Assessment of the Correlation Between Carotid Artery Plaque Density Determined by Histogram Analysis and Positive Remodeling on Computerized Tomography Angiography

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Abstract

Background: CT angiography (CTA) was routinely performed for carotid artery disease, but the plaque characterization based on measurement of density may be inaccurate, influenced by adjacent calcification and contrast agent. Remodeling ratio was one of the additional new objective indexes for plaque characterization. On coronary CTA, the utility of histogram analysis was reported in a few studies.

Objectives: The purpose of this study was to evaluate the diagnostic value of histogram analysis of carotid artery plaque density and positive remodeling on CTA for the diagnosis of pathologically proven complicated carotid artery plaques.

Patients and Methods: We retrospectively evaluated 29 patients with atherosclerotic carotid artery stenosis treated by carotid endarterectomy. On CTA, the boundaries of non-calcified plaques were manually traced at the site of the greatest stenosis. In addition to the mean plaque density, the percentage of pixels (PP) with a density of less than 30 Hounsfield units (HU) (PP < 30) was calculated using the histogram analysis. We calculated the remodeling ratio by dividing the cross-sectional artery area at the greatest stenosis by normal reference-segment artery area. These results of CTA analysis were compared with the results of histological analysis based on the American heart association criteria.

Results: Histologically, 13 of the 29 patients had complicated plaques. PP < 30 and the remodeling ratio were higher in patients with complicated plaques than in those with uncomplicated plaques (P = 0.023 and 0.002, respectively). Whereas, the mean plaque density did not differ between the two groups (P = 0.062). Correlation between PP < 30 and the remodeling ratio was stronger than the correlation between PP < 30 and the mean density (Spearman’s rs = 0.76 vs. 0.65, respectively).

Conclusion: Histogram analysis of the carotid artery plaque density may be more useful for the evaluation of atherosclerosis on CTA compared with the conventional analysis of plaque densities, and the combined analysis of histogram analysis and the remodeling ratio may help to predict future stroke events.

Keywords: Atherosclerotic Carotid Artery Plaque, CT Angiography, Histogram Analysis, Positive Remodeling

1. Background

Atherosclerotic disease of the extracranial carotid arteries is an important cause of stroke. Carotid endarterectomy (CEA) or stent placement is considered to prevent stroke for patients with symptomatic or asymptomatic carotid stenosis above a certain degree (1, 2). However, patients with mild stenosis in the internal carotid artery (ICA) can unexpectedly experience strokes. Vulnerable atherosclerotic plaques have been reported to be an additional risk of atherosclerotic disease (2-4). The vulnerability to rupture of atherosclerotic plaques is related to the intrinsic composition, such as the hemorrhage of intraplaque and lipid core size (2-6).

The coronary artery responds to the growth of atherosclerotic plaques in different ways: by shrinkage of vessel wall (negative remodeling) or by outward expansion (positive remodeling) (7). Plaques showing positive remodeling tended to show higher macrophage count and have large lipid core compared to those without positive remodeling (3). Positive remodeling was previously thought to be a delayed response of luminal stenosis during the progression of atherosclerosis (3), but it was
ment for informed consent was waived. The privacy of the
search ethics committee of our institution. The require-
3.1. Patients
3. Patients and Methods
sis of pathologically proven complicated carotid artery
plaque density and positive remodeling for the diagno-
sation and assessment of the risk of stroke.
Several imaging techniques and methods have demon-
strated the ability to predict cerebral ischemic events; how-
ever, there are no definite criteria and we need to evalu-
ate several factors as a whole. Multi-detector computed to-
mography (MDCT) allows evaluation of the carotid artery
with thin slice thickness (no more than 1 mm), and more
detailed analysis of carotid artery stenosis and plaque com-
ponents. Previous studies reported that differences in
Hounsfield unit (HU) on MDCT can characterize compo-
ents of atherosclerotic plaque (2, 4, 9). However, high
density influenced by luminal enhancement and calcifica-
tion of the plaque may limit calculation of the accurate
mean plaque density, leading to inaccurate characteriza-
tion of fibrous and lipid-rich plaques (10, 11). For the coro-
nary atherosclerotic plaque characterization, a few stud-
ies have reported the potential role of a quantitative his-
togram analysis for distribution of pixels showing low den-
sity (10, 11). Marwan et al. (11) reported the utility of his-
togram analysis for coronary artery plaque characteriza-
tion on CT angiography (CTA): the distribution of pixels
with density < 30 HU calculated by histogram analysis may
contribute to more reliable plaque classification. As in the
coronary arteries, the extent of positive remodeling of the
ICA may indicate underlying atherosclerotic plaque vul-
nerenability and ischemic symptoms (3, 5, 8). Therefore, both
histogram analysis of plaque density and positive remodel-
ing on CTA may contribute to carotid plaque characteri-
ization and assessment of the risk of stroke.

