High-Risk Plaque for Carotid Artery Stenting Evaluated With 3-Dimensional T1-Weighted Gradient Echo Sequence

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Background and Purpose—Preventing cerebral embolisms is a major concern with carotid artery stenting (CAS). This study evaluated 3-dimensional T1-weighted gradient echo (3D T1GRE) sequence to predict cerebral embolism related to CAS.

Methods—We performed quantitative analyses of the characteristics of 47 carotid plaques before CAS by measuring the signal intensity ratio (SIR) and plaque volume using 3D T1GRE images. We used T1-weighted turbo field echo sequence to obtain 3D T1GRE images. We also evaluated diffusion-weighted images (DWI) of the brain before and after CAS to detect ischemic lesions (DWI lesions) from cerebral emboli.

Results—SIR (2.17 [interquartile range 1.50–3.07] versus 1.35 [interquartile range 1.08–1.97]; \(P=0.010\)) and plaque volume (456 mm\(^3\) [interquartile range 256–696] versus 301 mm\(^3\) [interquartile range 126–433]; \(P=0.008\)) were significantly higher in the group of patients positive for DWI lesions (P-group: \(n=26\)) than DWI lesion-negative patients (N-group: \(n=21\)). In multivariate logistic regression analysis, SIR (\(P=0.007\)) and plaque volume (\(P=0.042\)) were independent predictors of DWI lesions with CAS. Furthermore, SIR (\(rs=0.42, P=0.005\)) and plaque volume (\(rs=0.36, P=0.012\)) were positively correlated with the number of DWI lesions. From analysis of a receiver-operating characteristic curve, the most reliable cutoff values of SIR and plaque volume to predict DWI lesions related to CAS were 1.80 and 373 mm\(^3\), respectively.

Conclusions—Quantitative evaluation of carotid plaques using 3D T1GRE images may be useful in predicting cerebral embolism related to CAS. (Stroke. 2013;44:105-110.)

Key Words: carotid arteries • intracranial embolism • plaque, atherosclerotic • stents

As the practice of carotid artery stenting (CAS) becomes more common, preventing cerebral embolism is a major concern with CAS. The CREST trial (Carotid Revascularization Endarterectomy versus Stenting) showed that there was a higher risk for stroke with CAS than carotid endarterectomy during the periprocedural period.\(^1\) In addition, there is an earlier report that asymptomatic ischemic lesions on diffusion-weighted image (DWI) are detected more often in CAS than carotid endarterectomy.\(^2\)

Recently, vulnerability of carotid plaque has been implicated in evaluating risk for plaque rupture that causes artery-to-artery embolism.\(^3,5\) Development of magnetic resonance (MR) imaging with high contrast and resolution enabled noninvasive assessment of carotid plaque vulnerability.\(^3,\) High signal intensity plaques on T1-weighted images are considered to correspond to vulnerable plaques that represent a lipid-rich necrotic core or intraplaque hemorrhage (IPH).\(^3,6,9-12,14,16,17\) Among T1-weighted sequences, 3-dimensional (3D) T1-weighted gradient echo (T1GRE) sequences demonstrated higher diagnostic capability to detect IPH,\(^19\) and now evaluating plaque vulnerability using 3D T1GRE images is gaining popularity in clinical settings.\(^3,4,6,9-11,14,16\) Evaluating plaque vulnerability also is important in CAS because mechanically ruptured plaques release debris from atherosclerotic plaque. Carotid plaque with T1 high intensity on 2-dimensional (2D) turbo spin echo images are reported to be predictive for cerebral embolism related to CAS,\(^20\) whereas the similar usefulness of T1 high intensity on 3D T1GRE images has not been evaluated. In addition, a larger plaque presumably carries a higher risk that more debris will be released during CAS as a result of its large burden. However, the impact of plaque volume on cerebral embolism related to CAS has not been examined. Accurate estimation of such plaque characteristics is important clinically to plan strategies that reduce cerebral embolism related to CAS.

In the present study, we retrospectively assessed the usefulness of quantitative plaque characteristics, including signal intensity on T1-weighted images and plaque volume...
evaluated with MR plaque imaging using 3D T1GRE sequence, in predicting cerebral embolism related to CAS.

**Methods**

**Study Population**

Our group performed 48 CAS from January 2008 to December 2009. Patients diagnosed with carotid lesions that were either symptomatic with >50% stenosis or those that were asymptomatic with >80% stenosis, by digital subtraction angiography according to the method used in the North American Symptomatic Carotid Endarterectomy Trial, met our criteria to perform CAS.21 Carotid artery stenosis was defined as symptomatic if the patient had a history of ipsilateral ischemic events attributed to the affected carotid artery within the previous 120 days before CAS. Outside of this window, carotid artery stenosis was considered asymptomatic. The patient characteristics were collected retrospectively through a review of the medical records. Laboratory parameters were examined within 1 month before CAS.

**Magnetic Resonance Imaging Protocol**

MR examinations, including DWI and 3D T1GRE carotid plaque imaging, were performed after diagnostic angiography on all patients within 3 days before CAS. There were no ischemic events, such as transient ischemic attack or stroke, between preprocedural DWI and CAS. DWI were obtained within 48 hours after CAS. Carotid plaque images and preprocedural DWI were achieved with a 3.0T MR imaging system (Achieva Quasar Dual, Philips Medical Systems, Best, The Netherlands). DWI after CAS was performed with a 1.5T MR imaging system (Intera Achieva Nova, Dual, Philips Medical System, Best, The Netherlands).

