Relationship Between Thin Cap Fibroatheroma Identified by Virtual Histology and Angioscopic Yellow Plaque in Quantitative Analysis With Colorimetry

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Background: Thin cap fibroatheroma (TCFA) is considered to be a vulnerable plaque. Virtual Histology-intravascular ultrasound (VH-IVUS) can precisely identify TCFA in vivo. Intense yellow plaque on angioscopy determined by quantitative colorimetry with $L^*a^*b^*$ color space corresponds with histological TCFA; in particular, a plaque of color b^* value >23 indicates an atheroma with a fibrous cap thickness $<100\mu\text{m}$. In the present study, the relationship between VH-TCFA and angioscopic plaque color determined by colorimetry was investigated.

Methods and Results: Fifty-seven culprit plaques in 57 patients were evaluated by VH-IVUS and angioscopy. VH-TCFA was defined as a plaque with a necrotic core $>10\%$ of plaque area without overlying fibrous tissue, and angioscopic TCFA was a plaque with b^* value >23 . The frequency of angioscopic TCFA was higher in the VH-TCFA group than in the VH-non-TCFA group (74% vs 23%, $P=0.0002$). Moreover, yellow color intensity (b^* value) significantly correlated with plaque classification on VH-IVUS. When TCFA detected with angioscopy was used as the gold standard, the sensitivity, specificity, and accuracy for TCFA with VH-IVUS was 68%, 81%, and 75%, respectively.

Conclusions: VH-TCFA strongly correlated with angioscopic TCFA determined by a quantitative analysis with colorimetry. (Circ J 2009; 73: 497–502)

Key Words: Angioscopy; Atherosclerosis; Imaging; Ultrasound

The major cause of acute coronary syndrome (ACS) is disruption of an atherosclerotic plaque and the subsequent formation of a thrombus.¹ Pathological examinations have revealed that thin cap fibroatheroma (TCFA) is frequently found in patients who die of ACS, and plaque rupture usually occurs in a lesion with an abundant necrotic core and an overlying thin fibrous cap.^{2–4} Recently, a spectrum analysis of intravascular ultrasound (IVUS)-derived radiofrequency data based on a pathological analysis has demonstrated more detailed quantitative information on plaque composition and morphology than a gray-scale analysis.^{5–8} TCFA identified by Virtual Histology (VH-TCFA) are recognized more frequently in patients with ACS than in those with stable coronary artery disease.^{6,8} Similarly, several coronary angioscopic studies have demonstrated that yellow plaques are commonly observed at the culprit lesion of ACS.^{9–13} Furthermore, quantitative evaluation of the yellow plaque could be available with newly developed software using $L^*a^*b^*$ color space.^{13–16} Angioscopic examination of ex vivo human tissue samples

has indicated that a coronary plaque with high-intensity, yellow color regions (b^* value >23) consists of lipid cores beneath a TCFA (fibrous cap thickness $<100\mu\text{m}$).¹⁵ However, there is no available comparison of plaque classification determined by VH-IVUS and by angioscopic findings. The present study investigated the characteristics of VH-TCFA in comparison with the angioscopic yellow color intensity as determined by quantitative colorimetry.

Methods

Patient Selection

Initially, we enrolled 67 patients who had a definable culprit plaque on pre-interventional IVUS and coronary angioscopic examinations. Ten disrupted plaques including ulceration on IVUS or massive thrombi on angioscopy (thrombus area $\geq 50\%$ of visual field) in 10 patients were excluded because the VH analysis may have provided unreliable tissue characterization and no established algorithm for thrombus. Finally, 57 plaques in 57 patients were analyzed. The Medical Ethics Committee at Chiba-Hokuso Hospital approved this study, and written informed consent was given by all patients before participation.

Clinical Demographics

The clinical data and information about clinical presentation were based on chart reviews. Stable angina pectoris (SAP) was defined as a positive stress test and no change in the frequency, duration or intensity of chest symptoms within 4 weeks. In each patient, the culprit lesion was identified by a combination of electrocardiographic findings,

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Figure 1. Plaque classification on Virtual Histology. (A) Pathological intimal thickening, composed of mainly fibrous and fibro-fatty tissue with no dense calcium and a necrotic core constituting 1% of the total plaque area. (B) Fibrocalcific lesions, featuring mainly fibrotic plaques with some dense calcium. (C) Fibrous cap atheroma: necrotic core with 18% of the total plaque area separated by fibrous tissue. (D) Thin cap fibroatheroma: superficial necrotic core rich plaque occupying 46% of the cross-sectional area without evident overlying fibrous tissue.

