Significance of Susceptibility Vessel Sign on T2*-Weighted Gradient Echo Imaging for Identification of Stroke Subtypes

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Background and Purpose—In contrast to platelet-rich white thrombi, red thrombi in the heart are rich in fibrin and trapped erythrocytes. The magnetic susceptibility effect of deoxygenated hemoglobin in red thrombi may result in hypointense signals on T2*-weighted gradient echo imaging (GRE). We tested the hypothesis that a GRE susceptibility vessel sign (SVS) is specific for cardioembolic stroke.

Methods—This retrospective study examined data from acute ischemic stroke patients who underwent diffusion-weighted imaging, GRE and magnetic resonance angiography (MRA) within 24 hours of stroke onset and who had symptomatic occlusion of large intracranial arteries in the circle of Willis. Hypointense signals within vascular cisterns on GRE corresponding to symptomatic vascular occlusion were termed “GRE SVS.” Recanalization was assessed on follow-up MRA performed within 7 days of onset. The relationships between GRE SVS and stroke subtypes and subsequent recanalization were explored.

Results—Of the 95 patients who met the inclusion criteria, GRE SVS was observed in 45 (47.4%). GRE SVS was more commonly associated with cardioembolic stroke patients (31 of 40, 77.5%) than with other stroke subtypes (14 of 55, 25.5%; \( P < 0.001 \)). In 66 patients who underwent follow-up MRA, GRE SVS was associated with subsequent recanalization (\( P < 0.001 \)). Multivariate analysis showed that GRE SVS was an independent predictor of cardioembolic stroke and subsequent recanalization (odds ratio, 10.75 and 4.26; 95% CI, 3.68 to 31.47 and 1.12 to 16.30).

Conclusions—GRE SVS may predict cardioembolic stroke and subsequent recanalization. Identifying clot composition may be important in choosing the optimal treatment based on clot characteristics. (Stroke. 2005;36:2379-2383.)

Key Words: diagnosis ■ magnetic resonance imaging ■ stroke, acute ischemic ■ stroke subtype

Autopsy studies show that thromboembolic stroke can be caused by a variety of thrombi, including white, red, and mixed.1,2 White thrombi are predominantly composed of platelet aggregates, whereas red thrombi are rich in fibrin and trapped erythrocytes. The composition of the thrombus is affected by local blood flow characteristics. White thrombi form in areas of high-shear stress, such as the arterial system, and, thus, develop on ruptured plaques. In contrast, red thrombi form in low-pressure systems, such as cardiac or venous systems. In areas of reduced blood flow, red thrombi result from activation of the coagulation cascade.3 Therefore, it is widely accepted that cardiac emboli are mainly composed of red thrombi.

Blood goes through sequential stages of degradation from oxyhemoglobin to deoxyhemoglobin, methemoglobin, and then hemosiderin, which can each be identified using MRI. In contrast to oxyhemoglobin, the presence of unpaired electrons in deoxyhemoglobin, methemoglobin, and hemosiderin gives them paramagnetic properties, which produce an inhomogeneity in magnetic fields.4 This property of paramagnetic molecules is termed the magnetic susceptibility effect and causes signal loss on MRI, which is best detected using T2*-weighted gradient echo imaging (GRE).5

Intraluminal clots evolve in stages similar to parenchymal hematomas.4 Thus, red thrombi in occlusive vessels may be seen as hypointense signals within vascular cisterns on GRE because of the paramagnetic property of deoxygenated hemoglobin components in trapped red blood cells. We termed this radiological finding the “GRE susceptibility vessel sign (GRE SVS)”6,7 In the present study, we tested the hypothesis that the presence of GRE SVS may predict cardioembolic stroke. We also sought to determine whether GRE SVS is associated with subsequent recanalization.