We used 3D T1-weighted turbo field echo (T1TFE) sequence to obtain 3D T1GRE images. This imaging was performed in the coronal plane with null blood conditions (effective inversion time 600 msec; TR/TE 5.0/2.3 msec) and the water excitation technique to suppress fat signals. Other scanning parameters were as follows: FOV 260 mm; voxel size = 0.68×0.68×1.00 mm; flip angle = 13°. 56 partitions, covering 70 mm around the carotid bifurcation; and data acquisition time of 4 min 2 sec.

Preprocedural DWI was performed with the following parameters: TR/TE shortest/60; slice thickness = 3 mm; spacing, 0 mm; \( b \) value = 1000 sec/mm²; and FOV = 230 mm. Postprocedural DWI was obtained with following parameters: TR/TE shortest/60 msec; slice thickness = 3 mm; spacing, 0 mm; \( b \) value = 1000 sec/mm²; and FOV = 230 mm.

**Quantitative Evaluation of Carotid Plaques Using 3D T1TFE Sequence**

All MR images were reviewed by 2 neurointerventionalists blinded to clinical data. Regions of interest were drawn manually on a workstation around the carotid plaque and adjacent sternocleid mastoid muscle with coronal 3D T1GRE images that detected a largest carotid plaque segment. The signal intensity ratio (SIR) was defined as a value of the signal intensity of carotid plaque divided by that of sternocleid mastoid muscle, and was measured in each patient.

Carotid plaques were contoured manually in long-axis reconstruction 3D T1GRE images of the carotid plaque on a workstation, and the area (mm²) of the carotid plaque was calculated automatically. The area measurement was repeated in all images that showed carotid plaques, and plaque volume (mm³) was then calculated as a sum of the areas (mm²) determined in each slice multiplied by the slice thickness (1mm).

**Detection of Cerebral Embolism Using DWI**

Pre- and postprocedural DWI images were compared, and any new ipsilateral hyperintense lesion (DWI lesion) was regarded as an ischemic lesion related to cerebral embolism related to CAS. The number of new ipsilateral DWI lesions was counted by section-to-section comparison of the pre- and postprocedural DWI.

### Table 1. Patient Characteristics With or Without Ischemic Lesions on Diffusion-Weighted Image

<table>
<thead>
<tr>
<th></th>
<th>P-Group (n=26)</th>
<th>N-Group (n=21)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>74.0±4.9</td>
<td>72.2±6.5</td>
<td>0.276</td>
</tr>
<tr>
<td>Degree of stenosis (%)</td>
<td>80.3±2.3</td>
<td>81.7±2.6</td>
<td>0.687</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>24 (92.3%)</td>
<td>19 (90.5%)</td>
<td>1.000</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic stenosis</td>
<td>13 (50.0%)</td>
<td>10 (47.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>4 (15.4%)</td>
<td>2 (9.6%)</td>
<td>0.687</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (76.9%)</td>
<td>14 (66.7%)</td>
<td>0.521</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (42.2%)</td>
<td>4 (19.1%)</td>
<td>0.121</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>18 (69.2%)</td>
<td>15 (71.4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (19.2%)</td>
<td>7 (33.3%)</td>
<td>0.270</td>
</tr>
<tr>
<td>Contralateral ICA occlusion</td>
<td>13 (50.0%)</td>
<td>10 (47.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Proximal balloon protection</td>
<td>15 (57.7%)</td>
<td>16 (76.2%)</td>
<td>0.227</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-Cholesterol, mg/dl</td>
<td>48.4 [42.3–54.4]</td>
<td>44.6 [37.8–58.3]</td>
<td>0.703</td>
</tr>
<tr>
<td>LDL-Cholesterol, mg/dl</td>
<td>111.0 [101.0–137.8]</td>
<td>98.0 [83.0–117.0]</td>
<td>0.040</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>142.0 [104.0–188.0]</td>
<td>127.0 [81.5–182]</td>
<td>0.451</td>
</tr>
<tr>
<td>C-reactive protein, mg/dl</td>
<td>0.23 [0.06–0.38]</td>
<td>0.15 [0.06–0.229]</td>
<td>0.870</td>
</tr>
<tr>
<td>Carotid plaque characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIR</td>
<td>2.17 [1.50–3.07]</td>
<td>1.35 [1.08–1.97]</td>
<td>0.010</td>
</tr>
<tr>
<td>Plaque volume (mm³)</td>
<td>477.7 [256.4–696.3]</td>
<td>300.7 [125.6–433.0]</td>
<td>0.008</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; ICA indicates internal carotid artery; LDL, low-density lipoprotein; and SIR, signal intensity ratio.
and 1133 mm³, respectively. Diffusion-weighted image after carotid artery stenting revealed multiple asymptomatic cerebral emboli.

