Characterization of Carotid Artery Plaque Components on Magnetic Resonance Imaging Using Signal Intensity of the Phantom as a Reference

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Aims and objectives

Atherosclerotic carotid disease is a major cause of cerebral ischemia [1]. It is generally accepted that mildly stenotic plaques with a thin or ruptured fibrous cap, large lipid core, and hemorrhage are more susceptible to rupture than plaques with a thick cap, high degree of fibrosis, and calcification. Plaque lesions characterized by a lipid-rich necrotic core, by the presence of a thinned fibrous cap, or by intra-plaque hemorrhage are regarded as high-risk unstable plaques that are likely to rupture and lead to cerebral ischemia [2-16]. In 1995, Stary et al. defined different atherosclerotic subtypes to allow pathological identification of plaques most likely to cause symptoms. The stepwise progression of atheroma, with or without symptoms, in its later accelerated phase is often associated with intra-plaque hemorrhage, thus providing further evidence for the importance of this form of complex plaque in atherosclerotic disease [3]. Therefore, it is important to evaluate not only stenosis rate but also the properties of vulnerable plaque.

Magnetic resonance imaging (MRI) provides a means of noninvasively characterizing and monitoring carotid atherosclerotic lesions over time. The sequences are optimized for vessel wall imaging of the carotid artery for two-dimensional (2D) black-blood imaging using double inversion recovery preparations, and three-dimensional (3D) black-blood imaging which 3D-FSE(fast spin echo) with variable refocusing pulse using small flip angle. [17, 18]. High-risk plaques (soft and intra-plaque hemorrhage) show high signal intensity on fat suppression T1-weighted images and/or fat suppression T2-weighted images [19-21]. To evaluate the properties of plaque, it is necessary to perform normalization relative to a material with stable signal intensity, because the signal intensity on MRI changes with the signal gain.

Watanabe et al. reported that comparison of signal intensities with those of muscle and the submandibular or parotid gland was useful for property evaluation of pathological specimens [5]. However, the signal intensities of muscle and submandibular/parotid glands in humans vary between individuals. Therefore, we used a small phantom set on the circumference of the neck as a reference.
Methods and materials

Ethical review board approval was obtained for this analysis, and all patients gave their informed consent.

1. Patients

Between 2010 and 2012, 52 consecutive patients who underwent MRI with suspected or confirmed atherosclerosis of the carotid artery based on the results of carotid magnetic resonance angiography (MRA) and cervical ultrasonography were enrolled in this study (41 men, 11 women, age 39 years old to 87 years old).

2. Phantoms

Three types of phantom were used for normalization in this study. The phantoms consisted of a column-shaped container 20 mm in diameter and 40 mm in length filled with water (phantom 1), 5 µmol Gd-DTPA (phantom 2), or 2.5 µmol Gd-DTPA (phantom 3)[fig.1].
3. Pathological grade classification

Sixteen patients were enforced CEA (carotid endarterectomy) after MRI examination. In all cases, CEA was performed by two experienced surgeons according to the standard procedure. The surgeons were blinded to the results of plaque MRI. Pathological grade was classified based on the results of CEA or ultrasonography, follow-up MRI examination, 2D time-of-flight magnetic resonance angiography (2D TOF-MRA) and a diagnosis on contrasting examination.

On the pathological grade classification, the grade 3 was that there was large necrotic core with intra-plaque hemorrhage more than 40% in plaque and lipid-rich plaque or the thing that fibrous cap was recognized, and the grade 2 was that there was large necrotic core with intraplaque hemorrhage more than 20% in plaque, and the grade 1 was under more than 20% in plaque.

4. MRI protocol
MRI was performed on a 1.5T clinical system (Achieva; Philips Medical Systems, Best, The Netherlands) with standard neck and head array coils. First, multislab 3D TOF-MRA was performed to determine the position of carotid stenosis. Plaque imaging was performed by 2D-BB(black-blood) imaging and 3D-FSE(fast spin echo) with variable refocusing pulse using small flip angle (VISTA). 2D-BB imaging acquisition was performed using fast spin echo sequence with double inversion recovery preparation pulse, yielding excellent contrast between the dark lumen and vessel wall. Electrocardiogram gating was used to reduce flow-related and motion-related artifacts. The disadvantage of this technique is that the electrocardiogram (ECG)-gated pulse sequence requires a long repetition time of at least one R-R interval, which limits the incorporated fast spin echo sequence to only proton density and T2-weighted imaging, and not true T1-weighted imaging. The double inversion recovery technique is time inefficient, because it acquires a single slice at a time due to the need for nulling the blood longitudinal magnetization. For effective data sampling, 3D-FSE(VISTA) was recently developed.

5. Image analysis

The region of interest (ROI) was set on the carotid plaques, sternocleidomastoid muscle, submandibular gland, and three phantoms. The size of the ROI was greater than 5 pixels in the plaque and 50 pixels on other tissues and phantoms.

