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Virtual Histology Study of Atherosclerotic Plaque Composition in Patients with Stable Angina and Acute Phase of Acute Coronary Syndromes without ST Segment Elevation

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SUMMARY

Introduction Rupture of vulnerable atherosclerotic plaques is the cause of most acute coronary syndromes (ACS). Postmortem studies which compared stable coronary lesions and atherosclerotic plaques in patients who have died because of ACS indicated high lipid-core content as one of the major determinants of plaque vulnerability.

Objective Our primary goal was to assess the potential relations of plaque composition determined by IVUS-VH (Intravascular Ultrasound – Virtual Histology) in patients with stable angina and subjects in acute phase of ACS without ST segment elevation.

Methods The study comprised of 40 patients who underwent preintervention IVUS examination. Tissue maps were reconstructed from radio frequency data using IVUS-VH software.

Results We analyzed 53 lesions in 40 patients. Stable angina was diagnosed in 24 patients (29 lesions), while acute phase of ACS without ST elevation was diagnosed in 16 patients (24 lesions). In the patients in acute phase of ACS without ST segment elevation IVUS-VH examination showed a significantly larger area of the necrotic core at the site of minimal lumen area and a larger mean of the necrotic core volume in the entire lesion comparing to stable angina subjects (1.84±0.90 mm^2 vs. 0.96±0.69 mm^2; $p<0.001$ and 20.94±15.79 mm^3 vs. 11.54±14.15 mm^3; $p<0.05$ respectively).

Conclusion IVUS-VH detected that the necrotic core was significantly larger in atherosclerotic lesions in patients in acute phase of ACS without ST elevation comparing to the stable angina subjects and that it could be considered as a marker of plaque vulnerability.

Keywords: atherosclerotic plaque; virtual histology; intravascular ultrasound; acute coronary syndrome; stable angina

INTRODUCTION

Postmortem studies which compared stable coronary lesions and atherosclerotic plaques in patients who have died because of acute coronary syndrome (ACS) indicate that a high lipid core content and the thickness of atheroma cap are the major determinants of plaque vulnerability [1-5].

Some studies have reported a high incidence of multiple plaque ruptures in ACS patients [6], while others have shown that plaque ruptures occur not only in ACS patients but also in patients with stable angina or asymptomatic ischemia [7]; thus, it is obvious that clinical presentation is related to atherosclerotic plaque stability which depends on its histological composition. Hence, accurate in vivo identification of plaque components may allow the detection of vulnerable atheroma before rupture and its consequences [8].

As tomographic imagining technique, intravascular ultrasound (IVUS) allows the visualization of atherosclerotic plaques in vivo as well as the determination of morphology of the whole vessel wall.

Virtual Histology (VH) is a diagnostic method which uses spectral analysis of IVUS radio frequency data to construct tissue maps that classify plaque into 4 major components. These different plaque components were assigned color codes. Calcified, fibrous, fibrolipid, and lipid core regions are labeled white, green, greenish yellow, and red, respectively. In addition to compositional data, IVUS-VH software provides geometric data of the vessel [8, 9].

OBJECTIVE

Our primary goal was to assess the potential relations of plaque composition determined by IVUS-VH in patients with stable angina and subjects in acute phase of ACS without ST segment elevation. Our secondary goal was to determine potential relation between the diagnosis of stable angina and acute phase of ACS and data from patients' histories of these two groups (age, sex, risk factors, previous and current diseases, laboratory parameters, medications).

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METHODS

The study population comprised of 40 consecutive patients prospectively enrolled into two groups. Chronic stable angina group (Group A) consisted of patients with typical exertional angina in functional Canadian Cardiovascular Class 2 or 3 and a positive result of ECG exercise tolerance test (ST depression >0.1 mV in at least 2 leads). None of the group A patients had diagnosed ACS nor experienced any spontaneous prolonged chest pain at rest within 12 months preceding examination. Group B consisted of patients in acute phase of ACS (unstable angina and non-ST elevation myocardial infarction) without ST segment elevation.

The study was approved by the local Ethics Committee and conformed to the ethical guidelines of the Declaration of Helsinki. Informed consent was obtained from all participants.

Interventional procedure and IVUS-VH imaging and image analysis

Forty patients underwent preintervention IVUS examination. Hemodynamically unstable patients were previously excluded.