CAS Procedure

All patients received the combination of aspirin (100 mg per day) with clopidogrel (75 mg per day) or cilostazol (200 mg per day) as an antiplatelet therapy at least 7 days before CAS. All CAS procedures were performed under local anesthesia via a percutaneous transfemoral route and by an experienced neurointerventional team. A heparin bolus of 100 U/kg was administered intravenously just after the introducer sheath was placed to increase the activated clotting time to a minimum of 300 sec. Two different types of distal embolic protection devices were used: Angioguard XP (Johnson & Johnson, Cordis, Minneapolis, MN; n=46) or Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA; n=2). In the 31 cases protected with Angioguard Xp, proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) was also performed. All of the patients were treated with self-expandable stents: Precise (Johnson & Johnson, Cordis, Minneapolis, MN; n=46) or Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA; n=2). In the 31 cases protected with Angioguard Xp, proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) was also performed. All of the patients were treated with self-expandable stents: Precise (Johnson & Johnson, Cordis, Minneapolis, MN; n=46) or Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA; n=2). In the 31 cases protected with Angioguard Xp, proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) was also performed. All of the patients were treated with self-expandable stents: Precise (Johnson & Johnson, Cordis, Minneapolis, MN; n=46) or Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA; n=2). In the 31 cases protected with Angioguard Xp, proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) was also performed. All of the patients were treated with self-expandable stents: Precise (Johnson & Johnson, Cordis, Minneapolis, MN; n=46) or Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA; n=2). In the 31 cases protected with Angioguard Xp, proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) was also performed. All of the patients were treated with self-expandable stents: Precise (Johnson & Johnson, Cordis, Minneapolis, MN; n=46) or Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA; n=2). In the 31 cases protected with Angioguard Xp, proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) was also performed. All of the patients were treated with self-expandable stents: Precise (Johnson & Johnson, Cordis, Minneapolis, MN; n=46) or Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA; n=2). In the 31 cases protected with Angioguard Xp, proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) was also performed. All of the patients were treated with self-expandable stents: Precise (Johnson & Johnson, Cordis, Minneapolis, MN; n=46) or Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA; n=2). In the 31 cases protected with Angioguard Xp, proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) was also performed. All of the patients were treated with self-expandable stents: Precise (Johnson & Johnson, Cordis, Minneapolis, MN; n=46) or Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA; n=2). In the 31 cases protected with Angioguard Xp, proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) was also performed. All of the patients were treated with self-expandable stents: Precise (Johnson & Johnson, Cordis, Minneapolis, MN; n=46) or Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA; n=2). In the 31 cases protected with Angioguard Xp, proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) was also performed. All of the patients were treated with self-expandable stents: Precise (Johnson & Johnson, Cordis, Minneapolis, MN; n=46) or Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA; n=2). In the 31 cases protected with Angioguard Xp, proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) was also performed. All of the patients were treated with self-expandable stents: Precise (Johnson & Johnson, Cordis, Minneapolis, MN; n=46) or Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA; n=2). In the 31 cases protected with Angioguard Xp, proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) was also performed. All of the patients were treated with self-expandable stents: Precise (Johnson & Johnson, Cordis, Minneapolis, MN; n=46) or Percusurge Guardwire (Medtronic AVE, Santa Rosa, CA; n=2).

Neurological examinations were carried out in each patient before CAS, the day after CAS, and 30 days after CAS. Thirty-day morbidity was defined as any new neurological deficit that persisted 30 days after CAS.

Statistical Analysis

Normally-distributed continuous variables were expressed as mean ± standard deviation (SD). Median values and the interquartile range (IQR) were computed for non-normally distributed variables. Because most of the continuous variables were not distributed normally, we made a common logarithmic or square-root transformation of these variables. Baseline characteristics were compared by using Student t test for continuous variables and Fisher exact test for categorical variables. A 2-sided P value of less than 0.05 was considered to indicate a statistically significant difference. Multivariate logistic regression analysis with DWI lesion-positive or -negative as the outcome was then performed using those variables with a P value < 0.25 from the univariate analysis. Factors included were as follows: diabetes mellitus, proximal balloon occlusion, SIR, plaque volume, and low-density lipoprotein cholesterol (LDL-C) were analyzed for the incidence of DWI lesion related to CAS. Then, with the variables in which significance was indicated by the multivariate logistic regression analysis, correlation with the number of DWI lesions was further analyzed by calculating Spearman’s correlation coefficients (rs). The cutoff values of SIR and plaque volume with the best sensitivity and specificity for evaluating the probability of newly appearing DWI lesions were identified by analyzing the receiver operating characteristic curve. To determine intra- and inter-reader reproducibility, the intraclass correlation coefficient (ICC) with 95% confidence interval (CI) was calculated for the level of agreement. All of the statistical analyses were performed with IBM SPSS Statistics 19 software.

Results

Forty-eight consecutive CAS procedures were completed successfully with satisfactory angiographic results. Thirty-day morbidity and mortality were 2.1% and 0%, respectively. No myocardial infarctions or adverse events related to devices were observed. Characteristics of patients with or without DWI lesions (DWI positive, P-group; or DWI negative, N-group) are shown in Table 1. One patient was excluded from evaluation because the quality of the 3D T1GRE images was inadequate for evaluation. In this case, flow artifact around the carotid plaque obscured the plaque–lumen interface. Thus, 47 carotid plaques were evaluated in this study. Representative 3D T1GRE images and DWI of P-group and N-group are presented in Figures 1 and 2.