The standard deviations of tissue ratios (muscle/submandibular gland, phantom 1/phantom 2, and phantom 2/phantom 3) on T1WIs for 52 patients were calculated to evaluate the dispersion of signal values. In addition, the standard deviations of tissue ratios (muscle/phantom 2 on T1WI, submandibular gland/phantom 1 on T2WI, and phantom 3/phantom 2 on T2WI) for 52 patients were calculated.

The signal intensity index (SII) was calculated from each signal intensity.

\[
\text{SII(plaque/muscle)} = \frac{\text{signal intensity of plaque}}{\text{signal intensity of muscle}}
\]

\[
\text{SII(plaque/phantom 2)} = \frac{\text{signal intensity of plaque}}{\text{signal intensity of 5 µmol Gd-DTPA phantom}}
\]

The correlation coefficient of SII (plaque/phantom 2) was compared with SII (plaque/muscle).

For SII(plaque/muscle) on 2DSE-BB-T1WI, SII>1.25 on unstable plaque was defined as grade 3, 1.25>SII>0.5 was defined as grade 2, and SII<0.5 was defined as grade 3 based on the previous report by Watanabe [6]. For SII(plaque/phantom 2) on 2DSE-BB-T1WI, SII>0.4 was defined as grade 3, 0.4>SII>0.3 was defined as grade 2, and SII<0.3 was defined as grade 1.
On the other hand, for SII(plaque/muscle) on 3DT1WI(VISTA), SII>2 was defined as grade 3, 2>SII>1 was defined as grade 2, and SII<1 was defined as grade 1. For SII(plaque/phantom 2) on 3DT1WI(VISTA), SII>0.3 was defined as grade 3, 0.3>SII>0.2 was defined as grade 2, and SII<0.2 was defined as grade 1 [Table 1].

<table>
<thead>
<tr>
<th>Grade classification using signal intensity index (SII)</th>
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<tbody>
<tr>
<td>2D SEBB–T1WI</td>
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<tr>
<td>SII (plaque/muscle)</td>
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<tr>
<td>SII &gt; 1.25</td>
</tr>
<tr>
<td>grade3</td>
</tr>
<tr>
<td>1.25 &gt; SII &gt; 0.5</td>
</tr>
<tr>
<td>grade1</td>
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<tr>
<td>0.5 &gt; SII</td>
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**Table 1**

**References:** Kyoto city hospital - Kyoto/JP

The correlation coefficients of the grades of SII(plaque/muscle) and SII(plaque/phantom 2) were evaluated.

The pathological grade was compared with the grade from SII, and the correlation was reviewed by statistical analysis.
**Fig. 1:** Images of T1-weighted carotid artery wall and three phantoms. A: phantom 1 (water); B: phantom 2 (5 µmol Gd-DTPA); and C: phantom 3 (Gd-DTPA 2.5 µmol).

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### Table 1

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Results

The standard deviations of tissue ratios (muscle/submandibular gland, phantom 1/phantom 2, and phantom 2/phantom 3) for 52 patients were shown for evaluation of an agenda to use for reference.[Fig. 2 on page 11]

The standard deviations of tissue ratios were: (muscle/submandibular gland) = 0.272; (plaque/phantom 2) = 0.161; and (phantom 3/phantom 2) = 0.165. In addition, the standard deviations of tissue ratios were: (muscle/phantom 2) on T1WI = 0.192; (submandibular gland/phantom 1) on T2WI = 0.284; and (phantom 3/phantom 2) on T2WI = 0.074 [Fig. 3 on page 11].

The correlation coefficient of SII(plaque/phantom 2) with SII (plaque/muscle) was 0.5657 [Fig. 4 on page 12].

Comparisons of pathological grade with SII(plaque/muscle) and SII(plaque/phantom 2) are shown in Fig. 5 on page 13 and Fig. 6 on page 14, respectively.

For 3D images, comparisons of pathological grade with SII(plaque/muscle) and SII(plaque/phantom 2) are shown in Fig. 7 on page 15 and Fig. 8 on page 16, respectively.

In addition, the agreement rates with grades from each SII and pathological grade for 2D and 3D images are shown in Table 2.

<table>
<thead>
<tr>
<th>the equality rates with grades supposed to be from each SII and pathological grade</th>
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<tbody>
<tr>
<td>2DSE-BB-T1WI</td>
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<tr>
<td>SII(plaque/phantom2)</td>
</tr>
<tr>
<td>0.86</td>
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Table 2

References: Kyoto city hospital - Kyoto/JP
The agreement rate with grades from SII (plaque/phantom 2) and pathological grade was 0.86, and that with grades from SII (plaque/muscle) and pathological grade was 0.63. For 3D images, the agreement rate with grades from SII (plaque/phantom 2) and pathological grade was 0.86, and that with grades from SII (plaque/muscle) and pathological grade was 0.71.
Fig. 2: Standard deviations of tissue ratios (muscle/submandibular gland, water/phantom 2, and phantom 2/phantom 3) in 52 patients. The standard deviations of tissue ratios were: (muscle/submandibular gland) = 0.272; (plaque/phantom 2) = 0.161; and (phantom 3/phantom 2) = 0.165.