2. Objectives

The purpose of this study was to evaluate the di-
agnostic value of histogram analysis of carotid artery
plaque density and positive remodeling for the diagno-
sis of pathologically proven complicated carotid artery
plaques.

3. Patients and Methods

3.1. Patients

This was a retrospective study approved by medical re-
search ethics committee of our institution. The require-
ment for informed consent was waived. The privacy of the
patients was fully protected. Between January 2009 and
February 2014, we selected the patients following search of
electronic medical records in our institution. We applied
the following inclusion criteria to patients: acquisition of
carotid CTA on the same CT scanner and imaging param-
eters within 3 months before CEA following the previous
study (2), and treatment of atherosclerotic carotid artery
stenosis by CEA. An exclusion criterion was the insufficient
quality of CTA due to artifacts or poor visualization of the
artery. One carotid artery was excluded from the study be-
cause of poor visualization of ICA due to near occlusion.
Twenty-nine patients (mean age: 69 ± 5 years) with a total
of 29 lesions were finally enrolled in this study. Character-
istics of the patients are summarized in Table 1. Clinical in-
formation of all patients was obtained from the electronic
medical records at our institution including other clinical
findings.

3.2. CT Examination

Carotid CTA was performed by a 64-slice dual source
CT scanner (SOMATOM Definition; Siemens Medical Solu-
tions, Forchheim, Germany). The imaging acquisition pa-
rameters for CTA were as follows: spiral mode 0.5-second
gantry rotation, 32 × 0.6 mm collimation, 0.9 - 1.5 pitch fac-
tor, 1.0 mm section thickness, 0.5 - 0.8 mm reconstruction
interval, 120 kVp tube voltage, a tube current of 400 - 650
mAs, and kernel B30-31f. 50 mL of iodine contrast medium,
ioamidol (Iopamiron 300; Bayer Schering Pharma, Berlin,
Germany) or iohexol (Omnipaque 300; Dainichi Sankyo,
Tokyo, Japan), was injected and followed by 20 mL of a
saline chaser at a flow rate of 4.0 mL/s. An automated bolus-
timing program determined optimal timing of CTA acquisi-
tion. Images were obtained from the level of the inferior
orbits to the aortic arch.

3.3. Image Data Analysis

CT images were analyzed by one neuroradiologist
(M.O.) who was blinded to the clinical and pathological
information. Multiplanar reconstruction (MPR) was per-
formed to produce two-dimensional images showing the
cross-sectional profile of a vessel along its length on a com-
puter workstation (Aquarius iNtuition, Version 4.4.7; Ter-
aRecon, Inc, San Mateo, CA, USA). Using a window level
of 250 and window width of 700, the region of maximal
luminal stenosis was visually identified on MPR and ax-
ial images on the workstation (Figure 1A and B). The de-
gree of stenosis was determined following the criteria of
the North American symptomatic carotid endarterectomy
trial (NASCET). The outer vessel contouring was manu-
ally performed to calculate the cross-sectional vessel area

recently presumed to be associated with plaque inflam-
mation and increased tendency for rupture (3, 5, 8). For
subjects with severe carotid artery stenosis, greater pos-
itive remodeling was observed in patients with cerebral
ischemic symptoms than in patients with no symptoms
in the previous study (3, 5). Plaque characterization or
positive remodeling provides accurate risk stratification
for future cerebral ischemic events.

