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Tissue Characterization of Coronary Plaques Using Intravascular Ultrasound/Virtual Histology

Jang-Ho Bae, MD, PhD[1], Charanjit S Rihal, MD, PhD[2] and Amir Lerman, MD, PhD[2]

[1]*Department of Cardiology, Heart Center, College of Medidine, Konyang University, Daejeon, Korea*
[2]*Cardiology, Mayo Clinic, Rochester, MN, USA*

ABSTRACT

Most studies related with plaque histopathology and/or morphology are based on the gray scale intravascular ultrasound (IVUS) and autopsy findings, although IVUS is limited for differentiating echolucent areas, and tissue shrinkage almost always occur during tissue fixation. In addition, autopsy studies can not establish the causal relationship between the autopsy findings and the clinical findings. Spectral analysis of the IVUS radiofrequency data may be a new and useful tool because it allows detailed assessment of plaque composition in vivo, with a high predictive accuracy of 87.1% to 96.5% in fibrous, fibrofatty, calcified and necrotic core regions with performing tissue mapping and geometric assessment like that for classic gray scale IVUS. This new imaging technique offers clear benefits compared with the results of classic IVUS and autopsy studies. This review will briefly discuss the methodology of spectral analysis of the IVUS radiofrequency data, the recent clinical studies that have used this technique and the future perspectives. **(Korean Circulation J 2006;36:553-558)**

KEY WORDS : Intravascular ultrasonography ; Diagnostic imaging ; Coronary arteriosclerosis ; Plaque.

Introduction

The ability to visualize and quantify the different components of atherosclerosis provides important information not only on the mechanism of coronary artery disease (CAD), but also on potential future therapeutic interventions to alter the disease process. Histological examination has been the only way to determine the exact pathology of coronary atherosclerotic plaques; however, it can not be done in vivo in humans, and some degree (15-80%) of tissue shrinkage occurs during tissue fixation.[1)] Postmortem contraction of arteries is an additional confounding factor.[2)] Recently, spectral analysis of the intravascular ultrasound (IVUS) radiofrequency data (IVUS-Virtual Histology [IVUS-VH]) has become a new and useful tool because it allows detailed assessment of plaque composition in vivo, with high predictive accuracy (89.5% to 92.8%) in the fibrous, fibrofatty, calcified and necrotic core regions via tissue mapping.[3)4)] The benefits of this new method over classic IVUS include 1) accurate differentiation of focal areas of microcalcification and necrosis, and also the calcified and dense fibrous regions and 2) differentiation of adjacent small areas that show heterogenous composition from the large homogenous regions such as a predominantly calcified area, and these small areas include plaques with a necrotic core and the adjacent areas with microcalcifications and lipids.[4)]

This review briefly considers the methodology and clinical significance of IVUS-VH findings and their potential clinical implications.

Correspondence : Jang-Ho Bae, MD, PhD, Department of Cardiology, Heart Center, College of Medidine, Konyang University, 685 Gasoowon-Dong, Seo-Gu, Daejeon 302-718, Korea
Tel: 82-42-600-9400, Fax: 82-42-600-9399
E-mail: janghobae@yahoo.co.kr

Methodological Overview of IVUS-VH

Intravascular ultrasound virtual histology examination

The methods of performing IVUS examinations are same as have been previously reported.[4)5)] An IVUS VH examination is performed with a dedicated IVUS VH console (Volcano Therapeutics, Rancho Cordova, California) after intracoronary administration of 100 to 200 μg nitroglycerin. A commercially available 20-MHz, 2.9F monorail, electronic Eagle Eye Gold IVUS catheter (Volcano Therapeutics, Rancho Cordova, California) is advanced distal to the coronary artery lesion and then automatic pullback is done at 0.5 mm/s. During pullback, the gray scale IVUS is recorded, as well as raw radiofrequency data, which is captured at the top of the R-wave for reconstruction of the color-coded map by a VH data recorder. The IVUS VH im-

age is recorded on a DVD-ROM for later offline analysis, and real-time analysis of the IVUS-VH image is also possible in regions of interest. The IVUS VH uses spectral analysis of the IVUS radiofrequency data to construct a tissue map.[4]

