Detection of Attenuated Plaque in Stable Angina With 64-Multidetector Computed Tomography
– A Comparison With Intravascular Ultrasound –
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Background: To clarify multidetector computed tomography (MDCT) findings of attenuated plaque detected by intravascular ultrasound (IVUS).

Methods and Results: One hundred and fifty-four patients with stable angina underwent MDCT before IVUS. The attenuated plaque was identified in the targeted artery with IVUS, and the same artery was analyzed with MDCT for the presence of a high density area (HDA) >130 Hounsfield units (HU), and a low density area (LDA) <30HU. A HDA in attenuated plaque was compared with that in calcified plaque. Ten attenuated plaques and 15 calcified plaques were identified in 9 of 154 patients (males=9, 66.2±9.5 years). Eight of the 10 attenuated plaques and all 15 calcified plaques were accompanied with a HDA on MDCT. The HDA ranged from 174 to 667 HU (mean 389.0±148.3HU) in the 8 attenuated plaques, and from 545 to 1,205 HU (mean 920.9±215.9HU) in 15 calcified plaques. There was a significant difference in CT density of the HDA between the attenuated and calcified plaque (P<0.001). All attenuated plaques contained LDA <30HU in the portions without HDA.

Conclusions: MDCT has the ability to demonstrate attenuated plaque as the combination of HDA (approximately 400HU on average) and LDA <30HU. The HDA can be differentiated from calcified plaque by its lower CT density value. (Circ J 2012; 76: 1182–1189)

Key Words: Attenuated plaque; Computed tomography; Coronary artery; Intravascular ultrasound; Vulnerability

Recently, attenuated plaque, which refers to deep ultrasound attenuation without calcification on intravascular ultrasound (IVUS), has been reported to be associated with plaque vulnerability. Lee et al suggested that attenuated plaque is observed more frequently in ST-elevated myocardial infarction, and might be part of the unstable lesion morphometric spectrum. Attenuated plaque is also thought to cause slow-flow or no-flow after percutaneous coronary intervention (PCI) because of its components such as lipid-laden atheromatous gruel mixed with foam cells and microcalcification, which might cause echo attenuation, per se. At present, IVUS is the only modality to detect attenuated plaque, and thus prior to PCI, we were unable to assume vulnerability by the existence of attenuated plaque. Multidetector computed tomography (MDCT) has enabled the evaluation of coronary plaque and the differentiation between calcified plaque and non-calcified plaque using differences in CT density. If attenuated plaque is composed of lipid-laden atheromatous and microcalcification, MDCT might have the potential to demonstrate attenuated plaque as a lesion with low density area (LDA; lipid-rich lesion) and high density area (HDA; calcified lesion), and enable the detection of attenuated plaque non-invasively.

In this study, we sought to clarify MDCT findings of attenuated plaque detected by IVUS.

Methods

Patient Population
The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was in agreement with the guidelines of the Ethics Committee of Keio University School of Medicine (Tokyo, Japan). Informed consent was obtained from all patients. Out of 154 cases who underwent ECG-gated 64-MDCT within 3 months prior to the IVUS investigation from September 2005 to February 2009, we identified 12 stable
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angina pectoris patients with attenuated plaque in the culprit artery. Three cases were excluded, 2 of which could not be analyzed by 64-MDCT due to severe calcification in the culprit artery, and the other had a motion artifact due to arrhythmia. As a result, 9 cases (males=9, 66.2±9.5 years) were enrolled in this study, which underwent 64-MDCT scanning at 31±25 days (1–77 days) before PCI was performed under IVUS guidance (Figure 1). Baseline clinical characteristics and procedural variables were recorded and entered prospectively.

Coronary Angiography

Angiographic analysis was performed to determine the locations of each example of attenuated and calcified plaque on the coronary artery in accordance with IVUS. This is useful for confirming the position of the plaque on coronary CT angiography. The coronary blood flow status was determined before and after PCI in accordance with the Thrombolysis In Myocardial Infarction (TIMI) flow grade.