Table 1. Comparison of Clinical Characteristics Between Type-VI and Non-Type-VI Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>All</th>
<th>Type-VI</th>
<th>Non-Type-VI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>29</td>
<td>13</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>69 ± 5</td>
<td>68 ± 5</td>
<td>70 ± 5</td>
<td>0.37</td>
</tr>
<tr>
<td>Male Gender</td>
<td>24 (83)</td>
<td>12 (92)</td>
<td>12 (75)</td>
<td>0.23</td>
</tr>
<tr>
<td>Symptoms</td>
<td>25 (86)</td>
<td>11 (85)</td>
<td>14 (88)</td>
<td>0.83</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (83)</td>
<td>11 (85)</td>
<td>14 (88)</td>
<td>0.83</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (31)</td>
<td>4 (31)</td>
<td>5 (31)</td>
<td>0.98</td>
</tr>
<tr>
<td>Smoking</td>
<td>22 (76)</td>
<td>11 (85)</td>
<td>11 (69)</td>
<td>0.33</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>16 (55)</td>
<td>9 (69)</td>
<td>7 (44)</td>
<td>0.18</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5 (17)</td>
<td>1 (8)</td>
<td>4 (25)</td>
<td>0.21</td>
</tr>
<tr>
<td>Stenosis (NASCET)</td>
<td>76.1 ± 13.9</td>
<td>73.9 ± 16.9</td>
<td>77.9 ± 11.1</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Abbreviation: NASCET, north american symptomatic carotid endarterectomy trial.

Values are expressed as Mean ± SD or No (%).

(CSA) on slices of maximum stenosis, reference CSA calculated at the nearest distal segments without atherosclerotic plaques (Figure 1B and C). According to previously reported methods (3, 5), the remodeling ratio was calculated as follows:

Remodeling ratio = (CSA at the point of maximum stenosis / reference CSA at the distal portion)

On the Image J program (Image J 1.48 v; national institutes of health, MD, USA), non-calcified plaques in cross sections at the point of maximum stenosis were manually traced at a short distance from calcification, vessel lumen, or wall to avoid partial volume effect, and histograms of the CT value distribution were obtained. Graphs were created using Excel (Microsoft, Redmond, Washington) (Figure 2). Based on the previous coronary CTA histogram study using a similar CT scanner (11), the percentage of pixels with density < 30 HU (PP < 30) and mean density of the carotid plaques were calculated.

We selected 30 HU as the cutoff for low-density plaques for the following reason. In the coronary CTA histogram analysis, Schlett et al. (10) and Marwan et al. (11) reported 60 and 30 HU as the cutoff, respectively. In a previous meta-analysis study, significant differences were found for the mean HU criteria of atherosclerotic plaques according to the CT vendor and number of detector rows with no correlation to the lumen contrast enhancement (12). Also, the HU criteria of carotid lipid-rich plaques may be lower than those of coronary arteries, caused by less partial volume effect or movement (12). Therefore, we selected 30 HU as the cutoff because Marwan et al. (11) used a CT scanner (SOMATOM Definition) similar to ours in their coronary CTA study.

3.4. Histological Grading of Carotid Artery Plaques Obtained by CEA

All lesion samples obtained by CEA were used to assess and categorize the histological classification of atherosclerotic plaques. The CEA specimens were fixed in 10% normal formaldehyde and cut into sequential 5-mm blocks, from the specimen base (common carotid or proximal end) to the bifurcation, until the whole specimen was cut. Sections of each block were stained with eosin and hematoxylin. Based on the American heart association (AHA) criteria, one experienced neurosurgeon (H.K.) who was blinded to the clinical information classified atherosclerotic plaques into either type VI or not. Complicated plaques (type VI) were graded based on the following criteria: 1, organized lamellar plaque or luminal adherent thrombosis (white blood cells, red blood cells, fibrin, platelets, and lines of Zahn); 2, free red blood cells within the media or intima not associated with lumen of vessel; 3, rupture or surface defects, or 4, macrophages containing hemosiderin.

3.5. Statistical Analysis

We used the StatView statistical package (StatView 5, SAS institute, Cary, NC, USA) for all statistical analysis. Spearman’s rank correlation was used to analyze correlations between two factors. To compare scores of unpaired samples, Mann-Whitney U test was used. Correlations between two factors were analyzed by Spearman’s rank correlation. A P value < 0.05 was considered to indicate statistical significance.
4. Results

Characteristic symptoms of the patients were transient ischemic attack, amaurosis fugax, or stroke, thought to be caused by the affected carotid artery. The definition of stroke and transient ischemic attack was based on the previously published criteria (13, 14). Amaurosis fugax was defined as transient acute onset of partial or complete monocular loss of vision (5).