Spectral analysis of intravascular ultrasound radiofrequency data

IVUS-VH uses 8 spectral parameters (maximum power, corresponding frequency, minimum power, corresponding power, slope, y-intercept, mid-band fit and integrated backscatter) with autoregressive classification schemes to identify each plaques' components.[4] These analyses were originally done in an in vitro left anterior descending coronary artery with using customized software (IVUSLab; Volcano Therapeutics, Rancho Cordova, California). Later, the accuracy was also verified in other in vivo coronary arteries, as well as in the left anterior descending coronary artery, by comparing the in vivo IVUS-VH findings with the in vitro histopathology of coronary atherosclerotic plaques that were obtained by directional coronary atherectomy. This IVUS-VH technique showed a high predictive accuracy of 87.1% to 96.5% in fibrous, fibrofatty, calcified and necrotic core regions.[6]

Regions of interest should first be defined for spectral analysis of the IVUS radiofrequency data. Both the lumen and the media-adventitia interface are then automatically detected. The border detection should be manually corrected again in all the frames after automatic border detection due to the poor automatic border detection. For each frame, the histologic findings are expressed in colors (green for fibrous, greenish-yellow for fibrofatty core areas, white for densely calcified core areas and red for necrotic core areas) (Fig. 1). In addition, the volume and percentage of each tissue component of a plaque are expressed in the segmental analysis. The predictive accuracy of this method with tissue mapping has been validated.[4)6)]

Coronary Artery Remodeling and Plaque Characterization

Positive (expansive) remodeling is known to be associated with unstable symptoms, lipid-rich plaque and ruptured plaques in the culprit lesions of acute coronary syndrome, and all of these findings are associated with vulnerable plaque.[7-9] IVUS-VH disclosed that positive remodeling was correlated with lipid cores in 41 vessels with non-significant stenosis (<50% diameter stenosis by angiography), and it was correlated with fibrofatty plaque areas in 77 lesions that had moderate or severe coronary stenosis, whereas negative remodeling was associated with fibrous plaque.[10)11)] Those results are consistent in terms of the association between positive remodeling and lipid-rich plaque, although there were some differences of results (lipid core vs. fabrofatty plaque) and the studies' populations. Those studies are consistent with the previous pathological findings in a postmortem study.[12)] However, that postmortem study did not imply a natural history of high-risk plaques, whereas the in vivo IVUS-VH studies may provide more information about the prognosis and natural history of such lesions.

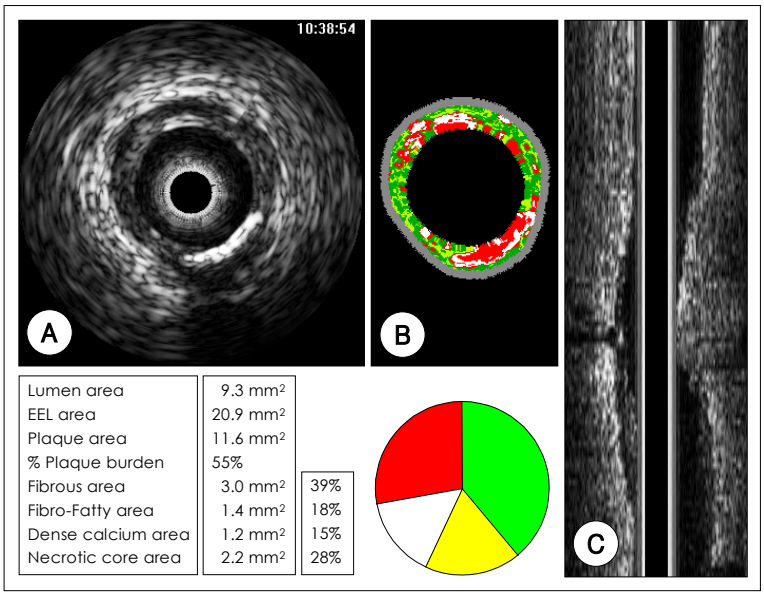

Fig. 1. One example of spectral analysis of intravascular ultrasound (IVUS) radiofrequency data of coronary atherosclerotic plaques, which is seen on the monitor screen (A: Gray scale IVUS image, B: Tissue map of IVUS virtual histology, C: Longitudinal view). The area and percentages of each coronary atherosclerotic plaques component are shown with different colors.

