Assessment of Carotid Plaque Stability Based on the Dynamic Enhancement Pattern in Plaque Components With Multidetector CT Angiography

Nobutaka Horie, MD, PhD; Minoru Morikawa, MD, PhD; Shunsuke Ishizaka, MD; Tomonori Takeshita, MD; Gohei So, MD; Kentaro Hayashi, MD, PhD; Kauzhiiko Suyama, MD, PhD; Izumi Nagata, MD, PhD

Background and Purpose—Recent studies have investigated plaque morphology to determine patients who are at high risk of carotid atherosclerosis. In this study, we investigated whether a difference in dynamic enhancement pattern in plaque components could be useful to assess plaque stability with multidetector CT angiography.

Methods—Fifty-nine lesions with moderate to severe carotid atherosclerosis in 51 patients (33 symptomatic, 18 asymptomatic) were consecutively included. Early- and delayed-phase images were obtained in 3 equivalent axial slices with multidetector CT angiography. Hounsfield units (HU) in the early phase were subtracted from those in the delayed phase in plaques (ΔHU) and compared with clinical features, MRI-based plaque characteristics, and histological findings with 20 surgical specimens acquired from carotid endarterectomy.

Results—The ΔHU was significantly higher in asymptomatic than that in symptomatic presentation (P=0.02). With MRI, a higher ΔHU was negatively correlated with signal intensity on T1-weighted imaging (r=−0.56, P<0.0001). Histology confirmed that ΔHU was positively correlated with fibrous tissue (r=0.67, P=0.001) and negatively correlated with a lipid-rich necrotic core with hemorrhage (r=−0.70, P<0.001). Moreover, less neovascularization and inflammation was found in plaques with a higher ΔHU.

Conclusions—Delayed-phase images provide information regarding the dynamic change in contrast media from the early arterial phase. An increase in HU from the early phase on multidetector CT angiography indicates plaque stability with more fibrous tissue and a less lipid-rich necrotic core, intraplaque hemorrhage, and neovascularization. (Stroke. 2012; 43:393-398.)

Key Words: carotid plaque ■ delayed phase ■ multidetector computed tomography angiography ■ stability

Carotid atherosclerosis is 1 of the major causes of cerebral stroke. This can contribute to hemodynamic impairment in intracranial circulation as well as artery-to-artery embolisms. Initially, studies focused on luminal stenosis because the risk of stroke in patients with carotid atherosclerosis is closely associated with the severity of luminal stenosis, and the degree of stenosis is used in therapeutic decision-making for carotid interventions such as carotid endarterectomy or carotid arterial stenting. The widespread use of this measure is primarily based on the results of several randomized clinical trials that demonstrated a reduction in the risk for ischemic stroke in patients with luminal stenosis of ≥70% after carotid endarterectomy compared with medical treatment alone.1-4 However, carotid stenosis of ≥70% occurs in <10% of patients, whereas <70% of carotid stenosis is extremely frequent in the general population.5 Recently, studies on carotid atherosclerotic plaques have revealed that plaque morphology could be an important additional feature in the risk assessment of patients with carotid stenosis.6-26 Certain morphological features of carotid plaques such as a large lipid-rich necrotic core (LRNC), intraplaque hemorrhage (IPH), neovascularization, inflammation, or thin fibrous caps are increasingly reported to be associated with a heightened risk of stroke. Therefore, the concept of the vulnerable or high-risk plaque, initially derived from coronary studies, has been increasingly shown to be applicable in the carotid circulation.

An increased number of reports have shown promising plaque imaging techniques, including ultrasound, positron emission tomography, MRI, and multidetector CT angiography (MDCTA), which can characterize vulnerable carotid plaque features as well as luminal stenosis.16 However, it remains

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unclear which modality is the most effective and reliable. MDCTA is fast emerging as 1 of the noninvasive modalities of choice for carotid stenosis because of its high spatial resolution, speed, and ready availability. However, the use of MDCTA on plaque vulnerability is controversial8–11,15,20,26,27 with some reports showing the limitation of evaluating Hounsfield units (HU) for the assessment of carotid plaques owing to the blooming effect of calcification and overlapping between plaque components.15,16,26,27

Recently, some reports have indicated that a dynamic study with contrast-enhanced MRI can differentiate plaque components such as fibrous tissue with a peak in a delayed venous phase and neovascularization with a peak in an early arterial phase.24,25,28–30 This concept is based on the difference in absorption of contrast media in each plaque component and therefore it also could be applied to MDCTA, which has not been performed yet. Moreover, this dynamic study has the potential to address the blooming effect of calcification on MDCTA if HU in the delayed phase are subtracted from those in the early phase.

