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In Vivo Intravascular Ultrasound-Derived Thin-Cap Fibroatheroma Detection Using Ultrasound Radiofrequency Data Analysis

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OBJECTIVES The purpose of this study was to assess the prevalence of intravascular ultrasound (IVUS)-derived thin-cap fibroatheroma (IDTCFA) and its relationship with the clinical presentation using spectral analysis of IVUS radiofrequency data (IVUS-Virtual Histology [IVUS-VH]).

BACKGROUND Thin-cap fibroatheroma lesions are the most prevalent substrate of plaque rupture.

METHODS In 55 patients, a non-culprit, non-obstructive (<50%) lesion was investigated with IVUS-VH. We classified IDTCFA lesions as focal, necrotic core-rich (≥10% of the cross-sectional area) plaques being in contact with the lumen; IDTCFA definition required a percent atheroma volume (PAV) ≥40%.

RESULTS Acute coronary syndrome (ACS) (n = 23) patients presented a significantly higher prevalence of IDTCFA than stable (n = 32) patients (3.0 [interquartile range (IQR) 0.0 to 5.0] vs. 1.0 [IQR 0.0 to 2.8], p = 0.018). No relation was found between patient's characteristics such as gender (p = 0.917), diabetes (p = 0.217), smoking (p = 0.904), hypercholesterolemia (p = 0.663), hypertension (p = 0.251), or family history of coronary heart disease (p = 0.136) and the presence of IDTCFA. A clear clustering pattern was seen along the coronaries, with 35 (35.4%), 31 (31.3%), 19 (19.2%), and 14 (14.1%) IDTCFAs in the first 10 mm, 11 to 20 mm, 21 to 30 mm, and ≥31 mm segments, respectively, p = 0.008. Finally, we compared the severity (mean PAV 56.9 ± 7.4 vs. 54.8 ± 6.0, p = 0.343) and the composition (mean percent necrotic core 19.7 ± 4.1 vs. 18.1 ± 3.0, p = 0.205) of IDTCFAs between stable and ACS patients, and no significant differences were found.

CONCLUSIONS In this in vivo study, IVUS-VH identified IDTCFA as a more prevalent finding in ACS than in stable angina patients. (J Am Coll Cardiol 2005;46:2038–42) © 2005 by the American College of Cardiology Foundation

Sudden cardiac death or unheralded acute coronary syndromes (ACS) are common initial manifestations of coronary atherosclerosis, and most such events occur at sites of non-flow limiting coronary atherosclerosis (1,2). Autopsy data suggest that plaque composition is a key determinant of the propensity of atherosclerotic lesions to provoke clinical events. Thin-cap fibroatheroma (TCFA) plaques with large avascular, hypocellular lipid cores seem particularly prone to rupture and result in epicardial occlusion (3–5).

Careful systematic evaluation, in a large series of victims of sudden cardiac death, suggested that ruptured TCFA was the precipitating factor for 60% of acute coronary thrombi. Furthermore, 70% of those patients had other TCFAs that had not ruptured (5).

Intravascular ultrasound (IVUS) is the gold standard for evaluation of coronary plaque, lumen, and vessel dimensions (6,7). However, although visual interpretation of gray-scale IVUS can identify calcification within plaques, it cannot reliably differentiate lipid-rich from fibrous plaque (7). Recently, spectral analysis of IVUS radiofrequency data (IVUS-Virtual Histology [IVUS-VH]) has demonstrated potential to provide detailed quantitative information on plaque composition and morphology and has been validated in studies of explanted human coronary segments (8).

In the present study, we evaluated the prevalence of IVUS-derived TCFA (IDTCFA) in coronary artery segments with non-significant lesions on angiography using IVUS-VH.

METHODS

In 55 patients, a non-culprit, de novo, angiographically non-obstructive (<50%) lesion was investigated with IVUS-VH. Written informed consent was obtained from all patients.

IVUS-VH acquisition and analysis. Details regarding the validation of the technique on explanted human coronary segments have previously been reported (8). Briefly, IVUS-VH uses spectral analysis of IVUS radiofrequency data to construct tissue maps that classify plaque into four major components (fibrous [labeled green], fibrolipidic [labeled greenish-yellow], necrotic core [labeled red], and calcium [labeled white]) which were correlated with a specific spectrum of the radiofrequency signal and assigned color codes (8).