Lesion Classification

The lesion classification system proposed by the American Heart Association (Table 1) is difficult to use because its long list of roman numerals is difficult to remember and its orderly linear pattern of lesion progression tends to be ambiguous.[13][14] In addition, its major limitation is the lack of direct, experimental testing in prospective human or animal models.[15] Thrombotic occlusion in the absence of rupture also raises a critical question about the central role of rupture in the current AHA classification. Thus, a modified AHA classification (Table 2) based on morphological description was proposed by Virmani et al.[15] This modified classification focuses on the AHA classification of type IV, V and VI lesions. There are 7 categories that are classified according to the accretion of lipid in relationship to formation of the fibrous cap, the changes over time in the lipid to form a necrotic core, thickening or thinning of the fibrous cap, and thrombosis.

This modified AHA classification of lesion may overcome several of the limitations of the current AHA classification. However, its simplified classification relies on descriptive morphology from autopsy. This is the inherent pitfall in the analysis of human arteries. The current clinical imaging methods to visualize the vessel

Table 1. Current AHA classification [13][14]

Terms for atherosclerotic lesions in histological classification		Other terms for the same lesions often based on appearance to the unaided eye	
Type I lesion	Initial lesion	Fatty dot or streak	Early lesion
Type II lesion			
IIa	Progression-prone type II lesion		
IIb	Progression-resistant type II lesion		
Type III lesion	Intermediate lesion (preatheroma)		
Type IV lesion	Atheroma	Atheromatous plaque, fibrolipidic plaque, fibrous plaque	Advanced lesions, raised lesions
Va	Fibroatheroma (type V lesion)		
Vb	Calcific lesion (type VII lesion)	Calcified plaque	
Vc	Fibrotic lesion (type VIII lesion)	Fibrous plaque	
Type VI lesion	Lesion with surface defect and/or hematoma/hemorrhage and/or thrombotic deposit	Complicated lesion, complicated plaque	

Table 2. Modified AHA classification based on morphological description[15]

	Description	Thrombosis
Nonatherosclerotic intimal lesions		
Intimal thickening	The normal accumulation of smooth muscle cells(SMCs) in the intima in the absence of lipid or macrophage foam cells	Absent
Intimal xanthoma, or fatty streak	Luminal accumulation of foam cells without a necrotic core or fibrous cap. Based on animal and human data, such lesions usually regress.	Absent
Progressive atherosclerotic lesions		
Pathological intimal thickening	SMCs in a proteoglycan-rich matrix with areas of extracellular lipid accumulation without necrosis	Absent
Erosion	Luminal thrombosis; plaque same as above	Thrombus mostly mural and infrequently occlusive
Fibrous cap atheroma	Well-formed necrotic core with an overlying fibrous cap	Absent
Erosion	Luminal thrombosis; plaque same as above; no accumulation of thrombosis with necrotic core	Thrombus mostly mural and infrequently occlusive
Thin fibrous cap atheroma	A thin fibrous cap infiltrated by macrophages and lymphocytes with rare SMCs and an underlying necrotic core	Absent; may contain intraplaque hemorrhage/fibrin
Plaque rupture	Fibroatheroma with cap disruption; luminal thrombus communicates with the underlying necrotic core	Thrombus usually occlusive
Calcified nodule	Eruptive nodular calcification with underlying fibrocalcific plaque	Thrombus usually nonocclusive
Fibrocalcific plaque	Collagen-rich plaque with significant stenosis usually contains large areas of clacification with few inflammatory cells; a necrotic core may be present	Absent

wall and to classify lesion are limited. IVUS-VH is a promising imaging tool for evaluating in vivo human coronary arteries. Lesion classification using IVUS-VH based on the modified AHA classification has also been suggested (Table 3) (Fig. 2).[10)16)]

One limitation of this type of lesion classification is related with image resolution. The axial resolution of IVUS-VH is between 100 to 150 μm; thus, it was assumed that the absence of visible fibrous tissue overlying a necrotic core suggested a cap thickness of below 100 to 150 μm and the absence of such tissue was used to define a thin fibrous cap.[16)17)] The threshold to define a thin cap was 65 to 200 μm in several studies.[18)19)]

