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Implication of Plaque Color Classification for Assessing Plaque Vulnerability

A Coronary Angioscopy and Optical Coherence Tomography Investigation

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Objectives The purpose of this study was to assess the relationship between plaque color evaluated by coronary angioscopy and fibrous cap thickness estimated by optical coherence tomography (OCT) in vivo.

Background Yellow color intensity of coronary plaque evaluated by coronary angioscopy might be associated with plaque vulnerability.

Methods Seventy-seven coronary artery plaques in patients with acute coronary syndrome were observed by angioscopy and OCT. Plaque color was graded as white, light yellow, yellow, or intensive yellow.

Results There were significant differences among the groups classified by plaque color with respect to the fibrous cap thickness estimated by OCT: 389 ± 74 μm in white plaques, 228 ± 51 μm in light yellow plaques, 115 ± 28 μm in yellow plaques, and 59 ± 14 μm in intensive yellow plaques ($p < 0.0001$). In Spearman rank-order correlation analysis, there was a significant negative correlation between yellow color intensity and fibrous cap thickness ($p < 0.0001$). Furthermore, 80% of intensive yellow plaques were thin cap fibroatheroma with a cap thickness of ≤65 μm.

Conclusions The plaque color in coronary angioscopy was determined by the fibrous cap thickness, which was assessed by OCT. Although coronary angioscopy remains a specialized research tool, it might allow us to evaluate plaque vulnerability. (J Am Coll Cardiol Intv 2008;1:74–80) © 2008 by the American College of Cardiology Foundation

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Based on the current knowledge, histological characteristics attributed to vulnerable plaques are a thin fibrous cap, a large lipid core, active inflammation within the fibrous cap, endothelial denudation with superficial platelet aggregation and fissured plaque (1). In the clinical setting, there are significant advantages to identifying the vulnerable plaques before acute coronary events. Coronary angioscopy is a useful imaging modality to assess the surface characteristics of vessel wall, such as plaque color, fibrous cap disruption, and thrombus (2). It has been suggested that yellow plaque was associated with acute coronary syndrome (ACS) and plaque color might be related to plaque vulnerability (2–11). Previous pathohistological studies demonstrated that yellow plaque was lipid-rich and white plaque was predominantly fibrous (9). One investigation using intravascular ultrasound (IVUS) combined with integrated backscatter analysis (11), which is useful to differentiate fibrous tissue and fatty tissue of coronary plaque, showed the relationship between plaque color and fibrous cap thickness. However, the thin cap fibroatheroma (TCFA) with a cap thickness of ≤65 μm might not be evaluated completely in this study because the resolution of IVUS is limited to be approximately 100 to 200 μm. Although the fibrous cap thickness of atheromatous plaque may be an important determinant of plaque color, it has not been fully examined yet. Recently, intravascular optical coherence tomography (OCT) has been developed as a high-resolution imaging method (12–18). It has a resolution of 10 to 20 μm and may allow us to estimate fibrous cap thickness accurately and to identify TCFA (15–17). The purposes of the present study were: 1) to evaluate the relationship between plaque color by coronary angioscopy and fibrous cap thickness of the plaque estimated by OCT; and 2) to assess the prevalence of TCFA in yellow plaques.

Methods

Patient selection. The consecutive ACS patients who underwent coronary catheterization were enrolled in the present study. Exclusion criteria were: 1) culprit lesion in the left main trunk or the osmium of the right, left anterior descending, or circumflex coronary artery; 2) extremely tight lesions or tortuous vessels where we expected difficulty in advancing the coronary angioscopy or OCT catheter; 3) target vessel reference diameter of ≥4 mm expected limitation in OCT evaluation; 4) congestive heart failure with left ventricular ejection fraction <40%; and 5) renal insufficiency with baseline serum creatinine >1.5 mg/dl. The institutional review board approved the study, and all patients provided informed consent before participation.