This study aimed to test (1) whether an increase in HU from early to delayed phases (ΔHU) on MDCTA is correlated with clinical presentation, MRI-based plaque morphology, and histological findings; and (2) to assess the hypothesis that a higher ΔHU indicates plaque stability with a lot of fibrous tissue and less LRNC, IPH, and neovascularization.

Methods

Study Population

Between April 2009 and December 2010, 59 lesions in 51 patients with >50% carotid stenosis on MDCTA (according to the North American Symptomatic Carotid Endarterectomy Trial [NASCET]) were consecutively included in this study. The patients were defined as “symptomatic” because they had an anterior circulation stroke or transient ischemic attack within 2 weeks of radiological analysis. The diagnosis of stroke was based on clinical presentation at admission and positive diffusion-weighted imaging at follow-up. The patients were defined as “asymptomatic” because they had no clinical symptoms and were found to have carotid stenosis in screening for atherosclerosis. Twenty patients underwent carotid endarterectomy based on the NASCET criteria3 and surgical specimens were analyzed for histology. This study was approved by our Institutional Review Board, and all patients gave written informed consent.

MDCTA Protocol and Analysis

All patients were scanned from the aortic arch to the head using a 64-MDCTA scanner (Aquilion 64®; Toshiba Medical Systems). MDCTA examinations were performed within 2 weeks of the surgical procedure to reduce potential errors in image and histopathologic correlations. Details of the protocol are described in the Supplemental Method (http://stroke.ahajournals.org). Two experienced readers (N.H. and M.M.) blindly rated and measured with free-hand segmentation the region of interest in each carotid plaque at 3 axial slices including the most stenotic site and 3.0 mm proximally and 3.0 mm distally. The mean HU in the region of interest was measured at 2 phases (early and delayed phase with an interval of 2 minutes). The equivalent level of the stenosis and region of interest were automatically defined at the early and delayed phases to avoid misregistration between the 2 phases (Figure 1A–C). HU in the early phase were then subtracted from those in the delayed phase (ΔHU) to assess delayed enhancement of the contrast media in relation to clinical, radiological, and histological findings. Severe calcified components covering the vessel wall were excluded from the region of interest. During the image review, the center level was set at 200 HU and window width was at 700 HU in both phases, which allowed for optimal plaque component distinction. Plaque ulceration was defined as outpouching of contrast into the plaque at least 2 mm deep.

MRI Protocol and Analysis

In all the patients, carotid atherosclerotic plaques were imaged in a 1.5-T MRI scanner (Signa; GE Medical System) using a phased-array coil with a diameter of 3 inches. MRI examinations were also performed within 2 weeks of the surgical procedure. Details of the MRI sequences are described in the Supplemental Method.

Figure 1. Sagittal section of the carotid plaque on MDCTA (A). Three transverse sections of the plaque including severe stenosis were selected, and the region of interest encompassing the plaque was drawn at the same slices automatically on early (B) and delayed (C) phases. MDCTA indicates multidetector CT angiography; JV, jugular vein; VB, vertebral body.
axial slices (including the most stenotic site and 3.0 mm proximal and 3.0 mm distal to the stenosis; these were the same slices analyzed on MDCTA) were selected, and then the mean signal intensity was quantified in the axial plaque area and ipsilateral sternocleidomastoid muscle. The T1-weighted imaging plaque/sternocleidomastoid muscle ratio was calculated for the assessment of LRNC with hemorrhage. \(^{11}\) The IPH was defined as the signal ratio of time of flight plaque/sternocleidomastoid muscle >2.0.\(^{11}\)

