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審査学位論文
（博士）
Evaluating middle cerebral artery atherosclerotic lesions in acute ischemic stroke using magnetic resonance T1-weighted three-dimensional vessel wall imaging

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Short title: 3D vessel wall imaging in acute stroke
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Disclosure Statement

M.S. and K.K. received honoraria from GE Healthcare. M.M and H.K. are employees of GE Healthcare.
Abstract

Background: Atherosclerotic lesions in intracranial arteries are a leading cause of ischemic stroke. Magnetic resonance (MR) angiography (MRA) is often used to assess atherosclerotic changes by detecting luminal narrowing, while it cannot directly visualize atherosclerotic lesions. Here, we used a three-dimensional vessel wall imaging (3D-VWI) technique to evaluate intracranial arterial wall changes in acute stroke.

Methods: Eighteen consecutive patients with acute non-cardioembolic stroke in middle cerebral artery (MCA) territory who were prospectively examined with a 1.5-T MR scanner were studied. T1-weighted (T1W) 3D-VWI was obtained using a flow-sensititized 3D fast spin-echo technique. Wall thickening of MCA which suggest atherosclerotic plaques was visually evaluated and the contrast ratio (CR) of signal intensity of the lesions to that of the corpus callosum was calculated and compared with stenotic changes by MRA.

Results: Wall thickenings of the MCA ipsilateral and contralateral to the lesion were observed in almost all patients on 3D-VWI (94.4% and 94.4%, respectively), while MRA showed stenotic changes of 50% only in 1 patient (5.9%) (p < 0.001). The CR of the thickened wall in the ipsilateral MCA was significantly higher than that in the contralateral MCA (median, 0.53 and 0.45, respectively; p = 0.028), suggesting of unstable plaques consisting of hemorrhage or lipid.

Conclusions: The T1W 3D-VWI can provide direct visualization of atherosclerotic lesions of the intracranial arteries in stroke patients, and it can detect signal change suggestive of unstable plaque.
Introduction

Atherosclerotic lesions in major intracranial arteries are a leading cause of ischemic stroke [1, 2]. Atherosclerotic plaques are frequently found at autopsy in the intracranial arteries in patients with fatal stroke [3]. However, it has not been fully determined which non-invasive imaging techniques are best to detect and evaluate these lesions. Several imaging modalities, such as magnetic resonance angiography (MRA), CT angiography (CTA), and digital subtraction angiography (DSA), have been widely applied for this purpose, but they only assess luminal narrowing and cannot directly visualize vessel wall lesions.

Recently, several studies have attempted to identify changes indicating atherosclerotic plaques of intracranial arteries using vessel wall imaging (VWI) techniques [4-12]. However, the results in these studies have varied, presumably due to partial volume effects of two-dimensional (2D) acquisition and differences in image contrasts among the studies, indicating that appropriate techniques for evaluating lesions of the intracranial arterial walls have not been fully established. Hence, we attempted to quantitatively assess atherosclerotic changes of intracranial vessel walls related to acute ischemic stroke using a T1-weighted (T1W) three-dimensional (3D) fast spin-echo (FSE) technique for 3D-VWI, which may allow minimization of partial volume effects and improved intraplaque contrast.

Methods

Patients

From October 2010 to September 2012, we prospectively enrolled 18 consecutive patients (11 men and 7 women; age range, 33 to 89 years; mean age, 69.8 years) with
acute non-cardioembolic stroke in middle cerebral artery (MCA) territory, which included infarcts mainly in perforating artery areas (17 cases), water shed areas (1 cases). The clinical characteristics of the patients before hospitalization included hypertension in 10 patients, hyperlipidemia in 6, and diabetes mellitus in 4. No patient had other uncommon causes such as intracranial arterial dissection, vasculitis, moyamoya disease, and hypercoagulation state. Patients received the following medications: anti-platelet agents in 3, angiotensin-2 receptor blockers in 4, statin in 2, and oral hypoglycemic in 1. No patient received insulin. All patients were non-candidates for thrombolytic therapies and received standard treatments for ischemic stroke, such as antiplatelet therapy, anticoagulants, neuroprotection, transfusion, and statin therapies. All patients were examined by T1W 3D-VWI and axial 3D time-of-flight (TOF) MRA, and the study was carried out after obtaining approval from the institutional review board and written informed consent from the patients.

