Two-Layered Susceptibility Vessel Sign on 3-Tesla T2*-Weighted Imaging Is a Predictive Biomarker of Stroke Subtype

Nobuaki Yamamoto, MD; Junichiro Satomi, MD, PhD; Yoshiteru Tada, MD, PhD; Masafumi Harada, MD, PhD; Yuishin Izumi, MD, PhD; Shinji Nagahiro, MD, PhD; Ryuji Kaji, MD, PhD

Background and Purpose—A susceptibility vessel sign (SVS) on 1.5-tesla (T)-T2*-weighted images may predict cardioembolism. It has also been detected in patients with large artery atherosclerosis. In patients with major vessel occlusion, the SVS was comprised 2 layers on 3T-T2*-weighted images. We assessed the efficacy of 2-layered SVS on 3T-T2*-weighted imaging scans for predicting cardioembolism.

Methods—Our study included 132 patients who had ischemic stroke within the preceding 24 hours and presented with internal carotid artery or middle cerebral artery occlusion because of cardioembolism or large artery atherosclerosis. We compared 2-layered SVS and SVS on 3T-T2*-weighted imaging scans for their sensitivity, specificity, and diagnostic odds ratio for predicting cardioembolism.

Results—We enrolled 132 patients (72 men; mean age, 74.5 years); of these, 63 (47.7%) were presented with cardioembolism. Although the sensitivity of SVS and 2-layered SVS for cardioembolism and large artery atherosclerosis was not statistically different (74.6% and 58.0%, respectively), the sensitivity of 2-layered SVS was significantly higher in patients with cardioembolism (42.9%) than those with large artery atherosclerosis (2.9%; P<0.001). The specificity and diagnostic odds ratio for 2-layered SVS for cardioembolism were 97.1% and 25.1; for SVS they were 42.0% and 2.1, respectively.

Conclusion—The specificity of 2-layered SVS for cardioembolism was high. It may be useful for predicting cardioembolism and for the management of patients with acute ischemic stroke. (Stroke. 2015;46:269-271. DOI: 10.1161/STROKEAHA.114.007227.)

Key Words: atherosclerosis ■ diagnostic imaging ■ internal carotid artery ■ intracranial embolism ■ magnetic resonance imaging ■ middle cerebral artery ■ occlusion

Cardioembolism and large artery atherosclerosis (LAA) are major factors in cerebral arterial occlusion. Identification of the ischemic stroke subtype is of utmost importance for the appropriate management of patients with acute stroke and 24-hour ECGs and echocardiograms are required. Although some MRI studies showed biomarkers of ischemic stroke, for example, the vessel status or penumbral enhancement, these markers did not help to identify the stroke subtype. However, MRI predictors of cardioembolism are useful because they are objective and yield information such as the infarct volume and the site(s) of arterial obstruction.

The composition of clots in obstructed arteries varies depending on whether the embolic source is cardioembolism or LAA. Although the susceptibility vessel sign (SVS) on 1.5T-T2*-weighted images (T2*-WI) was reported to be associated with cardioembolism, it was also detected in some patients with LAA. Some patients with acute cerebral arterial occlusion manifested 2-layered SVS on 3T-T2*-WI scans. We assessed the efficacy of the 2-layered SVS on 3T-T2*-WI scan for predicting cardioembolism and examined whether its value for predicting the stroke subtype is greater than of SVS.

Methods
This study was approved by the local ethics committee. Our inclusion criteria, MRI parameters, and statistical analysis methods are provided in the online-only Data Supplement. Only consecutive patients with internal carotid artery or middle cerebral artery occlusion because of cardioembolism or LAA were included in this study. We compared SVS and 2-layered SVS observed on 3T-T2*-WI scans for their sensitivity, specificity, and diagnostic odds ratio for cardioembolism. SVS was defined as a hypointense signal in a vessel cistern on T2*-WI scans that was larger than the contralateral arterial diameter, 2-layered SVS as an SVS that contained a low-intensity core surrounded by a signal of higher intensity (Figure 1).

