Chapter 9
Intravascular Ultrasound

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Introduction

In the half century since it was initially performed, coronary angiography has become the preferred imaging modality for the diagnosis of atherosclerotic coronary artery disease (CAD). Angiography has been employed to triage patients to a range of medical and revascularization therapies. At the same time, it has become apparent that conventional angiographic techniques are limited in their ability to evaluate atherosclerotic plaque. This has prompted the search to develop new imaging modalities to more extensively visualize atherosclerosis in order to gain further insight into the mechanisms driving the disease process and to facilitate the therapeutic approach to the patient with CAD. Intravascular ultrasound (IVUS) has emerged as a sensitive tool for the evaluation of the natural history of atherosclerosis.

Role of Angiography in the Evaluation of Atherosclerosis

A number of important observations suggest that angiography is limited in its ability to characterize atherosclerosis. While early studies demonstrated a relationship between the number of vessels diseased on angiography and clinical outcome, more recent data suggest that the angiographic severity of a lesion is a poor predictor of its propensity to cause clinical events.[1–3] Several groups have reported that culprit lesions are often mild-to-moderately stenotic in patients undergoing angiography during hospitalization for an acute myocardial infarction.[12] These observations have stimulated the concept of the importance of plaque composition, rather than its extent, in determining the likelihood of acute ischemic syndromes. In addition, while studies employing serial quantitative coronary angiography have demonstrated a beneficial impact of medical therapies on the rate of progression of obstructive disease, the degree of benefit appeared to be of a much smaller magnitude than the effect of these therapies on clinical events. These observations highlight the potential discord between studying the luminal stenoses and making conclusions about atherosclerosis.

Angiography provides a two-dimensional silhouette of the arterial lumen. It does not visualize the vessel wall, in which plaque accumulates. As a result, angiography does not image atherosclerotic plaque. This has important implications for the precise quantitation of the extent of atherosclerosis within the coronary arteries. Quantitative angiography compares the lumen diameter at the site of a lesion with a segment of artery that is presumed to be free of disease. Given that atherosclerosis is a diffuse process, this approach is limited by the likelihood that the "reference" segment is not normal. This is supported by the finding of necropsy studies that angiography underestimates the extent of atherosclerosis.[4–6]

Angiographic analysis is confounded by arterial remodeling. In the presence of early plaque accumulation, the external elastic membrane (EEM) typically expands, with relative preservation of the luminal diameter.[7] Contraction of the lumen does not typically occur until later stages of atherosclerosis. As a result, angiographic abnormalities may not appear until a substantial amount of atheroma is present within the artery wall. This is supported by the observation from imaging modalities that visualize the entire vessel that substantial plaque is often present in segments that appear normal or minimally diseased on angiography.[8] As a result, there is a need to develop imaging modalities that visualize the artery wall to gain a greater insight into the natural history of atherosclerosis and its regulation.

Intravascular Ultrasound

Technological advances in ultrasound technology permit the placement of transducers within the coronary arteries. The ability to place high-frequency ultrasound transducers (20–50 MHz) in close proximity to the endothelial surface generates high-resolution (axially 80 mm, laterally 200 mm) tomographic cross-sectional images of the entire artery wall (Fig. 9.1). Transducer

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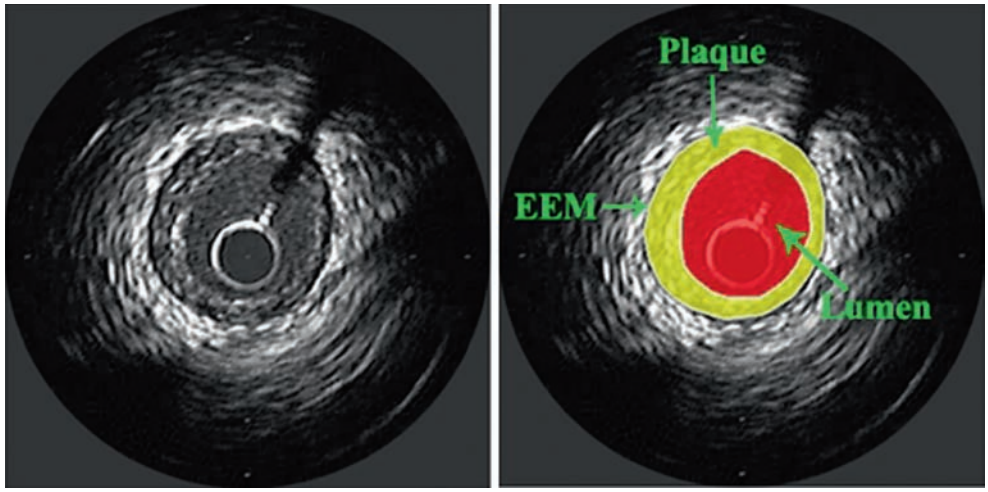

FIG. 9.1. IVUS Image: An intravascular ultrasound image demonstrating the external elastic membrane (EEM), plaque, and lumen areas

systems incorporate mechanically rotated devices or electronically switched multielement electronic arrays. Mechanical systems employ a single piezoelectric transducer, rotated at 1,800 rpm, generating 30 images per second. Electronic systems employ up to 64 transducer elements, organized in an annular array, which are sequentially activated to generate images. Mechanical rotation systems are preferred due to superior image quality.