Image acquisitions. Cardiac catheterization was performed by the conventional femoral approach, using a 7-F sheath and catheters. Intravenous heparin (100 U/kg) was administered at the beginning of catheterization. The culprit lesion was identified on the basis of the findings by a coronary angiogram. In patients with Thrombolysis In Myocardial Infarction (TIMI) flow grade ≤2, aspiration thrombectomy was performed by an aspiration catheter (Export catheter, Medtronic Tokyo, Japan) before intracoronary imaging, but pre-dilation by balloon catheter was not allowed. After getting TIMI flow grade 3, not only the culprit lesion but also non-culprit lesions (angiographic diameter stenosis ≥25%) in the culprit vessel were observed by angioscopy and OCT as described previously (2,16–18). First, angioscopic examination (Vecmova, Clinical Supply Co., Gifu, Japan) was performed while coronary blood flow was interrupted by occlusion balloon and blood was cleared away from view by the injection of 5 to 10 ml of warm saline. Second, a 0.016-inch OCT catheter (ImageWire, LightLab Imaging, Westford, Massachusetts) was advanced to the distal end of the lesion through a 3-F occlusion balloon catheter. To remove the blood from the field of view, the occlusion balloon was inflated to 0.6 atm at proximal site of the lesion and warm saline was infused into the coronary artery from the distal tip of the occlusion balloon catheter at 0.5 ml/s. The entire lesion length was imaged with an automatic pullback device moving at 1 mm/s and the OCT image clearly visualized the target lesion.

Abbreviations and Acronyms

ACS = acute coronary syndrome
AMI = acute myocardial infarction
IVUS = intravascular ultrasound
OCT = optical coherence tomography
SD = standard deviation
TCFA = thin cap fibroatheroma
TIMI = Thrombolysis In Myocardial Infarction

Image analysis. All images were stored digitally for subsequent analysis. Analysis of the angioscopic images were performed by 2 reviewers blinded to the results of the OCT analyses. Analysis of the OCT images was performed by 2 reviewers blinded to the results of the angioscopic analyses. When there was discordance between the observers, a consensus reading was obtained. The corresponding images of coronary angioscopy and OCT were identified by the distances from two landmarks, such as side branches. In the coronary angioscopic images, plaque color was evaluated and was graded as white, light yellow, yellow, or intensive yellow (Fig. 1, panels A-1, B-1, C-1, and D-1), as Ueda et al. (7,8) reported previously. OCT images were analyzed using validated criteria for plaque characterization, and fibrous cap thickness was determined as reported previously (12–17). Briefly, fibrous cap thickness was defined as the minimum distance from the coronary artery lumen to inner border of lipid pool, which was characterized by a signal-poor region in the OCT image (Fig. 1, panels A-3, B-3, C-3, and D-3). Cap thickness for each image was measured 3 different times, and the average value was computed. Lipid was semiquantified as the number of involved quadrants on the

