Intravascular Ultrasound in Cardiovascular Medicine

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Case presentation: A 38-year-old man underwent angiography 2 weeks after a non–ST-segment myocardial infarction. He was overweight and prehypertensive, with a blood pressure of 134/86 mm Hg. His biochemical parameters included low-density lipoprotein cholesterol (LDL-C) 127 mg/dL, high-density lipoprotein cholesterol (HDL-C) 38 mg/dL, and C-reactive protein (CRP) 3.2 mg/L. Angiography revealed mild disease throughout the coronary arteries and a hazy appearance that involved the proximal left anterior descending coronary artery. Intravascular ultrasound (IVUS) imaging revealed diffuse and extensive atherosclerosis with evidence of plaque rupture at multiple sites (Figure 1). In the presence of no significant luminal stenoses, the patient was treated medically with aspirin and low-dose statin therapy.

The application of IVUS in this case highlights a number of important points with regard to the natural history of atherosclerosis and its modification by use of established medical therapies. The ability to image the entire arterial wall represents a significant advantage over coronary angiography. In the presence of minimal luminal stenoses, IVUS imaging in patients with coronary symptoms typically reveals extensive and diffuse atherosclerosis. Application of serial IVUS imaging in prospective clinical trials has enabled a greater understanding of the impact of antiatherosclerotic interventions on patients with established coronary artery disease (CAD).

IVUS and the Natural History of Atherosclerosis

Ultrasonic coronary imaging has revealed essential details about the natural history of atherosclerosis. Atheroma formation begins at a surprisingly young age in a contemporary American population. IVUS studies in hearts of cardiac transplant donors reveal significant plaque in some individuals <20 years of age. By age 30, >50% of the population has at least 1 lesion of >0.5 mm in atheroma thickness. This finding, previously demonstrated in necropsy studies of Korean and Vietnam War casualties, confirms that atherogenic risk factors begin to affect coronary vascular anatomy many decades before symptoms appear.

In early coronary disease, the angiogram often remains normal or shows trivial irregularities. IVUS studies have helped to explain this conundrum. During the early phases of atheroma accumulation, outward expansion (“remodeling”) of the external elastic membrane compensates for plaque growth, thereby maintaining a normal lumen size. The initial report of expansion of the vascular wall in response to early plaque accumulation was derived from studies of necropsy specimens; this phenomenon has been confirmed and more fully defined by IVUS. In the later phases of CAD, plaque accumulation overcomes remodeling, and luminal stenoses appear.

Because most plaques are accompanied by outward expansion of the external elastic membrane (“expansive remodeling”), the true extent and severity of atherosclerosis are concealed during angiography. Thus, in nearly all CAD patients, IVUS shows more diffuse and extensive atherosclerotic plaque within the coronary arteries than is suggested by angiography. Angiography provides a 2-dimensional silhouette of the arterial lumen but does not image the vascular wall. The ability of IVUS to visualize the entire vessel wall thickness permits detection of atheroma long before it results in luminal compromise.

Arterial remodeling appears to be a critical determinant of the propensity

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of an atherosclerotic plaque to result in clinical symptoms. Several research groups have reported that culprit lesions in acute coronary syndromes are associated with expansive remodeling. In contrast, lesions accompanied by constrictive remodeling (reduction of external elastic membrane dimensions) are associated with a presentation of stable angina pectoris.6 This is consistent with the finding that expansively remodeled plaques contain greater amounts of metalloproteinases, a critical factor in fibrous cap rupture.7

As illustrated in the present case, IVUS imaging often demonstrates the presence of multiple sites of plaque rupture throughout the coronary arterial tree in patients with acute coronary syndromes.8,9 This finding supports the concept that atherosclerosis and its complications are a systemic, and not focal, process. IVUS has also provided insights into a number of vascular pathologies beyond traditional atherosclerosis. Coronary ultrasound has shown that restenosis after percutaneous intervention results from a combination of arterial recoil, remodeling, and neointimal formation.10 Ultrasound imaging has characterized different phases of coronary transplant vasculopathy, a pathological process responsible for most of the late morbidity and mortality after transplantation. As a result, serial IVUS examinations have become an integral component of the routine clinical surveillance of transplant recipients.11 A clinical trial that included IVUS end points established the beneficial impact of the antiproliferative agent everolimus on progression of vasculopathy, an effect that also resulted in improved clinical outcome.12