IVUS

IVUS was performed using the Boston Scientific (Minneapolis, MN, USA) system incorporating a 40 MHz single-element beveled transducer (Atlantis SR Pro2) rotating at 1,800 rpm coupled with either ClearView Ultra, or an Intra Focus HF (Terumo, Tokyo, Japan) with a Intramage TU-C200. All IVUS images were recorded after administration of 2–5 mg of intracoronary isosorbide dinitrate. The ultrasound catheter was advanced distally and was pulled back to the aorto-coronary ostium using a motorized transducer pullback at 0.5 mm/s. All IVUS images were recorded on s-VHS videotapes for offline analysis.

The IVUS data were analyzed in consensus by 2 experienced cardiologists who were blind to the result of 64-MDCT. The existence of attenuated plaque was identified in the culprit artery on IVUS and the existence of calcified plaque was also checked in the same coronary artery. Calcified plaque was identified by its echogenicity and acoustic shadowing. Attenuated plaque was defined as hypoechoic plaque with deep ultrasound attenuation without calcification. The location of each case of plaque was confirmed by measuring the distance from the aorto-coronary ostium or the nearest bifurcation point. The remodeling index was defined as the mean cross sectional area of external elastic membrane (EEM) over attenuated plaque divided by the mean cross sectional area of EEM of proximal reference sites. The proximal reference site was selected as a segment without plaque proximal to the respective lesion or, should there be no segments without plaque available, the least diseased segment between the lesion and the coronary ostium or major bifurcations. The EEM over attenuated plaque was measured through estimation. Positive remodeling was determined as a remodeling index >1.05.

MDCT

Coronary CT angiography was obtained by using a 64-detector row CT (LightSpeed VCT; GE Healthcare, Milwaukee, WI, USA). Glycerol trinitrate, 0.3 mg, was administered sublingually immediately before the scan. Metoprolol was administered orally 1 h before data acquisition to patients with a heart rate 65 beats/min, unless contraindicated. Patients with a heart rate between 65 and 75 beats/min received 25 mg metoprolol and patients with a heart rate 75 beats/min received 50 mg metoprolol. An unenhanced image of the whole heart was obtained with collimation of 64×0.625 mm, rotation time of 0.35 s, pitch between 0.20 and 0.22, tube current of 300 mA and voltage of 120 kV. These data were reconstructed as 1.25 mm thick sections and no overlap. The enhanced images were obtained with collimation of 64×0.625 mm, rotation time of 0.35 s, pitch between 0.20 and 0.22, tube current of 300–550 mA and voltage of 120 kV. Iodine contrast material (Iopamidol 370 mgI/ml) with a total amount of 0.7 ml/kg was injected at an injection duration of 10 s, immediately followed by 20 ml of saline at the same rate. The delay between the start of injection and scanning was determined by the test bolus technique with monitoring at the level of the ascending aorta (120 kVp, 20 mAs, 10 ml of contrast material followed by 20 ml of saline injected at the same injection rate as the main scanning). The delay applied...
for main scanning was calculated by the time to peak enhancement for the test bolus plus 3 s.

In patients with a heart rate >65 beats/min or a heart rate change >5 beats/min, the cardiac helical scan with an ECG trigger was used. In patients with a stable heart rate ≤65 beats/min, a prospective ECG triggered dose modulation (the tube current in the systolic phase was 25% of the maximal tube current) or a step-and-shoot method (at 75% of the R-R interval) was used. In patients with a cardiac helical mode, an estimated mean radiation dose was 17.4±3.2 mSv. In patients scanned with ECG modulation or the step-and-shoot method, the estimated mean radiation dose was 4.7±0.8 mSv. The estimated values were calculated using the dose-length product×0.017.15

