A Three-Vessel Virtual Histology Intravascular Ultrasound Analysis of Frequency and Distribution of Thin-Cap Fibroatheromas in Patients With Acute Coronary Syndrome or Stable Angina Pectoris

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The frequency and distribution of thin-cap fibroatheromas (TCFA) have important clinical implications. We evaluated the frequency and distribution of TCFA identified by virtual histology intravascular ultrasound (VH-IVUS) in acute coronary syndrome (ACS) and stable angina pectoris (SAP). Preintervention 3-vessel VH-IVUS was performed in 105 patients with ACS and 107 with SAP. The length of left anterior descending artery imaged was 72 ± 16 mm—54 ± 12 mm in the left circumflex and 92 ± 19 mm in the right coronary. VH-IVUS-derived TCFA (VH-TCFA) had a necrotic core ≥10% of plaque area without overlying fibrous tissue in a plaque burden ≥40%. There were 76 ruptured plaques (55 in ACS and 21 in SAP) and 439 VH-TCFA (262 in ACS and 177 in SAP, 2.5 ± 1.5 vs 1.7 ± 1.1 TCFA per patient with ACS and with SAP, respectively; p <0.001). Twelve patients with ACS and 1 with SAP had multiple ruptured plaques (p <0.001); 76 patients with ACS and 58 with SAP had multiple VH-TCFA (p = 0.009). Presentation of ACS was the only independent predictor for multiple ruptured plaques (p = 0.013) or multiple VH-TCFA (p = 0.011). Eighty-three percent of VH-TCFA were located within 40 mm of the coronary: 111 ≤10 (25%), 110 from 11 to 20 (25%), 83 from 21 to 30 (19%), and 61 from 31 to 40 mm (14%). The axial distribution of VH-TCFA was similar in patients with ACS and those with SAP and was similar to the axial distribution of ruptured plaques. In conclusion, 3-vessel VH-IVUS imaging showed a higher frequency of VH-TCFA in primary and secondary lesions in patients with ACS compared with those with SAP, but showed a similar clustering of VH-TCFA in the proximal 40 mm of each coronary artery.   © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101:568–572)

Pathology and autopsy studies have reported that rupture of a vulnerable plaque and subsequent thrombus formation is the most important mechanism leading to acute coronary syndrome (ACS).[1–3] The studies also indicated that thin-cap fibroatheromas (TCFA) are the most common type of vulnerable plaque and are the precursor of plaque rupture. Detection of TCFA before plaque rupture occurs could prevent development of ACS, but there are technical difficulties to identifying TCFA in vivo in real-world clinical practice. Intravascular ultrasound (IVUS) can safely detect plaque rupture in vivo[4–7]; however, conventional gray-scale IVUS has significant limitations in accurately assessing atheromatous plaque composition and identifying TCFA before plaque rupture occurs. The limitations of gray-scale IVUS have been partially addressed by virtual histology IVUS (VH-IVUS), which characterizes plaque as calcified, fibrotic, fibrofatty, and necrotic core.[8–10] We previously used gray-scale IVUS to report the frequency and axial distribution of plaque ruptures in patients with ACS and those with stable angina pectoris (SAP).[6,11] The purpose of the present study was to extend our previous observations by using 3-vessel VH-IVUS to evaluate the frequency and axial distribution of VH-IVUS-derived TCFA (VH-TCFA) in a large number of patients with ACS or SAP.

Methods

Study population: From July 2005 to December 2006, 3-vessel preintervention VH-IVUS was attempted in 216 nonconsecutive patients at Asan Medical Center and was successful in 212 patients (105 with ACS and 107 with SAP) without any complications. The ACS group included 47 patients with unstable angina, 22 patients with non–ST-elevation myocardial infarction, and 36 patients with ST-elevation myocardial infarction. Definitions of acute myo-