Angiographic exclusion criteria were:

- severe peripheral vascular diseases that precluded the use of a standard 8 F arterial sheath;
- other concomitant diseases or medical conditions that could impact patient/procedural outcomes such as history of bleeding diathesis, stroke or transient ischemic neurological attacks within the past year or hypersensitivity to heparin, ticlopidine or X-ray contrast media;
- a positive pregnancy test;
- significant left main stenosis (>50%);
- severe vessel stenosis that precluded IVUS examination;
- high vessel tortuosity.

IVUS-VH data were acquired using a commercially available 20-Mhz IVUS catheter Eagle Eye Gold, Volcano Corp. All measurements were performed by two experienced IVUS readers, blinded to the clinical data, with the use of standard software (Virtual Histology – Volcano Corp.). Disagreement was solved by consensus between the observers.

External elastic membrane, lumen and plaque plus media cross-sectional area were measured. Proximal and distal references were defined as single cross-section images with the largest lumen and smallest plaque burden within 5 mm proximally and distally, but before any large side branch [1, 10].

All plaques were excluded from this study if they met the following IVUS criteria:

- low quality images of the lesion as well as of the proximal and distal reference segments which precluded precise and accurate interpretation;
- presence of side branches inside the lesion and between the proximal and distal reference segment;
- extensive calcification that limits quantitative assessment of the vessel area – arc of calcium >180° (the total arc of calcium was measured with a protractor centered on the lumen);
- culprit lesions patients in acute phase of ACS and all lesions requiring intervention;
- atherosclerotic lesions with either angiographic or IVUS evidence of thrombus.

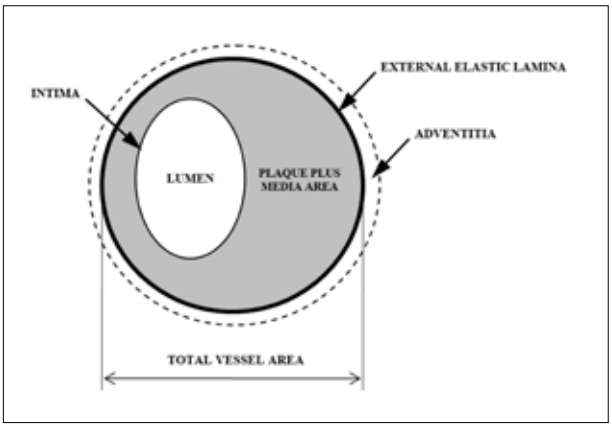


Figure 1. Scheme of basic IVUS-VH measurements

Minimum lumen cross-sectional area (MLA) site was also identified. If there were several images with equal lumen size, the one with the largest external elastic membrane (EEM) cross-sectional area was selected. Lesion length was defined as a distance between the proximal and the distal reference sites [10]. The vessel area was defined as a cross sectional area within the border between the hypoechoic media and the echoreflective adventitia. It was measured by tracing the leading edge of the media-adventitia boundary and represented a reproducible measure of the total vessel area [11]. The lumen area was determined by tracing the boundary between the lumen and the intimal leading edge. The contours of the external elastic membrane and the lumen-intima interface enclosed an area that was defined as the coronary plaque plus media area [11] (Figure 1).

IVUS-VH plaque morphology was characterized by the analysis of mean percentage area of tissues in the MLA site, as well as the mean percentage volume of tissues in the entire lesion. Geometric and compositional data were obtained for both MLA and the entire lesion. The calculations and IVUS-VH quantitative analysis were performed according to the criteria of the American College of Cardiology clinical expert consensus document on IVUS [12].

Statistical analysis was performed with t-test, ANOVA and Pearson correlation for continuous variables, chi-square test and Spearman correlation for nominal data. Because of the relatively small sample size results of t-test and ANOVA were confirmed with the non-parametric Kruskal-Wallis test. Commercially available software – SPSS statistical package (version 11.5; SPSS Inc., Chicago, Illinois, USA) was used.

RESULTS

We analyzed 53 lesions in 40 patients of average age 62.93±9.91 years, ranging from 45 to 85 years (13 women

of average age 68.05±8.90 and 27 men of average age 60.07±9.21).