Materials and Methods

Patients

A retrospective study was performed, which involved analysis of data obtained from all of the stroke patients admitted to the Stroke Center at the Asan Medical Center between November 1, 2002 and August 31, 2004. Stroke patients were identified by reviewing the registry, in which data had been prospectively collected. Patients were eligible if they met the following criteria: (1) a final diagnosis...
of definite acute ischemic cerebrovascular syndrome with diffusion-weighted imaging (DWI) confirmation of acute ischemia; (2) DWI, GRE, and magnetic resonance angiography (MRA) performed within 24 hours of symptom onset; and (3) symptomatic occlusion of large intracranial arteries in the circle of Willis (ie, distal internal carotid, anterior, middle, or posterior cerebral arteries). According to our MRA protocol, all of the patients were scheduled for scans acutely and at 3 to 5 days after stroke onset. Because of clinical care requirements or patient requests, follow-up scans were sometimes performed outside of the target range of times or not at all. The “time from stroke onset” was determined as the time patients were last known to be without new ischemic symptoms. Stroke severity at admission was measured using the National Institutes of Health Stroke Scale (NIHSS) score. The study was approved by the Institutional Review Boards of the Asan Medical Center. Patients’ informed consents were not obtained, because this study was retrospectively designed.

Imaging Analysis
MRI examinations were performed using a 1.5-T MR imaging unit (Signa; GE Medical Systems, Milwaukee, WI) with echo-planar capabilities. Included in the protocol for this study were DWI, GRE, 3D time-of-flight MRA, and 3D contrast-enhanced MRA. The common MRI parameters for DWI and GRE were a slice thickness of 5 mm, an interslice gap of 2 mm, 20 axial slices, and a field-of-view of 250 mm. DWI parameters included a repetition time (TR) of 7500 ms, an echo time (TE) of 84 ms, a matrix number of 128×128, and two b values of 0 and 1000 s/mm². GRE parameters were a TR of 400 ms, a TE of 30 ms, a flip angle of 20°, and a matrix number of 256×192. Common MRA parameters included a flip angle of 20°, a matrix number of 512×512, and a field-of-view of 250 mm. A 3D time-of-flight MRA of the circle of Willis was performed with a TR of 25 ms and TE of 2 ms. A 3D contrast-enhanced MRA from the aortic arch to the level of the central skull base was obtained using an IV bolus injection of 20 mL (3 to 4 mL/s) gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) with a TR of 6 ms and TE of 1 ms.

GRE interpretations were performed by an investigator (D-W.K.) blinded to clinical data and other magnetic resonance sequences other than information regarding the side of the index lesion. GRE SVS was defined as a hypointense signal on GRE within vascular cisterns in corresponding symptomatic occlusive vessels. The diameter of the hypointense signals should exceed the contralateral vessel diameter.¹,² Acute and follow-up MRA data were independently reviewed in different sessions. Significant recanalization was defined if follow-up MRA revealed complete visualization of branch arteries distal to occluded vessels with residual stenosis <50%.

Clinical Assessments
Clinical data were obtained by reviewing stroke registry and medical records. In addition to MRI studies, the following investigations were performed in all of the patients: complete blood count, erythrocyte sedimentation rate, chemistry, serology, coagulation tests, ECG, chest x-rays, and urinalysis. Transthoracic and transesophageal echocardiography and 24-hour ECG monitoring were performed in the following patients: (1) those with history of heart disease, irregular pulse on physical examination, clinical or radiological cardiac abnormalities, or rhythm abnormalities on ECG; (2) those who were young (<45 years) and without atherosclerosis risk factors; (3) those with suspected infective endocarditis or marantic endocarditis; or (4) those whose MRA did not indicate an extracranial source of stroke. Stroke subtypes were determined according to the classification of the Trial of Org 10172 in Acute Stroke Treatment (TOAST).³ TOAST diagnosis was made by 3 stroke neurologists (J.S.K., S.U.K., and D.-W.K.) blinded to the GRE findings, and discrepancies were settled by consensus discussion.