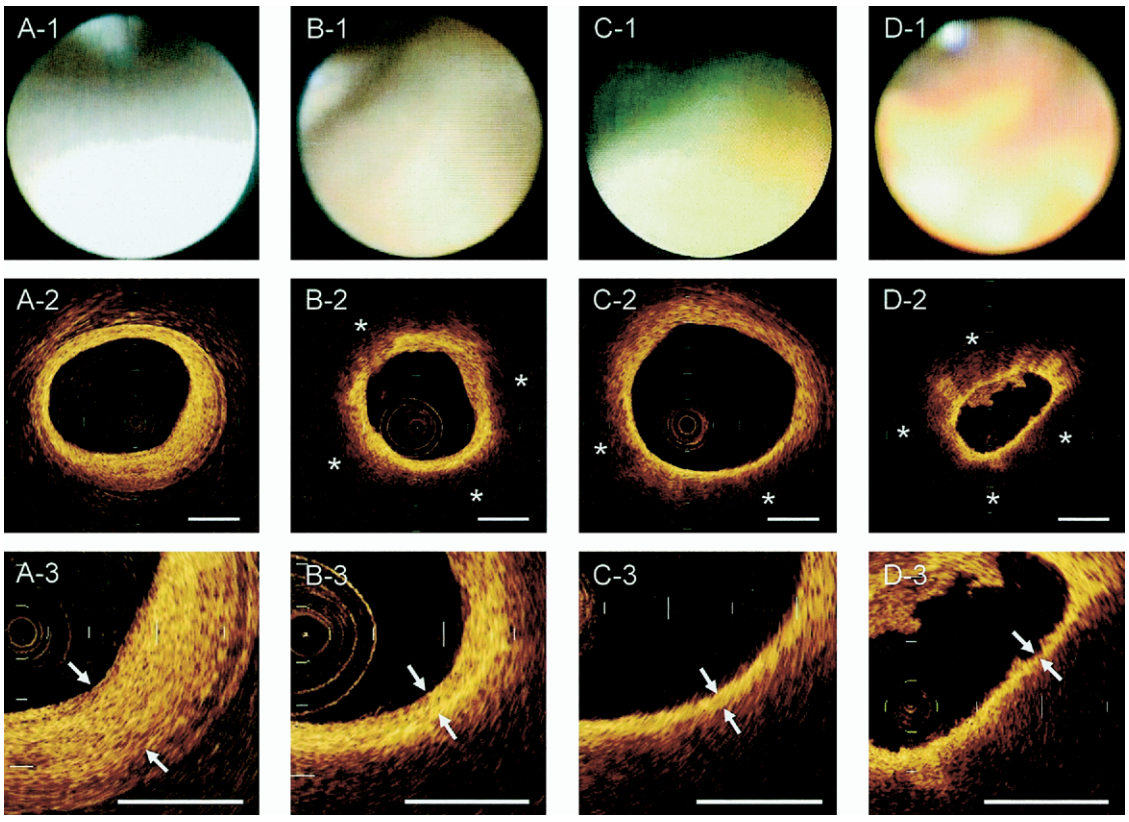

Figure 1. Corresponding Images of OCT and Coronary Angioscopy

In the angioscopic images, plaque color was graded as white **(A-1),** light yellow **(B-1),** yellow **(C-1),** or intensive yellow **(D-1).** A lipid pool **(*)** was characterized by a signal-poor region, and it was semiquantified as the number of involved quadrants on the cross-sectional optical coherence tomography (OCT) image **(A-2, B-2, C-2, D-2).** The fibrous cap was identified as a signal-rich region between the coronary artery lumen and inner border of lipid pool in the OCT image, and its thickness was measured at the thinnest part **(A-3, B-3, C-3, D-3; arrows)**.

cross-sectional OCT image (Fig. 1, panels A-2, B-2, C-2, and D-2) as reported previously (16). When lipid was present in ≥2 quadrants in any of the images within a plaque, it was considered a lipid-rich plaque. For each patient, the cross-sectional image with the thinnest fibrous cap was used for analysis. The TCFA was defined as a plaque with lipid content in ≥2 quadrants and the thinnest part of the fibrous cap measuring ≤65 μm, as Jang et al. (16) reported.

Statistical analysis. Continuous data are presented as mean ± standard deviation (SD). The fibrous cap thickness and percent diameter stenosis were compared between groups by 1-way analysis of variance. To test for significant differences of the number of quadrants involved by lipid with respect to the plaque color, a Kruskal-Wallis test was performed. If it was significant, pairwise comparisons by Bonferroni test were performed for multiple analyses. Relations between yellow color intensity of plaque and fibrous cap thickness or number of quadrants involved by lipid were analyzed by Spearman's rank-order correlation. The incidences of lipid-rich plaque or TCFA were compared among the groups by use of the chi-square test or Fisher exact test. The Fisher exact test was used if there was an expected cell value <5. For reproducibility of fibrous cap thickness and lipid size estimation, the intraobserver and interobserver differences were determined as mean and SD. Furthermore, correlation coefficients were assessed among observations and observers, respectively. All analyses were performed using Statview version 5.0 (Abacus Concepts Inc., Berkeley, California). A p value <0.05 was required for statistical significance.