Table 1. Baseline Characteristics and Angiographic Findings

	VH-TCFA (n=23)	Non-VH-TCFA (n=34)	P value
Age, years	63±10	61±14	0.7
Men	18 (78%)	28 (82%)	0.7
Diabetes	17 (70%)	9 (21%)	0.008
Hypertension	11 (48%)	23 (70%)	0.13
Hypercholesterolemia	18 (78%)	27 (79%)	0.92
Family history of coronary disease	7 (30%)	11 (32%)	0.9
Smoking	19 (83%)	17 (50%)	0.01
Observed coronary artery			
Right	7 (30%)	8 (25%)	0.6
Left anterior descending	11 (48%)	20 (63%)	0.4
Left circumflex	5 (22%)	4 (13%)	0.3
Acute coronary syndrome	14 (61%)	4 (13%)	<0.0001
Stable angina pectoris	9 (39%)	30 (87%)	
Quantitative angiographic analysis			
Reference vessel diameter, mm	2.7±0.6	2.8±0.8	0.8
Minimum lumen diameter, mm	0.9±0.4	0.9±0.3	0.9
Percent diameter stenosis, %	66.4±11.7	66.8±11.7	0.9
Lesion length, mm	11.6±4.6	10.5±4.4	0.6
AHA/ACC classification			
Type A	6 (26%)	11 (33%)	0.8
Type B1	11 (48%)	12 (35%)	0.39
Type B2 or C	6 (26%)	11 (32%)	0.8

Values are n (%) or the mean±SD.

VH-TCFA, thin cap fibroatheroma identified by Virtual Histology; AHA/ACC, American Heart Association/American College of Cardiology.

wall motion abnormalities on left ventriculography or echocardiography findings, and lesion morphology.

Angiographic Analysis

Quantitative angiographic measurements of the lesion were performed using digital angiograms that were analyzed with a computer-assisted, automated edge detection algorithm (CMS, Medis Medical Imaging System, Nuenen, The Netherlands). The reference vessel diameter, minimum lumen diameter, percent diameter stenosis, and lesion length were measured. The lesion type was categorized according to the American Heart Association/American College of Cardiology classification.

Analysis and Definition of VH-IVUS Imaging

VH-IVUS analysis was performed during a standardized pullback (0.5 mm/s) with the use of a VH-IVUS console and 3.5Fr imaging catheter that incorporated a 20-MHz phased-array transducer (Eagle Eye Gold catheter, Volcano Corp, Rancho Cordova, CA, USA). A statistical classification sorted the radiofrequency data based on combinations of the spectral parameters into 1 of 4 plaque components by color code: green (fibrous), yellow (fibro-fatty), white (dense

calcium) and red (necrotic core).⁴⁻⁷ VH-derived plaque classifications are based on histopathological analysis³ and these criteria have been previously reported.⁵⁻⁷ To classify the lesions, these criteria had to be met at the site of minimum lumen area plus the immediate distal and proximal cross-sections. Pathological intimal thickening (PIT) was classified as a plaque composed mainly of fibrous and fibro-fatty tissue, with a lipid core or dense calcium constituting <5% of the total plaque volume. A fibrocalcific lesion (FC) featured primarily a fibrotic plaque with dense calcium (>5% of total plaque volume) and a lipid core occupying <5% the total plaque volume. Fibrous atheroma (FA) was a plaque composed of fibrous and/or fibro-fatty tissue with confluent necrotic core >10% of the total plaque volume (the necrotic core covered by a cap of fibrous and/or fibro-fatty tissue). TCFA was a necrotic core rich plaque >10% of the cross-sectional area in 3 consecutive frames without evident overlying fibrous tissue in the presence of a plaque burden >40% (**Figure 1**). PIT, FC, and FA were categorized as VH-non-TCFA.

Analysis and Definition of Angioscopic Imaging

The angioscopic procedure using an imaging catheter

Table 2. Plaque Characteristics on Virtual Histology-Intravascular Ultrasound

	VH-TCFA (n=23)	Non-VH-TCFA (n=34)	P value
Lumen area, mm ²	4.7±1.3	5.6±2.0	0.19
External elastic lumen area, mm ²	15.7±5.9	17.1±4.2	0.51
Plaque area, mm ²	11.5±5.5	11.8±4.1	0.88
Plaque area, %	67.8±8.4	66.7±10.2	0.78
Fibrous, %	55.8±10.8	67.3±9.7	0.01
Fibro-fatty, %	10.4±5.8	21.6±14.4	0.02
Dense calcium, %	8.3±6.5	3.7±3.9	0.06
Necrotic core, %	25.5±9.5	8.6±5.9	0.0003
Plaque with b* >23 on colorimetry	17 (74%)	8 (24%)	0.0002

Abbreviation see in Table 1.

