV). Abbreviations as in Tables.

Figure 2. Plot illustrating the relationship between aortic PWV and WMHV for participants younger (n=83) and for participants older (n=84) than the median age of 52.7 years. The data points illustrate the predicted WMHV vs the aortic PWV, adjusted for age, sex, and BV, and for younger and older participants separately. P values indicate the significance levels for the corresponding linear regression analyses (using log-transformed WMHV). Abbreviations as in Tables.
might better reflect damage to the cerebral microcirculation than PP. Conversely, aortic PWV remained significantly related to WMHV and LACs after controlling for the MAP. Third, the inverse of arterial stiffness, ie, arterial compliance, is determined by the ratio of stroke volume:PP rather than PP alone.26 As such, PP only partly reflects arterial compliance (and, thus, stiffness), providing a further explanation for the lack of association with cerebral small-vessel disease.

The mechanisms linking large-artery stiffness and manifestations of (silent) cerebral small-vessel disease are complex and not well understood. Moreover, and contrary to large-artery stiffness, the role of small-artery stiffness has been studied less extensively.27 Our findings are consistent with the hypothesis that cerebral small-vessel disease results from abnormal flow pulsations into the brain microcirculation as a consequence of aortic stiffening, linking systemic large-artery to cerebral small-vessel disease.9 The brain is, under normal conditions, continuously perfused at high-volume flow throughout systole and diastole. Because vascular resistance and pulse wave reflection are very low, pulsations of pressure and flow extend well into the (micro)vascular bed.9 Exposure to highly pulsatile pressure and augmented flow, which exist in the carotid and vertebral arteries as a result of arterial stiffening, may, thus, lead to microvascular damage and eventually to stroke.9,28 In line with this hypothesis, reduced arterial wall compliance of large arteries has been associated with narrowing of retinal arterioles, which, in turn, has been related to the presence of WMHs and may reflect the state of the cerebral microcirculation.29

The present study has limitations. First, our study sample is relatively small, and with a cross-sectional study design, association does not imply causation. Accordingly, our observations need confirmation in longitudinal and adequately powered studies. Second, our study is carried out in a selected group of hypertensive patients referred to a university hospital, limiting the generalizability of our findings to other populations. Third, there are several methodologic limitations with respect to the measurement of arterial stiffness. Approximately 10% of our participants started antihypertensive treatment after ABPM but before PWV measurements, which might have influenced our findings. On the assumption that lowering BP reduces PWV, we believe that this most likely results in an underestimation of the observed associations between aortic PWV and WMHV, as well as LACs. Moreover, adjusting the regression models additionally for BP-lowering medication during the PWV measurements did not change our findings. Next, measuring the absolute distance between the carotid and femoral recording sites might overestimate the PWV. Although appropriate when being used within 1 study, the use of corrected distances, in which the carotid-femoral distance or the distance between the femoral artery and the sternal notch is adjusted for the distance between the sternal notch and the carotid artery, might be more accurate.3,30 Another important methodologic limitation is the lack of information on radial or carotid wave reflections. Radial and carotid waveforms enable the central PP and augmentation index to be determined as indices of the effects of aortic stiffening on cerebral blood flow. Also, MAP is best calculated from integration of waveforms rather than from brachial SBP and DBP.31 Accordingly, it is difficult to interpret the full hemodynamic profile of our participants from aortic PWV alone.3 Therefore, future studies investigating the relationship between arterial stiffening and cerebral small-vessel disease should implement both aortic PWV and central pressure measurements.3

Strengths of our study are that we included several manifestations of silent cerebral small-vessel disease, that the volumetric assessment of WMHs enabled us to explore the relation with arterial stiffness in continuous rather than in (arbitrary) categorical analyses, and that the associations were not biased by a history of symptomatic cardiovascular or cerebrovascular disease.

Perspectives

In this study we observed robust, cross-sectional associations between aortic stiffness and both WMHs and LACs. However, long-term follow-up studies are needed to evaluate whether arterial stiffening, determined by both aortic PWV and central pressure,3 really causes such manifestations of cerebral small-vessel disease and eventually stroke. Because both aortic stiffening and silent cerebral small-vessel disease increase the risk of future stroke,5,6,8 it is reasonable to consider that long-term reduction in arterial stiffness will reduce the risk of silent and eventually symptomatic cerebrovascular disease. We found higher aortic PWV to be associated with older age, male sex, long-standing hypertension, higher BP levels, and higher creatinine, cholesterol, and glucose levels. Consequently, arterial stiffness can be regarded as a summary measure for vascular damage caused by coexisting vascular risk factors.1 This implies, however, a multifactorial approach aimed at treating all reversible risk factors and, ultimately, prevention of progression of silent into clinically evident cerebrovascular disease.

