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TISSUE CHARACTERISTICS OF CULPRIT CORONARY LESIONS IN ACUTE CORONARY SYNDROME AND TARGET CORONARY LESIONS IN STABLE ANGINA PECTORIS: VIRTUAL HISTOLOGY AND INTRAVASCULAR ULTRASOUND STUDY

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ABSTRACT

Objective: coronary plaque composition cannot be assessed accurately using gray-scale intravascular ultrasound (IVUS). Using virtual histology IVUS (VH-IVUS), a comparison of coronary plaque composition between acute coronary syndromes (ACS) and stable angina pectoris (SAP) was performed.

Methods: pre-intervention IVUS of de novo culprit and target lesions was performed in 47 patients (25 with ACS and 22 with SAP). Using VH-IVUS, plaque was characterized as fibrotic, fibro-fatty, dense calcium, and necrotic core. VH-IVUS-derived thin-cap fibro-atheroma (VH-TCFA) was defined as necrotic core >10% of plaque area without overlying fibrous tissue in a plaque burden >40%. Lesions were classified into 3 groups: ruptured, VH-TCFA, and non–VH-TCFA plaque. Unstable lesions were defined as either VH-TCFA or ruptured plaque.

Results: compared with patients with SAP, those with ACS had significantly more unstable lesions. Planar VH-IVUS analysis at minimum lumen site shown that necrotic core and dense calcium by percentages and absolute quantities areas are significantly greater in ACS group compared with SAP group. Volumetric analysis over a 10-mm-long segment centered at the minimum luminal site showed that the percentage of necrotic core was significantly greater and that the percentage of fibrotic plaque was significantly smaller in patients with ACS.. VH-TCFA were more frequently observed in ACS patients than in SAP patients ($p = 0.006$).

Conclusions: culprit lesions in patients with ACS were more unstable and had greater amounts of necrotic core and smaller amounts of fibro-fatty plaque compared with target lesions in patients with SAP.

Keywords: intravascular ultrasound, coronary plaque, plaque components.

Introduction

Clinical symptoms and presentations, not lesion morphology, define acute coronary syndromes (ACS) and differentiate ACS from stable angina pectoris (SAP). However, unstable clinical symptoms in patients with ACS are associated with unstable plaque characteristics[1-4]. Conventional gray-scale intravascular ultrasound (IVUS) has significant limitations in accurately assessing atheromatous plaque composition. These limitations have been partially addressed by virtual histology IVUS (VH-IVUS), which provides detailed qualitative and quantitative information and it characterizes plaque as calcified, fibrotic, fibrofatty, or necrotic core [5-6]. The purpose of this study was to use VH-IVUS to compare coronary plaque composition between patients with ACS and patients with SAP.

Subjects and Methods

Patient population

A total of 47 consecutive patients who had undergone grayscale and VH-IVUS in culprit lesion in ACS patients and in target lesion in SAP patients between January, 2016 and October, 2016 were identified from the Lithuanian University of Health Sciences VH-IVUS registry database. We compared VH-IVUS findings between 25 ACS culprit lesions and 22 SAP target lesions. The presence of SAP was determined according to the Canadian Cardiovascular Society classification. Unstable angina and non-ST segment elevation myocardial infarction are considered to be closely related conditions whose pathogenesis and clinical presentations are similar, but of differing severity (i.e., they differ primarily in whether the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury, most commonly troponin I, troponin T, or the MB isoenzyme of creatine phosphokinase). Once it has been established that no biochemical marker of myocardial necrosis has been released, the patient with an ACS may be considered to have experienced unstable angina, whereas the diagnosis of non-ST segment elevation myocardial infarction is established if a marker of myocardial injury has been released [7]. ST-segment elevation myocardial infarction is a clinical syndrome defined by characteristic symptoms of myocardial ischemia, in association with persistent electrocardiographic ST-elevation and the subsequent release of biomarkers of myocardial necrosis. Diagnostic ST-elevation in the absence of left ventricular hypertrophy or left bundle-branch block is defined by the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction as a new ST-elevation at the J point in at least 2 contiguous leads of ≥2 mm (0.2 mV) in men or ≥1.5 mm (0.15 mV) in women in leads V 2-3, and/or of ≥1 mm (0.1 mV) in other contiguous chest leads or the limb leads [14]. We excluded patients with Thrombolysis in Myocardial Infarction (TIMI) 0-1 flow, coronary artery bypass graft lesion, chronic total occlusion, restenosis after stenting, important systemic disease such as systemic lupus erythematosus, amyloidosis, sarcoidosis, human immunodeficiency virus infection, and malignancies, and so on, or serum creatinine >2.5 mg/dL. Culprit lesion in ACS patients was defined as plaques viewed on an angiogram. Target lesion in SAP patients was defined as a coronary lesion whose diameter stenosis by quantitative coronary angiography (QCA) was greatest if the patient had multivessel disease. Plaques with more than a 30%