Figure 2. Relationship between plaque classification on Virtual Histology-intravascular ultrasound (VH-IVUS) and colorimetric analysis of angioscopic yellow intensity. Spearman's rank correlation analysis showed a yellow color as analyzed by quantitative colorimetry (b* value) to be significantly correlated with plaque classification on VH-IVUS ($P=0.019$). PIT, pathological intimal thickening; FC, fibrocalcific lesions; FA, fibrous cap atheroma; TCFA, thin cap fibroatheroma.

(Vecmova Neo, FiberTech Corp, Chiba, Japan) has been previously reported!¹⁰ The angioscopic images were digitally recorded for later analysis. The exact position of the angioscopic catheter at the observed segment was recorded on an angiogram to ensure a reliable comparison for IVUS observation. L*a*b* color space is widely used to describe all the colors visible to the human eye (<http://www.en.wikipedia.org/wiki/Lab-color-space>). In this color space, a yellow color intensity can be represented as the b* value (yellow color intensity 0–100, the color of blue –100–0) independent of such conditions as light intensity, the distance from the angioscope's lens to the object, and even the angle of the angioscope to the region of interest. Detailed examinations of L*a*b* color space have been reported previously^{13,14} and we used the same colorimetric system. Those reports revealed that a plaque of b* value >23 contains atheroma that has a fibrous cap thickness <100 μ m, and that such plaques are more frequently observed in the culprit lesions of ACS than in the culprit lesions of SAP. Therefore, we defined an angioscopic TCFA as a plaque with a measured b* value >23; otherwise it was deemed to be an angioscopic non-TCFA.

Statistical Analysis

Continuous variables are expressed as the mean±SD. Comparisons between 2 groups were performed with

Figure 3. Distribution of angioscopic thin cap fibroatheroma (TCFA) and non-TCFA in the plaque classification on Virtual Histology (VH)-intravascular ultrasound. Angioscopically analyzed plaques are divided into 25 TCFA and 32 non-TCFA. Of the VH-TCFA, 74% accounted for angioscopic TCFA, while 95% of the VH-fibrous cap atheroma (FA) are angioscopic non-TCFA. The frequencies of angioscopic TCFA and angioscopic non-TCFA are similar for pathological intimal thickening (PIT) and fibrocalcific lesion (FC).

unpaired Student's t-test. Comparisons of categorical variables presented as numbers (%) were performed by either chi-square test or Fisher's exact test. The relationship between plaque classification on VH-IVUS and angioscopic yellow color (b* value) was analyzed with Spearman's rank correlation. A P-value<0.05 was considered to be statistically significant.

Results

Patients Characteristics and Angiographic Findings

Baseline characteristics and angiographic findings are summarized in **Table 1**. There were 23 plaques classified as VH-TCFA and 34 as VH-non-TCFA. The frequencies of diabetes, smoking, and ACS were significantly higher in the VH-TCFA group (**Table 1**). There were no differences in the reference vessel diameter, minimum lumen diameter, percent diameter stenosis, lesion length, and type of lesion between the 2 groups.

Plaque Characteristics on VH-IVUS

Plaque characteristics on VH-IVUS are summarized in **Table 2**. There were no significant differences in lumen area, external elastic lumen area, plaque area, and % plaque

Figure 4. Corresponding Virtual Histology (VH)-intravascular ultrasound (IVUS) and angioscopic images of culprit plaques. (A) Angiogram shows 90% of stenosis (arrowhead) in the left anterior descending artery of a patient with stable angina pectoris (SAP). (B) There is no superficial necrotic core in this culprit plaque, and thick fibrous tissue covers the deep necrotic core (18% of total plaque area) and dense calcium. This plaque is categorized as VH-fibrous cap atheroma. (C) Colorimetry indicates the yellow color intensity (b^* value) of this plaque to be -3.5 , and the plaque is categorized as an angioscopic non-thin cap fibroatheroma (TCFA). (D) There is 75% stenosis in the right coronary artery of a patient with SAP (arrowhead). (E) In this culprit plaque, VH-IVUS shows a superficial large necrotic core (41% of total plaque area) without an overlying fibrous cap. This plaque meets the criteria of VH-TCFA. (F) The yellow color intensity of this plaque is 40.6 . This plaque is classified as an angioscopic TCFA.

area between the 2 groups. The fibrous and fibro-fatty areas were significantly smaller in the VH-TCFA group than in VH-non-TCFA group, whereas the dense calcium and necrotic core areas were greater in the VH-TCFA group than in VH-non-TCFA group. The prevalence of angioscopic-TCFA was significantly higher in the VH-TCFA group than in the VH-non-TCFA group.