Table 1
Baseline clinical characteristics

Variables	ACS (n = 105)	SAP (n = 107)	p Value
Age (yrs)	60 ± 11	60 ± 10	0.9
Men	90 (86%)	80 (75%)	0.046
Hypertension	44 (42%)	50 (47%)	0.5
Diabetes mellitus	20 (19%)	24 (22%)	0.5
Cigarette smoker	54 (51%)	27 (25%)	<0.001
Lipid profiles at baseline			
Total cholesterol (mg/dl)	182 ± 38	170 ± 34	0.024
HDL cholesterol (mg/dl)	41 ± 13	46 ± 15	0.015
LDL cholesterol (mg/dl)	112 ± 36	94 ± 28	<0.001
Triglycerides (mg/dl)	162 ± 128	158 ± 101	0.8
C-reactive protein (mg/dl)	0.6 ± 1.0	0.2 ± 0.2	0.001
Number of narrowed coronary arteries			0.11
1	66 (63%)	80 (75%)	
2	26 (25%)	21 (20%)	
3	13 (12%)	6 (5%)	

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2
Gray-scale intravascular ultrasound findings of culprit/target lesions in patients with acute coronary syndrome (ACS) or stable angina pectoris (SAP)

Variables	ACS (n = 105)	SAP (n = 107)	p Value
Minimum lumen area site			
External elastic membrane area (mm^2)	16.4 ± 4.2	14.9 ± 4.1	0.008
Lumen area (mm^2)	3.7 ± 0.7	3.8 ± 0.8	0.2
Plaque and media area (mm^2)	12.8 ± 4.2	11.1 ± 3.9	0.003
Remodeling index	1.06 ± 0.17	0.99 ± 0.18	0.010
Largest necrotic core site			
External elastic membrane area (mm^2)	16.9 ± 4.2	15.5 ± 4.4	0.017
Lumen area (mm^2)	4.4 ± 1.2	4.7 ± 1.7	0.13
Plaque and media area (mm^2)	12.5 ± 4.2	10.8 ± 3.8	0.002

Table 3
Virtual histology intravascular ultrasound findings of culprit/target lesions in patients with acute coronary syndrome (ACS) or stable angina pectoris (SAP)

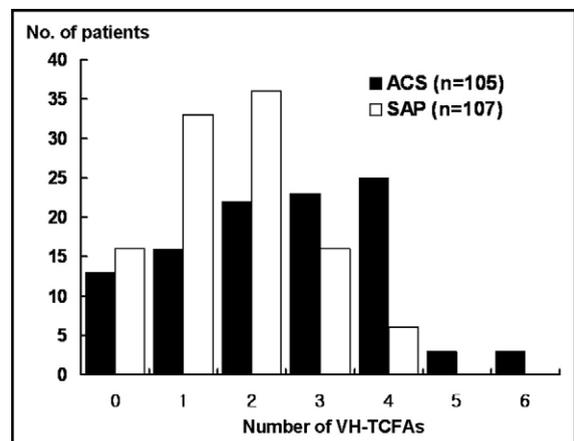| Variables	ACS (n = 105)	SAP (n = 107)	p Value
Minimum lumen area site			
Absolute areas (mm^2)			
Fibrotic (green)	4.9 ± 2.6	4.2 ± 2.5	0.059
Fibrofatty (yellow-green)	0.4 ± 0.5	0.5 ± 0.5	0.133
Dense calcium (white)	0.8 ± 0.7	0.6 ± 0.8	0.086
Necrotic core (red)	3.1 ± 1.5	2.3 ± 1.2	<0.001
Percentages			
Fibrotic	51 ± 15	53 ± 15	0.3
Fibrofatty	4 ± 4	6 ± 6	0.002
Dense calcium	9 ± 8	9 ± 8	0.8
Necrotic core	35 ± 12	32 ± 13	0.031
Largest necrotic core site			
Absolute areas (mm^2)			
Fibrotic	4.9 ± 4.6	4.0 ± 2.3	0.066
Fibrofatty	0.4 ± 0.4	0.5 ± 0.5	0.149
Dense calcium	0.9 ± 0.8	0.6 ± 0.6	0.004
Necrotic core	3.5 ± 1.7	2.5 ± 1.4	<0.001
Percentages			
Fibrotic	48 ± 14	52 ± 14	0.067
Fibrofatty	4 ± 4	5 ± 6	0.005
Dense calcium	10 ± 8	9 ± 7	0.180
Necrotic core	38 ± 11	34 ± 13	0.018

