Enlarged Perivascular Spaces on MRI Are a Feature of Cerebral Small Vessel Disease

Fergus N. Doubal, MRCP; Alasdair M.J. MacLullich, MRCP; Karen J. Ferguson, PhD; Martin S. Dennis, FRCP; Joanna M. Wardlaw, FRCR

Background and Purpose—Enlarged perivascular spaces in the brain are common but generally overlooked and of uncertain pathophysiology. They may reflect underlying cerebral small vessel disease. We determined whether enlarged perivascular spaces were associated with lacunar stroke subtype and white matter hyperintensities, markers of established small vessel disease.

Materials and Methods—We prospectively recruited patients with acute ischemic lacunar or cortical stroke. Age-matched nonstroke control subjects were also recruited. We rated basal ganglia and centrum semiovale enlarged perivascular spaces 0 to 4 (0=none, 4=>40) on T2-weighted MRI and white matter hyperintensities. We compared enlarged perivascular spaces between stroke subtypes and control subjects and assessed associations with vascular risk factors and white matter hyperintensities.

Results—We recruited 350 patients; 129 lacunar, 124 cortical stroke, and 97 age-matched control subjects. Adjusting for vascular risk factors and white matter hyperintensities, total enlarged perivascular spaces were associated with lacunar stroke subtype (P=0.04) in the acute stroke group (n=253); basal ganglia enlarged perivascular spaces were associated with lacunar stroke subtype (P=0.003), deep (P=0.02) and periventricular white matter hyperintensities (P=0.01); in all 350 subjects, total enlarged perivascular spaces were associated with deep (P<0.001) and periventricular (P<0.001) white matter hyperintensities.

Conclusions—Although prevalent in patients with vascular risk factors and stroke, enlarged perivascular spaces are specifically associated with lacunar ischemic stroke and white matter hyperintensities. Further studies should determine the mechanism of this association while including adequate controls to account for stroke and vascular risk factors. Enlarged perivascular spaces should not be overlooked in studies of small vessel disease. (Stroke. 2010;41:00-00.)

Key Words: enlarged perivascular spaces ■ lacunar infarcts ■ small vessel disease ■ white matter disease

Enlarged perivascular spaces (EPVS), or Virchow-Robin spaces, are cerebrospinal fluid-filled cavities that surround small penetrating cerebral arterioles and correspond with extensions of the subarachnoid space.1 EPVS are visible on axial T2-weighted cerebral MRI as characteristic small high-signal areas in the basal ganglia and centrum semiovale that follow the orientation of penetrating arterioles. They appear linear when parallel and dot-like when perpendicular to the imaging plane (see Figure).

Although it is common to see a few EPVS on T2-weighted MRI at all adult ages, EPVS are found in increased numbers in older people2 and have been associated with impaired cognitive function,3 depression,4 and diabetic retinopathy5 and are found in and around active lesions associated with inflammation in multiple sclerosis.6 A possible association with cerebral small vessel disease is suggested by their greater frequency in patients diagnosed as having vascular dementia as opposed to Alzheimer disease,7 their association with white matter hyperintensities (WMH) in patients with lacunar stroke,8 and their high frequency in patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy.9 However, vascular dementia is not per se a marker of small vessel disease, and a control group with stroke of a different etiology (eg, large artery stroke) would be required to demonstrate a specific association with lacunar stroke, something that no previous study has done. It is unclear therefore whether EPVS are a marker of small vessel disease or simply represent a generalized brain response to exposure to a range of vascular or other risk factors, for example inflammation or increasing age.

