Background and Purpose—The size variation of single subcortical infarcts (SSIs) may be because of differences in stroke mechanisms or branching patterns of perforators. We aim to investigate this issue using high-resolution MRI.

Methods—Patients with high-resolution MRI–identified SSI without significant (≥50%) middle cerebral artery stenosis were enrolled. Perforator stems were defined as perforators originating from the middle cerebral artery and perforator branches as linear structures inside the infarcted area, traceable from >2 adjacent slices. The branching index was calculated as the number of perforator branches divided by the number of perforator stems. Clinical and imaging characteristics were compared between large (≥20 mm in diameter) and small SSI groups.

Results—Forty-one patients (10 large and 31 small SSIs) were enrolled. Larger SSIs were more closely associated with diabetes mellitus and severe neurological dysfunction but not with the presence of middle cerebral artery plaque. Although there was no difference in the number of perforator stems, the number of perforator branches (4.8±2.2 versus 2.3±1.4; P=0.005) and branching index (2.9±1.0 versus 1.2±0.8; P<0.001) was higher in the large SSI group. SSI diameter showed a significant correlation with the number of perforator branches (r=0.630; P<0.001) and branching index (r=0.750; P<0.001).

Conclusions—SSI diameter seems to be associated with anatomic branching variation rather than the mechanism of stroke. Definition of small vessel disease with lesion diameter criteria may not be appropriate. (Stroke. 2014;45:00-00.)

Key Word: magnetic resonance imaging

Single subcortical infarctions (SSIs) with a diameter <15 or 20 mm occurring in a perforating artery territory have been classified as being caused by small vessel occlusion. Infarcts with a larger diameter are classified as stroke of undetermined cause.¹ However, there is controversy about whether SSI diameter is an appropriate criterion for classifying stroke subtypes.² ³ Although the varied size of SSIs may be because of different pathogenic mechanisms, variation in the branching pattern of middle cerebral artery (MCA) perforators is an alternative hypothesis.² This controversy is challenging to resolve because perforators are not readily visible by conventional MR angiography.

The aim of this study was to address these hypotheses by assessing the MCA plaque and the branching pattern of perforators with the use of high-resolution MRI in patients with SSI.

Methods

Patients

This study was performed in parallel with a previously published study, with a slight modification of the inclusion criteria.¹ Briefly, patients admitted to the Asan Medical Center between July 2011 and August 2012 were prospectively enrolled if they (1) had a single infarct identified with the diffusion-weighted image in the lenticulostriate arterial territory (basal ganglia, corona radiata, and internal capsule); (2) did not have significant (>50% stenosis) and relevant MCA disease; (3) had no identified source of the embolism (eg, embolic, cardiac disease or significant [≥50%] stenosis of the relevant artery); and (4) the MCA vessel and the infarcted area could be demonstrated by sagittal image of high-resolution MRI performed on the fifth day after the initial MRI. The study protocol was approved by the local institutional review board, and written informed consent was obtained from each patient.

Imaging Protocol and Analysis

The image sequences were described in the previous study.¹ The maximum diameter of the ischemic lesion was measured from the axial slice of the diffusion-weighted image. SSIs with a maximum diameter ≥20 mm were defined as large and others as small SSIs. The number of perforators was counted from the sagittal slice of the 3-dimensional reconstructed proton density image, which was acquired with a 1-mm thickness with 0.5-mm gap. Perforators branching from the MCA (perforator stem) and distal perforators shown inside the infarction (perforator branch) were separately counted. Although the diameter of perforator stem may reach 1 mm, the diameter of perforator branches is usually <0.5 mm.¹ Therefore, to
avoid multiple counts of a single perforator branch, longitudinal, linear, low-signal intensity structures traceable in adjacent slices were counted from a single slice that presented with the maximum number of perforator branches (Figure 1). The branching index was defined as the number of perforator branches over the number of perforator stems. The length of plaque was obtained as the number of continuous slices that showed evidence of plaque in the MCA. Indicators for small vessel disease (Fazekas scale of periventricular white and microbleeds) and atherosclerosis (presence of atherosclerosis in other cerebral vessels) were also investigated. A stroke neuroradiologist (B.J.K.) and a neuroradiologist (D.H.L.), who were blind to the MRI and clinical findings, evaluated the MCA plaques on high-resolution MRI. If any discrepancies were encountered, a third investigator (J.S.K.) adjudicated. The number of perforators in the sagittal MRI was calculated by B.J.K., and the mean number of 2 counts with a 1-week interval was used.

**Statistical Analysis**

Clinical and imaging variables were compared between patients with large and small SSIs. The χ² and Student t test were used as appropriate. The correlation between the maximum diameter and the branching index was evaluated. All statistical analyses were performed using SPSS for Windows (version 17.0; SPSS Inc).

**Results**

Forty-one patients (men 51.2%; mean age, 59.6±11.4 years) were enrolled. Thirty-one patients had small SSIs, and 10 had large SSIs. The large SSI was associated with diabetes mellitus and higher National Institutes of Health Stroke Scale score. Indicators for small vessel disease and atherosclerosis, the presence of MCA plaque, superiorly located plaque, and plaque length were not different between the groups.