Results
We included 132 patients (72 men; mean age, 74.5±12.1 years). Of these, 63 (47.7%) were in the cardioembolism
group. Their baseline characteristics differed significantly only with respect to atrial fibrillation at the time of admission (Table I in the online-only Data Supplement). The sensitivity of SVS was not statistically different in patients with cardioembolism (74.6%) or LAA (58.0%). However, the sensitivity of 2-layered SVS was significantly higher in the cardioembolism group than in the LAA group (42.9% versus 2.9%, P<0.001; Figure 2). In addition, the specificity and diagnostic odds ratio of 2-layered SVS were superior to SVS in patients with cardioembolism (specificity, 97.1% versus 42.0%; diagnostic odds ratio, 25.1 versus 2.1; Table).

The diagnostic indices are shown in Table II in the online-only Data Supplement. Of 45 patients without known atrial fibrillation at the time of admission in cardioembolism group, 9 (20%) manifested the 2-layered SVS and were diagnosed with cardioembolism. Representative cases are shown in Figure I in the online-only Data Supplement.

**Table. Diagnostic Accuracy of MRI Findings for Cardioembolism**

<table>
<thead>
<tr>
<th>MRI Findings</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVS</td>
<td>74.6%</td>
<td>42.0%</td>
<td>2.1</td>
</tr>
<tr>
<td>Two-layered SVS</td>
<td>42.9%</td>
<td>97.1%</td>
<td>25.1</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; DOR, diagnostic odds ratio; and SVS, susceptibility vessel sign.

**Discussion**

Although MRI can detect cerebral major vessel occlusion because of thrombus,

We looked for imaging biomarkers of the stroke subtype in patients with acute ischemic stroke. Although the SVS on 1.5T-T2*-WI was detected in 25.5% of patients with LAA,

the 2-layered SVS exhibited a higher specificity for cardioembolism than SVS (97.1% versus 74.5%) suggesting that the 2-layered SVS is useful for predicting cardioembolism.

We performed T2*-WI with a longer echo time to emphasize susceptibility differences among tissues. To our knowledge, no abnormal findings on 3T-T2*-WI with a long echo time have been reported. Our imaging parameters are useful for detecting paramagnetic materials and contributed to our findings. The appearance of SVS may depend on the amount of clots and the paramagnetic material content within the clots. The amount of clots originating from cardioembolism is thought to be larger than those because of LAA,

and this may contribute to the higher sensitivity of the SVS for cardioembolism than LAA reported by Cho et al.

We did not assess the histology of the endovascularly retrieved clots. Cardioembolism clots contain more fibrin than erythrocytes and LAA clots were associated with a high percentage of erythrocytes. Histologically, thrombi from patients with atrial fibrillation were heterogeneous and contained more fibrin than erythrocytes while LAA clots harbored a high proportion of erythrocytes. Deoxyhemoglobin and hemosiderin in the erythrocytes are paramagnetic materials that result in a signal reduction on T2*-WI scans. We suggest that 2-layered SVS reflects the heterogeneity of paramagnetic and diamagnetic materials within the clots.

Because the sensitivity of 2-layered SVS for predicting cardioembolism was not high (42.9%), we cannot exclude cardioembolism in our patients without such SVS. However, we demonstrated that the 2-layered SVS on MRI scans was highly specific and of positive predictive value and that this sign is useful for diagnosing cardioembolism even in patients without known atrial fibrillation. Kimura et al reported that the appearance of SVS on the middle cerebral artery after the administration of tissue-type plasminogen activator is predictive of no early recanalization. We did not assess the value of 2-layered SVS for therapeutic decision-making and studies to analyze its use for reperfusion therapy such as the administration of tissue-type plasminogen activator are underway in our laboratory. Finally, our study was conducted on a 3T scanner and as such instruments are not available at many centers, we are conducting additional studies using 1.5T scanners.