We investigated first whether MRI-defined EPVS (in the basal ganglia or centrum semiovale) were associated more with small vessel (lacunar) ischemic stroke than with large vessel stroke and second, whether EPVS were associated with WMH.
Patients and Methods
We recruited patients prospectively with clinical lacunar or mild cortical stroke at presentation to a teaching hospital within 3 months of symptom onset between April 2005 and December 2007. The hospital sees approximately 550 possible strokes/transient ischemic attacks (including severe and hemorrhagic stroke) per year of whom approximately 250 might have had a mild cortical or lacunar stroke. Exclusion criteria were: contraindications to MRI, unstable medical condition, and severe or hemorrhagic stroke. The main reasons for potentially eligible patients being excluded were that the diagnosis of stroke was not definite (only possible or probable), the patient had a severe stroke, or the patient declined or had contraindications to MRI scanning. All patients were examined by an experienced stroke physician and classified into lacunar or cortical stroke clinical syndromes according to the Oxfordshire Community Stroke Project classification.10 Diagnostic MRI at presentation (1.5-T MR scanner Signa LX; General Electric) with 22 mTm⁻¹ maximum strength gradients included axial diffusion-weighted, T2-weighted, fluid-attenuated inversion recovery, gradient echo, and sagittal T1-weighted sequences. Patients had carotid Doppler ultrasound, electrocardiogram, routine blood tests, and further clinical investigations as indicated.

We recorded severity of stroke (National Institutes of Health Stroke Scale), age, sex, race and history of diabetes, hypertension, ischemic heart disease, peripheral vascular disease, stroke, or transient ischemic attack. We defined symptomatic carotid stenosis as >50% in the relevant artery.11 We defined atrial fibrillation as history of atrial fibrillation or atrial fibrillation on electrocardiogram.

We defined lacunar syndromes as described in the Oxfordshire Community Stroke Project and mild cortical stroke syndromes as being equivalent to a partial anterior circulation stroke as described previously.10,12 Following initial clinical classification, we further classified stroke subtype using radiological criteria, that is, whether the recent infarct on MRI was cortical or lacunar, and used both the clinical and radiological classification to assign the final stroke subtype classification. When the classifications differed, the radiological classification was used because approximately 15% to 20% of cortical syndromes can arise from lacunar strokes and vice versa.13 If no definite recent lesion was visible on the scan, the clinical classification was used. We recorded the presence and characteristics of old stroke lesions but subtyped stroke based on the acute lesion. We compared EPVS in the lacunar and cortical strokes with healthy older male control subjects recruited and scanned as previously described on a 2T gradient echo Prestige scanner.3 These participants were free of vascular disease and were taking no regular medication. Note the sequences were optimized for both scanners used in this analysis to obtain the best possible quality diagnostic structural imaging and we performed regular quality assurance checks.

The study was approved by the local research ethics committee and all participants gave written, informed consent.

Image Analysis
All images were coded by an experienced neuroradiologist (J.M.W.) using a standardized classification system14 for the presence, size, and size of the recent infarct (increased signal on diffusion-weighted imaging, decreased signal on apparent diffusion coefficient, possibly also increased signal on fluid-attenuated inversion recovery and/or T2, decreased signal on T1), and also for the presence, site, and size of any old infarcts or hemorrhages. Scans were coded for deep and periventricular WMH according to the Fazekas scale15 from 0 to 3. Cerebral atrophy was defined as deep (enlargement of the ventricles) or peripheral (enlargement of the gyri) and rated on a subjective scale of 0 to 3 (0=absent, 1=mild, 2=moderate, 3=severe) against a reference MR brain template of normal subjects.16 EPVS were defined as small, sharply delineated structures of cerebrospinal fluid intensity on imaging that followed the orientation of the perforating vessels and ran perpendicular to the brain surface. Therefore, they appeared round in axial section (in the basal ganglia) and linear if in longitudinal sections (in the centrum semiouale) and were <3 mm wide. They were of high signal on T2 and low signal on T1 and fluid-attenuated inversion recovery sequences. They were distinguished from lacunes by the latter’s large size (>3 mm and spheroid shape). We did not count isolated small large invaginations of cerebrospinal fluid round perforating vessels. We assessed EPVS in the basal ganglia and centrum semiovale separately because it is possible that due to their different locations and features, they may have distinct pathophysiologies. EPVS in both the basal ganglia and centrum semiovale were coded with the following scale applied to standard axial images: 0= no EPVS, 1<10 EPVS, 2=11 to 20 EPVS, 3=21 to 40 EPVS, and 4= >40 EPVS. The numbers refer to EPVS on one side of the brain; the higher score was used if there was asymmetry between the sides and EPVS were counted in the slice with the highest number. We summed basal ganglia and centrum semiovale EPVS to form a total EPVS score (0 to 8). Although several other rating scales for EPVS have been described, these are either limited in their anatomic location or in the range of EPVS that they describe, so we developed our own scale. Limited intrarater reliability testing (15 scans) showed an excellent intrarater Cohen κ score of 0.82 for basal ganglia EPVS and Cohen κ of 0.78 for centrum semiovale EPVS.