There was no difference in the number of perforator stems (2.0±0.8 versus 2.2±1.1; P=0.57) between groups; however, the mean number of perforator branches (4.8±2.2 versus 2.3±1.4; P=0.005) and the branching index (2.9±1.0 versus 1.2±0.8; P<0.001) was higher in the large SSI group (Table). The results were similar when we used 15 mm as the cutoff value of large SSIs (Table I in the online-only Data Supplement). The number of perforator branches (r=0.630; P<0.001) and branching index (r=0.750; P<0.001) demonstrated a strong correlation with the maximum axial diameter of the lesion, whereas the length of plaque was not.

**Discussion**

We found that the number of perforator branches and branching index was greater in large SSIs. The maximum diameter of SSI was positively correlated with the number of perforator branches. Conversely, there were no differences in the indicators of atherosclerosis and the prevalence of MCA plaque between large and small SSIs. The prevalence of superiorly located plaque, which was reported to be more closely associated with SSI, was not different, either. Our data are consistent with a previous report showing that the axial diameter of diffusion-weighted image-identified SSI was not significantly different between patients with or without relevant MCA disease and support the hypothesis that the SSI size difference may be explained by variations in the branching pattern of perforators (Figure 2) rather than the pathogenic mechanism (large artery atherosclerosis versus small artery disease).

Previous pathology studies have shown that the number of perforator stems ranges from 2 to 12, 50% to 70% of the perforator branches share common trunks, and the calculated branching index is 1.66. In our study, the number of perforator stems ranged from 1 to 7, the mean branching index was 1.34, and 56.1% (23 of 41) of patients had a branching index >1. The relatively low branching index in our study may be attributed to the fact that we strictly counted only the traceable longitudinal structures from a single slice that contained the maximum number of perforator branches. Nevertheless, our results are generally in agreement with previous findings.

**Table. Clinical and Radiological Characteristics of Large and Small SSI**

<table>
<thead>
<tr>
<th></th>
<th>Large SSI</th>
<th>Small SSI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>62.8±10.2</td>
<td>58.6±11.7</td>
<td>0.31</td>
</tr>
<tr>
<td>Male</td>
<td>4 (40.0)</td>
<td>18 (58.1)</td>
<td>0.32</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (70.0)</td>
<td>16 (51.6)</td>
<td>0.31</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (40.0)</td>
<td>2 (6.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3 (30.0)</td>
<td>7 (22.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>Smoking</td>
<td>2 (20.0)</td>
<td>6 (19.4)</td>
<td>0.96</td>
</tr>
<tr>
<td>Previous stroke history</td>
<td>2 (20.0)</td>
<td>4 (12.9)</td>
<td>0.58</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>1 (10.0)</td>
<td>1 (3.2)</td>
<td>0.39</td>
</tr>
<tr>
<td>Initial NIHSS</td>
<td>6.0±1.4</td>
<td>3.6±2.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Concomitant cerebral atherosclerosis</td>
<td>3 (30.0)</td>
<td>16 (51.6)</td>
<td>0.23</td>
</tr>
<tr>
<td>Presence of plaque</td>
<td>5 (50.0)</td>
<td>22 (71.0)</td>
<td>0.22</td>
</tr>
<tr>
<td>Superior plaque</td>
<td>2/5 (40.0)</td>
<td>14/22 (63.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Plaque length</td>
<td>1.6±2.8</td>
<td>2.5±2.2</td>
<td>0.32</td>
</tr>
<tr>
<td>Fazekas grade of periventricular white matter</td>
<td>0.9±0.8</td>
<td>1.0±0.5</td>
<td>0.71</td>
</tr>
<tr>
<td>Presence of microbleeds</td>
<td>2 (20.0)</td>
<td>5 (16.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>No. of perforator stems</td>
<td>2.0±0.8</td>
<td>2.2±1.1</td>
<td>0.57</td>
</tr>
<tr>
<td>No. of perforator branches</td>
<td>4.8±2.2</td>
<td>2.3±1.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Perforator branching index</td>
<td>2.9±1.0</td>
<td>1.2±0.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results are presented as n (%) or mean±SD. NIHSS indicates National Institutes of Health Stroke Scale; and SSI, single subcortical infarction.
Our study has several limitations. First, the sample size was small and the results were not confirmed by pathology. Second, infarcts are presented as hyperintense lesions and may have exaggerated the visualization of perforator branches, especially in patients with large SSI. Third, we counted perforator branches only on 1 sagittal image, and our results may not represent the actual number of branches. Data obtained from coronal imaging could have supported our findings. Despite these limitations, our data suggest that lesion diameter may not be an appropriate criterion for definition of small vessel disease. Additional studies are required to confirm our preliminary findings.

Disclosures

None.

References

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SUPPLEMENTAL MATERIAL

Branching patterns determine the size of single subcortical infarctions

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Supplemental Table 1 Number of perforator stem and branches and branching index using 15 mm as a cut-off value for large and small single subcortical infarction
**Supplemental Table I** Number of perforator stem and branches and branching index using 15 mm as a cut-off value for large and small single subcortical infarction

<table>
<thead>
<tr>
<th></th>
<th>Large SSI (n=19)</th>
<th>Small SSI (n=22)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Perforator stems</td>
<td>2.0±0.8</td>
<td>2.3±1.2</td>
<td>0.32</td>
</tr>
<tr>
<td>No. of Perforator branches</td>
<td>4.1±2.0</td>
<td>1.9±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perforator branching index</td>
<td>2.4±1.0</td>
<td>0.9±0.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results are expressed as mean±SD