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Fig. 3: Standard deviations of tissue ratios (muscle/phantom 2) on T1WI, (submandibular gland/phantom 1) on T2WI, and (phantom 3/phantom 2) on T2WI in 52 patients. The standard deviations of tissue ratios were: (muscle/phantom 2) on T1WI = 0.192; (submandibular gland/phantom 1) on T2WI = 0.284; and (phantom 3/phantom 2) on T2WI = 0.074.

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**Fig. 4:** Correlation of SII(plaque/phantom 2) and SII (plaque/muscle). The correlation coefficient was 0.5657.

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Fig. 5: Comparison of SII(plaque/muscle) and pathological grade for 2D images.

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Fig. 6: Comparison of SII(plaque/phantom 2) and pathological grade for 2D images.

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**Fig. 7:** Comparison of SII(plaque/muscle) and pathological grade for 3D images.

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Fig. 8: Comparison of SII(plaque/phantom 2) and pathological grade for 3D images.

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Table 2

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Conclusion

Ultrasonography, computed tomography, and contrast-enhanced MRI are useful in differentiation of the characteristics of plaque in the carotid artery [22 - 24]. However, T1-weighted images and T2-weighted images are the most non-invasive and sensitive under the present conditions.

Two-dimensional reconstruction black-blood T1WI (2D-BB-T1WI) and T2WI (2D-BB-T2WI) are standard techniques. However, the disadvantage of these methods is that the ECG-gated pulse sequence requires a long repetition time of at least one R-R interval. Therefore, image contrast may be changed due to differences in repetition time (TR).

In addition, normalization is necessary because the pixel value on MRI depends on the signal gain during the scan. Therefore, the signal intensity of plaque was defined using signal intensity of adjacent tissue as a reference. However, there are problems with respect to precision in that the signal of the tissue differs between individuals. Figure 2[Fig. 2 on page 21] shows the wide variation in signal value ratio of muscle/submandibular gland comparison with phantoms in 52 patients. This is because the signal intensities of tissues in the human body are different between individuals and there are changes in contrast between phantoms due to differences in TR depending on R-R. The signal intensities of the submandibular gland differed markedly between individuals on T2WI [Fig. 3 on page 21].

The correlation coefficient of SII(plaque/muscle) and SII(plaque/phantom 2) was 0.5657. The agreement rate between SII(plaque/phantom 2) and pathological grade was higher than that between SII(plaque/muscle) and pathological grade (P < 0.001). These results were due to the differences in signal value of muscle between individuals.

Similarly, in 3D, the agreement rate with SII(plaque/phantom 2) and pathological grade was higher than with SII(plaque/muscle) and pathological grade (P < 0.001). These results suggested that the phantom is superior to muscle or submandibular gland as a reference. These are similar in T2WI.

In addition, 2D-BB is the standard technique for quantitative evaluation of the carotid plaque, but we understood that it was possible in the 3D-FSE method.

Keenan et al. reported that 3D fast spin echo carotid wall imaging showed similar performance to the conventional 2D technique, but with over twice the signal-to-noise ratio and a substantially reduced scan time [25]. In addition, 3D imaging can be performed in arbitrary sections and arbitrary projection view using multiplanar reconstruction (MPR) [25 - 27].
These SIIIs may be changed by system vendors and scanning parameters, and therefore further studies will be required in future.

This study using the phantom was limited by motion artifacts of the phantom related to movement on swallowing saliva and breathing, as well as changes in signal intensity due to convection of liquid in the phantom.

To address these limitations, a solid phantom may be fixed on the inside of a neck coil.

We examined the SII method as reference with phantoms signal setting close with carotid artery for discrimination of the properties of plaque in the carotid artery.

This method reduced error in comparison with use of tissue (e.g., muscle), and showed a good correlation with pathological grade.

The 3D-FSE method was also evaluated. For evaluation of the properties of plaque using a phantom as a reference with 3 D-FSE, SII showed good correlations with pathological grade. Therefore, the 3D method was more effective because it did not require ECG gating, and it can obtain arbitrary slice profiles in retro reconstruction.

However, further studies are required because the value of SII was affected by the scanning parameters.
**Fig. 2**: Standard deviations of tissue ratios (muscle/submandibular gland, water/phantom 2, and phantom 2/phantom 3) in 52 patients. The standard deviations of tissue ratios were: (muscle/submandibular gland) = 0.272; (plaque/phantom 2) = 0.161; and (phantom 3/phantom 2) = 0.165.

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Fig. 3: Standard deviations of tissue ratios (muscle/phantom 2) on T1WI, (submandibular gland/phantom 1) on T2WI, and (phantom 3/phantom 2) on T2WI in 52 patients. The standard deviations of tissue ratios were: (muscle/phantom 2) on T1WI = 0.192; (submandibular gland/phantom 1) on T2WI = 0.284; and (phantom 3/phantom 2) on T2WI = 0.074.

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