Results

Patient characteristics. A total of 30 patients with ACS were consecutively enrolled. Five patients were released according to exclusion criteria and 25 patients, including 14 patients with unstable angina and 11 patients with acute myocardial infarction (AMI), were finally presented in this study. The patient characteristics are demonstrated in Table 1. The mean age in these patients was 68 years old. In

Table 1. Baseline Characteristics of 25 Patients With Acute Coronary Syndrome

No. of patients	25
Age, yrs*	68 ± 7
Male gender	19 (76)
Clinical presentation	
Unstable angina	14 (56)
Acute myocardial infarction	11 (44)
Diabetes mellitus	6 (24)
Hypertension	20 (80)
Cigarette smoking	9 (36)
Hypercholesterolemia (total cholesterol >220 mg/dl)	15 (60)
Culprit vessel	
LAD	10 (40)
LCx	3 (12)
RCA	12 (48)
Culprit plaque observed by angioscopy and OCT	
No. of culprit plaque	25
Percent diameter stenosis, %*	89 ± 7
Nonculprit plaque observed by angioscopy and OCT	
No. of nonculprit plaque	52
Percent diameter stenosis, %*	56 ± 14

Values are given as n (%) or *mean ± SD.
LAD = left anterior descending coronary artery; LCx = left circumflex artery; RCA = right coronary artery.

coronary risk factors, the prevalence of hypertension, diabetes mellitus, and hypercholesterolemia were 80%, 24%, and 60%, respectively. The coronary angioscopic and OCT studies were completed in all patients and the corresponding images were obtained in 77 plaques, including 25 plaques of culprit lesions and 52 plaques of non-culprit lesions. In 10 culprit lesions with TIMI flow grade ≤2, aspiration thrombectomy was required before intracoronary imaging. Because reference vessel diameter was less than 4 mm in this population, clear OCT images were provided in spite of limited penetration of OCT signal. The coronary occlusion time necessary for angioscopic and OCT observation of a lesion was 17 ± 9 s and 36 ± 5 s, respectively. The averaged procedure time required to complete imaging by 2 methods, including imaging catheters exchanges, was <11 min. Although ST-segment re-elevation on the electrocardiogram was observed in all patients during imaging procedures, it disappeared soon after the procedures by releasing the coronary occlusion. No major complications and adverse events occurred in the present study.

Coronary angioscopy and OCT findings. The coronary angioscopic and OCT findings are summarized in Table 2. The number of white, light yellow, yellow, and intensive yellow plaques classified by angioscopy were 19 (25%), 21 (27%), 22 (29%), and 15 (19%), respectively. The number of culprit plaques was significantly different among the plaques for each plaque color (0%, 12%, 36%, and 52%, in the white, light yellow, yellow, and intensive yellow plaques, respectively, $p < 0.0001$). In pairwise comparison, the number of culprit plaques was significantly different between light yellow and yellow plaques ($p = 0.0452$) and between yellow and intensive yellow plaques ($p = 0.0142$), but not between white and light yellow plaques ($p = 0.2354$). The percent diameter stenosis in angiography was significantly different among the plaques for each plaque color (53 ± 14%, 53 ± 13%, 71 ± 16%, and 94 ± 8%, in the white, light yellow, yellow, and intensive yellow plaques, respectively, $p < 0.0001$). In addition, the difference of the percent diameter stenosis was significant between light yellow and yellow plaques ($p = 0.0091$) and between yellow and intensive yellow plaques ($p < 0.0001$), but not between white and light yellow plaques ($p = 0.8802$). There were significant differences among the groups classified by plaque color with respect to the fibrous cap thickness measured by OCT: 389 ± 74 μm in white plaques, 228 ± 51 μm in light yellow plaques, 115 ± 28 μm in yellow plaques and 59 ± 14 μm in intensive yellow plaques ($p < 0.0001$). In pairwise