### Histology Sample Processing and Analysis

In the patients who underwent carotid endarterectomy, whole specimens were formalin-fixed, sectioned in 3.0-mm transverse slices, decalcified, and embedded in paraffin. Subsequently, 5.0-μm sections (3 sections with an interval of 3.0 mm including most stenotic slices to match the MDCTA and MRI slices) were subjected to histopathological analysis of plaque phenotype after hematoxylin and eosin, Azan, elastic van Gieson (EVG), Alcian blue staining, and Berlin blue staining. The plaque component of fibrous tissue, or LRNC with hemorrhage, was separately calculated as a mean percentage of the total plaque area in the 3 axial slices (fibrous tissue or LRNC with hemorrhage/total plaque area×100). Fibrous areas were measured on sections stained with Azan and EVG (blue in Azan and pinkish in EVG) and LRNC with hemorrhage areas were measured on sections stained with Azan and EVG (purple in Azan and brown in EVG). Some sections with a massive LRNC were stained with Alcian blue to confirm mucopolysaccharide in the plaque. Neovascularization and inflammation were assessed with hematoxylin and eosin staining (>400). Initially, neovascularization on the shoulder of the plaque was classified as follows: Stage 1, mild (<5 vessels); Stage 2, moderate (5–10 vessels); and Stage 3, severe (>10 vessels). The area of inflammatory cells on the shoulder of the plaque was classified as follows: Stage 1, mild (<25% of the area); Stage 2, moderate (25%–50% of the area); and Stage 3, severe (>50% of the area).

### Image and Pathology Review and Data Analysis

The MDCTA and MR images were separately analyzed by 2 experienced readers (N.H. and G.S.). Statistical analysis was performed with GraphPad Instat (Version 3.05; La Jolla, CA) and SPSS (Version 15.0; SPSS Japan Inc, Tokyo, Japan). The independent samples t test and Fisher exact test were used to compare continuous and categorical characteristics, respectively, between symptomatic and asymptomatic patients. Correlations between MDCTA-based HU and MRI parameters or pathological tissue area (fibrous and LRNC with hemorrhage) were analyzed by the Pearson rank correlation test (which measures the linear relationship between 2 variables), because we expected a linear relationship. Differences were defined as significant at a probability level <0.05.

### Results

#### Patients’ Characteristics

The characteristics of the study population are listed in Table 1. Among the 51 patients, 33 were symptomatic (24 infarctions, 9 transient ischemic attacks) and 18 were asymptomatic. There were significant differences in some of radiological findings. Initially, the mean degree of stenosis was 82.2%±12.8% in symptomatic compared with 68.3%±14.8% in asymptomatic (\(P<0.001\)) presentation. In 5 cases, severe calcified adventitia was excluded from the region of interest in radiological analysis. Interestingly, not early-phase HU (53.0±19.4 versus 19.7±19.7), but the \(\Delta\)HU (5.6±10.2 versus 13.5±14.5) was significantly different between the 2 groups (\(P=0.02\)). With regard to MR findings, symptomatic plaques had higher signal intensity than those with asymptomatic presentation on time of flight (66.7% versus 22.2%, \(P=0.002\)) and for the T1-weighted image ratio (1.60±0.6 versus 1.26±0.3, \(P=0.02\)).

### Radiological Correlation Between MDCTA and MR Findings

We then assessed whether early-phase HU or \(\Delta\)HU correlates with MRI-based plaque vulnerability. Early-phase HU showed a very weak correlation (\(r=-0.08\), \(P=0.54\); Figure 2A) with the T1-weighted imaging ratio. However, \(\Delta\)HU showed a significant correlation (\(r=-0.56, P<0.0001\); Figure 2B) with the T1-weighted imaging ratio. On the other hand, there was no difference in early-phase HU for the presence of IPH defined by time of flight (Figure 2C). However, plaques without IPH had higher \(\Delta\)HU than plaques with IPH (\(P<0.0001\); Figure 2D). These results suggest that not early-phase HU but \(\Delta\)HU could be a marker of LRNC and IPH.

#### Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Symptomatic (n=33)</th>
<th>Asymptomatic (n=18)</th>
<th>(P)</th>
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<tbody>
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<td>Cardiovascular risk factor</td>
<td></td>
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</tr>
<tr>
<td>Age, y</td>
<td>71.8±8.5</td>
<td>67.8±9.1</td>
<td>0.16</td>
</tr>
<tr>
<td>Male gender (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td></td>
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<td></td>
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<tr>
<td>Hypertension (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Current or former smoker (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>32 (97.0)</td>
<td>14 (77.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>23.9±4.6</td>
<td>20.4±2.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>11 (33.3)</td>
<td>3 (16.7)</td>
<td>0.21</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>27 (81.8)</td>
<td>13 (72.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>11 (33.3)</td>
<td>4 (22.2)</td>
<td>0.41</td>
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<td>Male gender (%)</td>
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<td>Age, y</td>
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<td>Male gender (%)</td>
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<td>Male gender (%)</td>
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</table>
Correlation Between MDCTA and Pathological Findings

To confirm the significance of ΔHU for plaque vulnerability, pathological analysis was performed. Twenty surgical specimens obtained from carotid endarterectomy clearly showed fibrous tissue and LRNC with hematoxylin and eosin, Azan, EVG, and Alcian blue staining. The ΔHU, but not early-phase HU (Figure 3A–B), was positively correlated with fibrous tissue ($r = 0.67$, $P < 0.001$; Figure 3C) and negatively correlated with LRNC with hemorrhage ($r = -0.70$, $P < 0.001$; Figure 3D). Representative images are shown in Supplementary Figures I and II.

We then investigated neovascularization and inflammation on the shoulder of the plaque because these components might affect HU and plaque vulnerability. Overall, interobserver reproducibility (N.H. and G.S.) and intraobserver reproducibility (N.H.; interval of 7 days) were substantial to nearly perfect for neovascularization grade ($\kappa$ coefficient $= 0.68$ and 0.84, respectively) and inflammation grade ($\kappa$ coefficient $= 0.92$ and 0.85, respectively). Interestingly, plaques with lower ΔHU had lots of small vessels or large irregular vessels on the shoulder, and inflammatory cells were also observed (Supplemental Figure IIIA), which was different from plaques with higher ΔHU showing fewer vessels or less inflammatory cells (Supplemental Figure IIIB). The correlation between ΔHU and neovascularization (Supplemental Figure IIIIC) or inflammation (Supplemental Figure IIID) indicated that plaques with low-grade neovascularization and inflammation had higher ΔHU, although a large distribution of values was noted.

Discussion

Delayed Enhancement of the Contrast Media

In this study, we focused on plaque stability because fibrous components are stabilizing features of atherosclerotic plaques.
Table 2. Dynamic Change in the Enhancement Pattern Between Plaque Components

<table>
<thead>
<tr>
<th>Plaque Component</th>
<th>Early</th>
<th>Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous tissue</td>
<td>Low to iso</td>
<td>Moderately high</td>
</tr>
<tr>
<td>LRNC</td>
<td>Low to iso</td>
<td>Low to iso</td>
</tr>
<tr>
<td>IPH</td>
<td>Iso to moderately high</td>
<td>Iso to moderately high</td>
</tr>
<tr>
<td>Calcification</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>Neovascularization</td>
<td>Lumen</td>
<td>Low to iso</td>
</tr>
<tr>
<td>Extravascular extracellular space</td>
<td>Low to iso</td>
<td>Moderately high</td>
</tr>
</tbody>
</table>

LRNC indicates lipid-rich necrotic core; IPH, intraplaque hemorrhage.

plaque neovascularization with static imaging modalities. Only dynamic contrast-enhanced carotid ultrasound is able to show vasa vasorum and plaque neovascularization, which are associated with cerebrovascular events, but there have been no previous reports clearly showing intraplaque neovascularization with MRI or MDCTA. It was reported that plaque neovascularization could be identified using a threshold of 80% enhancement in fibrous tissue with MRI, but there was a high SD in percent enhancement of neovascularization. This could account for an overlap between the neovascularization with a peak in the early phase and the fibrous tissue with a peak in a delayed phase. Therefore, the interpretation of neovascularization depends on the timing of the scan in static imaging. Theoretically, contrast media can be observed in the lumen of new vessels in the early phase, and it gradually penetrates into the extravascular extracellular space circumferentially. Consistent with this, Kerwin et al showed that there is a rapidly enhancing component, which is parallel to a signal change in the vessel lumen (suggesting neovascularization), and a slowly enhancing component (suggesting fibrous tissue) in plaques with contrast-enhanced dynamic MRI.