Plaque Composition and Clinical Presentation

The underlying mechanism of acute coronary syndrome such as myocardial infarction and unstable angina is generally rupture of the plaque surface and subsequent luminal thrombus formation, and the risk of plaque rupture depends on plaque composition rather than on plaque size.[20)] A rupture-prone plaque is a vulnerable plaque, and this is characterized according to histopathologic data as a soft lipid-rich core, a thin cap and inflammation.[20)] However, these findings were mostly based on the postmortem study, which has inherent limitations related with tissue shrinkage. These concepts were recently disclosed, to some degree, by an in vivo study using IVUS-VH.[21)] The authors of that revealed that the percentage of lipid cores was significantly larger (12.26±7.0% vs. 7.40±5.5%, respectively, p=.006) in patients with acute coronary syndrome, whereas those cores with a high fibrotic content were larger (63.96±9.1% vs. 70.97±9.3%, p=.007) in the patients with stable angina. These results are compatible to the previously reported results,[20)] although the authors of that study examined the nonculprit lesions for evaluating the composition of plaques. Fig. 3 also shows the high content of necrotic cores in the culprit lesions in male patients who presented with ST elevation myocardial infarction in our hospital.

A necrotic core in contact with the lumen is associated with high strain, according to a study using IVUS-VH and IVUS palpography; this technique allows assessment of local mechanical properties such as a high strain.[22)] This study suggests that the tearing site

Table 3. Lesion classification by IVUS-VH[10)16)]

	Characteristics	% of lipid core
Pathological intimal thickening	Mainly fibrotic or fibrolipidic tissue	0-≤3%
Fibrocalcific lesion	Mainly fibrotic plaques with some calcium	3-10%
Fibrous cap atheroma	Lipid-rich plaques with overlying fibrous tissue	>10%
Thin-cap atheroma	Lipid-rich plaques without overlying fibrous tissue Percent atheroma volume ≥40%	>10%

IVUS-VH: intravascular ultrasound-virtual histology

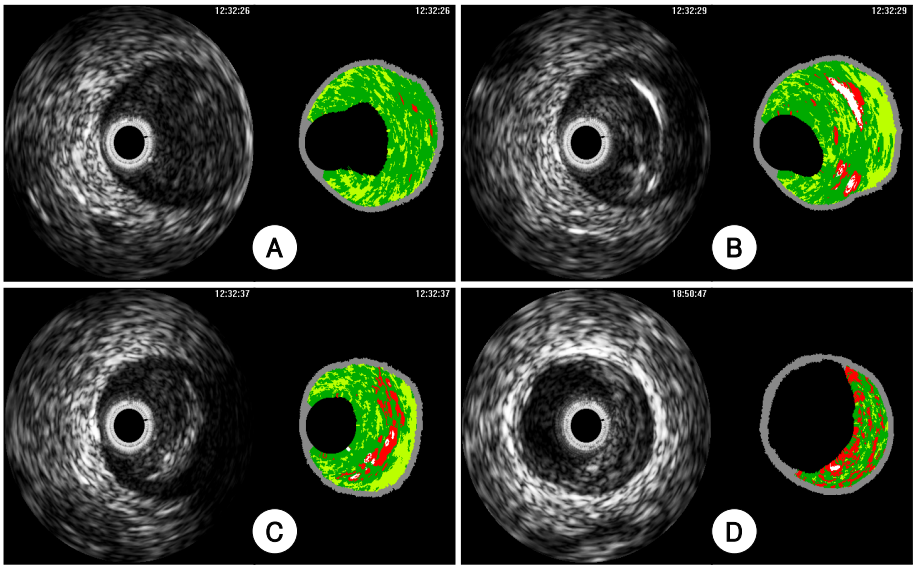

Fig. 2. Typical examples of lesion classification by intravascular ultrasound-virtual histology. A: pathological intimal thickening (fibrous area=76%, fibrofatty area=23%, dense calcium area=0%, and necrotic core area=1%), B: fibrocalcific lesion (fibrous area=62%, fibrofatty area=28%, dense calcium area=4%, and necrotic core area=7%), C: fibrous cap atheroma (fibrous area=59%, fibrofatty area=27%, dense calcium area=1%, and necrotic core area=13%), and D: thin-cap fibroatheroma (fibrous area=60%, fibrofatty area=7%, dense calcium area=1%, and necrotic core area=31%). See Table 3 for lesion characteristics of each lesion types.

