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Insights Into Echo-Attenuated Plaques, Echolucent Plaques, and Plaques With Spotty Calcification

Novel Findings From Comparisons Among Intravascular Ultrasound, Near-Infrared Spectroscopy, and Pathological Histology in 2,294 Human Coronary Artery Segments

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Objectives Three intravascular ultrasound (IVUS) signatures have been associated with coronary artery disease instability: echo attenuation, an intraplaque echolucent zone, and spotty calcification. The aim of this study was to investigate the substrates responsible for these IVUS signatures in a relatively large series of post-mortem human coronary samples.

Background The exact mechanisms and pathological correlates underlying echo attenuation, an intraplaque echolucent zone, and spotty calcification remain poorly understood.

Methods IVUS was compared with near-infrared spectroscopic detection of lipid core plaque and histopathology in 2,294 vessel segments from 151 coronary specimens from 62 patients at necropsy using the modified American Heart Association classification.

Results IVUS detected echo-attenuated plaques in 18.3% of segments, echolucent plaques in 10.5% of segments, and spotty calcification in 14.4% of segments. Histopathologically, 91.4% of echo-attenuated plaques corresponded to either a fibroatheroma (FA) with a necrotic core (NC) or pathological intimal thickening with a lipid pool; almost all segments with superficial echo attenuation indicated the presence of an FA with an advanced NC. Echolucent plaques indicated the presence of a relatively smaller lipid or NC compared with echo-attenuated plaques (thickness: 0.51 mm [interquartile range (IQR): 0.35 to 0.64 mm] vs. 0.70 mm [IQR: 0.54 to 0.92 mm] [$p < 0.001$]; arc: 74.5° [IQR: 59.0° to 101.0°] vs. 90° [IQR: 70.0° to 112.0°] [$p < 0.001$]), although 82.8% of superficial echolucent zones indicated an NC-containing FA. IVUS spotty calcification, especially when superficial in location (72.6%), was often associated with an FA with calcium deposits and had smaller arcs of calcium in the setting of FA compared with fibrocalcific plaques (37.5° [IQR: 23.0° to 53.0°] vs. 59.0° [IQR: 46.0° to 69.0°]; $p < 0.001$). Comparisons between IVUS and near-infrared spectroscopy revealed that echo-attenuated plaques contained the highest probability of near-infrared spectroscopy–derived lipid core plaque, followed by echolucent plaques and spotty calcifications.

Conclusions This study demonstrated that echo-attenuated plaque, especially superficial echo attenuation, was the most reliable IVUS signature for identifying a high-risk plaque (i.e., an FA containing a large NC). (J Am Coll Cardiol 2014;63:2220–33) © 2014 by the American College of Cardiology Foundation

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Intravascular ultrasound (IVUS) has played an important role in understanding the pathology and treatment of atherosclerotic disease in humans. Several grayscale IVUS features have been associated with either clinical instability or a high risk for cardiovascular events in patients with coronary artery disease undergoing percutaneous coronary intervention. These include atherosclerotic plaque with ultrasonic attenuation (echo-attenuated plaque) (1,2), an intraplaque echolucent zone (echolucent plaque) (3), and scattered spotty calcification (4,5). To date, however, the exact mechanisms or pathological correlates underlying these IVUS signatures and the associated risk for ischemic events remain poorly understood. More recently, near-infrared spectroscopy (NIRS) has been developed to detect lipid core plaque (LCP) (6,7); NIRS has been fused with IVUS in the first combined imaging system (8). In the present ex vivo study, we investigated the substrates responsible for echo-attenuated plaques, echolucent plaques, and IVUS spotty calcification on the basis of the modified American Heart Association histological classification scheme in a relatively large series of post-mortem human coronary samples.

Abbreviations and Acronyms

FA = fibroatheroma
IQR = interquartile range
IVUS = intravascular ultrasound
LCBI = lipid core burden index
LCP = lipid core plaque
NC = necrotic core
NIRS = near-infrared spectroscopy
PIT = pathological intimal thickening

Methods

Subjects. Human coronary specimens were obtained over a 2-year period from autopsied patients. With approval from the institutional review board, hearts were acquired from the National Disease Research Interchange (Philadelphia, Pennsylvania) or the International Institute for the Advancement of Medicine (Edison, New Jersey), which also provided information regarding age, sex, medical history, and cause of death. The following terms were designated as indicating a cardiovascular cause of death: "myocardial infarction," "cerebrovascular accident," "cardiac arrest," and "other cardiovascular." Hearts were received within 48 h of death, maintained on ice at 4°C, and imaged within 96 h of death. The major coronary arteries were harvested after in situ angioscopic screening to exclude occluded segments impassable by the IVUS catheter. Side branches were ligated to prevent loss of blood during perfusion; adventitial fat surrounding the arterial segments was kept intact. Each coronary specimen was mounted in a unique custom fixture with vertical guideposts at 2-mm intervals to be used as reference points when comparing imaging with histological studies. Both ends of the arterial segment were attached to Luer connectors that allowed fluid flow and catheter entry. A varistaltic pump (Manostat, Barnant Corporation, Barrington, Illinois) supplied pulsatile flow at 60 cycles/min and a flow rate of approximately 130 ml/min, with pressure inside the coronary artery maintained at physiological levels (80 to 120 mm Hg) at a body temperature of 37.0°C. IVUS, NIRS, and histopathologic analyses were performed without knowledge of the findings obtained from the other 2 methods.

IVUS image acquisition and analysis. An Atlantis SR Pro 40-MHz catheter attached to an iLab system (Boston Scientific Corporation, Fremont, California) was advanced along a 0.014-inch guidewire through the coronary specimen mounted in the fixture. IVUS imaging was performed using motorized pullback at 0.5 mm/s to include proximal and distal Luer connectors. Image data were archived onto a CD-ROM and sent to an independent IVUS core laboratory (Cardiovascular Research Foundation, New York, New York) for off-line analyses. Every IVUS frame was matched to its comparable histopathologic slice using vessel shape, side branches, perivascular structures, and distances from the Luer connectors.

IVUS analyses were performed using validated planimetry software (echoPlaque, INDEC Medical Systems, Santa Clara, California). Quantitative analyses were performed according to criteria from the American College of Cardiology consensus statement on IVUS (9). Echo-attenuated plaque, echolucent plaque, and IVUS spotty calcification were defined as previously published (1–5,10).

Echo-attenuated plaque was identified by the absence of the ultrasound signal behind plaque that was either hypoechoic or isoechoic to the reference adventitia but contained no bright calcium (10). The arc of attenuation was measured in degrees with a protractor centered on the lumen. The interobserver variability of this arc of attenuation measurement was 4.9 ± 2.8°. The location of attenuation was defined as superficial (leading edge of attenuation closer to the lumen than to the adventitia) or deep (leading edge of attenuation closer to the adventitia than to the lumen).

Echolucent plaque contained an intraplaque zone of absent or low echogenicity (lower than that of the reference adventitia) surrounded by tissue of greater echodensity (3,10). The arc of echolucent zone was measured in degrees with a protractor centered on the lumen. The interobserver variability of the arc of echolucent zone was 5.8 ± 3.4°. The location of the echolucent zone was defined as "superficial" if the leading edge of the echolucent zone was closer to the lumen than to the adventitia or "deep" if the leading edge of the echolucent zone was closer to the adventitia than to the lumen (3).

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