Ultrasonic imaging is performed following anticoagulation and administration of nitroglycerin. For adjunctive use during percutaneous coronary interventions, the catheter tip is advanced beyond the segment of interest. In the setting of clinical trials that assess the natural history of atherosclerosis, the catheter is typically placed as distally as possible in the longest and least angulated epicardial artery. The catheter is subsequently withdrawn through the coronary artery either manually or at a constant speed (0.5 mm s^{-1}) using a motorized pullback device.

The requirement for invasive cardiac catheterization limits the application of IVUS to the setting of percutaneous coronary interventions or evaluation of the patient undergoing a clinically indicated angiogram. Despite this, several studies have documented that IVUS can be performed safely, with reported complications varying from 1 to 3%.[9–11] The most commonly cited adverse reaction is transient, focal coronary spasm, which responds rapidly to administration of intracoronary nitroglycerin. Serious complications, including dissection and vessel closure, are rare (less than 0.5%), typically occurring during coronary intervention rather than diagnostic imaging. Sequential IVUS imaging has not been shown to accelerate vasculopathy in both transplant and nontransplant patients.[11,12]

Evaluation of Atherosclerosis by Intravascular Ultrasound

The ability to visualize the entire vessel wall permits the opportunity to detect the full extent of atherosclerosis within an imaged arterial segment. Invasive ultrasonic imaging has provided a number of important insights into the natural history of coronary atherosclerosis. Coronary ultrasound reveals more extensive and diffuse atherosclerosis than suggested by angiography. It also highlights that atherosclerosis is typically present much earlier than previously thought. In a study of 262 heart transplant recipients, shortly following their operation, macroscopic atheroma was detected in the coronary arteries of one in six teenage, apparently healthy, donors.[13] The prevalence of coronary plaque rises exponentially with age. This dispels the myth that atherosclerosis is a disease which commences in middle age.

IVUS has been extensively employed to characterize the in vivo remodeling response of the arterial wall in response to plaque accumulation. The typical expansive pattern of remodeling in early atherosclerosis, initially described on the basis of necropsy specimens, has been confirmed by ultrasonic imaging.[14] Further studies provided important insights into the interaction between atherosclerosis, remodeling, and the clinical expression of disease.[15] In particular, culprit lesions in the setting of acute ischemic syndromes are more likely to be associated with expansive remodeling. In contrast, patients with more stable, exercise-related symptoms are more likely to have culprit lesions with constrictive remodeling, promoting lumen contraction and obstruction. These findings are consistent with the observation that expansive remodeling is associated with higher systemic levels of matrix metalloproteinases, factors involved in fibrous cap rupture, the pathological stimulus of acute ischemic syndromes.[16]

IVUS has been employed to characterize the morphology of culprit lesions in the setting of acute coronary syndromes. Echolucent, lipid-rich plaques with evidence of rupture (Fig. 9.2) and luminal thrombus can be identified in the setting of unstable clinical syndromes.[17] Investigations in patients with unstable angina reveal the presence of multiple ruptured plaques, throughout the coronary tree.[18] This is consistent with the concept that acute ischemic syndromes are triggered by systemic inflammatory factors.

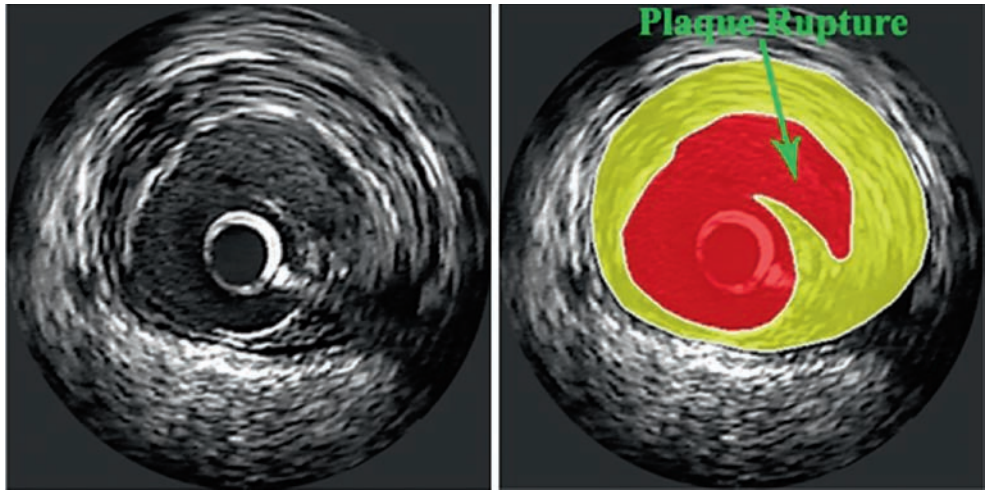

Fig. 9.2. Plaque Rupture: The site of plaque rupture can be identified in an IVUS image as a blood-filled recess in the plaque beginning at the luminal-intimal border