Table 2. Coronary Angioscopy and OCT Findings

Findings	White (n = 19)	Light Yellow (n = 22)	Yellow (n = 21)	Intensive Yellow (n = 15)	p Value
Angiographic findings					
No. of culprit plaque	0 (0)	3 (12)	9 (36)*†	13 (52)‡§	<0.0001
No. of nonculprit plaque	19 (37)	19 (37)	12 (23)*†	2 (4)‡§	<0.0001
Percent diameter stenosis, %‖	53 ± 14	53 ± 13	71 ± 16*†	94 ± 8‡§	<0.0001
OCT findings					
Fibrous cap thickness, μm‖	389 ± 74	228 ± 51¶	115 ± 28*†	59 ± 14‡§	<0.0001
Lipid plaque, no. of quadrants					
1/2/3/4	11/6/2/0	9/7/4/2	3/7/7/4*†	0/5/6/4‡	0.0002
Lipid-rich plaque (≥2 quadrants)	8 (42)	13 (59)	18 (75)*	15 (100)‡	0.0006
TCFA	0 (0)	0 (0)	0 (0)	12 (80)‡§	<0.0001

*p < 0.01 versus white; †p < 0.05 versus light yellow; ‡p < 0.01 versus white, p < 0.01 versus light yellow; §p < 0.05 versus yellow; values are given as n (%) or ‖mean ± SD; ¶p < 0.01 versus white. Categorical data were compared using chi-square statistics.
TCFA = thin cap fibroatheroma (lipid ≥2 quadrants and fibrous cap thickness ≤65 μm)

comparison, fibrous cap thickness was significantly different between white and light yellow plaques ($p < 0.0001$), between light yellow and yellow plaques ($p < 0.0001$), and between yellow and intensive yellow plaques ($p = 0.0010$). In Spearman rank-order correlation analysis (Fig. 2), there was a significant negative correlation between yellow color intensity and fibrous cap thickness ($p < 0.0001$). The number of quadrants involved by lipid was also significantly different among the 4 groups ($p = 0.0002$), but not in pairwise comparison between white and light yellow plaques ($p = 0.1286$) and between yellow and intensive yellow plaques ($p = 0.2327$). In Spearman rank-order correlation analysis (Fig. 3), there was a significant positive correlation between yellow color intensity and the number of quadrants involved by lipid ($p < 0.0001$). Furthermore, the frequency of lipid-rich plaque was significantly different among the plaques with each plaque color ($p = 0.0006$). In pairwise comparison using the chi-square test, however, the frequency of lipid-rich plaque was not significantly different between white and light yellow plaques ($p = 0.3543$), between light yellow and yellow plaques ($p = 0.0883$), and between yellow and intensive yellow plaques ($p = 0.2500$). TCFA was observed only in intensive yellow plaques, and its frequency was 80% of them ($p < 0.0001$). In pairwise comparison using the Fisher exact test, the frequency of TCFA was significantly different between yellow and intensive yellow plaques ($p < 0.0001$), but not between white and light yellow plaques ($p > 0.9999$) and between light yellow and yellow plaques ($p > 0.9999$). All TCFAs were detected in the culprit lesions. The frequencies of TCFA in AMI and unstable angina were 64% and 36%, respectively ($p = 0.2377$).

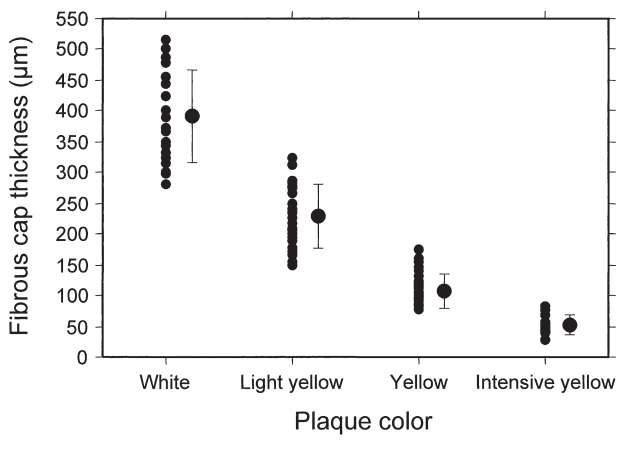

Figure 2. Relation Between Plaque Color and Fibrous Cap Thickness

The plaque color was graded as white, light yellow, yellow, or intensive yellow by coronary angioscopy. The fibrous cap thickness was estimated by optical coherence tomography. There was a significant negative correlation between yellow color intensity and fibrous cap thickness in Spearman rank-order correlation analysis ($p < 0.0001$).