IVUS and the Impact of Antiatherosclerotic Therapies

Randomized clinical trials have shown that modification of established atherosclerotic risk factors has a beneficial impact on clinical events. These findings have provided the scientific basis for the development of guidelines for cardiovascular prevention. However, these therapies fail to prevent the majority of clinical events. Imaging modalities that assess plaque burden and composition, such as IVUS, have become attractive tools in the search to identify new therapeutic strategies to further diminish cardiovascular risk. Serial coronary ultrasound imaging can accurately determine the volumetric extent of atheroma within an arterial segment at different time points, providing a powerful tool for defining the effect of existing and investigational therapies on plaque progression (Figure 2). Plaque progression has emerged as the primary end point in a number of clinical trials that target both established and emerging risk factors.

Although statins are an essential component of secondary prevention strategies, the optimal LDL level for treatment remains controversial. The first large prospective, randomized multicenter IVUS trial of statins, the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study,13 provided strong evidence that lower levels of LDL-C slow disease progression. An intensive lipid-lowering strategy (atorvastatin 80 mg daily, LDL-C 79 mg/dL) halted the progression of plaque com-
pared with a moderate lipid-lowering strategy (pravastatin 40 mg daily, LDL-C 110 mg/dL). This finding was subsequently confirmed by reports that intensive lipid lowering produces a beneficial impact on clinical events in patients with acute\textsuperscript{14} and chronic\textsuperscript{15} ischemic syndromes. The National Education Cholesterol Program (NCEP) lipid-lowering guidelines were amended to include the option to use an aggressive LDL-C therapeutic target for secondary prevention in high-risk individuals.\textsuperscript{16}

Despite a continuous relationship between changes in LDL-C and atheroma volume, the difference between the 2 therapeutic strategies could not be explained completely by LDL-C lowering alone. Atorvastatin-treated patients showed a greater lowering of CRP compared with pravastatin-treated patients. The finding of a continuous relationship between changes in CRP and atheroma volume suggests that part of the benefit was derived from a reduction in vascular inflammation.\textsuperscript{17} This complemented the finding in acute coronary syndrome patients that greater CRP lowering resulted in fewer clinical events. These results suggest that the incremental benefit on atherosclerotic plaque after use of high-dose statin therapy results from both LDL-C--lowering and non--lipid-lowering properties.

This was further extended by the findings of A Study To Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID).\textsuperscript{18} Twenty-four months of treatment with rosuvastatin 40 mg daily resulted in lowering of LDL-C to 61 mg/dL and an elevation of HDL-C by 14.7%. Significant reductions in each measure of atheroma burden were observed, consistent with unequivocal regression of coronary atherosclerotic plaque (Figure 3). This supports earlier reports of atheroma regression with statin therapy in small cohorts monitored by serial IVUS.\textsuperscript{19,20} Placed in the context of all large clinical IVUS trials, these results suggest that the direct relationship between the level of LDL-C achieved and change in atheroma volume extends to regression in the setting of very low LDL-C levels. The relative contribution of HDL-C elevation to atheroma regression warrants further investigation. The results have important implications for the development of therapeutic strategies

Figure 2. Cross-sectional tomographic image of the arterial wall containing atherosclerotic plaque obtained by IVUS (left panel). Standard measurements including planimetry of the leading edges of the lumen (inner circle) and external elastic membrane (outer circle) are illustrated in the right panel.

Figure 3. Illustrative example of regression of coronary atheroma in a patient who received intensive lipid-lowering therapy. Tomographic images at a matched site at baseline (left panels) and follow-up (right panels) are depicted. The atheroma area in each image is shaded in the bottom panels.
that aim to simultaneously lower LDL-C and elevate HDL-C.