Figure 1. Frequency distribution of the number of VH-TCFA in patients with ACS versus those with SAP.

cardial infarction and SAP and identification of culprit/target lesions have been described previously.[6] Chronic total occlusions, bifurcation lesions, lesions with severe angulations, and heavily calcified lesions were excluded in the present study. Preintervention 3-vessel VH-IVUS was attempted but not successfully performed in 4 patients due to the inability of the IVUS-imaging catheter to cross lesions into the distal vessels (heavy calcification in 2 patients and severe angulation in 2 patients). No IVUS-related complications occurred in these 4 patients, and they were excluded from this study.

IVUS imaging and analysis: VH-IVUS examination of all 3 major epicardial arteries was performed before any intervention and after intracoronary administration of 0.2 mg nitroglycerin. The 2.9Fr IVUS imaging catheter (Eagle Eye, Volcano Corp, Rancho Cordova, California) incorporated a 20 MHz phased-array transducer. In all 3 coronary arteries in each of the patients studied, the transducer was advanced into the distal coronary artery, and an imaging run

was performed back to the aorto-ostial junction using motorized transducer pullback (0.5 mm/s).

Conventional gray-scale quantitative IVUS analyses were performed according to criteria of the clinical expert consensus document on IVUS to include external elastic membrane, lumen, and plaque and media (external elastic membrane - lumen) areas.[4] A remodeling index was calculated as the external elastic membrane area of the lesion divided by the mean of the reference external elastic membrane area. IVUS signs of plaque rupture were a cavity that communicated with the lumen with an overlying residual fibrous cap fragment.[6,12]

Planar VH-IVUS analysis was performed at the site of the minimal lumen area and the site of the largest necrotic core using pcVH software (Volcano Corporation, Rancho

Table 4
Numbers of patients with ruptured plaques and virtual histology intravascular ultrasound (VH-IVUS)-derived thin-cap fibroatheroma (TCFA)

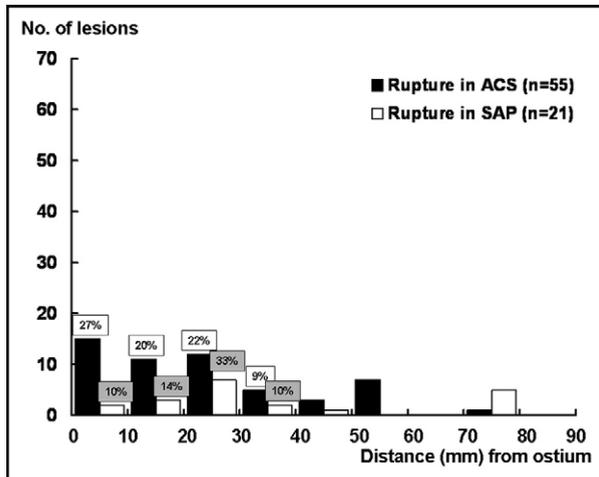|	Non–VH-TCFA	Single VH-TCFA	Multiple (≥2) VH-TCFA	Total
No ruptured plaques	16 (10%)	39 (25%)	99 (64%)	154
Single ruptured plaque	9 (20%)	6 (13%)	30 (67%)	45
Multiple (≥2) ruptured plaques	4 (31%)	4 (31%)	5 (38%)	13
Total	29	49	134	212

Figure 2. Axial distribution of ruptured plaques in patients with ACS versus those with SAP.
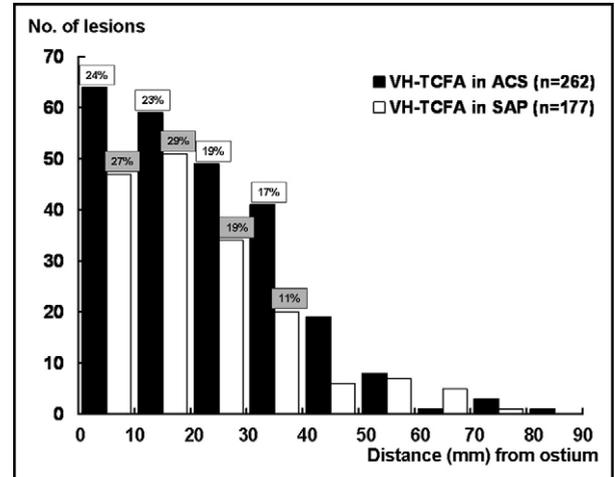

Figure 3. Axial distribution of VH-TCFA in patients with ACS versus those with SAP.