Basic demography and laboratory characteristics of the studied groups are summarized in Table 1. There were no differences in demographics and the occurrence of atherosclerosis risk factors between the groups. We also did not observe statistically significant differences in laboratory means except for fibrinogen which was statistically higher ($p<0.05$) in Group B patients. Medication was statistically better in Group A patients for all the drugs except for clopidogrel which was on the border of statistical significance ($p=0.051$). Statin therapy was particularly better in Group A patients ($p=0.001$).

Quantitative coronary-angiographic analysis (QCA) and results of IVUS-VH are summarized in Table 2. No statistically significant differences in the location and angiographic features of lesions were observed between the study groups.

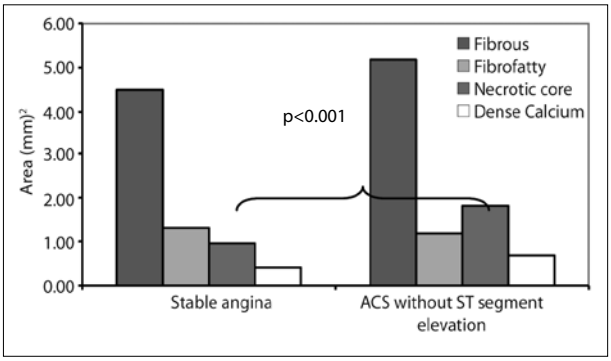
Using IVUS-VH examination we did not find statistically significant differences in atheroma morphology and geometrical parameters measured in MLA CSA. However, plaque structure in MLA CSA differed between the groups. In patients in acute phase ACS without ST segment elevation we discovered significantly larger mean and higher percent of necrotic core area than in stable angina subjects (1.84±0.90 mm^2 vs. 0.96±0.69 mm^2; $p<0.001$ and 22.28±8.90% vs. 15.00±10.19%; $p<0.01$ respectively) (Graphs 1 and 2).

By using IVUS-VH volumetric analysis of lesions we did not find statistically significant differences in geometrical parameters between the two study groups. In patients in acute phase of ACS without ST segment elevation we

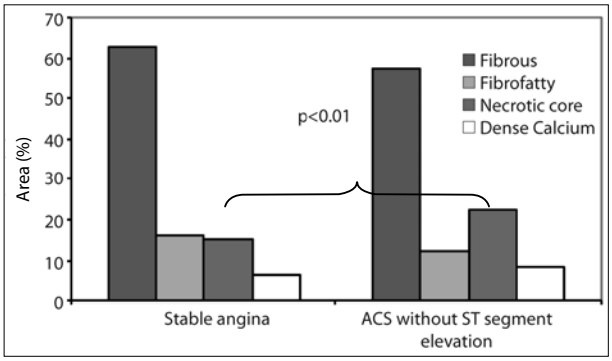
Table 1. Baseline clinical and laboratory characteristics of studied groups (n=40)

Characteristics		Stable angina	ACS without ST segment elevation – acute phase	Statistical significance
Number of patients		24	16	/
Age (years±SD)		61.21±8.64	65.50±11.37	0.183
Male sex		16 (66.67%)	11 (68.75%)	0.890
Risk factors	Hypertension	19 (79.16%)	13 (81.25%)	0.872
	Diabetes mellitus	6 (25.00%)	2 (12.5%)	0.333
	Hypercholesterolemia	20 (83.33%)	12 (75.00%)	0.339
	Smoking	8 (33.33%)	7 (43.75%)	0.505
History	History of stroke	4 (16.67%)	1 (6.25%)	0.329
	Previous PCI	7 (29.16%)	3 (18.75%)	0.456
	Previous AMI	3 (12.50%)	4 (25.00%)	0.308
	Chronic renal failure	4 (16.67%)	0 (0.00%)	0.085
	COPD	0 (0.00%)	0 (0.00%)	/
Laboratory analysis	White blood count	7.96±2.05	8.50±2.49	0.470
	Fibrinogen	436.81±97.51	523.25±119.01	0.031*
	Glucose	104.91±20.14	94.31±13.50	0.076
Lipid profiles	Total cholesterol	173.62±43.23	198.77±45.81	0.117
	Triglycerides	151.62±78.07	156.54±84.38	0.864
	LDL cholesterol	85.88±37.21	93.14±10.38	0.621
	HDL cholesterol	53.86±13.59	45.30±13.70	0.113
Medication	Acetylsalicylic acid (aspirin)	23 (95.83%)	9 (56.25%)	0.002**
	Clopidogrel	5 (20.83%)	0 (0.00%)	0.051
	Beta-blocker (labetalol)	21 (87.50%)	8 (50.00%)	0.009**
	Statins	22 (91.67%)	7 (43.75%)	0.001***
	ACE inhibitors	18 (75.00%)	4 (25.00%)	0.002**