Statistical Analysis
Total EPVS was normally distributed and analyzed with multiple linear regression. Basal ganglia EPVS and centrum semiovale EPVS were not normally distributed and, to permit binary logistic regression, we dichotomized basal ganglia and centrum semiovale EPVS into 0 (EPVS scores 0, 1) and 1 (EPVS scores 2, 3, 4). We used t tests, Mann–Whitney U tests, and differences in proportions for association to test for differences between the lacunar and cortical groups. We used multiple regression to assess effects of potential explanatory variables in predicting numbers of EPVS, both total EPVS in the acute stroke group and healthy control subjects combined, and basal ganglia and centrum semiovale EPVS separately within the acute stroke group. We entered both stroke subtype (lacunar versus cortical) and WMH separately into the model because WMHs are found commonly in patients with cortical stroke and normal older people. The α value for statistical significance was set at 0.05. All analyses were performed with Minitab software (Version 14, Minitab
Table 1. Baseline Characteristics of Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lacunar Stroke (n=129)</th>
<th>Cortical Stroke (n=124)</th>
<th>Difference (95% CI) and P Value Between Lacunar and Cortical Groups</th>
<th>Healthy Control Subjects (n=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), years</td>
<td>66.3 (11.6)</td>
<td>70.0 (11.5)</td>
<td>3.6 (0.8, 6.5) P=0.01</td>
<td>66.9 (1.4)</td>
</tr>
<tr>
<td>Median NIHSS</td>
<td>3</td>
<td>2</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>77 (60%)</td>
<td>88 (70%)</td>
<td>10% (-1%, 22%) P=0.06</td>
<td>97 (100%)</td>
</tr>
<tr>
<td>AF</td>
<td>6 (4.6%)</td>
<td>16 (12.90%)</td>
<td>8% (1, 15) P=0.02</td>
<td>0</td>
</tr>
<tr>
<td>Carotid stenosis &gt;50% (NASCET)</td>
<td>5 (3.88%)</td>
<td>14 (11.29%)</td>
<td>7% (1, 13) P=0.02</td>
<td>0</td>
</tr>
<tr>
<td>History of previous TIA</td>
<td>19 (14.96%)</td>
<td>13 (10.48%)</td>
<td>4% (-4, 12) P=0.29</td>
<td>0</td>
</tr>
<tr>
<td>History of previous stroke</td>
<td>9 (6.98%)</td>
<td>14 (11.38%)</td>
<td>4% (-3, 12) P=0.23</td>
<td>0</td>
</tr>
<tr>
<td>History of IHD</td>
<td>17 (13.18%)</td>
<td>34 (27.42%)</td>
<td>14% (4, 24) P=0.004</td>
<td>0</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>84 (65.32%)</td>
<td>70 (56.59%)</td>
<td>9% (-3, 20) P=0.15</td>
<td>0</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>22 (17.05%)</td>
<td>14 (11.29%)</td>
<td>6% (-3, 14) P=0.19</td>
<td>0</td>
</tr>
<tr>
<td>History of peripheral vascular disease</td>
<td>5 (3.88%)</td>
<td>6 (4.84%)</td>
<td>1% (-4, 6) P=0.71</td>
<td>0</td>
</tr>
<tr>
<td>Median deep white matter Fazekas score (IQR)</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>P=0.92</td>
<td>1 (0–1)</td>
</tr>
<tr>
<td>Median Periventricular white matter Fazekas score (IQR)</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>P=0.50</td>
<td>1 (0–1)</td>
</tr>
<tr>
<td>Mean total EPVS score (SD)</td>
<td>3.81 (1.76)</td>
<td>3.46 (1.72)</td>
<td>0.3 (-0.1, 0.8) P=0.11</td>
<td>1.02 (0.89)</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; AF, atrial fibrillation; NASCET, North American Symptomatic Carotid Endarterectomy Trial; TIA, transient ischemic attack; IHD, ischemic heart disease; IQR, interquartile range.