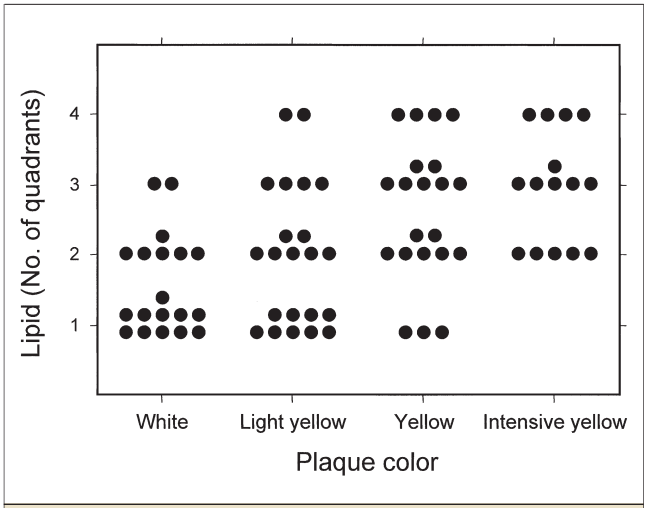

Figure 3. Relation Between Plaque Color and Lipid Size

The plaque color was graded as white, light yellow, yellow, or intensive yellow by coronary angioscopy. The lipid size was semiquantified as the number of involved quadrants on the cross-sectional optical coherence tomography image. There was a significant negative correlation between the 2 variables in Spearman rank-order correlation analysis. ($p < 0.0001$).

Intraobserver and interobserver variability. For reproducibility of the measurements of the fibrous cap thickness by OCT, both intraobserver (17 ± 9 μm) and interobserver (28 ± 16 μm) differences were low. Correlation coefficients were high for repeated measurements by the same observer ($r = 0.99$) and measurements by 2 different observers ($r = 0.97$). In addition, for semiquantification of lipid size as the number of involved quadrants, the intraobserver (0.04 ± 0.20) and interobserver (0.08 ± 0.27) differences were low, and correlation coefficients yielded acceptable ($r = 0.98$ and $r = 0.96$, respectively).

Discussion

In the present study we demonstrated the significant relationship between plaque color grade in coronary angioscopy and fibrous cap thickness estimated by OCT in vivo, and 80% of intensive yellow plaques were proved to be TCFA. Lipid size, estimated as the number of involved quadrants in the OCT image, was also positively correlated with yellow color intensity, but there were not significant differences with adjacent color graded plaques. These results suggested that fibrous cap thickness might be a more important determinant of plaque color in comparison with lipid size of plaque, and the color grade classification of plaques by angioscopy might be a simple and useful method to evaluate the vulnerability of coronary plaques.

Coronary angioscopy has the unique ability to observe the endoluminal surface of coronary arteries, and there are many reports on the importance of plaque color for assessing plaque vulnerability. In the clinical study, the relationship

between the yellow color of the plaque and ACS has been already established (2–4). In addition, the glistening yellow color of the plaque has been demonstrated to be predictive of early adverse coronary events (5,6). Furthermore, it has been suggested that yellow plaques with higher color grades have a higher incidence of intracoronary thrombus (7,8). Therefore, the grading of yellow color might emphasize the predictive value of the angioscopic examinations for future coronary events.

Based on the current knowledge, a thin cap with a large lipid core is one of the important characteristics attributed to vulnerable plaques (1). As noted previously, yellow plaques correlate with lipid-rich atheromas in a histopathological study by directional coronary atherectomy (9) and tend to have thin fibrous caps in the experimental investigation (10). Recently, Kawasaki et al. (11) revealed that the plaque color reflected not the size of the lipid core but the thickness of the fibrous cap using an integrated backscatter IVUS. However, the relationship between the plaques with intensive yellow color and the plaques with cap thicknesses <100 μm, which might be highly vulnerable, were not clarified in the IVUS study because of a limitation of its resolution (11).