The protective properties of HDL-C are well established, but it remains a secondary target for management in the NCEP guidelines. Infusing reconstituted HDL containing apolipoprotein A-I Milano weekly for 5 weeks promoted regression of coronary atheroma in subjects with a recent acute coronary syndrome.21 This extends reports that infusing reconstituted HDL in humans improves endothelial function22,23 and that apolipoprotein A-I Milano is protective.24 The findings of plaque regression, rather than halting of progression, and the rapid time course of this effect are of particular importance in comparison with other therapeutic strategies. This result provides evidence that interventions that promote HDL can have a beneficial impact on coronary atheroma. Further studies are required to assess the potential impact of infusing HDL on clinical events.

Although epidemiological studies demonstrated that increasing levels of systolic blood pressure within the normal range confer a greater cardiovascular risk, there is no consensus with regard to the optimal management of blood pressure in patients with CAD who are deemed to be normotensive. The Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study25 demonstrated that administration of the antihypertensive amlodipine to CAD patients with a mean blood pressure of 129/77 mm Hg resulted in a reduction in the combination of hospitalization for angina, coronary revascularization, and nonfatal myocardial infarction. Serial IVUS imaging in a subset of patients revealed that amlodipine halted plaque progression compared with placebo-treated patients. A continuous relationship was shown between the changes in systolic blood pressure and atheroma volume. These results suggest that patients with established CAD and a blood pressure considered to be normal, as illustrated, might derive considerable clinical benefit from the use of antihypertensive therapies and intensive blood pressure lowering.

Serial IVUS studies have been extended to assess the impact of strategies directed against emerging targets in atheroma formation. Administration of pactimibe, an inhibitor of acyl-coenzyme A:cholesterol acyltransferase (ACAT), a major factor in foam cell formation, has a potentially deleterious influence on plaque progression.26 This contrasts with a large body of evidence from animal studies that ACAT inhibition is beneficial and supports a previous report that the early-generation ACAT inhibitor avasimibe had no impact on plaque progression.27 The results also highlight the importance of imaging atherosclerotic plaque with ultrasound in evaluating the potential benefit or harm of emerging therapies.

**Future of IVUS and Imaging Modalities in General**

Ultrasonic imaging of coronary atheroma is limited by suboptimal characterization of plaque composition, need for invasive catheterization, and lack of correlation with clinical outcome. Technological developments of radio-frequency analysis of ultrasound backscatter enhance the ability of IVUS to characterize plaque components.28 With the use of this approach, it was reported that LDL-C lowering with atorvastatin is accompanied by a reduction in lipidic components and increase in fibrotic components of coronary atheroma.29 Additional intravascular techniques, including optical coherence tomography and the assessment of plaque temperature and compressibility, identify lipidic and inflamed atheroma. None of these imaging modalities has been employed in a large-scale assessment of antiatherosclerotic therapies. Advances in MR and CT provide an exciting opportunity to assess serial changes in atheroma burden and composition noninvasively.

The fundamental aim of all experimental agents is to result in fewer clinical events. Although there is a strong suggestion that changes in atheroma burden are indicators of clinical outcome, the proof for such a relationship is yet to be established. The ability to demonstrate that regression or slowing of plaque progression results in lower clinical event rates remains an important priority to further validate the use of modalities that visualize atherosclerotic plaque in the development of novel therapies.

**Clinical Implications**

The findings from studies that use IVUS assessments of coronary atheroma burden in a serial fashion have important implications for the management of the patient who presents with an acute coronary syndrome. These studies suggest that secondary prevention in the patient presented should aim at much more aggressive treatment goals, including use of aspirin, high-dose statin therapy to lower LDL-C levels as low as possible, and lowering of blood pressure in patients who do not appear to have elevated blood pressures. The development of therapeutic agents that elevate HDL-C levels may provide another strategy to further reduce cardiovascular risk in such patients.

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