Results

We recruited 350 patients in total, 253 patients with acute stroke and 97 normal healthy age-matched control subjects (Table 1). Of the 253 patients with stroke, the mean age was 68.1 years (SD, 11.6 years; range, 34 to 95 years), median National Institutes of Health Stroke Scale 2 (interquartile range, 2 to 3), 65% were male, and there were 129 patients with lacunar stroke and 124 patients with cortical stroke. No patients had concurrent acute lacunar and cortical infarcts. The mean age of the healthy control subjects was 66.9 years (SD, 1.4 years) and they were all male. Among the patients with acute stroke, those with cortical stroke were older (70 versus 66 years P=0.01) and had a higher prevalence of atrial fibrillation (P=0.02), carotid stenosis >50% (P=0.02), and ischemic heart disease (P=0.004) than the patients with lacunar stroke (Table 1).

EPVS in Ischemic Stroke Subtypes

In the 253 patients with acute stroke, total EPVS (basal ganglia and centrum semiovale combined) were independently and significantly associated with lacunar stroke subtype after correction for important confounders, including vascular risk factors, age, WMH, and deep atrophy, in keeping with our primary hypothesis (Table 2). Basal ganglia EPVS were modeled simultaneously with centrum semiovale EPVS to look at separate associations despite being correlated at Spearman rho 0.47 (P<0.001). Basal ganglia EPVS were associated with lacunar stroke subtype after correcting for other confounders, including WMH and deep atrophy (Table 3). Centrum semiovale EPVS did not differ between ischemic stroke subtypes.

EPVS and WMHs

In all 350 patients, total EPVS were associated with deep and periventricular WMH after adjusting for age, presence of stroke, hypertension, diabetes, and sex (Table 4). Furthermore, in the acute stroke group of 253 patients, we found that basal ganglia EPVS were associated with deep and periventricular WMH adjusting for lacunar stroke subtype, age, and deep atrophy. Centrum semiovale EPVS were not associated with any explanatory variables (after correcting for basal ganglia EPVS).

EPVS and the Presence of Stroke

In all 350 patients, EPVS were associated with the presence of any stroke on univariate analysis, but this association was reduced to below statistical significance after adjustment for WMH.

EPVS, Vascular Risk Factors, and Demographics

In all 350 patients, EPVS were associated with increasing age on univariate analysis, but this association was attenuated to below statistical significance after adjustment for WMH. After full adjustment for other variables, only deep and periventricular WMH remaining were significantly associated with EPVS.

Table 2. Multivariate Associations With Total EPVS as the Dependent Continuous Variable Correcting for All the Other Explanatory Variables in the Table in the Subgroup of 253 Patients With Acute Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.02</td>
<td>0.08</td>
</tr>
<tr>
<td>Lacunar stroke subtype (compared with cortical stroke)</td>
<td>0.38</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.06</td>
<td>0.76</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.067</td>
<td>0.79</td>
</tr>
<tr>
<td>Deep WMH</td>
<td>0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Periventricular WMH</td>
<td>0.46</td>
<td>0.01</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.01</td>
<td>0.96</td>
</tr>
<tr>
<td>Deep atrophy</td>
<td>-1.4</td>
<td>0.29</td>
</tr>
</tbody>
</table>
### Discussion

Our novel findings are that total and basal ganglia EPVS are independently and significantly associated with lacunar compared with cortical ischemic stroke in keeping with the hypothesis that EPVS and lacunar stroke share a common etiology. EPVS were also independently and significantly associated with deep and periventricular WMH after correcting for increasing age and vascular risk factors.