In our study, plaques with a lower ΔHU had multiple irregular or large vessels, and they also had massive inflammatory cells on the shoulder, although there was a wide distribution of values. Therefore, our results also suggest that plaques with low ΔHU can show plaque neovascularization and surrounding inflammation as well as LRNC and IPH, which all indicate vulnerable plaques (Table 2). Therefore, an increase in HU from the early to delayed phase indicates a lot of fibrous tissue and less LRNC, IPH, and neovascularization, which suggest plaque stability (Figure 4).

Limitations
Several limitations in this study should be addressed. First, disadvantages of MDCTA are radiation exposure and the need to administer radiological contrast. Second, this study did not quantify HU for the entire plaque volume because of technical difficulty. Care should be taken in interpreting the data because atherosclerotic components could be heterogeneous in the carotid plaque. We further confirmed that ΔHU in all individual locations of the plaque showed a significant (P<0.0001) correlation with MRI and histological findings (Supplemental Figure IV). Multislice analysis with MDCTA...
is recommended to obtain overall understanding of the plaque. Third, it is difficult to evaluate each plaque component separately with MDCTA. Nevertheless, MDCTA using the difference in HU between phases has great potential to determine plaque stability or vulnerability. It is worth reconsidering the role of MDCTA using the difference in HU between phases for the assessment of carotid plaque stability.

Conclusions

This study is the first to show the dynamic assessment of contrast media in the plaque components to evaluate plaque stability. Considering the role of MDCTA using the difference in HU, the difference in HU between phases has great potential to determine plaque stability. Nevertheless, MDCTA using the difference in HU between phases is recommended to obtain overall understanding of the plaque.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Supplemental Methods

MDCTA protocol

Radiation parameters were 300 mA, 120 kV, a matrix of 512 × 512, a field of view of 15 cm, a section thickness of 0.5 mm, and a pitch of 1.0. The acquisition time was 11 to 13 seconds. Unenhanced and two-phase contrast-enhanced helical scans of the carotid artery were obtained. Patients were instructed to hold their breath with inhalation during scanning. Two-phase contrast-enhanced CT of the carotid artery was performed in the early arterial phase and delayed phase with an interval of 2 minutes. An automatic bolus-tracking program (Sure Start, Toshiba Medical Systems, Japan) was used to start acquisition after contrast injection. First and second phase acquisition was started 10 and 130 seconds, respectively, after triggering. Intravenous contrast (Iohexol, Omnipaque 350®; Daiichi-Sankyo Co., Japan) was administered by using a double power injector (Dualshot ®; Nemoto Kyorindo Co., Tokyo, Japan) and a 20-gauge intravenous catheter inserted into the antecubital vein. The injection rate was 3.5 ml/s, for a total
volume of 70 ml followed by a saline chaser of 40 ml.

**MRI protocol**

After a survey to determine the position of the carotid plaque, the following MR imaging sequences were used: (1) T1WI: 2-dimensional fast spin echo, repetition time (TR)/echo time (TE) = 800/11 milliseconds, echo train length = 4; (2) 2-dimensional time of flight (TOF): TR/TE = 50/4.2 milliseconds, flip angle = 45°, field-of-view = 13 cm, matrix size = 256 × 128, and slice thickness = 3.0 mm.
Supplemental Figure 1: Representative images showing the vulnerable plaque. A three-dimensional reconstructed image shows severe stenosis at the left internal carotid artery (A). A transverse section of the plaque (white contour) shows similar HU in the early and delayed phases (B), and this section shows a high signal on T1WI and TOF images (C). Histological images (D) showing a massive LRNC component.