* p<0.05; ** p<0.01; *** p≤0.001
COPD – chronic obstructive pulmonary disease



Graph 1. Average content of specific plaque component in MLA CSA site in patients with stable angina and ACS without ST segment elevation

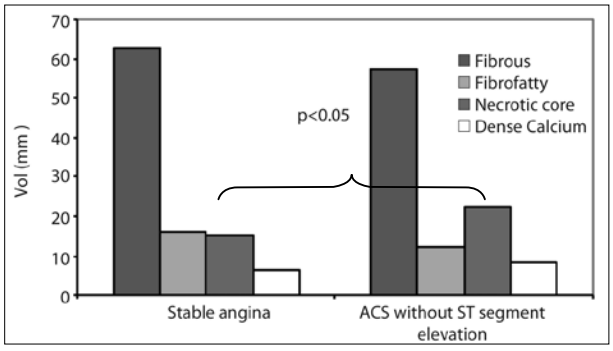


Graph 2. Percentage of specific plaque component in MLA CSA site in patients with stable angina and ACS without ST segment elevation

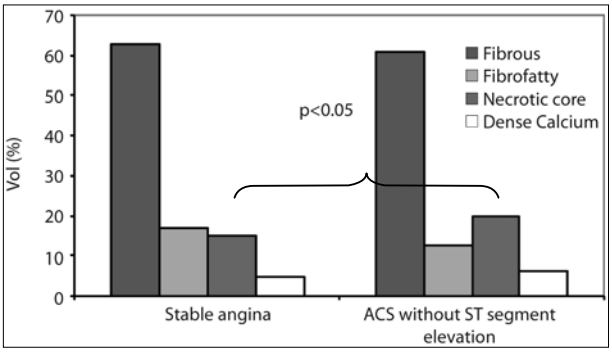
Table 2. QCA and IVUS-VH analysis

Characteristics			Stable angina	ACS without ST segment elevation – acute phase	Statistical significance
Number of examined lesions			29	24	
Vessel		Right coronary artery	8 (27.58%)	5 (20.84%)	0.841
		Left main coronary artery	2 (6.90%)	2 (8.33%)	
		Left anterior descending	18 (62.07%)	15 (62.50%)	
		Left circumflex	1 (3.45%)	2 (8.33%)	
Angiographic type of lesion		<40% (insignificant) and 40-70% (borderline)	28 (96.55%)	21 (87.50%)	0.214
		>70% (significant)	1 (3.45%)	3 (12.50%)	
Minimal Lumen Area analysis	Atheroma morphology by IVUS	Hypoechoic (soft)	10 (34.48%)	9 (37.50%)	0.983
		Mixed	7 (24.14%)	5 (20.83%)	
		Hyperechoic (fibrous)	3 (10.35%)	3 (12.50%)	
		Calcified	9 (31.03%)	7 (29.17%)	
	Geometrical parameters	EEM CSA area (mm^2)	15.79±5.39	17.25±4.73	0.311
		Lumen area (mm^2)	5.23±2.65	4.98±1.64	0.691
		Plaque area (mm^2)	7.19±4.01	8.87±4.02	0.135
		Plaque plus media CSA (mm^2)	10.56±4.40	12.36±4.36	0.143
		Plaque burden	0.66±0.11	0.67±0.16	0.883
		Remodeling index	1.05±0.26	1.05±0.21	0.915
		Positive remodeling	14	11	0.903
	Compositional parameters	Fibrous tissue area (mm^2)	4.50±2.79	5.18±2.78	0.379
		Fibrofatty tissue area (mm^2)	1.35±1.47	1.20±1.28	0.700
		Necrotic core area (mm^2)	0.96±0.69	1.84±0.90	0.0002***
		Calcified area (mm^2)	0.39±0.48	0.66±0.71	0.097
		Fibrous tissue area (%)	62.7±13.16	57.20±9.14	0.090
		Fibrofatty tissue area (%)	15.87±12.61	12.10±9.05	0.226
		Necrotic core area (%)	15.00±10.19	22.28±8.90	0.009**
		Calcified area (%)	6.42±7.61	8.42±6.64	0.318
Volumetric analysis of lesion	Geometrical parameters	Lesion length	13.99±4.31	16.37±5.05	0.093
		Vessel volume (mm^3)	227.18±161.05	286.38±154.25	0.189
		Lumen volume (mm^3)	98.55±60.93	121.29±70.17	0.221
		Plaque plus media volume (mm^3)	128.63±107.08	165.09±90.66	0.201
		Plaque volume in the whole lesion (mm^3)	80.33±82.84	106.82±71.01	0.232
		Plaque burden in the whole lesion	0.54±0.08	0.57±0.08	0.189
	Compositional parameters	Fibrous tissue volume (mm^3)	51.11±55.29	65.62±44.63	0.315
		Fibrofatty tissue volume (mm^3)	13.92±13.57	13.49±12.26	0.908
		Necrotic core volume (mm^3)	11.54±14.15	20.94±15.79	0.030*
		Calcified volume (mm^3)	3.76±4.34	6.77±8.85	0.120
		Fibrous tissue volume (%)	62.74±6.59	60.87±7.77	0.357
		Fibrofatty tissue volume (%)	17.16±10.11	12.61±8.03	0.086
		Necrotic core volume (%)	14.99±7.90	20.02±7.52	0.025*
		Calcified volume (%)	5.12±3.66	6.49±4.88	0.255