Cordova, California). VH-IVUS analysis coded tissue as green (fibrotic), yellow-green (fibrofatty), white (dense calcium), and red (necrotic core).[8–10] VH-IVUS analyses were reported in absolute amounts and as percentages (relative amounts) of plaque area. VH-TCFA was defined as a necrotic core ≥10% of plaque area at either the minimal lumen area site or largest necrotic core site in at least 3 consecutive frames without overlying fibrous tissue in the presence of ≥40% plaque burden (plaque and media divided by external elastic membrane).[9]

According to both the gray-scale and VH-IVUS findings, lesions were classified into 3 groups: ruptured plaque, VH-TCFA (without evidence of plaque rupture), and non–VH-TCFA plaque.[13] With the use of automated transducer pullback, the distance from each plaque rupture or VH-TCFA back to the respective coronary ostium was calculated (pullback speed multiplied by number of seconds).

Statistical analysis: Statistical analysis was performed with SPSS (SPSS Inc., Chicago, Illinois). Data are presented as frequencies or as mean ± SD. Comparison was performed with chi-square statistics and unpaired Student's t test or Mann-Whitney U test or analysis of variance. Multiple stepwise logistic regression analysis was performed to assess independent predictors for multiple VH-TCFA and multiple ruptured plaques. A p value <0.05 was considered statistically significant.

Results

Baseline clinical characteristics are listed in Table 1. The majority of patients (69% overall) had single vessel disease.

In Table 2 gray-scale IVUS findings of culprit/target lesions in patients with ACS or SAP are compared. External elastic membrane, plaque and media areas, and remodeling indices were significantly larger in patients with ACS compared with patients with SAP. In Table 3 VH-IVUS analysis of culprit/target lesions in patients with ACS or SAP are compared. Planar VH-IVUS analysis at the minimum lumen site and at the largest necrotic core site showed significantly greater percentages of necrotic core areas and smaller percentages of fibrofatty plaque areas in patients with ACS compared with patients with SAP.

Overall, combining gray-scale and VH-IVUS analysis of culprit/target lesions and nonculprit/nontarget lesions, there were 76 ruptured plaques (55 in patients with ACS and 21 in patients with SAP), 439 VH-TCFA (262 in patients with ACS and 177 in patients with SAP), and 252 non–VH-TCFA (75 in patients with ACS and 177 in patients with SAP). Culprit lesions in patients with ACS had 32 ruptured plaques (31%), 64 VH-TCFA (61%), and 9 non–VH-TCFA (9%). Conversely, target lesions in patients with SAP had 11 ruptured plaques (10%), 55 VH-TCFA (51%), and 41 non–VH-TCFA (38%) (p <0.001). In secondary lesions in patients with ACS there were 23 ruptured plaques (8%), 198 VH-TCFA (69%), and 66 non–VH-TCFA (23%); in secondary lesions of patients with SAP, there were 10 ruptured plaques (4%), 122 VH-TCFA (45%), and 136 non–VH-TCFA (51%) (p <0.001).