A and B: MDCTA. C: MR imaging. The scale bar indicates 1 mm. JV: jugular vein, VB: vertebral body.
Supplemental Figure 2: Representative images showing the stable plaque. A three-dimensional reconstructed image shows severe stenosis at the left internal to common carotid artery (A). A transverse section of the plaque (white contour) shows increased HU from early to delayed phase (B), and this section shows iso signal on T1WI and a low signal on TOF images (C). Histological images (D) showing fibrous components.

A and B: MDCTA. C: MR imaging. The scale bar indicates 1 mm. JV: jugular vein, VB: vertebral body.
Supplemental Figure 3: HE staining showing many small and irregular vessels on the shoulder in the plaque with a lower ΔHU (A: ΔHU=-11.2). Inflammatory cells were also observed in the plaque. On the other hand, the shoulder of a plaque with a higher ΔHU shows few vessels and inflammatory cells (B: ΔHU=46.7). The asterisk indicates a necrotic core. The scale bar indicates 200 μm. The bar graphs showing that a higher ΔHU tends to have low grade neovascularization (C: p=0.05) and inflammation (D: p=0.17).
Supplemental Figure 4: The DHU in all individual locations of the plaque showing significant correlation (p<0.0001) with T1WI ratio on MR imaging (A) and histological findings (B: fibrous tissue, C: lipid rich necrotic core with hemorrhage).
多検出器 CT 血管造影法で検出されるプラーク成分の動的増強パターンに基づく頸動脈プラークの安定性評価

Assessment of Carotid Plaque Stability Based on the Dynamic Enhancement Pattern in Plaque Components With Multidetector CT Angiography

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背景および目的：最近の研究で、頸動脈硬化症のリスクが高い患者を判定するためプラーク形態が調べられている。本研究では、プラーク成分の動的増強パターンの差が多検出器 CT 血管造影法によるプラークの安定性評価に有用であるかどうかを検討した。

方法：51例の患者（症候性33例、無症候性18例）の中等度から重度の頸動脈硬化症を呈する59の病変を連続して組み入れた。多検出器 CT 血管造影法により、3つの対応する軸位断スライスで早期相および遅延相の画像を取得した。早期相の Hounsfield 単位（HU）をプラークの遅延相の HU から減算し（ΔHU）、臨床的特徴、MRI に基づくプラークの特徴、および頸動脈内膜剥離術で得た20個の外科検体の組織学的所見と比較した。

結果：ΔHU は無症候性の場合の方が症候性の場合より有意に高かった（p = 0.02）。MRI では、ΔHU の高さは T1 強調画像の信号強度と逆相関した（r = -0.56, p < 0.0001）。組織学的検査で、ΔHU は線維組織と正相関し（r = 0.67, p = 0.001）、出血のある脂質に富む壊死性コアと逆相関することが確認された（r = -0.70, p < 0.001）。さらに、ΔHU の高いプラークほど血管新生および炎症は少なかった。

結論：遅延相の画像から早期動脈相からの造影剤の動的変化に関する情報が得られた。多検出器 CT 血管造影で早期相からの HU の上昇は、線維組織が増加し、脂質に富む壊死性コア、プラーク内出血、血管新生の減少した、プラークの安定性を示す。

表2 プラーク成分間の増強パターンの動的変化

<table>
<thead>
<tr>
<th>プラーク成分</th>
<th>早期相</th>
<th>遅延相</th>
</tr>
</thead>
<tbody>
<tr>
<td>線維組織</td>
<td>中程度高</td>
<td>高～等</td>
</tr>
<tr>
<td>LRNC</td>
<td>中程度高</td>
<td>高～等</td>
</tr>
<tr>
<td>IPH</td>
<td>高～等</td>
<td>高～等</td>
</tr>
<tr>
<td>石灰化</td>
<td>非常に高</td>
<td>非常に高</td>
</tr>
<tr>
<td>血管新生</td>
<td>非常に高</td>
<td>増加中</td>
</tr>
<tr>
<td>内腔</td>
<td>非常に高</td>
<td>高～等</td>
</tr>
<tr>
<td>血管外の細胞外空間</td>
<td>高～等</td>
<td>増加中</td>
</tr>
</tbody>
</table>

LRNC：脂質に富む壊死性コア、IPH：プラーク内出血。