Data Analysis
The raw data of the optimal phase were reconstructed as

<table>
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<th>Table. Baseline Patient Characteristics</th>
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<tr>
<td>M/F</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Hypertension</td>
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<td>Hyperlipidemia</td>
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<td>Diabetes mellitus</td>
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<td>Smoking</td>
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<tr>
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<tr>
<td>Prior history of percutaneous coronary intervention</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Prior history of coronary artery bypass graft surgery</td>
<td>0</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Hemodialysis</td>
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Figure 2. A 67-year-old man with attenuated plaque accompanied by a high density area on MDCT in the right coronary artery. (A) An instance of attenuated plaque is demonstrated in longitudinal- and cross-sectional images with IVUS. White arrows indicate the plaque positions. (B) A plaque with linear high density is demonstrated in the same position with attenuated plaque on IVUS in the curved MPR and cross-sectional (C) images with MDCT. The length of high density is identical to the length of attenuated plaque on IVUS. The maximum density is averaged as 480HU in the enhanced cross-sectional CT image. The arrow head (C) shows enhanced coronary lumen. (D) The high density corresponding to this area is also seen in the unenhanced cross-sectional CT image. MDCT, multidetector computed tomography; IVUS, intravascular ultrasound; MPR, multiplanar reconstruction; CT, computed tomography.
Figure 3. A 56-year-old man with attenuated plaque accompanied by a high density area and a low density area on MDCT in the left anterior descending artery. Instances of attenuated plaque (A: long arrows) and calcified plaque (B: short arrows) are demonstrated in longitudinal- and cross-sectional image with IVUS. Instances of attenuated plaque (C-F: long arrows) and calcified plaque (C-G: short arrows) are demonstrated in stretched MPR (C) and cross-sectional (D-G) images with MDCT in the same positions as on IVUS. The length (4 mm) of high density (C: long arrow) is smaller than the length (6 mm) of attenuated plaque on IVUS. The maximum density is averaged at 370 HU (D) in attenuated plaque and averaged at 1,105 HU (G) in calcified plaque on enhanced CT. The mean attenuation of the 3 regions of interest (ROI) in the center of the calcification density was calculated (G). The high density area of attenuated plaque corresponding to the enhanced CT image is also seen in the unenhanced CT image (E). The portions of the attenuated plaque without a high density area included areas of CT density value <30 HU (F). The arrow head (C) indicates the partial image of another calcified plaque. Instances of measurement of cross-sectional vessel areas in MDCT are demonstrated in the reference segment (H) and lesion (I). The Remodeling index was 1.2. MDCT, multidetector computed tomography; IVUS, intravascular ultrasound; MPR, multiplanar reconstruction; CT, computed tomography.
0.625 mm thick sections and with no overlap. Axial images of both unenhanced and enhanced CT images were transferred to a standard commercially available workstation (GE Advantage Workstation 4.4). Curved multiplanar reconstruction (MPR) was initially displayed with a default window setting (level, 100 Hounsfield units [HU]; window, 700 HU). The window and level of the evaluated images could then be adjusted by the observer.

One experienced technologist, who was blinded to the results of conventional coronary angiography, rendered stretched MPRs of the targeted coronary artery in both unenhanced and enhanced images. Two radiologists (9 years and 1 year of experience in cardiac CT, respectively) independently evaluated the MDCT findings. They first confirmed the range scanned with IVUS and the location of attenuated plaque on IVUS images was then confirmed by measuring the distance from the aorto-coronary ostium or the nearest bifurcation point on stretched MPR images, and the angle on cross-sectional images. The areas corresponding to the plaque demonstrated by IVUS were reported as either accompanied by calcification density (this being defined as a HDA >130 HU) or a LDA <30 HU (considered to be soft plaque). The mean attenuation of the 3 regions of interest (ROI) in the center of the calcification density was calculated. The size of the ROI was 1 mm². To rule out the possibility that areas depicting a high density of >130 HU might simply be due to the enhancement of plaque, the same area was confirmed for HDA on unenhanced images. The remodeling index was calculated by dividing the cross-sectional vessel area at the site of maximum luminal narrowing by the cross-sectional vessel area in the reference segment. Using a fixed image display setting (window 700 HU, level 250 HU), the image that displayed maximum luminal narrowing was identified by visual estimation and the outer vessel contour (border to low-signal epicardial fat) was manually traced to measure the cross-sectional vessel area. Similarly, the cross-sectional vessel area was determined in a reference segment without detectable plaque proximal to and as close as possible to the respective coronary lesion (in the absence of a segment without plaque, the least diseased segment between the lesion and the coronary ostium or major bifurcations). We also identified all calcified plaques that were detected with IVUS and determined the mean attenuation of the lesion based