Comparison of Plaque Characteristics on VH and Angioscopy

A comparison of the b^* value among plaque classifications on VH-IVUS is shown in **Figure 2**. Spearman's rank correlation analysis showed a yellow color as analyzed by quantitative colorimetry (b^* value) to be significantly correlated with plaque classification on VH-IVUS ($P=0.019$). There were 25 angioscopic TCFAs and 32 angioscopic non-TCFAs. In the angioscopic TCFA, 17 (68%) were classified by VH-IVUS as TCFA, 1 (4%) was FA, 3 (12%) were FC, and 4 (16%) were PIT. Angioscopic non-TCFA were categorized as 6 TCFA (19%), 19 FA (59%), 2 FC (6%), and 5 PIT (16%) (**Figure 3**). VH-TCFA was more common in the angioscopic-TCFA group than in the angioscopic non-TCFA group; 17 of 23 plaques (74%) in the VH-TCFA group accounted for angioscopic TCFA. In contrast, FA was more common in the angioscopic non-TCFA group than in the angioscopic TCFA group. In VH-FA, 19 of 20 plaques (95%) were characterized as angioscopic non-TCFA. In plaque types PIT and FC, the frequencies of angioscopic TCFA and angioscopic non-TCFA were

similar (**Figure 3**). Typical corresponding plaque images on VH-IVUS and angioscopy are shown in **Figure 4**. When TCFA detected with angioscopy was used as the gold standard, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for TCFA with VH-IVUS was 68%, 81%, 74%, 76%, and 75%, respectively.

Discussion

This study demonstrated that VH-TCFA has a more intense yellow color on the plaque surface than VH-non-TCFA. Moreover, VH-TCFA closely correlated with angioscopic TCFA, as determined by quantitative analysis with colorimetry.

Angioscopic yellow plaque is frequently observed at the culprit lesion in patients with ACS⁹⁻¹⁵. Furthermore, some prospective studies have indicated that the number of yellow plaques in the coronary arteries, or the presence of intense yellow plaques, is a predictor of future cardiac events, such as ACS.^{16,17} Therefore, atherosclerotic yellow plaques, especially intense yellow plaques identified by angioscopy, are believed to be vulnerable. Although angioscopic evaluation of plaque color has a major limitation because of its qualitative or semi-quantitative analysis based on visualization by the naked eye, the newly developed colorimetry enables a quantitative assessment of color with computer assistance. Comparative examination of histopathology and angioscopy findings revealed that an atheroma with fibrous cap thickness $\leq 100\mu\text{m}$ presented as an intense yellow plaque of

b* value >23 on colorimetry.¹⁴ Moreover, the typical vulnerable plaque is considered to be a TCFA with a fibrous cap thickness <100 μ m.¹⁸ In this study, therefore, a yellow plaque of b* value >23 (angioscopic TCFA) was used as the gold standard for comparison with VH-IVUS findings for tissue characterization. Coronary plaque classification using another imaging system, VH-IVUS, has been established by corresponding histopathological investigations, and this imaging modality can provide detailed information on the plaque composition in vivo.⁵⁻⁸ The present study focused on a comparison of the identification of TCFA between VH-IVUS and angioscopy.

In this analysis of the culprit plaques, VH-IVUS identified TCFA more frequently in patients with ACS than in those with SAP. On the other hand, VH-non-TCFA was found more frequently in SAP than in ACS cases. These results are consistent with those of a previous report⁶ and the components of the culprit plaque may differ in patients with different clinical conditions. In this study, VH-TCFA was more prevalent in patients with diabetes and smoking. A previous investigation using VH-IVUS demonstrated high-frequency recognition of VH-TCFA in diabetic patients.¹⁹ Smoking induces endothelial dysfunction, thereby increasing the level of circulating oxidized low-density lipoprotein cholesterol,^{20,21} so not only diabetes but also cigarette smoking probably contributes to acceleration of atherosclerotic changes of coronary plaque and may contribute to the development and formation of a necrotic core.