**Figure 1.** Patients with susceptibility vessel sign (SVS) and 2-layered SVS. Case A, A 68-year-old man with right internal carotid artery (ICA) occlusion because of cardioembolism. (1) Magnetic resonance angiography (MRA) showing the occlusion site (arrowhead), (2) 3-Tesla (T)-T2*-weighted imaging (T2*-WI) scan (white arrow) showing a 2-layered SVS with a low-intensity signal core (arrowheads) surrounded by a higher intensity signal. Case B, A 72-year-old woman with left ICA occlusion because of cardioembolism (CE). (1) MRA showing the occlusion site (arrowhead), (2) 3T-T2*-WI showing 2-layered SVS at the ICA. Case C, A 76-year-old man with middle cerebral artery occlusion because of large artery atherosclerosis (LAA). (1) MRA showing the occlusion site (arrowhead), (2) 3T-T2*-WI shows SVS without a low-intensity core.

**Figure 2.** Comparison of 2-layered susceptibility vessel sign (SVS) and SVS for their sensitivity for cardioembolism (CE) and large artery atherosclerosis (LAA). n.s indicates not significant.
Conclusions
The 2-layered SVS on 3T-T2*-WI scans can predict cardioembolism. Additional studies are needed to assess the value of this sign for the selection of the appropriate reperfusion treatment.

Disclosures
None.

References
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Stroke. 2015;46:269-271; originally published online December 4, 2014;
doi: 10.1161/STROKEAHA.114.007227

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SUPPLEMENTAL MATERIAL

The two-layered susceptibility vessel sign on 3-tesla T2*-weighted imaging is a predictive biomarker of stroke subtype

Running head: Two-layered SVS predicts the stroke subtype

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Key words: 3-tesla magnetic resonance imaging, T2*-weighted imaging, susceptibility vessel sign, two-layered susceptibility vessel sign, stroke subtype, imaging biomarker
Supplemental Methods

Inclusion criteria

This retrospective study was based on a prospectively collected register of consecutive patients seen between April 2009 and December 2013. We extracted patient data from the registry. Included were only patients manifesting occlusion of the internal-carotid artery (ICA), the horizontal-portion of the middle-cerebral artery (MCA), or the insular-portion of the MCA due to cardioembolism (CE) or large-artery atherosclerosis (LAA) within 24 hr of ischemic stroke onset. The occlusion site was determined by magnetic resonance angiography (MRA).

The stroke subtypes were defined according to the Trial of ORG 10172 in the Acute Stroke Treatment criteria. Baseline characteristics at the time of admission were compared between patients with CE and LAA (Supplemental Table I).

Definition of complicating diseases

Continuous variables are expressed as the mean ± standard deviation (S.D.). Atrial fibrillation (AF) was defined as a positive finding on electrocardiograms performed at the time of admission, diabetes mellitus as a hemoglobin A1C level greater than 6.5% or the current use of drugs for hyperglycemia, dyslipidemia as a total cholesterol concentration greater than 5.70 mmol/L and/or triglyceride greater than 2.26 mmol/L or the current use of drugs for hyperlipidemia, and hypertension as a systolic and diastolic blood pressure greater than 140 mmHg and 90 mmHg, respectively, or the current use of depressor drugs.

MR imaging

Magnetic resonance imaging (MRI) was on a 3-tesla scanner (Discovery MR 750; GE Healthcare, Milwaukee, WI) equipped with an 8-channel phased-array head coil. All patients underwent diffusion-weighted imaging (DWI), MRA and T2*-weighted imaging (T2*-WI). For T2*-WI gradient echo sequences the parameters were field of view, 24 cm; matrix, 320 x 192; repetition time (TR), 400 ms; echo time (TE), 28 ms; flip angle, 28°; slice thickness, 6 mm; gap, 1.5 mm; number of slices, 18.

A neurologist and a neurosurgeon independently evaluated the T2*-WI scans; both were blinded to all patient information.