New ipsilateral DWI lesions were detected after 26 CAS procedures (55%). The majority of new ipsilateral DWI lesions were asymptomatic; however, 1 patient experienced a minor stroke from a cerebral embolism related to CAS. To clarify the ability of SIR and plaque volume to predict cerebral embolism related to CAS, the relationship between these variables and DWI lesions with CAS were investigated. The results of univariate analysis are summarized in Table 1. Among the
clinical variables, SIR (2.17 [IQR 1.50–3.07] and 1.35 [IQR 1.08–1.97], respectively; \(P = 0.010\)), plaque volume (456 mm\(^3\) [IQR 256–696] and 301 mm\(^3\) [IQR 126–433], respectively; \(P = 0.008\)), and LDL-C (111 mg/dL [IQR 101–138] versus 98 mg/dL [IQR 83–117] respectively; \(P = 0.040\)) were significantly related to new ipsilateral DWI lesions (Figure 3). The multivariate logistic regression analysis that we subsequently performed, with DWI lesion-positive or –negative as the outcome, indicated SIR (\(P = 0.007\)), plaque volume (\(P = 0.042\)), and LDL-C (\(P = 0.021\)) as independent predictors of new ipsilateral DWI lesions (Table 2).

We then calculated Spearman correlation coefficients between those independent predictors and the numbers of DWI lesions and found significant correlation for SIR (\(r_s = 0.42, P = 0.005\)) or plaque volume (\(r_s = 0.36, P = 0.012\)), but not for LDL-C (\(r_s = 0.23, P = 0.110\); Figure 4).

Receiver operating characteristic curves indicated that the most reliable cutoff values of SIR and plaque volume to predict new ipsilateral DWI lesions related to CAS were 1.80 and 373 mm\(^3\), respectively (areas under the curve were 0.70 and 0.73, respectively). When the cutoff value of SIR was 1.80, the sensitivity, specificity, and positive and negative predictive values were 69%, 71%, 75%, and 65%, respectively. When the cutoff value for plaque volume was 373 mm\(^3\), the sensitivity, specificity, and positive and negative predictive value were 69%, 71%, 75%, and 65%, respectively.

Intrareader reproducibility (ICC, 95% IC) was excellent for the number of DWI lesions (0.996; 0.993 to 0.998), SIR (0.971; 0.948 to 0.984), and plaque volume (0.913; 0.850 to 0.951).

**Discussion**

The present study demonstrated that MR plaque imaging using the 3D T1GRE images could identify plaques representing high risk for cerebral embolism related to CAS. SIR and plaque volume were significantly higher in the P-group than the N-group. In addition, the numbers of new ipsilateral DWI lesions were correlated positively with SIR and plaque volume. Because the number of new DWI lesions after CAS has been reported to have a clear association with the incidence of minor or major stroke, SIR and plaque volume could be a useful predictors not only for DWI lesions but also for minor or major stroke. To our knowledge, this is the first report that describes the relationship between carotid plaque characteristics evaluated with 3D T1GRE sequence and risk of cerebral embolism related to CAS.

Preventing cerebral embolisms is a major concern with CAS. In contrast to carotid endarterectomy, CAS could mechanically rupture a plaque by applying high-pressure balloons and stents and could release plaque debris and soluble factors into the circulating blood. Therefore, accurate evaluation of carotid plaque characteristics is clinically important to reduce cerebral embolisms related to CAS, especially when the targeted carotid plaque is vulnerable. Vulnerable plaques that contain lipid-rich necrotic core or IPH as determined by ultrasonography or MR imaging are considered to be 1 of the risk factors for ischemic complications after CAS. Recent developments in MR imaging with high-contrast resolution have enabled noninvasive assessment of carotid plaque vulnerability. Yamada et al evaluated the usefulness of T1 high intensity in the 2D T1 turbo spin echo images to predict cerebral embolism related to CAS and concluded that an SIR of 1.25 was the most reliable cutoff value.

Recently, 3D T1GRE sequences have been used in clinical settings and attracted considerable attention for evaluating vulnerability of carotid plaques. Those sequences vary depending on the vendor, including 3D fast spoiled gradient recalled echo, 3D TFE, and magnetization prepared rapid acquisition with gradient echo. 3D
T1GRE sequences could overcome several limitations of 2D T1 turbo spin echo sequence, including imaging direction restricted to the cross-sectional transaxial plane, lack of contiguous anatomic coverage, quantification errors resulting from partial volume effect, requirement for electrocardiogram or peripheral pulse unit for pulse-synchronized image acquisition to minimize effects of intraluminal flow signals, and inadequate examination time-efficiency. Therefore, 3D T1GRE is more practical in clinical settings. In addition, 3D T1GRE sequences have been reported to demonstrate higher diagnostic capability to detect IPH compared with the 2D fast spin echo or turbo spin echo sequences. Although 3D T1GRE sequences are gaining popularity for evaluation of plaque vulnerability, no studies have been performed to determine the usefulness of those sequences in predicting cerebral embolism related to CAS. Our results demonstrated that 3D T1GRE images are useful in predicting the risk of cerebral embolism related to CAS and the most reliable cutoff value to predict cerebral embolism related to CAS was 1.80. Because the plaque signal on T1-weighted images varies considerably with different magnetic field strength, TR, and sequence, no reported cutoff value, including ours, achieved general validity. However, higher T1 intensity is certainly a risk factor for cerebral embolism related to CAS.