The current results showed that a quantitative yellow intensity, the mean value of b* on colorimetry, significantly correlated with plaque classification on VH-IVUS. Moreover, 74% of VH-TCFA was diagnosed as angioscopic TCFA. These findings suggest that VH-TCFA closely correlates with angioscopic TCFA, and that the consistent rate of identification of TCFA was high between VH-IVUS and angioscopy. Recently, an in vivo combination study using angioscopy and optical coherence tomography (OCT) certified that the determinant factor of plaque color was not the lipid area, but the fibrous cap thickness. Most angioscopic yellow plaques were lipidic atheroma with thin fibrous caps identified by OCT, whereas atheromas with thick fibrous caps were angioscopically visualized as white plaques.²² It is possible that VH-TCFA, defined as plaque with a superficial necrotic core, was recognized as an intense yellow plaque.

The remaining 26% of the VH-TCFA disagreed with the angioscopic TCFA, which may be explained by several reasons. (1) Angioscopic TCFA is not always composed of a necrotic core, but rather a superficial lipid deposition, such as a fatty streak or calcified nodule.¹⁴ Although it is unclear whether a fatty streak would be categorized into the plaque type of VH-IVUS, 12% of angioscopic TCFA were actually fibro-calcific plaques on VH-IVUS. (2) According to a previous histopathological investigation, analysis based on these data showed that the predictive accuracy of VH-IVUS for a necrotic core was limited to 85.5% in vitro and 88.3% in vivo.^{5,23} Moreover, recent histological analysis suggested that the diagnostic accuracy of VH-IVUS was inferior in comparison with integrated backscatter IVUS.²⁴ Therefore, VH-IVUS can not detect perfectly such a lipid plaque component, and so limitations of diagnostic accuracy still exist. (3) Although an angioscopic TCFA frequently contains lipid components, all of the lipid areas may not be recognized as necrotic core by VH-IVUS. Moreover, the necrotic core may not exceed 10% of the cross-sectional plaque area nor satisfy the criteria of VH-

TCFA. (4) The axial resolution of IVUS is between 100 μ m and 200 μ m. In the case of an atheroma that has a fibrous cap thickness between 100 μ m and 200 μ m, the atheroma may be presented as VH-TCFA because the fibrous cap overlying the necrotic core is invisible on an IVUS image. However, this type of atheroma is possibly validated as an angioscopic non-TCFA, based on determination by colorimetry. (5) In several cases, a mural thrombus on the culprit plaque may interfere with the correct plaque classification by VH-TCFA.

From the viewpoint of angioscopic diagnosis, 95% of FA were angioscopic non-TCFA, which suggests that angioscopy thus has a limited ability to detect a profoundly lipid or necrotic core. Moreover, the distribution of angioscopic TCFA and angioscopic non-TCFA was similar for FC and PIT on VH-IVUS classification. These findings suggest that angioscopic yellow intensity is irrelevant to these plaque types.

Study Limitations

First, the comparative findings were based on observations in a relatively small number of patients. Second, 10 plaques with angioscopically massive thrombi were excluded because there is no algorithm for thrombus imaging on VH-IVUS analysis. However, this exclusion may have influenced the high consistency between VH-TCFA and angioscopic TCFA. In the future it will be necessary to develop a VH-IVUS algorithm for thrombi. Last, the images for quantitative colorimetry were obtained from stored digital-videotapes, so the image acquisition process could have affected the “absolute” b* values. However, these values could be compared in all images, because they were recorded and stored in the same manner. Furthermore, b* values acquired from the digital-videotape were compared with those acquired from the previously described process without the original color correction circuit,¹⁵ using 16 standard calibration color samples (ColorChecker, X-Rite Inc, Grand Rapids, MI, USA), and there were no significant differences in the b* values between the 2 types of image (P=0.2 by a paired t-test, R=0.999). Therefore, the “absolute” b* values (=23) are thus considered to be acceptable in the present analysis.

Up to now, several imaging modalities to detect TCFA, such as VH-IVUS, OCT and angioscopy, have been available for clinical use. Although IVUS and angioscopy are invasive imaging techniques, analyses using VH and colorimetry enable quantitative validation of coronary plaque, and they may provide prognostic information on the natural history of high-risk plaques. Large-scale prospective studies using these imaging techniques are required to characterize true vulnerable plaques in vivo.

In conclusion, angioscopic TCFA with an intense yellow color as analyzed by quantitative colorimetry was found to be closely correlated with VH-TCFA. TCFA, a type of high-risk plaque, is likely to be identified by VH-IVUS and angioscopy with colorimetry.

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