Intravascular Ultrasound-Virtual Histology data were acquired after intracoronary administration of nitrates using a continuous pullback (Ultracross 2.9-F 30-MHz catheter, Boston Scientific, Santa Clara, California), by a dedicated

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Abbreviations and Acronyms

ACS = acute coronary syndrome
IDTCFA = intravascular ultrasound-derived thin-cap fibroatheroma
IQR = interquartile range
IVUS = intravascular ultrasound
IVUS-VH = Intravascular Ultrasound-Virtual Histology
LAD = left anterior descending coronary artery
LCX = left circumflex artery
PAV = percent atheroma
RCA = right coronary artery
ROI = region of interest
TCFA = thin-cap fibroatheroma

IVUS-VH console (Volcano Therapeutics, Rancho Cordova, California). The IVUS-VH data were stored on a CD-ROM and sent to the imaging core lab for offline analysis. Intravascular ultrasound B-mode images were reconstructed from the radiofrequency data by customized software (IVUSLab, Volcano Therapeutics, Rancho Cordova, California). Manual contour detection of both the lumen and the media-adventitia interface was performed, and the radiofrequency data were normalized using a technique known as "blind deconvolution," an iterative algorithm that deconvolves the catheter transfer function from the backscatter, thus accounting for catheter-to-catheter variability (9). Geometric and compositional data were obtained for every slice and expressed as mean percent for each component. The plaque eccentricity index (EI) was calculated by dividing the minimum plaque thickness by the maximum plaque thickness. Percent atheroma volume (PAV) was defined as: $EEM_{area} - lumen_{area}/EEM_{area} \times 100$, where EEM refers to external elastic membrane.

Subsequently, we evaluated the presence of IDTCFA lesions along the interrogated vessels, and their incidence and characteristics were determined. Finally, the spatial distribution of IDTCFA along the coronaries was evaluated starting from the ostium and dividing the vessel in 10-mm segments, evaluating a minimal length of 30 mm.

Definition of IDTCFA. Two experienced, independent IVUS analysts defined IDTCFA as a lesion fulfilling the following criteria in at least three consecutive frames: 1) necrotic core ≥10% without evident overlying fibrous tissue (Fig. 1); and 2) PAV ≥40%.

We selected this cutoff value because TCFA lesions are very unlikely present in segments with <40% occlusion (10). Cross sections with non-uniform rotational distortion artifact were excluded from the analysis.

Statistical analysis. Discrete variables are presented as counts and percentages. Continuous variables are presented as medians (25th, 75th percentile) or mean values ± SD when indicated. Pearson's chi-square or Fisher exact test, Student *t* test, and Wilcoxon rank-sum tests were performed, as indicated. A two-sided p value of <0.05 indicated statistical significance. Logistic regression analysis was performed to identify potential predictors of the presence of IDTCFA. Statistical analyses were performed with use of 11.5 SPSS software (SPSS Inc., Chicago, Illinois).

RESULTS

The baseline characteristics of the patients (n = 55) we studied are presented in Table 1. Thirty-four (61.8%) patients had at least one IDTCFA in the region of interest (ROI).

The population was prospectively divided into two groups, stable patients and patients presenting with ACS (defined as unstable angina, non–ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction).

IDTCFA incidence and predictors. Acute coronary syndrome patients had a significantly higher incidence of IDTCFA than stable patients (3.0 [interquartile range (IQR) 0.0 to 5.0] vs. 1.0 [IQR 0.0 to 2.8], p = 0.018). When corrected for the length of the ROI, the density of

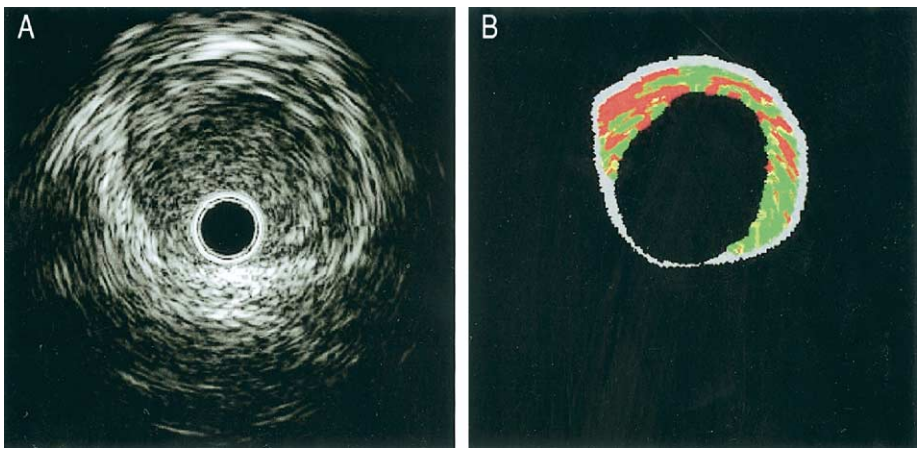

Figure 1. Left anterior descending artery depicted by Intravascular Ultrasound-Virtual Histology, where calcified, fibrous, fibrolipidic, and necrotic core regions are labeled **white**, **green**, **greenish-yellow**, and **red**, respectively. **Panel A** shows an intravascular ultrasound cross-sectional area reconstructed from backscattered signals. **Panel B** shows the corresponding tissue map depicting a necrotic core-rich plaque with necrotic core tissue in contact with the lumen.