Intravascular OCT has recently been proposed as a high-resolution imaging method for plaque characterization (12–18). OCT is an optical analogue of intravascular ultrasound and its resolution is approximately 10 to 20 μm, which is about 10 times higher than IVUS. In an autopsy study, Kume et al. (14) demonstrated that OCT allows us to measure intima-media thickness of normal coronary arteries more accurately than IVUS. Furthermore, they revealed a good correlation between OCT and histological examination in the measurements of fibrous cap thickness of the atherosclerotic plaques including TCFA ($r = 0.90$, $p < 0.001$; mean difference, -24 ± 44 μm) (15). In an in vivo OCT investigation, Jang et al. (16) defined a plaque with lipid area ≥ 2 quadrants and cap thickness ≤ 65 μm as TCFA and showed the fibrous cap thickness (47.0 [25.3 to 215.5] μm, 53.8 [18.7 to 184.3] μm, and 102.6 [22.0 to 291.1] μm, in AMI, ACS, and stable angina, respectively; $p < 0.034$) and the frequency of TCFA (72%, 50%, and 20%, in AMI, ACS, and stable angina, respectively; $p < 0.012$) in living patients with various clinical presentations. Recently, we also evaluated the culprit lesion in AMI by OCT and reported that fibrous cap thickness (49 ± 21 μm) and frequency of TCFA (83%) reproduced well (17). In the present study using coronary angioscopy and OCT, we revealed that yellow plaques of higher color grade might have a thinner fibrous cap, and 80% of intensive yellow plaque was TCFA. The ability of coronary angioscopy and OCT to identify TCFA might allow a better understanding of vulnerable plaque.

To date, coronary angioscopy has had an impact on the quest to identify the vulnerable plaque. It is an available imaging technique that has been reported to predict the occurrence of ACS (4–6); however, the challenge remains to make it a clinically useful and practical tool for the interventionalist. The present study clarified the relationship between high-risk plaque evaluated by angioscopy and TCFA identified by OCT. Although both techniques are invasive and performed in a similar fashion, OCT may be a more quantitative and less subjective modality for assessing plaque vulnerability than angioscopy. The investigation for natural history of TCFA identified by OCT may lead to advances in high-risk plaque detection. If treatment strategies emerge to stabilize vulnerable plaques effectively, the need for vulnerable plaque diagnostic modalities could increase. We anticipate that the unique capabilities of angioscopy and OCT as investigational tools for vulnerable plaque will contribute to detection of the high-risk lesions and development of effective treatment strategies.

Study limitations. First, the evaluation of plaque color by coronary angioscopy was rather subjective, although this kind of often-used grading system is easy and practical. Recently, some reports suggested the usefulness of computer-generated algorithms to measure plaque color by pixel quantification (2). The application of quantitative colorimetry would provide a more convincing and reproducible type classification. Second, a border between fibrous tissue and lipid tissue is diffuse in an OCT image. Although it may have some bias in measurement of the fibrous cap thickness, both the intraobserver and interobserver variability yielded acceptable concordance in the present study. Third, the penetration depth of the OCT signal is limited to within 2 mm. Therefore, this limited ranging depth presents difficulties assessing the entire plaque and lipid burden in the thick atherosclerotic lesions. In the present study, the lipid was semiquantified as the number of involved quadrants on the cross-sectional OCT image according to previous reports (16,17). Although still in a relatively early stage of development, frequency domain OCT imaging has already been shown to be a powerful enabling technology, including higher resolution, higher penetration depth, improvements in interrupted blood flow and faster image acquisition rates (19). These next-generation OCT systems may eliminate many of the technical limitations of the present study.

Conclusions

The plaque color in coronary angioscopy was determined by the fibrous cap thickness, which was assessed by OCT in vivo, and 80% of intensive yellow plaques were demonstrated as TCFA. Therefore, the angioscopic color grading of plaque might be useful to assess the plaque vulnerability. These angioscopic and OCT findings of the present study may help to establish benchmarks for approaches in the diagnosis and treatment of vulnerable plaques in patients with coronary artery disease.

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