Larger plaques have more atherosclerotic burden and exposed surface, and hence presumably carry a higher risk of releasing more plaque debris during CAS. However, to date, no study has evaluated the association between carotid plaque volume and increased risk for cerebral embolism related to CAS. The severity of carotid stenosis is an important risk factor for stroke and is used to decide which patients could benefit from carotid intervention. Unfortunately, luminal stenosis does not necessarily reflect the amount of atherosclerotic plaque. Degree of stenosis could underestimate the plaque volume, because enlarged arterial lumen resulting from positive remodeling cannot be accounted for with angiography. Long and continuous lesions with mild to moderate stenosis might have more atherosclerotic plaque materials than a severe stenosis that covers only a short segment. Our results clearly show that carotid artery stenosis with higher plaque volume carries more risk for cerebral embolism related to CAS, and that the cutoff value of plaque volume that most reliably predicts cerebral embolism related to CAS was 373 mm$^3$. We propose that plaque volume should also be considered a risk factor of cerebral embolism related to CAS.

Several limitations must be considered for the present study. First, it was performed retrospectively, and the number of patients enrolled was too small to evaluate the association with the incidence of stroke. A prospective study that includes an analysis for incidence of stroke with a larger number of patients would provide more evidence for the association we indicate in the present study. Second, the choice of embolic protection devices and other variables, such as the pressure applied for pre/post dilatation, differed in each case. Third, all the patients were treated with an open-cell–type stent. In a recent study, patients treated with open-cell–type stents had significantly higher stroke and death rates after CAS than those treated with closed-cell–type stents, indicating that the latter type of stent might have an intrinsically greater potential to prevent cerebral embolism of plaque debris. Therefore, we might have experienced more embolism cases with CAS. Use of closed-cell–type stents would further help decreasing incidence of cerebral embolism related to CAS. Finally, assessment of carotid plaque using signal intensity might fail to diagnose vulnerable plaques when they are composed of large lipid-rich necrotic core without IPH, because the regional signal intensity of lipid-rich necrotic core without IPH may not be demonstrated with high intensity signals on T1-weighted images.

**Conclusion**

The 3D T1GRE sequence was useful to identify vulnerable plaques at high risk for cerebral embolism related to CAS. Higher SIR and plaque volume evaluated with 3D T1GRE images correlated significantly with the appearance of DWI lesions related to CAS. We suggest that higher T1 intensity and larger plaque volume on 3D T1GRE images should be recognized as additional risk factors for cerebral embolism related to CAS.

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**Disclosures**

None.
References

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3D T1 強調グラディエントエコーーシーケンスにより評価した頚動脈ステント留置に伴う高リスクのプラーカ

High-Risk Plaque for Carotid Artery Stenting Evaluated With 3-Dimensional T1-Weighted Gradient Echo Sequence

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Key Words  頚動脈, 脳塞栓, プラーク, アテローム硬化性, ステント
本研究では、CAS 関連の脳塞栓予測におけるプラックの量的特徴の有用性を後向きに評価した。プラックの量的特徴として、T1 強調画像のシグナル強度、3D T1GRE シーケンスを用いた MR プラーク画像で評価したプラック容積を用いた。

### 方法

#### 研究対象集団

2008 年 1 月から 2009 年 12 月までに CAS を実施した 48 例を研究対象とした。

North American Symptomatic Carotid Endarterectomy Trial で使用された方法に従って、デジタルサブトラクション血管造影により、狭窄が 50% の症候性頸動脈病変または狭窄が 80% の無症候性頸動脈病変と診断された患者が CAS 実施の適格例であった。頸動脈狭窄症において、CAS 実施後の 120 日以内に、頸動脈病変に起因する同側虚血性イベントを発症している場合は症候性と定義した。これら以外は、無症候性頸動脈病変とみなした。患者特性は診療記録のレビューを通じて後向きに収集した。

CAS 実施前 1 カ月以内に臨床検査パラメータを評価した。

#### CAS 実施前 3 日以内に全患者に対し診断的血管造影を実施した後、DWI および 3D T1GRE による頸動脈プラークイメージングを含む、MR 検査を実施した。CAS 実施前の DWI から CAS 実施までの間、一過性脳虚血発作または脳卒中などの虚血性イベントはみられなかった。CAS 実施後 48 時間以内に DWI を取得した。頸動脈プラーク画像および CAS 実施前の DWI は、3.0T MR 検査システム (Achieva Quasar Dual, Philips Medical Systems 社, Best, オランダ) により得た。CAS 実施後の DWI は、1.5T MR 検査システム (Intera Achieva Nova, Dual, Philips Medical System 社, Best, オランダ) を使用した。

3D T1 ターボフィールドエコー (T1TFE) シーケンスを用いて 3D TIGRE 画像を取得した。3D TIGRE は、血液を null ポイントに設定して、冠状面において実施し、実効反転時間 600 msec, TR/TE 5.0/2.3 msec, 水エコー法により脂肪信号を抑制した。その他のスキャンングパラメータ: FOV 260 mm, ボクセルサイズ = 0.68 × 0.68 × 1.00 mm, フリップ角 = 13°, パーセッション 56, 頸動脈分岐部の周囲 70 mm をカバー、データ取り込み時間 4 分 2 秒。