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Table 1. Baseline Characteristics (n = 55)

	n (%)
Age (yrs ± SD)	57.6 ± 9.5
Male gender	44 (80.0)
Diabetes	5 (9.1)
Hypertension	20 (36.4)
Current smoking	15 (27.3)
Previous smoking	14 (25.5)
Hypercholesterolemia	46 (83.6)
Family history of coronary disease	30 (54.5)
Vessel	
Right coronary artery	22 (40.0)
Left anterior descending	23 (41.8)
Left circumflex	10 (18.2)
Clinical presentation	
Stable	32 (58.2)
Acute coronary syndrome	23 (41.8)

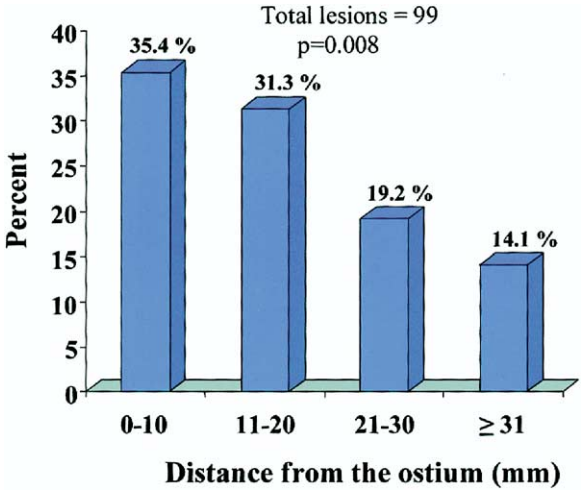

Figure 2. Bar graphs illustrating the frequency of intravascular ultrasound-derived thin-cap fibroatheroma (IDTFCA) starting from the ostium.

IDTCFA remained statistically significant (0.7 [IQR 0.0 to 1.3] IDTCFA/cm vs. 0.2 [IQR 0.0 to 0.7] IDTCFA/cm, p = 0.031) (Table 2).

No relation was found between patient's characteristics such as gender (p = 0.917), diabetes (p = 0.217), smoking (p = 0.904), hypercholesterolemia (p = 0.663), hypertension (p = 0.251), or family history of coronary heart disease (p = 0.136) and the presence of IDTCFA.

Characteristics and location. We compared the severity (mean PAV 56.9 ± 7.4% vs. 54.8 ± 6.0%, p = 0.343) and the composition (mean percent necrotic core 19.7 ± 4.1% vs. 18.1 ± 3.0%, p = 0.205) of IDTCFAs between ACS and stable patients, and no significant differences were found. Although not significantly, the left anterior descending coronary artery (LAD) (73.9% of the LADs, n = 23) was the most frequent location, followed by the left circumflex artery (LCX) (60.0% of the LCXs, n = 10) and the right coronary artery (RCA) (50.0% of the RCAs, n = 22, p = 0.254).

Four patients were excluded from the spatial distribution subanalysis, three because the IVUS assessment of the ROI was shorter than 30 mm and the last one because the pullback did not reach the ostium. A total of 99 IDTCFA were present in vessels that met the aforementioned criteria. A clear clustering pattern was seen along the coronaries, with 35 (35.4%), 31 (31.3%), 19 (19.2%), and 14 (14.1%) IDTCFAs in the first 10 mm, 11 to 20 mm, 21 to 30 mm, and ≥31 mm segments, respectively, p = 0.008 (Fig. 2). The results showed a clear clustering pattern of the lesions along the coronaries, with 66 (66.7%) IDTCFA located in the first 20 mm, whereas further along the vessels the incidence was significantly lower (33, 33.3%, p = 0.008).

DISCUSSION

Post-mortem observations have documented several characteristic histological patterns that are substrates for sudden death related to epicardial coronary occlusion, of which the most common is TCFA (5,11,12). The same studies have demonstrated that plaque rupture at TCFAs may also occur without clinical consequences. The ability to identify TCFA in patients would both help clarify the natural history of TCFA and provide the means to assess the effects of pharmacological, or other, intervention.

Until recently, no technique could identify TCFA in vivo. However, spectral analysis of IVUS radiofrequency (IVUS-VH) data has demonstrated potential to provide detailed quantitative information both on overall plaque composition and on the anatomic relation of specific plaque components to the lumen of the vessel, and it has been validated in studies of explanted human coronary segments (8).

IDTCFA definition. It is well established that tissue shrinkage occurs during tissue fixation (13). Shrinkage of up to 60%, 15%, and 80% can occur during critical-point drying, free drying, and air drying, respectively (14). Furthermore, postmortem contraction of arteries is an additional confounding factor (15).