Figure 4. A 50-year-old man with attenuated plaque accompanied by a low density area on 64-MDCT. An example of attenuated plaque is demonstrated with IVUS in the left anterior descending artery in longitudinal- and cross-sectional images (A: arrows). A plaque unaccompanied with a high density area is demonstrated in the curved MPR (B, arrow) and cross-sectional (C, long arrows) image with 64-MDCT in the same position with attenuated plaque on IVUS. The arrow head (C) shows enhanced coronary lumen. The predominant density is <30HU in the cross-sectional enhanced CT image. MDCT, multidetector computed tomography; IVUS, intravascular ultrasound; MPR, multiplanar reconstruction; CT, computed tomography.
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Figure 2. Comparison of CT density between attenuated plaque and calcified plaque, which are demonstrated as calcification densities. A box-and-whiskers plot showing ranges and quartiles. The box extends from the 25th percentile to the 75th percentile, with a line at the median. The whiskers extend above and below the box to show the highest and lowest values. CT, computed tomography.

Figure 3

Figure 5

Results

Coronary Angiograph and IVUS Findings

Ten attenuated plaques and 15 calcified plaques were identified in 9 of 154 (6%) patients (males=9, 66.2±9.5 years). The baseline characteristics of these 9 patients are shown in Table 1. All but 1 had some kind of coronary risk factor, which included a prior history of PCI (n=2) and chronic renal failure (n=3). These plaques were located in the left anterior descending artery in 4 patients, in the left circumflex artery in 1 patient, and in the right coronary artery in 4 patients. The lesion length of the attenuated plaque was 5.1±4.1 mm and calcified plaque was 5.7±4.9 mm. The remodeling index of attenuated plaque was 1.1±0.1 at IVUS. PCI sites were not included in the target lesion. Four of 10 attenuated plaques were present within culprit lesions and 6 were remote from culprit lesions. All 15 calcified plaques were remote from culprit lesions.

Four cases accompanying a HDA of approximately 400HU in this study suffered from temporary flow deterioration at the time of the PCI procedure (TIMI flow grade 0/1: 3; grade 2: 1).

MDCT Findings

Among 10 attenuated plaques, 8 demonstrated a high density of >130 HU on MDCT. The mean CT density of 8 attenuated plaques was 389.4±152.4 HU (ranged from 180 to 680 HU) in 1 reader, and 388.5±144.8 HU (ranged from 168 to 654 HU) in the other reader. Interobserver agreement was excellent (κ=0.99, P<0.001). The averaged CT density of the 2 readers was 389.0±148.3 HU (ranged from 174 to 667 HU) (Figures 2, 3). In these 8 attenuated plaques, the HDA of >130 HU detected on enhanced CT was also detected in the same area on unenhanced CT. Of the 8 attenuated plaques with a high density of >130 HU, the length of the HDA was perfectly identical to the length of the attenuated plaque on IVUS in 5 patients (Figure 2), whereas the high density of >130 HU was detected in a part of the segment of attenuated plaque in 3 patients (Figure 3). There were no cases that displayed a HDA of >130 HU to be longer than the segment of attenuated plaque.

Among the 10 attenuated plaques, 2 were completely unaccompanied and 3 were partially unaccompanied with a HDA of >130 HU on MDCT. These 2 entire plaques and portions of 3 plaques without a HDA of >130 HU all included areas of CT density value <30 HU (Figures 3, 4). The remodeling index of the 10 attenuated plaques was 1.1±0.1 at MDCT. The averaged CT density value in the coronary lumen area at the attenuated plaques was 343.1±34.1 HU (the range of 280 and 380 HU).

All 15 calcified plaques detected on IVUS demonstrated a HDA of >130 HU. The mean CT density of 15 calcified plaques was 902.6±193.7 HU (ranged from 540 to 1,160 HU) in 1 reader, and 939.1±241.4 HU (ranged from 550 to 1,250 HU) in the other reader. Interobserver agreement was excellent (κ=0.97, P<0.001). The averaged CT density of the 2 readers was 920.9±215.9 HU (ranged from 545 to 1,205 HU). There was a significant difference in the averaged CT density value of the HDA between attenuated and calcified plaque (Figure 5).

Among 23 plaques accompanied by a HDA (8 attenuated plaques and 15 calcified plaques), the sensitivity, specificity, positive predictive value and negative predictive value for the detection of attenuated plaque was 87.5%, 100%, 100%,
93.8%, respectively, when HDA between 130 and 500HU was defined as attenuated plaque.