CAS 実施前の DWI は以下のパラメータで実施した: TR/TE 最短/60 msec, スライス厚 = 3 mm, スペーシング、

#### 表1 拡散強調画像における虚血性病変を有するまたは有さない患者の特性

<table>
<thead>
<tr>
<th></th>
<th>P 群 (n = 26)</th>
<th>N 群 (n = 21)</th>
<th>p 値</th>
</tr>
</thead>
<tbody>
<tr>
<td>年齢平均値、歳</td>
<td>74.0 ± 4.9</td>
<td>72.2 ± 6.5</td>
<td>0.276</td>
</tr>
<tr>
<td>狭窄率 (%)</td>
<td>80.3 ± 2.3</td>
<td>81.7 ± 2.6</td>
<td>0.687</td>
</tr>
<tr>
<td>男性、n (%)</td>
<td>24 (92.3%)</td>
<td>19 (90.5%)</td>
<td>1.000</td>
</tr>
<tr>
<td>既往歴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>症候性狭窄</td>
<td>13 (50.0%)</td>
<td>10 (47.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>冠動脈疾患</td>
<td>4 (15.4%)</td>
<td>2 (9.6%)</td>
<td>0.687</td>
</tr>
<tr>
<td>高血圧</td>
<td>20 (76.9%)</td>
<td>14 (66.7%)</td>
<td>0.521</td>
</tr>
<tr>
<td>糖尿病</td>
<td>11 (42.2%)</td>
<td>4 (19.1%)</td>
<td>0.121</td>
</tr>
<tr>
<td>高コレステロール血症</td>
<td>18 (69.2%)</td>
<td>15 (71.4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>喫煙</td>
<td>5 (19.2%)</td>
<td>7 (33.3%)</td>
<td>0.270</td>
</tr>
<tr>
<td>対側性ICA閉塞症</td>
<td>13 (50.0%)</td>
<td>10 (47.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>近位パルーンプロテクション</td>
<td>15 (57.7%)</td>
<td>16 (76.2%)</td>
<td>0.227</td>
</tr>
<tr>
<td>臨床検査値</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL コレステロール、mg/dl</td>
<td>48.4 [42.3 ～ 54.4]</td>
<td>44.6 [37.8 ～ 58.3]</td>
<td>0.703</td>
</tr>
<tr>
<td>LDL コレステロール、mg/dl</td>
<td>111.0 [101.0 ～ 137.8]</td>
<td>98.0 [83.0 ～ 117.0]</td>
<td>0.040</td>
</tr>
<tr>
<td>トリグリセリド、mg/dl</td>
<td>142.0 [104.0 ～ 188.0]</td>
<td>127.0 [81.5 ～ 182]</td>
<td>0.451</td>
</tr>
<tr>
<td>C 反応性タンパク質、mg/dl</td>
<td>0.23 [0.06 ～ 0.38]</td>
<td>0.15 [0.06 ～ 0.229]</td>
<td>0.870</td>
</tr>
<tr>
<td>頚動脈プラークの特徴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIR</td>
<td>2.17 [1.50 ～ 3.07]</td>
<td>1.35 [1.08 ～ 1.97]</td>
<td>0.010</td>
</tr>
<tr>
<td>プラーク容積 (mm³)</td>
<td>477.7 [256.4 ～ 696.3]</td>
<td>300.7 [125.6 ～ 433.0]</td>
<td>0.008</td>
</tr>
</tbody>
</table>

HDL: 高比重リポタンパク, ICA: 内頸動脈, LDL: 低比重リポタンパク, SIR: 信号強度比。
抗血小板療法として全患者にアスピリン（100 mg/日）とクロピドグレル（75 mg/日）の併用、またはアスピリン（100 mg/日）とシロスタゾール（200 mg/日）の併用でCAS実施前に7日間以上投与した。CASはすべて、局所麻酔下で経験豊富な脳神経系血管内治療チームにより経皮的大腿動脈経由で実施された。イントロデューサーのシースを留置した直後にヘパリン100 U/kgを静脈内にポーラス投与し、活性化凝固時間（ACT）を300秒以上に延長した。2種類の遠位塞栓予防デバイス[Angioguard XP (Johnson & Johnson, Cordis 社, ミネアポリス, ミネソタ州, n = 46), または Percusurge Guardwire (Medtronic AVE 社, サンタローザ, カリフォルニア州, n = 2)]を使用した。患者31例は、Angioguard XPにより遠位塞栓を予防し、近位塞栓予防にはバルーンカテーテル、Optimo（東海メディカルプロダクツ社、愛知、日本）を使用した。全患者に対し、バルーンカテーテルで拡張後、自己拡張型ステント[Precise (Johnson & Johnson, Cordis 社, ミネアポリス, ミネソタ州)]による治療を実施した。ポスト拡張は必要に応じて実施した。CAS終了後、ヘパリンのリバースは実施せず、作用を自然に消失させた。

図1
P群患者の頸動脈フラクの典型的な画像。[A] 3D T1 GRE画像。[B] 拡散強調画像。画像は重度の無症候性頸動脈狭帯を有する70歳男性から取得した。高信号の頸動脈フラクが長軸再構成3D T1 GRE 画像において確認されている。頸動脈フラクの信号強度は3.07、およびプラク容積は1,133 mm³であった。頸動脈ステント留置術後の拡散強調画像において、多発性・無症候性脳塞栓が判明した。

図2
N群患者の頸動脈フラクの典型的な3D T1 GRE 画像。画像は、重度の症候性頸動脈狭帯を有する65歳男性から取得した。等強度の頸動脈フラクが長軸再構成3D T1 GRE 画像において描出されている（白矢印）。頸動脈フラクの信号強度は1.04、およびプラク容積は100 mm³であった。頸動脈ステント留置術後の拡散強調画像において、脳塞栓は認められなかった。