Disclosures

None.

References

Increased Aortic Pulse Wave Velocity Is Associated With Silent Cerebral Small-Vessel Disease in Hypertensive Patients


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AORTIC PULSE WAVE VELOCITY IS ASSOCIATED WITH SILENT CEREBRAL SMALL-VESSSEL DISEASE IN HYPERTENSIVE PATIENTS

Léon H.G. Henskens a, Abraham A. Kroon a, Robert J. van Oostenbrugge b, Ed H.B.M. Gronenschild c, Monique M.J.J. Fuss-Lejeune a, Paul A.M. Hofman d, Jan Lodder b, Peter W. de Leeuw a

Departments of Internal Medicine (Division of General Internal Medicine, Subdivision Vascular Medicine) a, Neurology b, Psychiatry and Neuropsychology c and Radiology d, Maastricht University Medical Centre and Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands.
Expanded Methods

Quantification of white matter hyperintensity and brain volumes

All imaging data were transferred to a Macintosh workstation and analyzed using the in-house developed (E.G.) image-processing software package GIANT (General Imaging and Analysis Tools; Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, The Netherlands).

Figure S1 shows an example of severe WMHs on both T2-weighted and corresponding FLAIR images.

Images were preprocessed by standardization of the MRI intensity scale for both the FLAIR and T2-weighted scan data. For deriving the parameters (training) we used a random selection of 16 data sets. The result of this nonlinear intensity transformation is a consistent correspondence between intensity and tissue meaning for all our MRI data. The next training step was to derive the parameters describing the region of WMHs in a two-dimensional feature space (scatter plot) in which one axis was defined by the T2 intensity and the other axis by the FLAIR intensity. For this step, the WMHs were manually segmented by one of us (L.H.) in 10 other randomly selected data sets. In the scatter plot the WMHs showed up as a cluster with high signal intensities for both T2 and FLAIR.

The actual quantification of WMHs was performed semi-automatically. The axial FLAIR and T2 image stacks were displayed and aligned side by side in synchrony on the computer monitor, and the contrast and brightness were automatically optimized. This allowed visual inspection of the scan data and easy identification of WMHs. In each slice, a WMH had to be indicated manually by clicking in its region. This position served as a seed point for a region growing operation based on the
parameters derived in the above step. The volume of this WMH was calculated as the segmented area times the slice thickness including the interslice gap. We obtained the total WMHV by summing the volumes of all individual hyperintensities located in both the periventricular and deep white matter. Figure S2 shows an example of the semi-automatic detection of periventricular and deep WMHs using GIANT.

The brain volume, defined as the total volume of the white and gray matter, was derived fully automatically by means of skullstripping followed by tissue classification. Skullstripping was performed by a custom tool using both T2 and FLAIR data. The method is based on a series of mathematical morphology operations and active contours. Tissue classification involved thresholding by means of a probability function derived from the image histograms of the skullstripped data.

Figure S3 and Figure S4 show examples of a silent LAC and BMBs, respectively.
References


Supplemental Figures

Figure S1

Example of severe white matter hyperintensities on T2-weighted (A) and corresponding fluid-attenuated inversion recovery (FLAIR) (B) magnetic resonance imaging sequences. Hyperintensities extend from the regions surrounding the lateral ventricles (periventricular regions) into the deep, subcortical white matter.
T2-weighted (A) and corresponding fluid-attenuated inversion recovery (FLAIR) (B) magnetic resonance imaging sequences showing advanced hyperintensities in the periventricular and deep white matter. Panel B shows the results of the semi-automatic detection of periventricular (turquoise) and deep (red) white matter hyperintensities (WMHs) using GIANT. Total WMH volume is obtained by summing the volumes of all individual hyperintensities located in both the periventricular and deep white matter.
Example of a silent lacunar infarct on T2-weighted (A) and corresponding fluid-attenuated inversion recovery (FLAIR) (B) magnetic resonance imaging sequences. The white arrow head indicates a silent lacunar infarct in the basal ganglia; note the hyperintense (white) rim surrounding the lacune characteristic for infarction (gliotic tissue).
Figure S4

Examples of brain microbleeds on T2*-weighted gradient echo magnetic resonance imaging sequence. The punctate signal loss (hemosiderin-laden macrophages) is characteristic of microbleeds. Panel A indicates a single microbleed (black arrow head) in the basal ganglia. Panel B indicates five microbleeds in the cerebellum.