* p<0.05; ** p<0.01; *** p<0.001



Graph 3. Average volume of specific plaque component in the whole lesion in patients with stable angina and ACS without ST segment elevation



Graph 4. Percentage volume of specific plaque component in the whole lesion in patients with stable angina and ACS without ST segment elevation

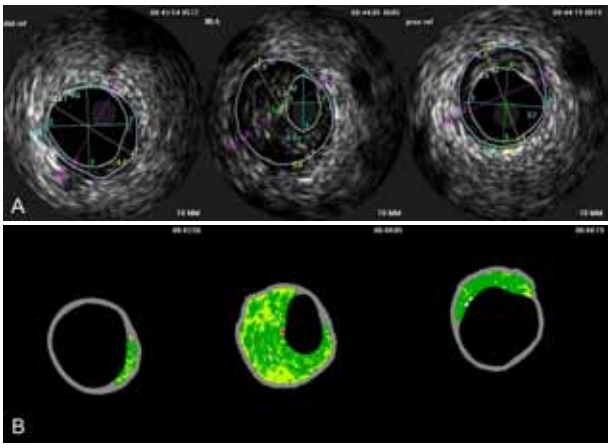


Figure 2. A 68-year-old male patient with diagnosed stable angina

A. IVUS of lesion (from left to right) – distal reference (dist ref), MLA, proximal reference (prox ref). Lumen edge and media-adventitia border are marked. In MLA site significant stenosis (<4 mm^2).
B. VH of lesion (from left to right) – distal reference, MLA, proximal reference (fibrous – green; fibrofatty – greenish yellow; necrotic – red; dense calcium – white). In MLA site, a large plaque predominantly composed of fibrous tissue.