diameter stenosis as compared with the reference diameter by IVUS were included in our study. Each plaque was separated by at least 5 mm from the edge of any other plaque or implanted stent edge. The protocol was approved by the institutional review board. Hospital records of all patients were reviewed to obtain clinical demographics and medical history.

Laboratory analysis

Peripheral blood samples were obtained before coronary angiography using direct venipuncture. The blood samples were centrifuged, and serum was removed and stored at -70°C until the assay could be performed. The serum levels of total cholesterol, triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured using standard enzymatic methods. Serum N-terminal pro-B-type natriuretic peptide was measured using an electrochemiluminescence sandwich immunoassay method with an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany).

Coronary angiographic findings

Coronary angiogram was analyzed with validated a QCA system. With the outer diameter of the contrast- filled catheter as the calibration standard, the reference diameter and minimal lumen diameter were measured in diastolic frames from orthogonal projections. Perfusion was evaluated according to TIMI criteria.

Intravascular ultrasound imaging and analysis

VH-IVUS examination was performed before any intervention and after the intracoronary administration of nitroglycerin 0.2 mg using a motorized transducer pullback system (0.5 mm/s). A 2.9Fr IVUS imaging catheter (Eagle Eye; Volcano Corporation, Rancho Cordova, California) incorporated a 20-MHz phased-array transducer. Conventional gray-scale quantitative IVUS analyses were performed according to criteria of the clinical expert consensus document on IVUS to include external elastic membrane (EEM), luminal, and plaque and media (P&M; defined as EEM minus luminal) areas [8]. Plaque burden was defined as P&M area divided by EEM area. A remodeling index was calculated as the lesion EEM divided by the mean reference EEM area. IVUS signs of plaque rupture were a cavity that communicated with the lumen with an overlying residual fibrous cap fragment [9;10]. Planar VH-IVUS analysis was performed at the site of the minimal luminal area. Volumetric VH-IVUS analysis was performed along a 10-mm segment centered on the minimal luminal area; calculations were made using Simpson's rule. VH-IVUS analysis classified and color-coded tissue as green (fibrotic), yellow-green (fibrofatty), white (dense calcium), and red (necrotic core) [5;6]. VH-IVUS analyses are reported in absolute amounts and as percentages (relative amounts) of plaque area and volume. VH-IVUS derived thin-cap fibroatheroma (VH-TCFA) was defined as a necrotic core ≥10% of plaque area at the minimal luminal area site in ≥3 consecutive frames without evident overlying fibrous tissue in the presence of ≥40% plaque burden [6]. Because plaque rupture is 1 of the final fates of TCFA, and the identification of TCFA before the rupture of plaque occurs is clinically significant, plaque rupture has different characteristics from TCFA. Differentiation between TCFA and non-TCFA is also clinically important because plaque rupture occurs mainly in TCFA lesions rather than non- TCFA lesions. Therefore, according to gray-scale and VHIVUS findings, culprit and target lesions were classified into 3 groups: ruptured plaque, VH-TCFA, and non–VH-TCFA plaque. Unstable lesions contained either VH-TCFAs or ruptured plaques.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) for Windows,(SPSS Inc., Chicago, IL, USA) was used for all analyses. Continuous variables were presented as the mean value±1SD; comparisons were conducted by a Student's t-test or nonparametric Wilcoxon test if the normality assumption was violated. Discrete variables were presented as percentages and relative frequencies. Comparisons were conducted by chi-square statistics or Fisher's exact test as appropriate. Multivariate analysis was performed to determine the independent predictors of TCFA. All variables with $p<0.1$ in the univariate analysis were entered into the multivariate analysis. A p of <0.05 was considered statistically significant.

