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Coronary plaque tissue characterization: Evaluation with intravascular ultrasound

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Over the past decade, a keen interest has developed in the imaging of atherosclerosis in patients. Intravascular ultrasound (IVUS) has evolved as a valuable adjunct to angiography, providing insights that are significantly altering conventional paradigms in diagnosis and therapy. IVUS translates the strength (amplitude) of reflected ultrasonic transmissions at the tip of an intravascular catheter equipped with a tiny transducer into gray-scale pixels, which are then combined to create circumferential images representing the anatomical structure of the coronary arteries. Angiography allows evaluation only of the geometry of the unobstructed part of lumen; it cannot provide information on the structure of the coronary artery wall, which is essential to understand the processes leading to plaque progression or regression. IVUS can provide the necessary structural information *in situ* and the development and refinement of IVUS have provided a powerful *in vivo* method to assess plaque morphology.[1)] The "grey scale" IVUS offers clinicians the ability to detect luminal borders, plaque volumes and calcium deposits within the coronary artery. Extensive research has been conducted on IVUS image analysis for determining plaque composition and compared the ultrasound appearance of plaques to histology.[2–7)] Lipid-laden lesions appear hypoechoic, fibromuscular lesions generate low-intensity echoes, and fibrous or calcified tissues are relatively echogenic. Fibrous plaques are generally thought of as advanced lesions that contain dense fibrous tissue, elastin fibers, and proteoglycans. Calcium obstructs ultrasound penetration, obscuring the underlying vessel wall as acoustic shadowing. The angle subtended by the calcified arc can be used to quantify the severity of calcification.[1, 8)]

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Coronary artery tissue characterization with standard grey-scale IVUS image

1. Normal coronary artery

IVUS has the capability to distinguish between muscular (i.e. coronary arteries, external iliac and femoral arteries) and elastic arteries like the aorta and pulmonary arteries. IVUS is capable of discovering intimal thickening, if it exceeds 150 to 200 μm. The intimal thickening increase with age, with average values of 60 μm from 1 to 5 years, 220 μm at 30 and 250 μm at 40 years, which leads to a typical three-layer (intima, media and adventitia) appearance of the coronary arteries (Fig. 1, A). The lumen-intima border and the media-external elastica lamina region can be imaged in great detail, while the external elastica lamina-adventitia border is almost newer to distinguish.[9, 10)]

2. Plaque calcification

Calcification of the coronary arteries is a well-recognized occurrence in the atherosclerotic process and usually signifies complex plaque formation. The deposition of calcium may occur after plaque rupture or thrombosis and is thought to represent a more "mature" point in the natural history of the atherosclerotic lesion.[11)] Calcification is easily identified by IVUS because of its high echogenicity. Calcified regions are defined as bright signals (brighter than the reference adventitia) with distal shadowing of underlying tissue (Fig. 1, B). Arcs of calcification can be easily identified on IVUS images, and the location within the atheroma may be characterized as either superficial or deep.

3. Fibrous plaque

The fibrous plaque is generally an advanced lesion that contains dense fibrous tissue, collagen and elastic fibers, proteoglycans, and necrotic debris with or without calcification.[11)] Dense fibrous plaque, often with small regions of early calcification (Fig. 1, C), may be relatively "senescent," causing stable anginal symptoms that can readily be treated with medical therapy, catheter-based intervention, or possible bypass surgery. Similar to calcified regions of plaque, dense fibrous plaque components are generally bet-