Tables 1 and 2 show the comparison of clinical and imaging findings between 13 patients with and 16 patients without type VI lesions. There were no significant differences between the two groups regarding degree of stenosis or clinical characteristics including age, sex, symptoms, and prevalence of stroke risk factors. In contrast to the mean plaque density ($P = 0.062$), patients with type VI lesions exhibited significantly higher $PP < 30$ and remodeling ratios than those without type VI lesions ($P = 0.023$ and $0.002$, respectively). $PP < 30$ was more significantly correlated with the remodeling ratio than with the mean density (Figure 3; Spearman’s $rs = 0.76$ vs. $0.65$; $P < 0.0001$ and $P = 0.0007$, respectively). Most of the clinical parameters were not correlated with these imaging findings, except for smoking history ($P = 0.032$).

5. Discussion

We demonstrated that the percentage of the low density plaques of less than 30 HU calculated by histogram analysis and the remodeling ratio were correlated with the AHA type VI lesions, indicating vulnerable and complicated plaques. Of note, these complex plaques are associated with a higher incidence of cerebrovascular events (4-6).

Recently, the advanced imaging modalities have enabled visualizing atherosclerotic plaques. US, MRI, and CTA were non-invasive imaging modalities compared with...
Table 2. Comparison of Radiographic Parameters Between Type-VI and Non-Type-VI Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>All</th>
<th>Type-VI</th>
<th>Non-Type-VI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remodeling ratio</td>
<td>2.2 ± 1.4</td>
<td>3.1 ± 1.7</td>
<td>1.6 ± 0.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean density, HU</td>
<td>56.3 ± 32.9</td>
<td>44.8 ± 22.8</td>
<td>66.4 ± 36.7</td>
<td>0.062</td>
</tr>
<tr>
<td>PP &lt; 30, %</td>
<td>21.1 ± 26.0</td>
<td>29.5 ± 26.7</td>
<td>14.2 ± 23.2</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Abbreviation: HU, Hounsfield Unit.

Values are expressed as means ± SD.

In previous studies, carotid plaque density was associated with recent ischemic neurologic events (9). It was reported that lipids, hemorrhage, and necrotic debris (called “soft tissue” by the authors) had the lowest tissue densities on CT and intraplaque hemorrhage was found in AHA type VI (4). However, the density of other tissue components (fibrosis or calcifications) and contrast agent or calcified portions in the adjacent lumen influenced the plaque densities, which affected the mean plaque densities and decreased the accuracy of plaque classification (4, 10, 11). For the coronary atherosclerotic plaque characterization, a few studies have reported the potential role of a quantitative histogram analysis for distribution of pixels showing low density (10, 11). For the carotid atherosclerotic plaques, the correlation between MDCT images for measurement of lipid core area and histological sections was poor for calcified plaques in a previous study (2). In our carotid artery study, histogram analysis showed significant differences between the type VI and non-type VI groups, but mean plaque densities showed no significant differences. Also, histogram analysis showed a more significant correlation with the remodeling ratio than the analysis of mean plaque density. As the extent of expansive remodeling may indicate underlying atherosclerotic plaque vulnerability of the ICA (3, 5), histogram analysis may be helpful for the carotid atherosclerotic plaque evaluation on the CTA. Furthermore, the extent of the remodeling ratio correlated well with the plaque evaluation as previously reported (5).

This study had several potential limitations. First, the
presence of neurological symptoms showed no significant correlation with the remodeling ratio, PP < 30, or AHA plaque types. As we selected patients treated by CEA, there were only four (14%) asymptomatic patients, leading to the small sample bias. Second, as we have already mentioned in the “Patients and Methods”, we selected the cutoff for low-density plaques based on the previous coronary CTA histogram study (11) using a similar scanner to ours. However, the cutoff may be less because the HU criteria of coronary plaques were reported to be significantly higher than those of carotid plaques, which are caused by more partial volume effects from lumen contrast enhancement and the surrounding tissue due to the smaller plaque size (12). In addition, the cutoff may be different according to CT vendor or number of detector rows (12). Thus, further evaluation is necessary.

In conclusion, histogram analysis of the carotid artery plaque density may be more useful for the evaluation of atherosclerosis on CTA compared with the conventional analysis of mean plaque density, and the combined analysis of histogram analysis and remodeling ratio may help to predict future stroke events.

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Footnotes

Authors’ Contributions: Masaki Ogawa, study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis, and study supervision; Yoshiyuki Ozawa, critical revision, technical support, and study supervision; Masahiro Muto, critical revision, and technical support; Hiroyuki Katano, analysis and interpretation of data, and technical support; Kazuo Yamada, critical revision; Toshiyuki Miura, study concept and design, critical revision; Noriyuki Matsukawa, critical revision; Yuta Shibamoto, critical revision, and study supervision.

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