Results

The baseline characteristics are summarized in Table 1. Patients with ACS had higher age, total cholesterol, low-density lipoprotein cholesterol, cardiac specific troponin and NT-pro-BNP levels compared with those with SAP.

Table 1. Baseline clinical characteristics

	SAP (n=22)	**ACS (n=25)**	**p**
Age (years)	60.9±10.4	61.3±10.1	**0,048**
Male gender	12 (35,3)	22 (64,7)	0,512
Diabetes mellitus, n (%)	1(4,5)	2 (8)	**0,049**
Hypertension, n (%)	21 (95,5)	22 (88,0)	0,611
Family history of coronary artery disease,n (%)	11 (50,0)	16 (64,0)	0,342
Prior myocardial infarction n, (%)	1 (4,5)	2 (8,0)	0,6
Dyslipidemia,n (%)	19 (86,4)	23 (92,0)	**0,021**
Low physical activity, n (%)	13 (59,1)	17 (68,0)	0,141
Smoking, n (%)	4 (18,2)	9 (36,0)	0,621
Total cholesterol, mmol/l	4,85±1,3	5,02±1,7	**0,051**
Low-density lipoprotein cholesterol, mmol/l	2,84±1,0	3,08±1,2	**0,044**
High-density lipoprotein cholesterol, mmol/l	0,98±1,0	0,75±1,2	0,352
Cardiac specific troponin - I, µg/l	0,007	0,19±0,1	**0,001**
Glukose, mmol/l	5,64±0,9	5,58±0,5	0,624
Creatinin, µmol/l	83,05±13,8	88,32±16,8	0,430
NT-pro-BNP ng/mL)	192±428	248±502	**0,04**
Triglyceride	1,82±0,4	2,42±0,07	0,441

ACS: acute coronary syndrome, SAP: stable angina pectoris.

Gray-scale IVUS results are summarized in table 2. Luminal area and luminal volume were significantly smaller at the minimum lumen site in ACS group

compared with SAP group. The P&M area and P&M volume were significantly greater at the minimum lumen site in ACS group compared with SAP group. Also EEM volume were significantly greater at at the minimum lumen site in ACS group compared with SAP group.

Table 2. Gray-scale intravascular ultrasound findings between acute coronary syndromes and stable angina pectoris in minimum luminal area.

Variable	SAP (n=22)	ACS (n=25)	p
Planar analysis:			
EEM area (mm^2)	15,2±3.9	16.4±3.8	0.5
Luminal area (mm^2)	3.9±0.8	3.5±0.9	**0.02**
P&M area (mm^2)	10.8±4.1	14.3±4.1	**0.001**
Remodeling index	1,01 ±0.18	1,09±0.18	0.251
Volumetric analysis:			
EEM volume (mm^3)	144.9±38.7	165.4±40.8	**0.001**
Luminal volume (mm^3)	61.5±14.7	58.6±14,9	**0.05**
P&M volume (mm^3)	92.4±33.5	107.9±36.1	**0.002**

Virtual histology – intravascular ultrasound cross section result are summarized in Table 3. At minimum lumen site planar analysis shown that areas of necrotic core and dense calcium by percentages and absolute quantities are significantly greater in ACS group compared with SAP group. In contrast, absolute fibro-fatty area in ACS group were smaller compared with SAP group.

Table 3. Virtual histology intravascular ultrasound findings at minimum luminal area site between acute coronary syndromes and stable angina pectoris, planar analysis.

Variable	SAP (n=22)	ACS (n=25)	p
Absolute areas (mm^2)			
FT (green)	4,4±3.0	5.5±2.2	0.912
FF (yellow-green)	0.7±0.8	0.9±0.9	**0.08**
DC (white)	0.6±0.4	0.8 ±0.5	**0.001**
NC (red)	2.2 ±1.8	4.3±1.8	**0.025**
Percentages (%)			
FT	61±14	52±14	0.075
FF	11±5	9±5	0.06
DC	9±6	11±6	**0.002**

NC	19±12	28±12	**0.001**

FT – fibrotic; FF – fibro-fatty; DC – dense calcium; NC – necrotic core;

Virtual histology – intravascular ultrasound volumetric results are summarized in Figure 1 and Figure 2. At minimum lumen site necrotic core volume and dense calcium volume in absolute quantities were significantly greater in ACS group compared with SAP group. In contrast, necrotic core in percentages were significantly greater and fibrotic volume were significantly smaller in ACS group compared with SAP group.