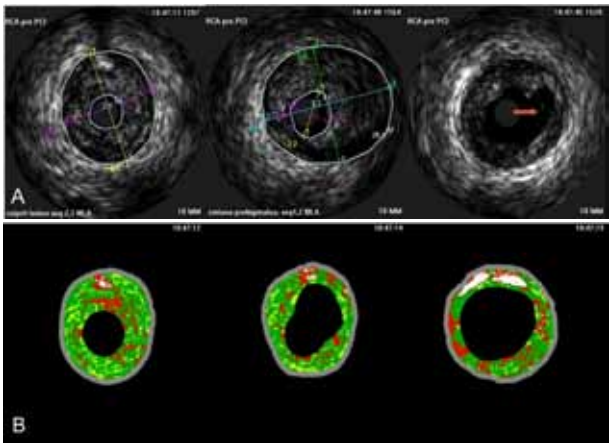


Figure 3. A 63-year-old male patient in acute phase ACS

A. IVUS of lesions (from left to right) – MLA of distal, middle and proximal lesion where plaque cavity is visible (arrow), thus it is not included in our study. Lumen edge and media-adventitia border are marked. Significant stenosis (<4 mm^2) in MLA sites of all lesions.
B. VH of distal lesion (from left to right) – MLA site, inserted CSA, proximal reference (fibrous – green; fibrofatty – greenish yellow; necrotic – red; dense calcium – white). Diffuse distribution of necrotic core component is evident.

discovered significantly larger mean and percentage of necrotic core volume in the whole lesion than in stable angina subjects (20.94±15.79 mm^3 vs. 11.54±14.15 mm^3; p<0.05 and 20.02±7.52% vs. 14.99±7.90%; p<0.05, respectively) (Graphs 3 and 4).

Examples of both group of patients with angiographic and IVUS images and VH reconstructions are shown in Figures 2 and 3.

DISCUSSION

The number of patients interviewed during our research is relatively small. However, the results obtained from the demographic data of patients are expected and concordant with the literature and reference textbooks [13]. As a whole, medical therapy was statistically significantly less intense in patients with ACS, and this is certainly one of the reasons which led to ACS episodes. Apart from the tendency that the total cholesterol and LDL levels were higher in ACS patients, as well as the fact that the HDL level in these patients was lower compared to patients with a stable angina, significant statistical differences were not determined in our study.

It was noted that statin therapy was significantly less administered in patients who developed ACS. This observation corresponds with the results of recent studies which have shown that aggressive lipid reduction therapy (high dosages of atorvastatin or rosuvastatin) induces a regression of plaques and that pioglitazone has favorable effects on coronary atherosclerosis [14, 15, 16].

Almost 2/3 of the total number was located in the left anterior descending artery (LAD) which, in addition to the number of plaques we tested in other coronary arteries, corresponded with the frequency of certain coronary arteries involvement in the development of ACS [14]. The literature contains additional descriptions of lesions in LAD with a worse phenotype compared to that of LCx and RCA. The cited results may present us with an explanation of a high frequency of restenosis encountered in LAD, especially its proximal segments, compared to LCx and RCA [17, 18, 19].

The main result of this study is that there is a significant difference in the structure of the atherosclerotic plaque in patients with an acute phase of ACS, without the elevation of ST segments, compared to the patients with a stable angina. The first exhibits a significantly higher portion of the necrotic core, which correlates to the subsequent research. [9,20] A significantly higher portion of the necrotic core in the lesions not directly accountable for the occurrence of ACS supports the fact that ACS is a multifocal process [9].

By comparing stable and vulnerable plaques, Sano et al. [2] have established a greater percentage of the lipid-necrotic component in vulnerable plaques. Previous pathological studies of vulnerable plaques after ACS showed that the share of the necrotic core represents a marker of plaque vulnerability [2].

Kubo et al. [21] used serial IVUS-RF imaging to investigate the natural evolution of non-obstructive plaques and showed that in contrast to fibrous and calcified plaques, which remained unchanged, the intimal thickening and thick cap fibroatheromas may evolve to thin cap fibroatheromas at 12 months follow-up.

Furthermore, in tumors researches, it is well-known that subpopulations of macrophages present in atherosclerotic plaques promote angiogenesis [22]. However, these newly formed blood vessels frequently lack the appropriate structural integrity and may cause bleeding inside the plaque, which leads to lesion growth and jeopardizes the stability of the plaque [23].

Of all parameters pertaining to the vulnerability of the atherosclerotic plaque, the most significant are the presence of the necrotic core and a thin fibrous cap which sep-

arates it from the lumen [2, 20]. Plaque ruptures are most frequently formed from the previously angiographically insignificant lesions [24]. Out of all of examined lesions, in our study only four were angiographically diagnosed as significant (>70% stenosis). Therefore, an IVUS-VH analysis may be used for the purpose of revealing vulnerable lesions [9, 25]. The fact that IVUS-VH has a reduced axial resolution (range: 100-200μm) limits its ability to identify some of these characteristics (e.g. plaque disruption, macrophage infiltration) and measure the thickness of the fibrous cap [26].