Frequency of ruptured plaques and VH-TCFA: The average number of ruptured plaques per patient was 0.5 ± 0.8 in patients with ACS and 0.2 ± 0.5 in patients with SAP (p <0.001). The average number of VH-TCFA per patient was 2.5 ± 1.5 in patients with ACS and 1.7 ± 1.1 in
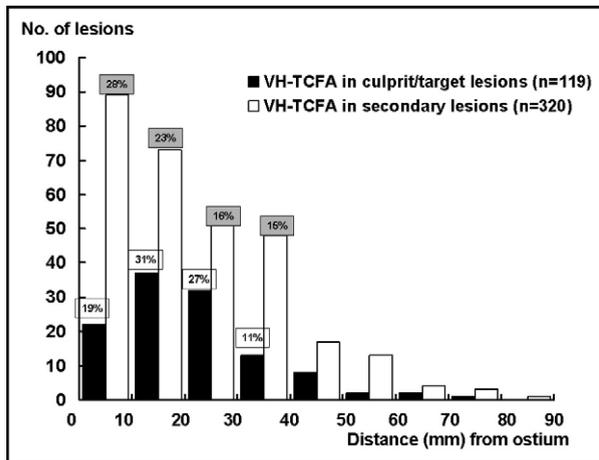
Figure 4. Axial distribution of VH-TCFA in culprit/target lesions versus secondary lesions.

patients with SAP (p <0.001). The average number of VH-TCFA was 2.7 ± 1.7 per patient in patients with unstable angina, 2.7 ± 1.4 per patient in patients with non–ST-elevation myocardial infarction, and 2.1 ± 1.4 per patient in patients with ST-elevation myocardial infarction (p = NS). The frequency distribution of the number of VH-TCFA in patients with ACS and those with SAP is shown in Figure 1.

Multiple (≥2) ruptured plaques were found in 12 patients with ACS (11%) and in only 1 patients with SAP (1%) (p <0.001). Multiple (≥2) VH-TCFA were found in 76 patients with ACS (72%) and in 58 patients with SAP (54%) (p = 0.009). There was a trend for patients with multiple ruptured plaques not to have multiple VH-TCFA (p = 0.056, Table 4) presumably because these plaques had already ruptured. Clinical and angiographic variables with p <0.2 in univariate analysis were entered into multiple logistic regression models: presentation of ACS and number of narrowed coronary arteries for multiple ruptured plaques and age, low-density lipoprotein cholesterol level, ACS presentation, and number of narrowed coronary arteries for multiple VH-TCFA. Presentation of ACS was the only independent clinical predictor for multiple ruptured plaques (odds ratio 13.67, 95% confidence interval 1.75 to 107.12, p = 0.013). It was also the only independent clinical predictor for multiple VH-TCFA (odds ratio 2.18, 95% confidence interval 1.20 to 3.97, p = 0.011).

Axial distribution of ruptured plaques and VH-TCFA: The total length of the coronary artery imaged by VH-IVUS was 72 ± 16 mm in the left anterior descending artery, 54 ± 12 mm in the left circumflex artery, and 92 ± 19 mm in the right coronary artery.

Overall, 75% (n = 57) of the ruptured plaques were located within the first 40 mm of the coronary ostium: 17 within the first 10 (22%), 14 from 11 to 20 (18%), 19 from 21 to 30 (25%), and 7 from 31 to 40 mm (9%). The axial distribution of ruptured plaques was similar in patients with ACS and patients with SAP: 27% versus 10% in the first 10, 20% versus 14% from 11 to 20, 22% versus 33% from 21 to 30, and 9% versus 10% from 31 to 40 mm (Figure 2).

Overall, 83% VH-TCFA (n = 365) were located within the first 40 mm of the coronary ostium: 111 within the first 10 (25%), 110 from 11 to 20 (25%), 83 from 21 to 30 (19%), and 61 from 31 to 40 mm (14%). The axial distribution of VH-TCFA was also similar in patients with ACS and patients with SAP: 24% versus 27% within the first 10, 23% versus 29% from 11 to 20, 19% versus 19% from 21 to 30, and 17% versus 11% from 31 to 40 mm (Figure 3). The axial distribution of VH-TCFA was also similar in culprit/target lesions and secondary lesions (Figure 4).

There were 2 ruptured plaques (3%) in the left main coronary artery (1 in a patient with ACS and 1 in a patient with SAP); 23 VH-TCFA (5%) were located in the left main coronary artery (17 in patients with ACS and 6 in patients with SAP).

