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iREVIEWS

STATE-OF-THE-ART PAPERS

Intravascular Imaging of Coronary Calcification and its Clinical Implications

Gary S. Mintz, MD

ABSTRACT

Calcium impacts the natural history and treatment of coronary artery disease in many ways. Intravascular imaging studies, mostly intravascular ultrasound, but more recently studies using optical coherence tomography, have been instrumental in increasing our understanding of the relationship between calcium and coronary atherosclerosis, the predictors, the natural history of this relationship, and the impact on treatment. On one hand, stable coronary lesions are associated with more calcium than unstable lesions; and the amount of calcium may affect the success of percutaneous coronary intervention. On the other hand, calcium correlates with plaque burden; unstable lesions are associated with focal calcium deposits; and calcific nodules are one of the morphologies of vulnerable plaque. This review focuses on more than 20 years of intravascular imaging studies of the relationship between calcium and coronary atherosclerosis. (J Am Coll Cardiol Img 2015;8:461–71) © 2015 by the American College of Cardiology Foundation.

The extent of coronary artery calcium strongly correlates with the degree of atherosclerosis and, therefore, with the rate of future cardiac events. Coronary angiography has low-to-moderate sensitivity compared with grayscale intravascular ultrasound (IVUS) or optical coherence tomography (OCT), the gold standard for coronary calcium detection; but coronary angiography has a relatively high positive predictive value. Stable coronary lesions are associated with more calcium than unstable lesions, and the amount of calcium may affect the success of percutaneous coronary intervention. Unstable lesions are associated with focal calcium deposits that may be related to fibrous cap disruption, and calcific nodules are one of the morphologies of vulnerable plaque. Certain patient populations are at higher risk for greater amounts of coronary calcium. This review summarizes the data that has been acquired with intravascular imaging.

DETECTION AND QUANTIFICATION OF CALCIUM

IVUS. Calcium is a powerful reflector of ultrasound; little of the beam enters or even penetrates calcium so that calcium casts a shadow over deeper arterial structures. The IVUS signature of calcium is echodense (hyperechoic) plaque that is brighter than the reference adventitia with shadowing (**Figure 1**); however, dense fibrous tissue is also echodense and can sometimes cast a shadow. Calcium, but not dense fibrous tissue, produces reverberations, multiple reflections from oscillation of ultrasound between the transducer and calcium to cause concentric arcs at reproducible distances, especially after calcium is treated with rotational or orbital atherectomy (**Figure 2**). Hyperechoic plaque with shadowing is highly sensitive, whereas reverberations are highly specific (1). With the exception of microcalcifications, IVUS is sensitive and specific for detecting calcium

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ABBREVIATIONS AND ACRONYMS

CKD = chronic kidney disease

CrCl = creatinine clearance

CTO = chronic total occlusion

DICOM = digital imaging and communications in medicine

IVUS = intravascular ultrasound

MI = myocardial infarction

OCT = optical coherence tomography

RF-IVUS = radiofrequency intravascular ultrasound

IVUS-VH = intravascular ultrasound-virtual histology

within a plaque. In 1 recent in vitro study, IVUS did not detect calcium in 14.8% of segments containing histopathologic calcium; reasons included microcalcium deposits (9.4%) and deep calcium hidden behind a large necrotic core that produced echo-attenuation (5.4%) (2). Although IVUS frequently shows a large block of calcium, pathologically this is an uncommon finding; instead, there are more often multiple smaller fragments of calcium that coalesce on IVUS imaging.

Calcium is assessed quantitatively with IVUS according to the arc (measured in degrees, using a protractor centered on the lumen) and length (using motorized transducer pullback). Semiquantitative grading classifies calcium as absent or subtending 1, 2, 3, or 4 quadrants. Calcium is described qualitatively according to its location: lesion versus reference and superficial (leading edge of acoustic shadowing within the most shallow 50% of the plaque and media thickness) versus deep (leading edge of acoustic shadowing within the deepest 50% of the plaque and media thickness). Because little of the ultrasound beam penetrates the calcium, only the leading edge of the calcific deposit is seen; and the apparent "thickness" of the calcium reflection in a grayscale IVUS image is a function of transducer saturation by the reflected ultrasound energy and not of anatomic thickness, although a volumetric "index" of calcium can be calculated by integrating the arc and length of calcium.

DICOM-based grayscale IVUS signal intensity analysis (Indec Medical Systems, Santa Clara, California) has been used to assess calcium. In an in vitro analysis, the sensitivity was 86.7%, the specificity was 93.3%, and the predictive accuracy was 92.3% for detecting calcium. However, it was unclear whether this approach adds to the visual assessment of calcification. In addition, the predictive accuracy behind calcium (in areas of shadowing) fell from 82.7% to only 53.3% (3).

RADIOFREQUENCY-IVUS. There are 3 radiofrequency (RF)-IVUS technologies. All 3 have been validated in vitro; and sensitivity, specificity, and predictive accuracy are high. However, each approach to tissue classification is very different; they should not be lumped together but should be considered distinct technologies; comparisons among them can yield discordant results; and only IVUS virtual histology (IVUS-VH) (Volcano Corporation, San Diego, California) is widely available (4).

IVUS-VH applies a mathematical autoregressive model to 8 amplitude or RF spectral parameters, and a statistical classification tree sorts combinations of these parameters to create 4 plaque components that are then color coded as fibrous tissue (dark green), fibrofatty tissue (light green), necrotic core (red), and dense calcium (white) (**Figure 3**) (5). IVUS-VH detects calcium as part of a fibrocalcific plaque or in the setting of a necrotic core (calcified fibroatheroma) (6). There is ongoing controversy whether IVUS-VH can "see" behind calcium. If calcification is nonconfluent with gaps of approximately 100 μm (as is common), then there is some level of ultrasound energy that, depending on the density and thickness of the calcium, is greater than random noise in the majority such that IVUS-VH assessment of calcium thickness, area, and volume as well as the composition of plaque within shadowed areas may be possible. However, in individual cases, it difficult to predict whether there is a definable signal versus mostly noise; the current hardware and software do not make this distinction, and therefore, the accuracy of tissue classification should be assumed to be reduced in such areas (7).

Implanted stents have an appearance that can be misclassified by IVUS-VH as "calcium with or without necrotic core" (8). Finally, an automated computational system has been developed to assess the spatial distribution with regard to location within the plaque as well as the relationship to the plaque-lumen border of each IVUS-VH plaque component, including calcification (9).

Integrated backscatter-IVUS (Visiwave, Terumo, Japan) uses just a single parameter, intensity of the backscatter or reflection of ultrasound, to assess plaque composition. There are significant differences in backscatter among: 1) thrombi; 2) fibrous tissue; 3) mixed lesions; 4) calcification; and 5) lipid core, intimal hyperplasia, and media that have similar values. Current systems color code tissue as red (calcium, −11 to −29 dB), dense fibrosis (yellow, −29 to −35 dB), green (fibrosis, −35 to −49 dB), and blue (lipid or intimal hyperplasia, −49 to −130 dB) (10).

iMAP (Boston Scientific, Fremont, California) is based on a mathematically defined measure of similarity comparing in vivo spectra versus a library of spectra that have been acquired in vitro and includes only regions with a high degree of confidence in matching geometry and well-defined tissue composition. iMAP also provides a measure of confidence for each region of interest. Although fibrous tissue is color coded light green, lipidic tissue is color coded yellow, necrotic core is color coded pink, and calcium is color coded blue, confidence regarding tissue classification is represented as transparency with high confidence characterizations shown with more opaque color (4).