**Discussion**

Schroeder et al first reported that IVUS echogenicity correlated well with CT density measurement in coronary plaque, meaning that the CT density values for hypoechoic, hyperechoic and calcified lesions were significantly different. Since then, many papers have also concluded that CT density values might reflect the major plaque composition. However, to the best of our knowledge, no study has yet evaluated the detection of attenuated plaque with MDCT.

Our data revealed that 8 of 11 attenuated plaques included a HDA ranging from 174 to 667HU, with an average of 389.0±148.3HU. These averaged values were often obtained with enhanced CT in the coronary artery lumen, so these density values might be due to enhancement. However, the HDA in these cases of plaque was also seen on unenhanced images. It could therefore be concluded that these values were due to some kind of calcification.

The CT density of a HDA in attenuated plaque was significantly lower than that of calcified plaque. This result suggested that the characteristics of calcification in attenuated plaque was different from that of typical calcified plaque, and might have been due to microcalcification, which has been reported to be a component part of attenuated plaque. Our results also suggest that some specific CT density value ranges might indicate the existence of attenuated plaque and that MDCT could become a non-invasive modality for detecting instances of attenuated plaque.

All attenuated plaques contained a LDA <30HU in the portions without a HDA. The presence of lipid rich plaque was described earlier as a lesion with <50HU, which was reported to be lower than that of fibrous plaque. However, it is considered that the large variability of these measurements makes it difficult to achieve an accurate classification of non-calcified ‘plaque types’.

So far, attenuated plaque has been regarded as a part of the morphometric spectrum, which includes unstable lesions. The present study showed that attenuated plaque was also found in stable angina, even though the frequency was significantly lower compared with a case of acute coronary syndrome (5.1% vs. 25.6%). Attenuated plaque in the present study had vessel positive remodeling as shown by the remodeling index of 1.1±0.1 in both IVUS and MDCT, which has also been reported to be associated with plaque vulnerability. Actually, 4 cases accompanying a HDA of approximately 400HU in this study suffered from temporary flow deterioration at the time of the PCI procedure. Attenuated plaque might still be a predictive factor for plaque vulnerability and flow deterioration even in stable angina cases, although the slow-flow phenomenon is also affected by the stent diameter or inflation pressure. If MDCT could be used pre-procedurally to actually classify attenuated plaque noninvasively through assessing a specific calcification density in cases of stable angina, the clinical value of MDCT should not be ignored.

Several previous studies described the findings of CT suggesting plaque vulnerability. Motoyama et al have reported that the CT characteristics of plaques associated with ACS include positive vascular remodeling, low plaque attenuation value, and spotty calcification. Kashiwagi et al and Nakazawa et al reported that a ring-like sign was related to plaque rupture and a no-reflow phenomenon during PCI, which is the CT finding of a ring of high attenuation around certain plaque caused by the difference in attenuation between a lipid-rich necrotic core and fibrous plaque tissue. Though, although plaque imaging from current CT technology still includes a lot of measurement errors, MDCT is remarkably developing, and has the potential to become a useful tool for the prediction of plaque vulnerability in the future by the improvement of spatial and time resolution. The findings of our study (a combination of a HDA as high as approximately 400HU and a LDA <30HU on MDCT) might also be one of the CT findings suggesting high-risk plaque features.

This study has several limitations. First, this was a study using a low number of patients from a single center. Accordingly, the results need to be confirmed by a large multicenter study. Second, in this study, we retrospectively evaluated MDCT findings of attenuated plaque detected on IVUS imaging. Thus, the study did not investigate whether all non-calcified plaques with an average HDA of approximately 400HU could be demonstrated as attenuated plaque on IVUS. Finally, both of the patients in whom the IVUS imaging did not include the whole length of the targeted artery and attenuated plaque overlying stents were also eliminated, so the frequency of the incidence of attenuated plaque in patients with stable angina might have been underestimated.

In conclusion, MDCT has the ability to demonstrate attenuated plaque as the combination of a HDA (approximately 400HU on average) and a LDA (<30HU). The HDA can be differentiated from calcified plaque by its lower CT density value. MDCT therefore would show promise as a noninvasive approach before PCI procedures in detecting attenuated plaque based on the difference in density values.

**Disclosures**

There is no grant for this study.

**References**

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