Although the most accepted threshold to define a cap as "thin" has been set at 65 μm (16), a number of important

Table 2. Incidence and Characteristics of IDTCFA Lesions in Stable and ACS Patients

	Length of ROI	IDTCFA	IDTCFA/cm	% PAV	% NC	EI
Stable (n = 32)	35.41 ± 11.6	1.0 (0.0, 2.8)	0.2 (0.0, 0.7)	54.8 ± 6.0	18.1 ± 3.0	0.23 ± 0.1
ACS (n = 23)	33.90 ± 15.0	3.0 (0.0, 5.0)	0.7 (0.0, 1.3)	56.8 ± 7.4	19.7 ± 4.1	0.27 ± 0.2
p value	0.684	0.018	0.031	0.343	0.205	0.35

Continuous variables are presented as medians (25th, 75th percentile) or mean values ± SD when indicated.

ACS = acute coronary syndrome; EI = plaque eccentricity index (defined as minimum plaque thickness divided by maximum plaque thickness); IDTCFA = intravascular ultrasound-derived thin-cap fibroatheroma; % PAV = percent atheroma volume (defined as $EEM_{area} - lumen_{area}/EEM_{area} \times 100$, where EEM refers to external elastic membrane); ROI = region of interest; % NC = percent necrotic core of the cross-sectional area.

ex vivo studies have used higher (>200 μm) thresholds (4,17,18). Indeed, one of these studies identified a mean cap thickness of 260 and 360 μm for "vulnerable" and "non-vulnerable" plaques, respectively (18). Because the axial resolution of IVUS-VH is between 100 to 150 μm, we assumed that the absence of visible fibrous tissue overlying a necrotic core suggested a cap thickness of below 100 to 150 μm and used the absence of such tissue to define a thin fibrous cap (19). Figure 1 depicts a typical example of IDTCFA.

Incidence, characteristics, and distribution of IDTCFA. The major findings of our study were first that IVUS-VH findings, compatible with IDTCFA, were common in non-culprit lesions of patients undergoing percutaneous intervention in another vessel. Second, the prevalence of IDTCFA was significantly higher in patients who presented with ACS compared to stable patients. In addition, the distribution of IDTCFA lesions along the coronary vessels was clearly clustered. Finally, we found no significant correlation between the presence of conventional risk factors and the occurrence of IDTCFA.

In vivo studies established that a multifocal instability process is present in ACS (20,21). Rioufol et al. (20) found at least one plaque rupture remote from the culprit lesion in 80% of patients and from the culprit artery in 71% of patients (20). The significantly higher prevalence of IDTCFA in non-culprit coronaries of patients presenting with an ACS supports the theory that holds ACS as multifocal processes.

The distribution of the IDTCFA in the coronaries was in line with previous ex vivo and clinical studies, with a clear clustering pattern from the ostium, thus supporting the non-uniform distribution of vulnerable plaques along the coronary tree (22,23). Of note, the mean PAV and the mean necrotic core percentage of the IDTCFAs detected by IVUS-VH were also similar to previously reported histopathological data (55.9% vs. 59.6% and 19% vs. 23%, respectively) (10).

The large number of high-risk plaques found throughout the coronary tree by means of angiography, angioscopy, IVUS, and palpography, in addition to the unpredictability of the natural history of such lesions and the uncertainty about whether vulnerable plaque characteristics will subsequently lead to fatal or non-fatal ischemic events, suggests that potential local preventive strategies could not be cost-effective (12,20,21,24,25). On the contrary, a systemic "plaque stabilization" approach including statins and angiotensin-converting enzyme inhibitors could be capable of "cooling-down" the inflammatory burden.

To our knowledge, this is the first study to detect in vivo the presence of an IVUS surrogate of TCFA. This novel intravascular diagnostic tool could potentially aid the assessment of the effect of antiatherosclerotic drugs, and allow a more comprehensive pathophysiologic approach towards natural history studies.

Study limitations. The present was an observational study where we evaluated only one coronary artery per patient. The inferior axial resolution of IVUS-VH in comparison to histology could influence our results. This study does not directly assess the incremental value of IVUS-VH over visual identification of plaque characterization. The main finding of the study (IDTCFA) is only a surrogate of a histopathological finding. Besides, the lack of a direct comparison between IVUS-VH and histopathology renders our observation to some extent only exploratory. Accordingly, interpretation of our findings must be cautious. Prospective studies are needed in order to evaluate the prognostic value and natural history of such finding. The seemingly high prevalence of IDTCFA in comparison with histopathological studies is mainly driven by the sampling limitation of such studies and has previously been acknowledged (26).

Conclusions. In this in vivo study, IVUS-VH identified IDTCFA as a more prevalent finding in ACS than in stable angina patients. Prospective studies are needed in order to evaluate the prognostic value of such finding in natural history studies.

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