DWI を使用した脳塞栓の特定
CAS実施前と実施後で取得したDWI画像を比較し、実施後の新規の同側性の超高信号病変（DWI病変）は、すべてCAS関連の脳塞栓と結びつく虚血性病変とみなした。新規の同側性DWI病変の数、セクションごとに実施前と実施後のDWI画像を比較して数えた。
CAS実施前、実施の翌日および30日後に各患者に対して神経学的検査を実施した。30日有病率は、CAS実施後30日時点で残存する何らかの新規神経学的徴候と定義した。

統計解析
正規分布する連続変数は、平均値±標準偏差（SD）で示した。非正規分布する変数に関しては、中央値および四分位範囲（IQR）を算出した。連続変数の大部分は、正規分布を示さなかったため、これらの変数を対数変換または平方根変換した。ベースライン特性は、連続変数に関してStudent t検定を用いて比較し、分類変数に関してはFisherの正確確率検定を用いて比較した。両側のp値が0.05未満の場合、統計的有意差を示すとみなした。单変量解析から得たp<0.25の変数を用いて、転帰としてのDWI陽性およびDWI陰性について多変量ロジスティック回帰分析を実施した。糖尿病、近位バルーン閉塞、SIR、プラック容積、LDL-Cを因子としてCAS関連のDWI病変の発生に関して解析した。その後、多変量ロジスティック回帰分析により有意性が示された変数と、DWI病変の数との相関関係をSpearmanの相関係数（rs）によりさらに解析した。

表2 多変量ロジスティック回帰分析の結果による統計値。CASに関連する新規のDWI病変に対する独立予測因子を示す。

<table>
<thead>
<tr>
<th>因子</th>
<th>係数</th>
<th>標準誤差</th>
<th>p値</th>
</tr>
</thead>
<tbody>
<tr>
<td>糖尿病</td>
<td>0.644</td>
<td>0.442</td>
<td>0.145</td>
</tr>
<tr>
<td>近位バルーン閉塞保護</td>
<td>0.687</td>
<td>0.456</td>
<td>0.132</td>
</tr>
<tr>
<td>LDLコレステロール（log）</td>
<td>3.300</td>
<td>3.703</td>
<td>0.021</td>
</tr>
<tr>
<td>SIR（log）</td>
<td>4.207</td>
<td>1.828</td>
<td>0.007</td>
</tr>
<tr>
<td>プラック容積（√）</td>
<td>0.157</td>
<td>0.056</td>
<td>0.042</td>
</tr>
</tbody>
</table>

LDL:低比重リポタンパク。SIR:信号強度比。
うプラークを特定し得ることを示した。SIR およびプラーク容積は、N 群よりも P 群において有意に高値であった。さらに、新規の同側性 DWI 病変の数は、SIR およびプラーク容積と正の相関を示していた。CAS 実施後の新規の DWI 病変の数に関しては、軽度または重度の脳卒中発症との明確な関連性が報告されていることから 22, SIR よりもプラーク容積は DWI 病変の有用な予測因子であるのみならず、軽度または重度の脳卒中予測にも有用であると考えられる。我々の知る限り、本研究は、3D T1GRE シーケンスを用いて評価した頸動脈プラークの特徴と CAS に伴う脳塞栓リスクとの関連性を示した最初の研究である。

脳塞栓予防は、CAS に伴う大きな課題である。頸動脈内膜剥離術と比較して、CAS では、バルーンおよびステントの高圧によりプラークが機械的に破壊し、プラーク片および可溶性因子が循環血中に放出される可能性がある。したがって、頸動脈プラークの特徴を正確に評価することは、CAS に伴う脳塞栓を減少させることの上で臨床的に重要であり、標的とする頸動脈プラークが不安定である場合は、特に重要である。超音波検査または MR 画像法により確認された脂質に富んだ壊死性コアまたはIPH を有する不安定プラークは、CAS 実施後の虚血性合併症の危険因子の 1 つである 20,23。最近の、高コントラスト分解能をもつ MR 画像法の開発により、頸動脈プラークの不安定性を非侵襲的に評価することが可能となった 3–18。Yamada 氏らは 20, CAS 関連の脳塞栓リスクを予測する上で、2D T1 ターボスピンエコー画像における T1 高信号の有用性を評価し、SIR の最も信頼できるカットオフ値は 1.25 であると結論付ける。

検者内の再現性は、DWI 病変の数 (ICC = 0.998, 95% CI: 0.996 ～ 0.999), SIR (ICC = 0.985, 95% CI: 0.973 ～ 0.991) およびプラーク容積 (ICC = 0.949, 95% CI: 0.911 ～ 0.971) において優れていた。検者間の再現性は、DWI 病変の数 (ICC = 0.996, 95% CI: 0.993 ～ 0.998), SIR (ICC = 0.971, 95% CI: 0.948 ～ 0.984) およびプラーク容積 (ICC = 0.913, 95% CI: 0.850 ～ 0.951) において優れていた。

考察

本研究では、3D TIGRE 画像を使用した MR プラークイメージングにより、CAS 関連の脳塞栓の高リスクを伴うプラークを特定し得ることを示した。SIR およびプラーク容積は、N 群よりも P 群において有意に高値であった。さらに、新規の同側性 DWI 病変の数は、SIR およびプラーク容積と正の相関を示していた。CAS 実施後の新規の DWI 病変の数に関しては、軽度または重度の脳卒中発症との明確な関連性が報告されていることから 22, SIR よりもプラーク容積は DWI 病変の有用な予測因子であるのみならず、軽度または重度の脳卒中予測にも有用であると考えられる。我々の知る限り、本研究は、3D T1GRE シーケンスを用いて評価した頸動脈プラークの特徴と CAS に伴う脳塞栓リスクとの関連性を示した最初の研究である。