Statistical analysis

Comparisons were performed using the Mann-Whitney U-test for continuous- and the \( \chi^2 \)-test for categorical variables. Statistical significance was defined as \( p < 0.05 \). The kappa statistic value was used to assess interobserver and intraobserver variability for evaluating the susceptibility vessel sign (SVS) and two-layered SVS. For diagnostic accuracy assessment we used the diagnostic odds ratio, sensitivity, specificity, and
negative- and positive predictive value (NPP, PPP). All statistical analyses were with the SPSS program, version 20.0 software package (SPSS, IBM Corporation, Tokyo) for Windows 7.

**Supplementary result**

*Comparison of the baseline characteristics*

Supplemental Table I is a comparison of the baseline characteristics of patients with CE and LAA. All variables except complicated atrial fibrillation at the time of admission were not different significantly between CE and LAA.

*Diagnostic accuracy of SVS and two-layered SVS*

Supplemental Table II shows the diagnostic accuracy of the susceptibility vessel sign (SVS) and the two-layered SVS. The positive predictive value of the two-layered SVS was higher than that of the SVS. The kappa value for interobserver and intraobserver agreement for evaluating the two-layered SVS was 0.79 and 0.91, respectively, indicating good agreement.
### Supplemental Table I. Comparison of the baseline characteristics of the 132 patients

<table>
<thead>
<tr>
<th></th>
<th>CE, n = 63</th>
<th>LAA, n = 69</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>75.2 ± 11.7</td>
<td>73.9 ± 12.5</td>
<td>0.564</td>
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<tr>
<td>Sex, male, n (%)</td>
<td>34 (54.0)</td>
<td>38 (55.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Time from onset to MRI, min</td>
<td>349.8 ± 398.8</td>
<td>661.8 ± 1308.5</td>
<td>0.424</td>
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<tr>
<td><strong>Laboratory data</strong></td>
<td></td>
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<tr>
<td>Glucose, mmol/L</td>
<td>8.20 ± 3.75</td>
<td>7.68 ± 2.55</td>
<td>0.662</td>
</tr>
<tr>
<td>Leukocytes, 10^3/μL</td>
<td>7.7 ± 3.1</td>
<td>8.4 ± 3.2</td>
<td>0.116</td>
</tr>
<tr>
<td>Platelets, 10^3/μL</td>
<td>201.9 ± 78.0</td>
<td>221.1 ± 83.6</td>
<td>0.135</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>133.5 ± 22.4</td>
<td>134.7 ± 21.6</td>
<td>0.846</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.96 ± 0.54</td>
<td>4.95 ± 0.58</td>
<td>0.895</td>
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<tr>
<td>Low density lipoprotein, mmol/L</td>
<td>2.90 ± 1.03</td>
<td>2.92 ± 0.78</td>
<td>0.874</td>
</tr>
<tr>
<td>High density lipoprotein, mmol/L</td>
<td>1.42 ± 0.76</td>
<td>1.40 ± 0.44</td>
<td>0.686</td>
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<tr>
<td>Blood urea nitrogen, mmol/L</td>
<td>6.57 ± 2.61</td>
<td>8.25 ± 7.32</td>
<td>0.185</td>
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<td>Creatinine, mmol/L</td>
<td>86.6 ± 20.3</td>
<td>106.1 ± 106.0</td>
<td>0.555</td>
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<tr>
<td>Na, mmol/L</td>
<td>139.2 ± 2.7</td>
<td>139.2 ± 3.1</td>
<td>0.592</td>
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<tr>
<td>K, mmol/L</td>
<td>4.1 ± 0.6</td>
<td>4.1 ± 0.6</td>
<td>0.376</td>
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<tr>
<td>Cl, mmol/L</td>
<td>102.3 ± 14.0</td>
<td>103.7 ± 2.8</td>
<td>0.769</td>
</tr>
<tr>
<td>Aspartate aminotransferase, IU/L</td>
<td>28.9 ± 18.7</td>
<td>27.1 ± 14.6</td>
<td>0.238</td>
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<tr>
<td>Alanine aminotransferase, IU/L</td>
<td>28.9 ± 18.7</td>
<td>20.0 ± 12.7</td>
<td>0.387</td>
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<td>γ-glutamyl transpeptidase, IU/L</td>
<td>39.4 ± 42.4</td>
<td>40.3 ± 81.9</td>
<td>0.160</td>
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<td>Amylase, IU/L</td>
<td>78.5 ± 44.3</td>
<td>72.7 ± 26.5</td>
<td>0.828</td>
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<tr>
<td>Total bilirubin, μmol/L</td>
<td>16.2 ± 9.7</td>
<td>14.5 ± 8.2</td>
<td>0.294</td>
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<tr>
<td>Creatine kinase, IU/L</td>
<td>111.6 ± 94.6</td>
<td>170.4 ± 457.6</td>
<td>0.694</td>
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<tr>
<td>Total protein, g/L</td>
<td>69.2 ± 9.5</td>
<td>71.1 ± 7.3</td>
<td>0.101</td>
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<td><strong>Clinical findings</strong></td>
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<tr>
<td>Systolic BP, mmHg</td>
<td>153.3 ± 23.9</td>
<td>154.7 ± 28.8</td>
<td>0.626</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>85.3 ± 18.2</td>
<td>85.8 ± 17.9</td>
<td>0.922</td>
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<tr>
<td>NIHSS score</td>
<td>9.9 ± 8.2</td>
<td>8.1 ± 6.6</td>
<td>0.309</td>
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<tr>
<td><strong>Complicated disease, preference</strong></td>
<td></td>
<td></td>
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<tr>
<td>Atrial fibrillation, n (%)</td>
<td>18 (28.6)</td>
<td>0 (0.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>48 (76.2)</td>
<td>49 (71.0)</td>
<td>0.749</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>13 (20.6)</td>
<td>11 (15.9)</td>
<td>0.222</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>19 (30.1)</td>
<td>14 (20.3)</td>
<td>0.129</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>4 (6.3)</td>
<td>7 (10.1)</td>
<td>0.130</td>
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</table>
Supplemental Table II. Diagnostic accuracy of susceptibility vessel sign (SVS) and two-layered SVS