**Imaging protocols**

Magnetic Resonance Imaging (MRI) examinations were performed in a 1.5 Tesla scanner and an 8-channel head coil (Signa HDxt, GE Healthcare, Milwaukee) at 0 to 14 days after onset (mean 6.3 days). The following pulse sequence and parameters were used for 3D-VWI: sagittal flow-sensitized T1W 3D-FSE with variable flip angles (FA); repetition time (TR), 500 ms; echo time (TE), 18.3 ms; echo train length, 24; b-value of the flow sensitizing gradients along 3 axes, 2.2 s/mm²; field of view (FOV), 25 × 19 cm²; matrix size, 512 × 512 (after zero-fill interpolation [ZIP]); slice interval, 0.5 mm (after ZIP); partition, 248; voxel size, 0.5 × 0.5 × 0.5 mm³; parallel imaging factor, 2; number of excitations, 1; and acquisition time, 3 min 54 s. Axial 3D TOF MRA was
obtained with the following parameters: TR, 36 ms; TE, 6.9 ms; FA, 20°; FOV, 24 × 19 cm²; matrix size, 512 × 224; slice interval, 0.5 mm (after ZIP); partition, 150; number of excitations, 1; and acquisition time, 4 min 56 s. Axial T2-weighted and diffusion-weighted images were also obtained to evaluate acute infarct lesions.

Data processing and statistical analysis

Consecutive reformatted images along the short axis of bilateral horizontal portions of MCA (M1) were generated with 0.5 mm intervals and 2× magnifications from 3D-VWI datasets with a 3D workstation (Ziostation2, Ziosoft, Tokyo). For qualitative evaluation, 1 author (T.N.) who was blinded to patient information visually assessed the presence and shape of the wall thickening at the ipsilateral and contralateral M1 regions. For quantitative evaluation, the same blinded interpreter measured the signal intensity of the thickened vessel wall (Svw) 3 times with a region-of-interest (ROI) manually-placed by a cross-hair cursor at the location at which signal intensity was the highest on a liquid crystal display, and the values obtained were averaged. Signal intensity of the corpus callosum (Scc) was also measured on the midsagittal section of VWI with a manually-traced ROI using a polygon cursor (Fig. 1B). We excluded the areas showing abnormal signal intensity due to ischemia or axonal degeneration from the measurement. The contrast ratio (CR) of the vessel wall against the corpus callosum was calculated using the following equation: CR = (Svw/Scc) × 100. The degree of stenosis of bilateral M1 regions was also measured 3 times on MRA using the same workstation according to the method described in the Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis (TOSS) study [13, 14], and the values were averaged. Stenosis of 50% or more was defined as substantial.
Differences in positive findings between 3D-VWI and MRA and between ipsilateral and contralateral M1 regions were examined using McNemar’s test, and differences in the CRs of 3D-VWI and degrees of stenosis on MRA were compared by Wilcoxon’s matched-pairs signed-rank test. The performance of the CR for discriminating between changes in relevant and non-relevant arteries was evaluated by a receiver operating characteristic (ROC) analysis. Youden index was used to determine cutoff values as well as sensitivity and specificity. Intra-operator agreements of the measurements were determined by calculating the intraclass correlation coefficient (ICC). The alpha level used was 0.05.

**Results**

MR images with sufficient quality were successfully obtained from all patients, and all were eligible for further analyses. On 3D-VWI, wall thickening suggesting atherosclerotic plaque was observed in 17 (94.4%) and 17 (94.4%) of 18 patients at the ipsilateral and contralateral M1, respectively; the shape was crescent in 7 and 6 patients or circumferential in 10 and 11, respectively (Table 1, Fig. 2, 3). In distinction to this, the MRA studies revealed a substantial stenotic change of 50% only in the ipsilateral MCA of 1 patient (5.9%), a significantly lower frequency as compared with wall thickening detected on VWI (p < 0.001; McNemar’s test) (Table 1, Fig. 2, 3). There were no significant differences in these findings between the ipsilateral and contralateral MCA (p = 1; McNemar’s test, Fisher’s exact test).

The median CRs of the thickened arterial walls in the ipsilateral and contralateral M1 segments on 3D-VWI were 52.5% (interquartile range, 49.2 to 56.7%) and 44.8% (41.8 to 47.0%), respectively. The former was significantly higher than the latter (p =
0.028, Wilcoxon’s test) (Table 1, Fig. 2). The median degrees of M1 stenosis detected on MRA were 13.4% (interquartile range, 6.1 to 22.0%) and 10.5% (3.5 to 18.3%), respectively, and there was no significant difference between these findings (p = 0.25, Wilcoxon’s test) (Table 1, Fig. 2). ROC analysis showed that the areas under the curve (AUC) of the CR in 3D-VWI in terms of discrimination of ipsilateral from contralateral M1 was 0.801. Sensitivity and specificity were 0.824 and 0.882, respectively, when the CR cutoff value was set as 48.5%.