本研究に登録した全患者 (n = 47) の新規の同側性 DWI 病変と (A)：SIR (B)：プラーク容積 (C)：LDL-C の散布図。Spearman 統計学的相関係数により、 DWI 病変数と SIR およびプラーク容積の間に有意な正の相関が認められた。DWI：拡散強調画像、LDL-C：低比重リポタンパクコレステロール、SIR：信号強度比。
3D T1 強調グラディエントエコーシーケンスは、脳卒中の発症率を評価する高リスクの kurulu

T1GRE シーケンスは、2D T1 ターボスピンエコーシーケ

スの欠点とされる断層横断面に限定された画像の方向、

近接部位の解剖学的カバー度の欠如、部分体積効果に起

因する定量化誤差、血管内血流の血流による信号を最小化するバ尔斯同期化画像のための心電図または末梢脈

拍ユニットの必要性、不適切な検査時間の短縮などを克服し得る。したがって、臨床現場においては 3D T1GRE の方が実用的である。さらに、3D T1GRE シーケンスは、IPH の特徴において、2D ファーストスピンエコーまたはターボスピンエコーのシーケンスよりも高い診断能力を示すといわれている。3D T1GRE シーケンスが、ブラークの不安定性評価において好評を博しているにもかかわらず、CAS に伴う脳塞栓予防に関する 3D T1GRE シーケンスの有用性を判定する研究は、実施されていなかった。本研究の結果では、3D T1GRE 画像が CAS に伴う脳塞栓のリスク予防において有用であること、さらに、CAS に伴う脳塞栓を予測する、最も信頼性できるカットオフ値 1.80 であることを示した。T1 強調画像におけるブラーク信号はかなり多様であり、磁場強度 24, TR25, シーケンス 26 により異なるため、我々も含めて、一般的妥当性のあるカットオフ値を示すことができなかった。しかし、T1 信号強度が上昇するほど、CAS 関連の脳塞栓のリスク因子として確実になる。

ブラークが大きくなるほど、アテローム性動脈硬化の負荷および露出面は大きくなり、これにより、CAS 実施中により多くのブラーク片を放出するリスクが高くなると推定される。しかし、現在までに、顕動脈ブラーク容積と CAS に伴う脳塞栓のリスク上昇との関係性を評価した研究はなかった。顕動脈狭窄の重症度は、脳卒中の危険因子として重要であり、顕動脈介入者が患者に有益であるか否かの判断に使用される。残念ながら、脳塞栓発症は、アテローム性ブラークの量を必ずしも反映するわけではない。狭窄率からブラーク容積を評価するに過小評価する恐れがあるのは、再構築により拡大した動脈内径を、血管造影的に評価することができないためである。軽度から中等度の狭窄を認める場合、短いセグメントの狭窄の有無よりも、アテローム性ブラーク物質を多く含んでいる可能性がある。本研究の結果から明らかになったのは、顕動脈狭窄のブラーク容積が増加するほど、CAS 関連の脳塞栓リスクが上昇するということと、CAS に伴う脳塞栓を予測する上で、ブラーク容積の最も信頼できるカットオフ値は 373 mm³ であったということである。ブラーク容積もまた CAS に伴う脳塞栓の危険因子であるとみなすことを探す。

本研究において、脳卒中発症率との関連を評価できなかったため、脳卒中発症率との関連を評価できなかったことである。より多くの患者を登録して脳卒中発症率を解析する研究であれば、本研究において我々が示した関連性に対するエビデンスをより多く提供できたと考える。2 番目は、塞栓予防デバイスの選択および拡張の前後に加えた変数など他の数変数の選択が症例ごとに異なっていたことである。3 番目は、全患者をオープンセルタイプのステントで治療したことである。最近の研究では、オープンセルタイプのステント治療を受けた患者の CAS 実施後の脳卒中発症率および死因率が、クローズドセルタイプのステント治療を受けた患者と比べて有意に高かったとしており、ブラーク片に起因する脳塞栓の予防において、実質的にはクローズドセルタイプのステントのほうがより有用である可能性が示唆される。したがって、我々はより多くの CAS 関連の脳塞栓を経験したのである。クローズドセルタイプのステントの使用により、CAS 関連の脳塞栓の発生はさらに減少すると考える。最後に、顕動脈ブラークが大きな脳卒中群に占した壊死性病変を有し、IPH を伴わない場合、シグナル強度による評価では、不安定ブラークの診断を誤る可能性がある。これは、脂肪に含有する壊死性病変を有し、IPH を伴わない病変の場合、T1 強調画像において高信号を示さない可能性があるためである。

結 論

3D T1GRE シーケンスは、CAS に伴う脳塞栓の危険が高い不安定ブラークの特定に有用である。3D T1GRE 画像の評価では、SIR およびブラーク容積の増加が CAS 関連の DWI 病変の発現と有意に相関していた。3D T1GRE 画像における T1 信号強度の上昇およびブラーク容積の増加は、CAS 関連の脳塞栓の危険因子が増加したと認識されるべきであることが示唆された。

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情報開示

なし。
References