The strengths of this study are that we directly compared EPVS in ischemic stroke subtypes and between patients with stroke and healthy age-matched control subjects. The sample size was large and we were thus able to investigate several explanatory variables with multivariate regression to correct for confounders, including those identified with multi-sequence MRI. The recruitment for this study was prospective and consecutive and patients were carefully characterized by a stroke physician. The patients had carefully standardized MRI brain imaging on a dedicated research scanner as part of the study assessment rather than using either retrospectively recruited patients or those who had had clinically indicated brain MRI. All MRI scans were assessed by one experienced neuroradiologist using a standard EPVS rating scale.

This study has some limitations. The healthy control group did not have basal ganglia and centrum semiovale EPVS characterized separately (although we were able to use a combined total EPVS score to compare groups) and the healthy control group was all male (although sex was not shown to have an independent association with EPVS in the acute stroke group). This is a cross-sectional study and therefore can only determine associations, not causation nor the sequence of development of small vessel disease features.

The exact causes of EPVS are uncertain but the perivascular space is an important conduit for drainage of interstitial fluid to the ventricles and could be affected by various factors, including abnormalities at the blood brain interface and inflammation. EPVS are associated with increased blood–brain barrier permeability in lacunar stroke, are found in patients with active multiple sclerosis lesions, and are associated with WMH which are associated with increased blood brain barrier permeability.

WMH are more common in lacunar than cortical stroke, again supporting a common small vessel disease pathophysiology. In the case of multiple sclerosis, the EPVS were associated with inflammation and blood–brain barrier breakdown and resolved as the active inflammation subsided. Endothelial inflammation may be associated with small vessel disease also. It is therefore plausible that EPVS are a manifestation of a cerebral small vessel pathology associated with, and a possible marker for, altered blood–brain barrier function. A possible link with venular pathology in small vessel disease and inflammation is suggested by our (and others’) previous observations that retinal veins are wider in lacunar compared with cortical stroke, and cerebral venous insufficiency secondary to collagenosis has been implicated in the etiology of white matter disease.

Basal ganglia EPVS were associated on multivariate analysis with periventricular (but not deep) WMH and increasing age in lacunar stroke (n = 165). Although this study included patients with large artery stroke (n = 41) as well as lacunar stroke, they did not report the EPVS association for cortical stroke thereby making it impossible to say that the EPVS were specifically associated with lacunar stroke. A study of 816 patients using clinically indicated brain MRI showed that EPVS were strongly associated with age but not WMH, hypertension, or dementia.

The clinically indicated MRI scan, retrospective design, wide age range, and a low rate of WMH may explain the differences with our results. EPVS and WMH were more frequent in patients with vascular dementia than other types of dementia but...
with possible confounding by higher rates of white matter disease in vascular dementia and study size (n=95).7

Beyond confirming that EPVS seen on MRI are indeed enlarged spaces around the perforating arterioles or venules, pathological studies of white matter disease produce conflicting information and shed little light on their etiology.24 EPVS were present at all Fazekas grades of deep and periventricular WMH.25 In the brains of 19 patients >60 years who had died of nonbrain disease causes, comparison of MRI and pathological appearance suggested that arteriosclerosis leads to demyelination, and then axonal loss and then subsequent dilatation of perivascular spaces and WMH.26 However, it is difficult to infer a sequence of events often late in their time course from a static picture obtained postmortem. It is not clear therefore if EPVS precede, follow, or appear concurrently with WMH. Variation in methods for assessing EPVS may account for the discrepancies between studies and points to the need for a robust and reliable classification scheme for EPVS.

EPVS are relatively underresearched but easy to recognize. Among older people, they are part of the spectrum of small vessel disease associated with widespread white matter lesions, lacunar stroke, and cognitive impairment. We propose that EPVS should be incorporated into white matter rating scales because the associations and significance of EPVS will only be elucidated once EPVS have been studied in more depth. Future research should investigate longitudinal associations among EPVS, WMH, stroke, and cognitive function to fully ascertain temporal associations between these common and important abnormalities. More information is needed to provide accurate prognostic indicators and guide development of future therapies for small vessel disease.

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Disclosures
None.

References
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