<table>
<thead>
<tr>
<th></th>
<th>SVS</th>
<th>Two-layered SVS</th>
</tr>
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<tbody>
<tr>
<td>Negative predictive value, %</td>
<td>64.4 (52.6-75.1)</td>
<td>65.0 (61.3-66.4)</td>
</tr>
<tr>
<td>Positive predictive value, %</td>
<td>54.0 (47.9-59.5)</td>
<td>93.1 (79.7-98.1)</td>
</tr>
<tr>
<td>Interobserver kappa value</td>
<td>0.81 (0.67-0.88)</td>
<td>0.79 (0.70-0.85)</td>
</tr>
<tr>
<td>Intraobserver kappa value</td>
<td>0.94 (0.89-0.97)</td>
<td>0.91 (0.83-0.95)</td>
</tr>
</tbody>
</table>

*Abbreviations; CE: cardioembolism, LAA: large artery atherosclerosis, MRI: magnetic resonance imaging, BP: blood pressure, SVS: susceptibility vessel sign, two-layered SVS: SVS comprised of two layers on 3T-T2*-WI, NIHSS: National Institutes of Health Stroke Scale*
Supplemental Figure I. A 75-year-old male with acute ischemic stroke.

A. The white arrow indicates the two-layered susceptibility vessel sign (SVS) and the arrow head the low-intensity core.

B. Magnetic resonance angiography. The arrow head shows the occlusion site on the internal carotid artery.

C. Diffusion-weighted imaging (DWI).

D. A digital subtraction angiography obtained after endovascular treatment confirms complete recanalization and the absence of stenosis in the infarcted artery. Based on the distribution of DWI-positive lesions, we initially predicted that this patient had large-artery disease.\(^1\) A two-layered SVS was detected. The patient needed urgent treatment because of progressive clinical deterioration. Post-treatment identification of the stroke subtype resulted in a diagnosis of cardioembolism.
Reference