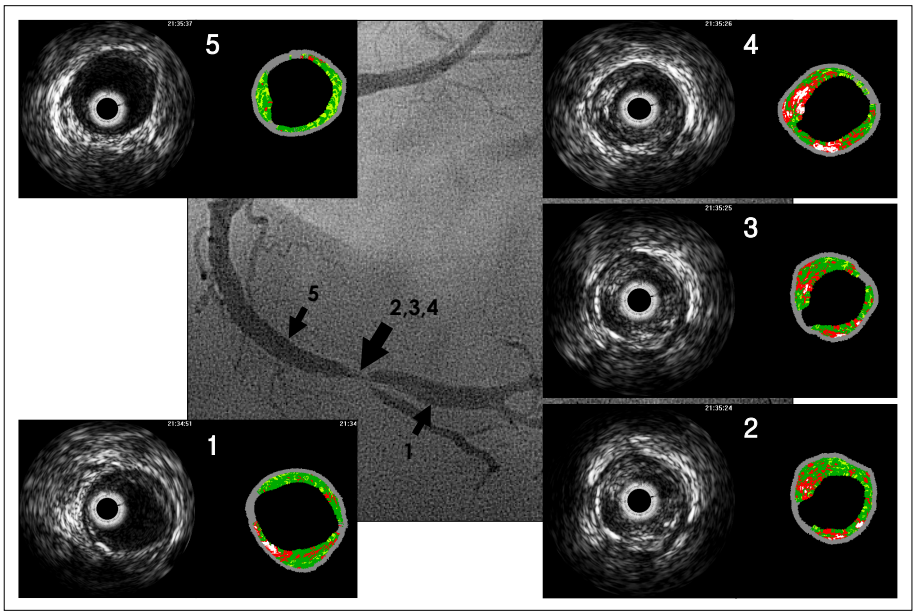

Fig. 3. Angiographic, gray scale intravascular ultrasound (IVUS), and IVUS-virtual histology findings in 37 years old man presented with ST-elevation myocardial infarction in Konyang university hospital. IVUS examination was performed during primary angioplasty after wiring without ballooning. Image frames 2, 3, and 4 show ruptured plaques composed of high content of necrotic core and some calcium, and luminal thrombus (asterisk).

(high-strain region) of a fibrous cap can be predicted by IVUS-VH, although the sensitivity and specificity were only 75.0% and 44.4%, respectively.

Other Studies with IVUS-VH

The sites of plaque rupture showed clustering in the proximal left anterior descending coronary artery, whereas these sites were located in the proximal and distal segments of the right coronary artery and the entire left circumflex coronary artery.[23] These findings are somewhat explained by a study showing that the distance of plaque from the coronary ostium is an independent determinant of the relative lipid content, which is associated with plaque vulnerability in humans.[24] Plaque rupture sites showed a higher content of necrotic cores compared with the sites with minimal lumen areas (17.48±10.8% vs. 13.10±6.5%, respectively, p=03) and there was a trend towards a more calcified component in the plaque rupture sites.[25]

Necrotic core plaques are an important component of plaque vulnerability, and they are associated with low-density lipoprotein cholesterol and the time after transplantation in cardiac allograft vasculopathy patients.[26] This result suggests that controlling lipid is important for preventing the development of necrotic core in cardiac allograft vasculopathy patients.

Future Perspectives

This new imaging technique has, for the first time, elucidated several factors related with the in vivo histopathology of coronary atherosclerotic plaques in humans. Those findings are undoubtedly important for understanding and guiding new catheter-based treatments for patients with coronary artery disease. This promising technique will be especially helpful in understanding the pathogenesis of atherosclerosis in vivo, as well as for guiding treatment decisions and obtaining information with using gray scale IVUS.

It is well known that there are differential responses of the arterial wall to systemic risk factors, and that there are significant associations between the extent of coronary atherosclerosis and carotd intima media thickness (Arterioscler Thromb Vasc Biol 2006).[27-29] However, there are still many things to disclose about the relationships among noninvasive atherosclerosis surrogates, the clinical outcomes, and in vivo plaque composition in humans.

Conclusions

Spectral analysis of IVUS radiofrequency data is a useful tool because it allows detailed assessment of plaque composition with a high predictive accuracy when conducting tissue mapping. Recent studies have demonstrated that this technique may serve as a useful imaging tool for determining the tissue characteristics of patients with coronary artery disease. It has definitely advantages over classic gray scale IVUS or postmortem study for understanding the pathophysiology of coronary artery disease, although better image resolution and greater accuracy for predicting plaque composition are still needed.

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