ICC values in the measurements of CR of the thickened arterial walls on 3D-VWI and degree of luminal stenosis on MRA were 0.999 and 0.991, respectively, indicating a high level of intra-operator agreement.

**Discussion**

Luminal stenosis of intracranial arteries on MRA or other imaging studies is widely accepted as a marker of atherosclerosis, and its presence and temporal changes are accepted as predictors of the risk of stroke events or as a means to evaluate efficacy of medical treatments [14, 15]. However, in this study, we found wall thickening of the MCA, either crescent or circumferential in shape, on 3D-VWI in almost all of the patients with acute stroke of the MCA territory, even though in all but one of the patients there was no substantial stenosis detected at the same locations on MRA. This suggests that thickened intracranial arterial walls indicating atherosclerotic plaques are frequently present even if stenotic changes are minimal, presumably because of an outward, “positive,” remodeling of the vessel wall. This assumption is supported by an autopsy study in which intracranial plaques were found in nearly 90% of patients with atherothrombotic infarction and were more frequent than stenotic changes [3]. Hence,
3D-VWI can be considered more sensitive to detect atherosclerotic changes of major intracranial arteries than MRA, and the technique is useful to assess subtle changes that were previously overlooked. Stenotic intracranial arteries have been a main target of previous studies using VWI [5, 8, 10], some of which reported that wall thickening was more frequent than luminal stenosis in acute stroke patients. However, the incidence of the wall lesions in these studies was lower than that reported in the present study [9]. One reason for this tendency could be the 2D imaging techniques that many of the previous studies adopted. The 3D imaging technique with isotropic voxels reported here is thought to improve the ability to detect subtle vessel wall lesions by minimizing partial volume effects.

In this study, we did not detect any significant differences in occurrence of wall thickening between ipsilateral and contralateral MCA in the affected regions. Plaques are commonly found at autopsy in intracranial arteries after fatal stroke [3]. Various studies using VWI also have detected wall lesions, even in asymptomatic or non-causal arteries in patients with stroke or intracranial vessel stenosis [8-10]. Thus, wall thickening on VWI *per se* cannot be utilized as a marker to determine lesions relevant to infarcts, and although we evaluated shapes of the wall lesions, there were again no apparent differences between relevant and non-relevant arteries.

Hence, assessment of the signal intensity also appears to be needed to adequately characterize wall lesions of intracranial arteries. In this study, the signal intensity on T1W VWI of the plaques in the M1 segment ipsilateral to the acute infarcts tended to be significantly higher than those in the contralateral arteries. It is well known that high-signal plaques on T1W images of appropriate parameter settings in the cervical carotid arteries reflect unstable plaques that mainly consist of hemorrhagic
and/or lipid components[16]. Thus, high-intensity wall lesions in this study may also suggest unstable plaques, although at this point we have no direct evidence to support this assumption. There have been a few imaging studies that have attempted to evaluate intraplaque signal changes of intracranial arteries [8, 10]. In these studies, high signal wall lesions were found in some patients, however, the detailed results varied among the studies and were also different from those of present study. These discrepancies can be attributed to disparate imaging parameters and analysis methods for assessing signal changes. In the present study, we used the signal intensity of the corpus callosum as a reference for quantitative assessment to normalize signal intensity of the vessel wall lesions because the corpus callosum is large enough to measure and stable in terms of signal intensity in majority of stroke patients. According to the results of ROC analysis of our results, vessel wall lesions with relative signal intensities of approximately half of that of the corpus callosum or greater can be suggestive of unstable plaques that are relevant to stroke events with relatively high sensitivity and specificity.