Discussion

The present 3-vessel VH-IVUS analysis of 212 patients (105 with ACS and 107 with SAP) showed a greater frequency of ruptured plaques, VH-TCFA, multiple ruptured plaques, and multiple VH-TCFA in patients with ACS compared with patients with SAP. Ruptured plaques and VH-TCFA were clustered in the first 40 mm of each coronary artery in both patients with ACS and patients with SAP.

In previous pathologic studies ruptured plaques were found in approximately 70% of the culprit lesions of patients with coronary artery disease who died suddenly.[1,2,14] Previous IVUS studies have reported a 16% to 66% incidence of ruptured plaques in the culprit lesions of patients with ACS[6,7,15] and a 22% to 32% incidence of ruptured plaques in the target lesions of patients with SAP.[6,7,16] Compared with these previous studies, the present study showed a slightly lower frequency of ruptured plaques; this might be explained in part by different resolution powers of the IVUS systems used in these studies—20 MHz in the present study versus 30 or 40 MHz in previous studies, which includes other studies from our laboratory.

Using a VH-IVUS definition of TCFA similar to that used in the present study, Rodriguez-Granillo et al[9] reported that 23 patients with ACS had a threefold higher frequency of VH-TCFA within secondary, nonobstructive lesions (diameter stenosis <50%) than did 32 patients with SAP. However, Rodriguez-Granillo et al[9] performed only single vessel VH-IVUS analysis in a small number of patients, analyzed nonobstructive lesions only, and did not tabulate actual plaque ruptures (the ultimate consequence of TCFA).

The present VH-IVUS study was designed to extend the observations of Rodriguez-Granillo et al[9] by including 3-vessel imaging in a large number of patients, studying primary and secondary lesions, and tabulating IVUS-detected ruptured plaques and VH-detected TCFA. In the present study the overall frequency of VH-TCFA was 2.5 per patient with ACS and 1.7 per patient with SAP (p <0.001). In a pathologic study by Kolodgie et al[17] there was an average of ≥1.5 TCFA in patients dying with acute myocardial infarction and/or acute plaque rupture and an average of ≥1.1 TCFA in patients dying with stable plaque. Another pathologic study with 21 patients showed an average number of 6.8 TCFA in patients with acute myocardial infarction and of 0.8 TCFA in patients with SAP.[18] The

different frequency of TCFA in the pathologic and VH-IVUS studies may be because of different diagnostic methods, clinical presentations or demographics of the study population, number of study patients, and definitions of a TCFA. Furthermore, VH-IVUS may overestimate or underestimate the number of TCFA compared with pathology. VH-IVUS examines the coronary arteries in 0.5 mm long segments. However, the technology of VH-IVUS and its definitions continue to evolve, and VH-IVUS does not detect thrombus that may fill a plaque cavity, overlay a necrotic core, or be coded as fibrotic tissue, which can obscure the identification of a ruptured plaque or TCFA. Nevertheless, we reported that primary VH-TCFA were more common in patients with ACS than in patients with SAP; in the present report and the study by Rodriguez-Granillo et al,[9] secondary VH-TCFA were also more common in patients with ACS than in patients with SAP, and in the present report presentation of ACS was the only independent predictor of multiple VH-TCFA.

Previous angiographic studies of acute coronary thromboses, IVUS studies of ruptured plaques, and pathologic studies of ruptured plaques showed that these unstable lesions were distributed predominantly in the proximal 40 to 50 mm of each coronary artery.[11,17,19] In the report by Rodriguez-Granillo et al,[9] there was a similar clustering pattern of VH-TCFA. The present study showed a similar distribution pattern of IVUS-detected plaque ruptures (75% of ruptured plaques occurred within the first 40 mm) and VH-TCFA (83% of VH-TCFA occurred within the first 40 mm). Thus, the axial location of VH-TCFA was similar to the location of plaque rupture and acute coronary thrombosis, the worst consequences of TCFA. Of note is that this anatomic clustering was independent of clinical presentation (ACS vs SAP).

This study was a single center, retrospective study. VH-IVUS cannot determine the presence of thrombus, which may obscure the identification of ruptured plaques and TCFA. In lesions with thrombus in patients with ACS, preintervention VH-IVUS examination was done after thrombus suction was done using thrombectomy catheter without use of balloon dilation or occlusion.

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