These limitations of IVUS-VH may be overcome by the use of optical coherence tomography (OCT). The high resolution of OCT enables the identification of lipid pools and, unlike IVUS-VH, detection of the internal and external elastic lamina [27, 28]. OCT further enables a precise quantification (measurement) of fibrous cap thickness, enables a reliable evaluation of the cap disruption and erosion and can clearly visualize the presence and type of the thrombus [26, 29]. The limitation of this model is the reduced axial penetration which may aggravate the estimate of lipid pool dimensions and the identification of positive remodeling. For overcoming these limitations, it has been suggested that a combined use of IVUS-VH and OCT be used [30].

Finally, an aggressive lipid defense therapy should also be administered for the purpose of stabilizing other plaques, independent of angiographically significant stenoses. Possible new episodes of ACS may be prevented in this manner [31].

Study limitations

The relatively small population included may limit this study. IVUS analysis was not performed in all segments of all coronary arteries in all patients. Small ruptures, ruptures masked by overlying thrombus and the lack of assessment of minor branches may lead to an underestimation of the prevalence of vulnerable plaques [18]. Unfortunately, the used version of IVUS-VH software is unable to differentiate thrombus [1]. The applied IVUS-VH analysis software does not have a tool to assess quantitatively the amount of contact of necrotic core with the lumen [32].

Although nitroglycerin was administered before IVUS imaging, occurrence of vasospasm may not be excluded completely. Because of a relatively small number of patients we included in our study both ostial and bifurcation lesions for which some authors suggest not to be examined [1]. Finally, prioritizing patients' safety, the decision to perform preintervention IVUS was at the discretion of the operator, potentially inducing a selection bias [10, 18].

CONCLUSION

In the present study, the IVUS-VH detected necrotic core was significantly larger in atherosclerotic lesions in patients in acute phase of ACS without ST elevation compared to the stable angina subjects and it could be considered a marker of plaque vulnerability.

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Виртуелнохистолошка студија структуре атеросклеротског плака код болесника са стабилном ангином пекторис и акутном фазом акутних коронарних синдрома без елевације *ST*-сегмента

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КРАТАК САДРЖАЈ

Увод Руптура атеросклеротског плака је најчешћи узрок већине акутних коронарних синдрома (АКС). Постмортална испитивања коронарних артерија у којима су упоређивани стабилни атеросклеротски и плакови болесника који су умрли од последица АКС показују да је постојање липидно-некротичног језгра у плаку један од главних параметара његове вулнерабилности.

Циљ рада Примарни циљ студије био је усмерен на ИВУЗ-ВХ (интраваскуларни ултразвук – виртуелна хистологија) анализу структуре атеросклеротског плака код болесника са стабилном ангином пекторис и болесника у акутној фази АКС без елевације *ST*-сегмента.

Методе рада Истраживање је обухватило 40 болесника подвргнутих преинтервенционом ИВУЗ испитивању. Атеросклеротски плакови су реконструисани спектралном анализом радио сигнала употребом ИВУЗ-ВХ програмског софтвера.

Резултати Анализиране су 53 лезије код 40 болесника. Стабилна ангина је дијагностикована код 24 болесника (29 лезија), док је 16 болесника (24 лезије) било у акутној фази АКС без елевације *ST*-сегмента. Код болесника у акутној фази АКС без елевације *ST*-сегмента ИВУЗ-ВХ анализом је установљен статистички значајно већи удео некротичног језгра на попречном пресеку с најмањом површином лумена и запремине некротичног језгра у целој лезији (1,84±0,90 mm^2 према 0,96±0,69 mm^2; $p<0,001$ и 20,94±15,79 mm^3 према 11,54±14,15 mm^3; $p<0,05$).

Закључак Студија је показала да је удео некротичног језгра у атеросклеротском плаку статистички значајно већи код болесника у акутној фази АКС у односу на болеснике са стабилном ангином, као и да се тај удео може сматрати параметром вулнерабилности лезије. ИВУЗ-ВХ се као дијагностичка метода може употребити у откривању ових лезија.

Кључне речи: атеросклеротски плак; виртуелна хистологија; интраваскуларни ултразвук; акутни коронарни синдром; стабилна ангина

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