This study had several limitations. First, there is no gold standard by which to validate findings of intracranial arterial wall changes suggested by 3D-VWI. We found substantial discrepancies between findings on VWI and those on MRA and significant differences in signal intensity of the vessel wall lesions between the affected and unaffected sides. However, the precision of our method in terms of presence and characteristics of the wall lesions cannot be confirmed. There have been a few postmortem studies [17], however, correlations between imaging and histopathological findings are generally not feasible, in contrast to studies regarding plaque imaging of cervical arteries. Intravascular ultrasonography techniques may solve this issue [18], although this method is not generally applicable to assessment of intracranial arterial
wall lesions. Second limitation is a relatively small number of the patients enrolled in this study. Hence, it was difficult to determine the relationships between imaging findings and stroke etiology, patient demographics, or clinical outcomes. We also did not compare findings between patients with acute stroke and those with chronic ischemia or examine their temporal changes. During the acute stage of the stroke, image findings of the intracranial vessel walls may dynamically influenced by altered hemodynamics, recanalization, or intensive medication, although responsible lesions may be evident as compared with the chronic stage. Further longitudinal studies with a larger sample size including subjects of acute and chronic stages with various stroke subtypes are needed to determine clinical significances of findings on 3D-VWI. Third, we did not obtain post-contrast images in this study, mainly due to ethical and economical considerations, although the 3D-FSE technique we used appears to be suitable for this purpose. Since contrast enhancement of intracranial arterial walls is reported to suggest atherosclerotic changes [4, 11], direct comparisons between non-contrast and post-contrast images are necessary to determine the ideal imaging protocols for detecting high-risk changes in the intracranial arterial walls. Another limitation that should be mentioned is a technical issue. Although the capability of acquiring 3D whole brain scan by isotropic voxels with a relatively short acquisition time is an advantage of the imaging techniques we used, the signal-to-noise ratio and spatial resolution at 1.5 T appear to be somewhat insufficient for precise evaluation of minute intramural lesions in intracranial arteries. To overcome this issue, imaging at 3 T would probably be effective, and we are now investigating this. Finally, we did not perform optimization of flow-sensitized gradients, which is crucial to enhance the black blood effect. When the gradients are too weak or strong, slow flow can be confused with
thickening of arterial wall or motion artifacts and T2 contrast can be increased. Although the value of the gradient strength in this study was larger than previously reported [19], validation studies are still required for further optimization.

In conclusion, T1W 3D-VWI can potentially provide direct visualization of atherosclerotic lesions of the intracranial arteries in patients with acute non-cardioembolic stroke, and it can detect signal changes suggestive of unstable plaque.
References


**Table 1.** Middle cerebral artery findings in acute stroke patients on T1-weighted three-dimensional vessel wall imaging (T1W 3D-VWI) and three-dimensional time-of-flight magnetic resonance angiography (3D-TOF MRA).

<table>
<thead>
<tr>
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<th>(n = 18)</th>
<th>T1W 3D-VWI</th>
<th>3D-TOF MRA</th>
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<tbody>
<tr>
<td></td>
<td>Wall thickening</td>
<td>Shape</td>
<td>Contrast ratio</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crescent</td>
<td>Circumferential</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>17 (94.4%)</td>
<td>7 (41.2%)</td>
<td>10 (58.8%)</td>
</tr>
<tr>
<td>Contralateral</td>
<td>17 (94.4%)</td>
<td>6 (35.3%)</td>
<td>11 (64.7%)</td>
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</tbody>
</table>

IQR, interquartile range; T1W 3D-VWI: T1-weighted three-dimensional vessel wall imaging; 3D-TOF MRA: three-dimensional time-of-flight magnetic resonance angiography; *p = 0.028, Wilcoxon’s test
Figure legends

Fig. 1. T1-weighted three-dimensional vessel wall imaging (T1W 3D-VWI)
A: Reconstructed image along the short axis of the horizontal portion of the middle
cerebral artery (M1). B: reconstructed image at midsagittal section.
Crescent-shaped wall thickening is evident at M1, and the signal intensity was measured
by placing a cross hair cursor at the highest part (A). Signal intensity of the corpus
callosum was measured by manual tracing with a polygon cursor (B).

Fig. 2. Signal intensity of thickened vessel wall on T1-weighted three-dimensional
vessel wall imaging (T1W 3D-VWI) and degree of stenosis on three-dimensional
time-of-flight magnetic resonance angiography (3D-TOF MRA) at M1.
On T1W 3D-VWI, contrast ratios of the vessel wall were significantly higher in
the M1 segment ipsilateral to the infarct than those in the contralateral side. On MRA,
the difference in stenosis ratios was insignificant between ipsilateral and contralateral
M1.

Fig. 3. T1-weighted three-dimensional vessel wall imaging (T1W 3D-VWI) and
three-dimensional time-of-flight magnetic resonance angiography (3D-TOF MRA) at
M1 in an acute stroke patient.
An 84-year-old woman with acute infarct in the territory of perforating arteries of the
right M1 (1 day after onset). A: diffusion-weighted imaging (DWI); B: 3D-TOF MRA;
C: T1W 3D-VWI.
Hyperintensity area in the right basal ganglia and corona radiata is seen on DWI (A).
MRA detected minimal stenotic change (stenosis ratio of 8.1%) in the right M1 (B, arrow). 3D-VWI depicted crescent-shaped lesions in the right (ipsilateral to the infarct) and left (contralateral) M1 walls. Signal intensity of the former (contrast ratio of 55.5%) appeared to be greater than that of the latter (34.6%) (arrows).