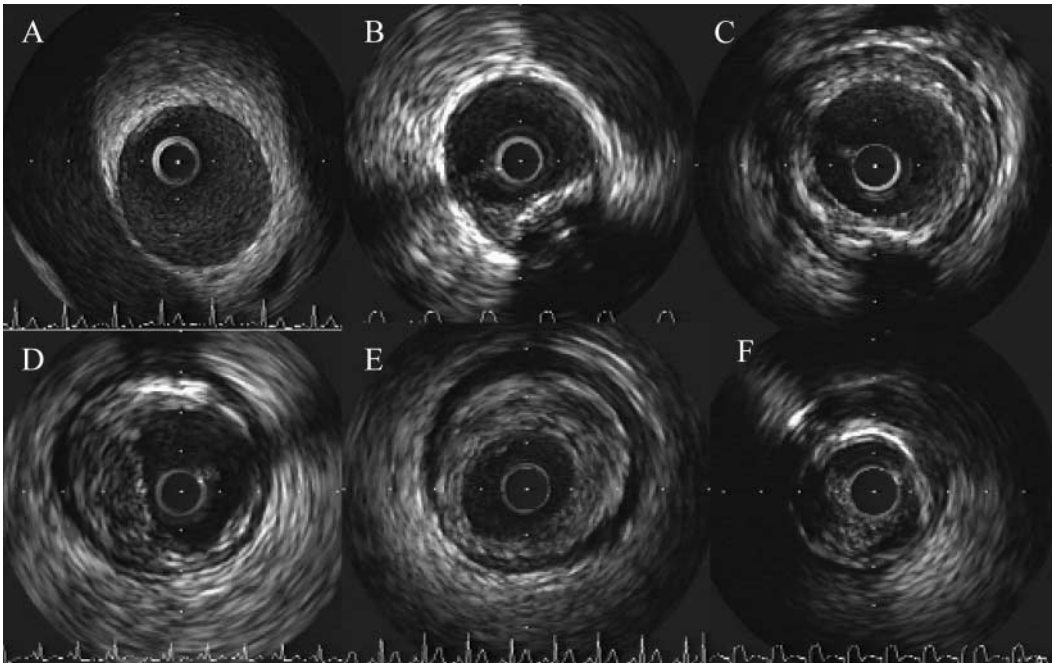

Fig. 1 A, normal coronary artery; B, calcified plaque; C, thin concentric fibrous plaque mixed with calcium; D, eccentric fibro-fatty plaque mixed with calcium; E, eccentric fibro plaque with lipid pool; F, calcified plaque with thrombus in the lumen.

ter reflectors of ultrasound energy, thus appearing bright and homogeneous on the resultant image.

4. Lipid-filled plaque

Low echogenic plaque consists of a large amount of lipid, thrombus, cellular components, and loose connective tissue. Regions of low-echo reflectance or actual echolucency define the soft plaque by IVUS criteria (Fig. 1, D and E). Echolucent regions are believed to be lipid pool. Atherosclerotic plaque stability is related to plaque composition. Acute coronary syndromes are usually caused by rupture or erosion of fibrous caps that cover the lipid-rich necrotic cores of vulnerable plaques.[12–18] Identification of plaques that have a high likelihood of causing clinical events will undoubtedly create new opportunities for treatment before the onset of acute ischemic syndromes. IVUS has the capacity of identifying plaque rupture and vulnerable plaques. Large eccentric plaque containing an echolucent zone, compensatory enlargement of vessel wall can be at increased risk of instability.[19] Plaques seem to be prone to rupture when the echolucent area is larger than 1 mm^2, the echolucent area/plaque ratio greater than 20% and the fibrous cap thinner than 0.7 mm.[20]

5. Thrombus

The need to detect thrombus and differentiate it from underlying residual soft plaque may be crucial in the evaluation and interventional treatment of acute coronary syndromes such as unstable angina or myocardial infarction. The use of IVUS to determine the amount of clot contributing to an angiographic stenosis would greatly assist clinical decision making in interventional cardiology. Thrombus appears variable echogenicity but usually is weak homogenous echoes in acute phase and brighter than moving blood (Fig. 1, F). Conventional IVUS image sometimes remains difficult to differentiate acute thrombus from surrounding soft plaque.

Limitations of conventional IVUS gray-scale images

Although IVUS play important role in evaluating plaque tissue characterization as we described above, there are some limitations in conventional IVUS images. Although the gray-scale images indicate the overall composition of large homogeneous regions, such as a predominantly calcified area, they are unreliable in differentiating adjacent smaller areas with heterogeneous composition.[21, 22] However, coronary atherosclerotic plaques are most frequently heterogeneous. In particular, plaques with a necrotic core, which is an accepted histological finding of unstable plaques, have adjacent areas of microcalcification and lipid.[12] The other major problem of conventional IVUS is the dependence on plaque brightness as a discrimination of plaque content. As this parameter is highly dependent on the gain setting (including time gain compensation and intensity) of IVUS console and its transmit power, direct comparison of brightness in IVUS images may not be possible and operator depended variability could increase.[4] The signal produced by the adventitia may be significantly

attenuated by the intervening tissue and consequently produce a dimmer image. The visual interpretation is limited and does not allow real-time assessment of quantitative plaque composition.[21, 23]

IVUS radiofrequency data analysis

There are two approaches to transducer construction: electronic arrays and mechanically rotating single element devices. Both of them produce images by emitting and then receiving ultrasound pulse. This technique is known as the pulse-echo mode of imaging. The pulse-echo mode of ultrasound imaging is the most common method of visualizing tissues, and is also modus operandi with IVUS. The ultrasound transducer is excited with a certain voltage, which makes it resonate and produce an ultrasound pulse. This wave propagates through the tissue and is reflected or scattered by the media back to the transducer where it is converted back to a voltage. This voltage is known as the backscattered or radiofrequency (RF) data. This backscatter signal is acquired by the transducer, which then processes the data to form the 512 (electronic) or 256 (mechanical) scanlines required to make up one image. It is the analysis of these scanlines that holds potential for tissue characterization.[4] One scanline is thus a signal that contains information about the tissue that reflected the ultrasound energy. By analyzing the frequencies and amplitude of the backscattered signal, it is possible to determine plaque composition. This method of analysis is known as spectral analysis. One of the prerequisites for spectral analysis of RF ultrasound data is access to the RF source. Both the Boston Scientific (mechanical) and the Volcano Therapeutics (electronic) systems provide access to these data.[4]

Recent studies have proven that spectral analysis of IVUS RF data can provide more detailed information regarding the size and composition of plaque components than image analysis of digitized videotape images does, and it can be potentially employed in real-time.[23–28] Spectral analysis of IVUS backscattered data allows reliable characterization of atherosclerotic coronary plaques. Composition could be predicted in individual regions in plaques as confirmed by histology. The computation of the classification schemes permits reconstruction of tissue maps of plaques.