Data Analysis
First, we tested the association of GRE SVS with stroke subtypes and subsequent recanalization. Then we explored whether GRE SVS predicts cardioembolic stroke and recanalization independent of demographics, risk factors, admission NIHSS score, time to MRI scan from onset, site of vessel occlusion, and thrombolytic treatment (Table 1). For univariate analysis, Pearson χ² test using the exact method, Student t test, or the Mann-Whitney test were applied where appropriate. Multiple logistic regression analysis was performed to estimate the independent contributions of variables to dependent variables (ie, cardioembolism and recanalization). Variables were selected for entry into the model based on the results of univariate analysis (P<0.1). The odds ratio and 95% CI were obtained. The Hosmer-Lemeshow goodness-of-fit test was used to assess how well the model accounted for outcomes. SPSS for Windows (version 11.5, SPSS Inc) was used for statistical analysis. A 2-tailed P value of <0.05 was considered to indicate a significant difference.

Results
Ninety-five patients met the eligibility criteria; they were composed of 44 women and 51 men with a median age of 69 years (mean, 67.8±12.3; range, 23 to 91). The median NIHSS score at admission was 10 (range, 1 to 32). Twenty patients were given thrombolytic therapy, with IV tissue plasminogen activator (tPA) in 7, intraarterial urokinase in 7, and a combination of both in 6. Echocardiography was performed in 59 patients (62.1%), with both transthoracic and transesophageal echocardiography in 25 patients. Follow-up MRA was performed in 66 patients (69.5%) within 1 week of onset (median, 3.7 days; mean, 3.8±1.3 days; range, 1.4 to 6.6 days). In the comparison between patients who had follow-up MRA and those who did not, there was no difference in demographics, risk factors, stroke subtypes, or the incidence of GRE SVS, except that patients who underwent follow-up MRA had a milder stroke severity (median NIHSS 9) than those who did not (median NIHSS 16; P=0.004).

Symptomatic occluded vessels were middle cerebral artery (MCA) stem in 46 patients, MCA branch in 19, distal internal carotid artery in 15, posterior cerebral artery in 14, and anterior cerebral artery in 1. GRE SVS was identified in 45.7% of patients (21 of 46) with MCA stem occlusion, 73.7% (14 of 19) of those with MCA branch occlusion, 26.7% (4 of 15) of those with distal internal carotid artery occlusion, 42.9% (6 of 14) of those with posterior cerebral artery occlusion, and 0% (0 of 1) of those with anterior cerebral artery occlusion (P=0.063). Demographics, risk factors, and admission NIHSS score were not different between patients with and without GRE SVS.

Association Between GRE SVS and Stroke Subtypes
GRE SVS was identified in 45 (47.4%) of the total 95 patients. GRE SVS was significantly associated with cardioembolic stroke. Of the 40 cardioembolic stroke patients, 31 (77.5%) had GRE SVS, whereas for the 55 patients with other stroke subtypes, only 14 (25.5%) had GRE SVS (P<0.001, Figure 1). Among these 14 patients, 6 had intracranial large artery atherosclerosis (LAA), 1 had extracranial LAA, and the remaining 7 had cryptogenic etiology.

Current smoking (P=0.058), time-to-initial MRI (P=0.076), and site of occlusion (P=0.062) were also marginally associated with cardioembolic stroke (Table 1). In multiple logistic regression analysis, GRE SVS and absence of current smoking independently predicted cardioembolic stroke (Table 2).
Association Between GRE SVS and Subsequent Recanalization

In a subgroup of 66 patients who underwent follow-up MRA, 30 (45.5%) demonstrated significant recanalization, and 29 (43.9%) showed GRE SVS. Among all of the clinical and radiological variables, cardioembolic stroke ($P<0.001$), GRE SVS ($P<0.001$), time-to-initial MRI ($P=0.01$), site of vessel occlusion ($P=0.093$), and thrombolytic treatment ($P=0.052$) were associated with subsequent recanalization, with $P=0.1$ according to univariate analysis (Table 1). Of the 30 patients who showed recanalization, 21 (70%) had GRE SVS (see Figure 2 for example). In multiple logistic regression

![Figure 1. Association between GRE SVS and stroke subtypes. CE indicates cardioembolism.](https://www.ahajournals.org/doi/10.1161/01.to.101.31.2381)
analysis, cardioembolic stroke and GRE SVS were independent predictors of subsequent recanalization (Table 2).