Figure 1. Virtual histology intravascular ultrasound findings at minimum luminal area site between acute coronary syndromes and stable angina pectoris, volumetric analysis; absolute volumes (mm^3).

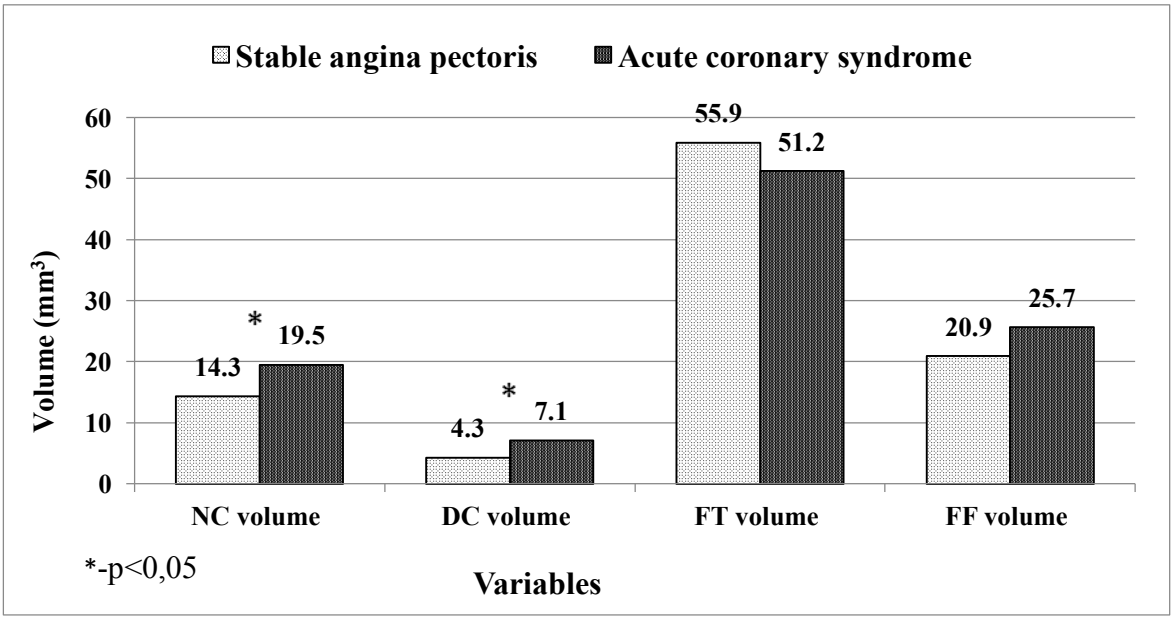


Figure 2. Virtual histology intravascular ultrasound findings at minimum luminal area site between acute coronary syndromes and stable angina pectoris, volumetric analysis; percentages (%).