Virtual Histology

Spectral analysis is commercially available on the Volcano Therapeutics consoles. This system has RF spectral analysis built in to the console, termed Virtual Histology—the first technology to enable real time compositional assessment of atherosclerotic plaques in coronary arteries.

Virtual Histology (VH) technology uses advanced spectral analysis techniques to allow simplified interpretation of ultrasound images and provide detailed information on

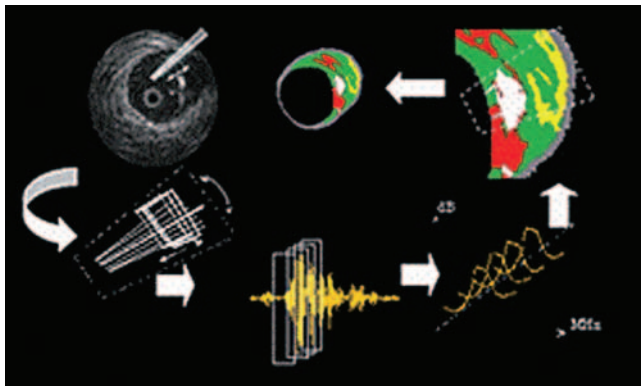

Fig. 2 The above schematic shows the conversion of raw radiofrequency data from intravascular ultrasound into color-coded parametric images of plaque boundary features, potentially providing additional information on plaque composition. (Courtesy of Volcano™ Therapeutics Inc.)

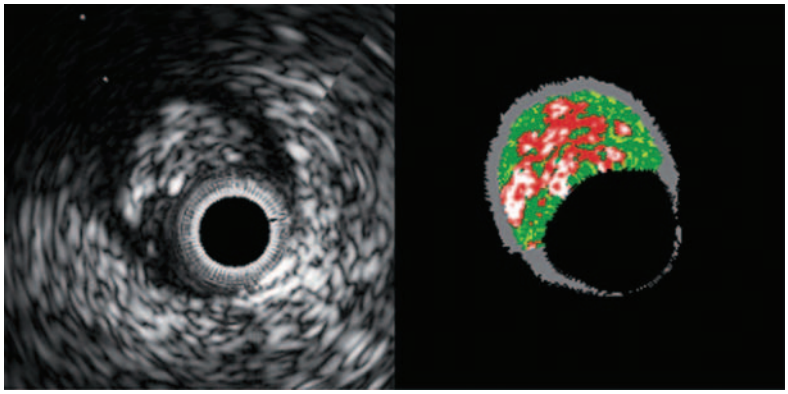

Fig. 3 Left: Conventional grey-scale intravascular ultrasound image. Right: Virtual Histology image. Green, fibrous; Yellow, fibro-lipidic; White, calcium; Red, lipid core.

the composition of each patient's atherosclerotic plaques. The colorized VH images show four plaque component types: fibrous, fibro-fatty, dense calcium, and necrotic core.[23] This novel technology provides automated measurement tools to simplify image interpretation and employs a pre-determined color key to display plaque composition at a specific point in the artery or across a region of interest. By simplifying IVUS use and by providing important new information to the interventional cardiologist, VH could improve the treatment of patients and help to further expand IVUS use in percutaneous coronary interventions. VH has the potential to revolutionize the management of coronary artery disease by providing more information about atherosclerosis in the form of arterial plaque composition assessment.[4, 23]

By analyzing eight spectral parameters of the reflected ultrasound signal (in addition to amplitude, which generates grey-scale IVUS data and images), Volcano's Virtual Histology IVUS identifies unique boundary features within the plaque and vasculature (Fig. 2). With this information, images can be created that provide additional information about the possible composition of atherosclerotic plaques (Fig. 3), which could only otherwise be assessed at autopsy.

Conclusion

Defining the composition of atherosclerotic plaque real-time may be possible by using IVUS techniques. In conventional grey-scale image, gray level will represent some tissue acoustic properties directly related to biochemical constituents such as lipids, collagen, or calcium. In recent years, the progress of spectral analysis of the RF signal allows a more detailed analysis of plaque tissue characterization. Analysis of IVUS RF signals is a robust technique for the classification of atheroma based on multiple spectral parameters. The developed technique makes real-time analysis of IVUS data conceivable, enabling plaque characterization and further increasing the utility of IVUS.

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