**Discussion**

The present study shows that GRE SVS is associated with cardioembolic stroke. To the best of our knowledge, this is the first study to link GRE SVS with a stroke subtype. Analogous to the hyperdense MCA signs on computed tomography (CT), early vessel signs on MRI have been described on fluid attenuation inversion recovery image and less frequently on GRE in acute ischemic stroke patients. Such signs can improve the diagnostic and prognostic strength of MRI by providing additional information with regard to vessel patency, hemodynamic status, and thrombus composition. A recent study showed that MCA susceptibility signs on MRI had a higher sensitivity than hyperdense MCA signs on CT for the identification of MCA thromboembolism proven by catheter angiography. In contrast, a more recent study found that the sensitivities of CT hyperdense MCA signs, fluid attenuation inversion recovery vessel signs, and GRE SVS were 40%, 66%, and 34%, respectively, compared with vessel status on MRA or perfusion-weighted images. We believe the differences between these studies in terms of GRE SVS sensitivity are related to the composition and aging of clots associated with stroke etiology.

This study also showed that GRE SVS was associated with subsequent recanalization, independent of other clinical and radiological characteristics. Although the natural course of spontaneous recanalization according to stroke subtypes is understudied, cardioembolic occlusion has been shown to more frequently recanalize than other stroke subtypes. A recent study evaluated the sonographic patterns of clot lysis during tPA infusion among stroke subtypes and found that vessel recanalization was more frequent and more complete in patients with cardioembolic stroke. Given the high-binding affinity of tPA for fibrin, tPA may penetrate and distribute homogeneously, leading to effective dissolution of emboli from the heart, which is characterized by more uniform fibrin-rich clots. Now our results provide evidence of a link among GRE SVS, cardioembolic stroke, and subsequent recanalization.

Identification of GRE SVS may help guide therapeutic decisions in terms of indicating whether an occlusive clot is susceptible or resistant to fibrinolytic therapy. In acute coronary syndrome, obstructive arterial thrombi that are platelet rich are resistant to thrombolysis and have an increased tendency to reocclude after initial reperfusion. In these circumstances, an antiplatelet agent used in combination with a thrombolytic agent not only offers the potential for

<table>
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<th>Variable</th>
<th>Cardioembolism OR (95% CI)</th>
<th>P Value</th>
<th>Recanalization OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRE SVS-positive</td>
<td>10.75 (3.68–31.47)</td>
<td>&lt;0.001</td>
<td>4.26 (1.12–16.30)</td>
<td>0.034</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.21 (0.07–0.70)</td>
<td>0.01</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Time to initial MRI (hr)</td>
<td>0.97 (0.88–1.07)</td>
<td>0.51</td>
<td>0.94 (0.80–1.11)</td>
<td>0.48</td>
</tr>
<tr>
<td>MCA branch occlusion</td>
<td>2.73 (0.78–9.56)</td>
<td>0.12</td>
<td>3.41 (0.67–17.26)</td>
<td>0.14</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>...</td>
<td>...</td>
<td>7.58 (1.95–29.45)</td>
<td>0.003</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>...</td>
<td>...</td>
<td>4.01 (0.86–18.71)</td>
<td>0.077</td>
</tr>
</tbody>
</table>

Variables were selected for entry into the models based on the results of univariate analyses (P<0.1). Hosmer-Lemeshow goodness-of-fit tests showed χ²=2.7 and 5.2 and P=0.95 and 0.64, respectively, demonstrating a good fitness of the models.