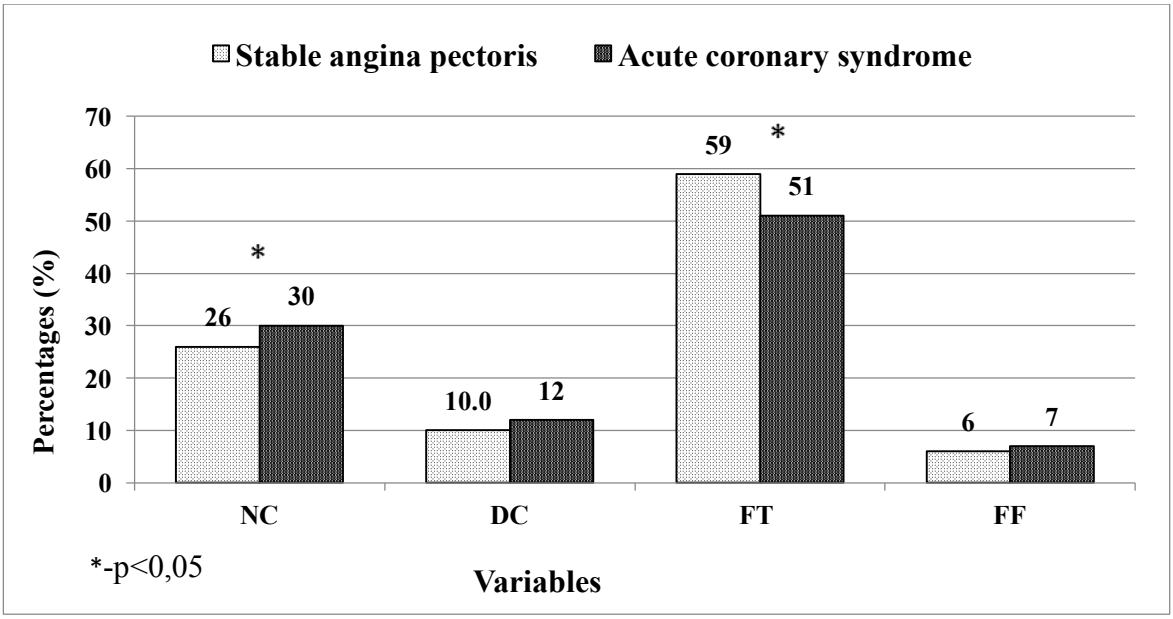
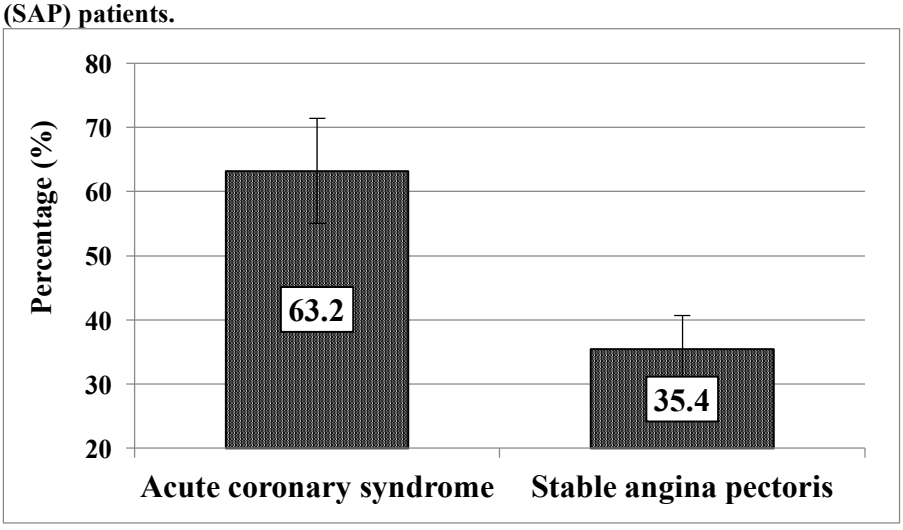


Figure 3. Presence of VH-TCFA in acute coronary syndrome (ACS) patients and stable angina pectoris (SAP) patients.



VH-TCFA were more frequently observed in ACS patients than in SAP patients (p = 0.006).

Table 4. Incidence of unstable and stable plaques in patients with ACS compared with those with SAP.

	SAP (n=22)	ACS (n=25)	p
Lesion, n (proc.)			
Unstable lesion	12 (35,3)	22 (64,7)	**0,020**
Stable lesion	10 (76,9)	3 (23,1)	**0,020**

Compared with patients with SAP, those with ACS had significantly more unstable lesions

Discussion

In the present study using VH-IVUS, ACS patients had a higher ratio of dense calcium and necrotic core components in culprit lesions in minimum lumen site compared with SA patients. VH-TCFA was more frequently observed in ACS patients. Recently, Rodriguez-Granillo et al.[11;12] have reported that ACS patients had a significantly higher prevalence of culprit lesions containing more necrotic core and TCFA compared with SA patients. A clinical study using optical coherence tomography has reported that the frequency of TCFA was 50%–70% in ACS patients and 20% in SAP patients [13]. Our results are in line with their results, showing the higher prevalence of vulnerable plaques in ACS patients.

Limitations

Several limitations should be noted. This is a single center study with a small number of patients, thus possibly posing a risk of patient selection bias. Our results of plaque components were not evaluated by histology or other diagnostic modalities such as optical coherence tomography and angioscopy.

Conclusions

The present study using VH-IVUS analysis have shown that ACS patients had higher prevalence of vulnerable plaque. These results have suggested that VH-IVUS has clinical implication for identifying vulnerable patients as well as vulnerable plaques. Further studies are needed to evaluate the impact of VH-TCFA on future clinical events.

All authors have no financial conflicts of interest to disclosure concerning the manuscript.

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