Figure 2. (A) A 61-year-old female patient with atrial fibrillation presented with right hemiparesis and aphasia. There are acute left MCA infarcts on DWI, a left MCA occlusion on MRA, and SVS in the occluded vessel on GRE (arrow) on acute scans (1 hour after onset). The patient was treated with IV tPA. Follow-up MRA shows complete recanalization of the left MCA. (B) A 56-year-old male patient presented with left hemiparesis. There are right striato-capillary infarcts on DWI and a right MCA occlusion on MRA, but no GRE SVS on acute scans (2 hours after onset). The patient was also treated with IV tPA. Follow-up MRA shows the right MCA is still completely occluded. The patient did not have cardioembolic sources and was classified as having large artery atherosclerosis.
enhancing thrombolysis and reducing the risk of reocclusion but also permits this to be accomplished with reduced doses of thrombolitics and heparin. Therapeutic decisions with regard to clot composition may facilitate thrombolysis and reperfusion. In addition, in acute stroke syndrome, from a mechanistic perspective, it may be that vessel occlusion with GRE SVS is more sensitive to fibrinolytic therapy, although the results of such investigations are not yet conclusive. The present study did not investigate the relationship between different thrombotic response patterns and GRE SVS because of the limited number of patients who received thrombolysis. Future studies using a larger sample size are required to explore this issue.

Of the 40 cardioembolic stroke patients in this study, we could not identify GRE SVS in 9 patients. It is likely that small-sized red thrombi might have been missed because of the GRE interslice gap, because GRE SVS was diagnosed if the hypointense signals exceeded the contralateral vessel diameter. Clot age and hemoglobin oxidation state may also explain these findings. Hemoglobin desaturation from oxyhemoglobin to deoxyhemoglobin occurs within a few hours. Thus, in hyperacute clot cases, the main component may still be deoxyhemoglobin, which does not produce a magnetic susceptibility effect. If oxyhemoglobin had not sufficiently degraded to deoxyhemoglobin, hyperacute clots would not have been identified as hypointense signals on GRE.

Fourteen patients with GRE SVS were eventually classified as having stroke etiology other than cardioembolism. Seven of the 44 LAA patients had GRE SVS. We suggest that this is probably attributable to the process of clot formation, which occurs similarly in coronary vessels. White thrombi initially form as the result of deep fissuring of atherosclerotic plaques or extensive endothelial erosion. This initial intraplaque thrombus, which is composed predominantly of platelets, leads to a local reduction in blood flow and additional thrombosis within the arterial lumen. Ultimately, completely occlusive thrombi consist of a fibrin network with numerous enmeshed red blood cells superimposed on the underlying platelet-rich clot. Our results also support this idea, because 6 of the 7 LAA patients with GRE SVS had intrinsic intracranial arterial disease.

Seven of the 9 patients with cryptogenic stroke etiology also showed GRE SVS. Based on our pathway for stroke etiology work-up, 6 of these patients were not completely evaluated for cardiogenic causes. In these patients, occult unidentified cardioembolic sources might have been present. Thus, it may be reasonable to initiate detailed cardiac evaluation in patients with GRE SVS, even if cardiac abnormalities are not suspected.

This study has several limitations. Although our stroke center has a clinical pathway for diagnosis and management of stroke patients, the investigative work-ups for stroke etiology were not identical in all of the patients. Echocardiography and follow-up MRA were not performed on all of the patients. The choice of MRA as a reference for vessel occlusion and recanalization is less accurate than catheter angiography. Our study is more heterogeneous with regard to the time window from onset compared with previous studies, although the sample size is larger. Long-term follow-up data for assessing the prognostic value of GRE SVS are lacking in the present study.

In conclusion, the present study indicates that GRE SVS may predict cardioembolic stroke and subsequent recanalization. Identifying thrombi composition may be important in choosing the optimal treatment based on clot characteristics.

Acknowledgments

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