IVUS provides an important role in the diagnostic assessment of lesions which cannot be accurately evaluated by angiography.[8] Overlapping contrast-filled structures on angiography may obscure ostial and bifurcation lesions. IVUS has been employed in the catheterization laboratory to characterize these segments and other indistinct lesions, including those at sites of aneurysms, focal spasm, and angiographic haziness.[8,19] The left main coronary artery can be a challenge to accurately assess angiographically, as a result of its short length, aortic cusp opacification obscuring the ostium, and concealment of the distal part by bifurcation or trifurcation branches.[20] Slow withdrawal of the ultrasound catheter into the aorta, with the guiding catheter disengaged from the left main ostium, facilitates accurate characterization of the left main coronary artery.[21,22]

IVUS has also been employed to investigate the natural history of other pathological processes within the coronary arteries. The development of vasculopathy as result of neointimal hyperplasia is the leading cause of poor clinical outcome following heart transplantation. Given that the transplanted heart is denervated and patients tend to be asymptomatic until late stages, surveillance for development of vasculopathy in recipients is imperative. IVUS is the most sensitive modality for the detection and quantitation of the extent of vasculopathy in transplant patients.[23] As a result, IVUS has been incorporated into clinical surveillance strategies of heart transplant recipients in many large centers.

Utility of Intravascular Ultrasound in Interventional Cardiology

IVUS has been used extensively in the setting of percutaneous coronary interventions. Ultrasonic imaging has characterized that restenosis following interventions results from a combination of arterial recoil, remodeling, and neointimal hyperplasia.[8] IVUS has provided an important tool for the guidance of coronary interventions and to evaluate the efficacy of new devices. Lesions of intermediate stenosis are often difficult to evaluate using angiography. Assessment is also difficult in the setting of atypical symptoms, vessel tortuosity, plaque eccentricity, and severe calcification. IVUS facilitates the decision whether to proceed with revascularization in such patients. Correlation with functional studies, such as fractional flow reserve, has provided guidelines from IVUS measurements, to identify hemodynamically significant lesions.[24] The presence of a minimum lumen cross-sectional area of at least 4.0 mm^2 typically suggests that the lesion can be medically managed.[25,26] Additional criteria, including the presence of a percent cross-sectional area stenosis greater than 70%, provide increasing support for the need for intervention in the setting of a minimum lumen area between 3.0 and 4.0 mm^2.[24,25]

Adjunctive imaging with IVUS guides the appropriate choice of intervention required for management of a specific lesion. The choice of intervention is often dependent on the extent and distribution of plaque, extent of calcification, and the presence of thrombi or dissections. Ultrasonic imaging provides valuable information for the treatment of ostial lesions and coronary artery dissections, which are not sufficiently discernable on angiography. Accurate imaging of the full longitudinal extent of a lesion reduces the requirement to deploy multiple stents to achieve adequate lesion coverage.

Directional coronary atherectomy (DCA) employs a mechanically driven cutter to shave off plaque. IVUS identifies specific lesions, which are suitable for this approach. As calcification impedes tissue removal by DCA, and its detection by ultrasonic imaging minimizes the chance of procedural failure. Calcified lesions are more amenable to high-speed rotational atherectomy, in which a rotating burr debulks plaque. IVUS imaging has demonstrated that rotablation selectively removes less compliant plaque material.[27]

Advances in stent technology have revolutionized the interventional approach to coronary lesions. Early stents were complicated by significant rates of acute thrombosis, requiring the use of

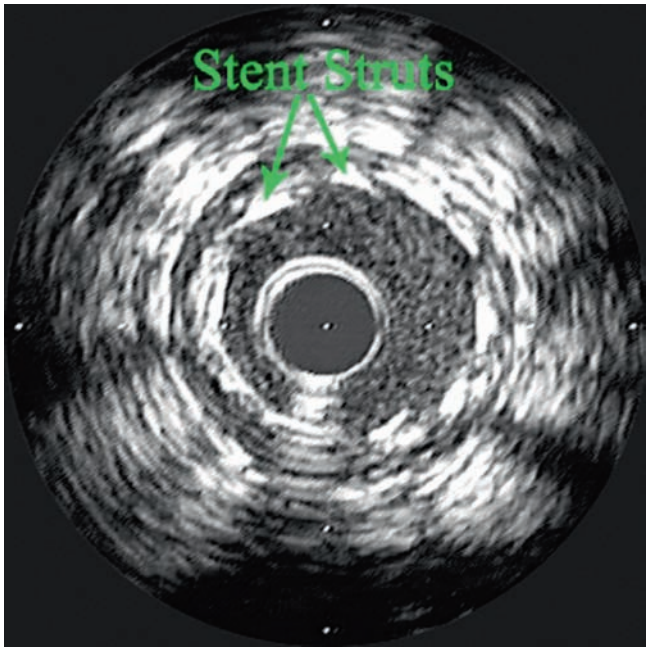

Fig. 9.3. Stent: An IVUS image demonstrating an implanted stent

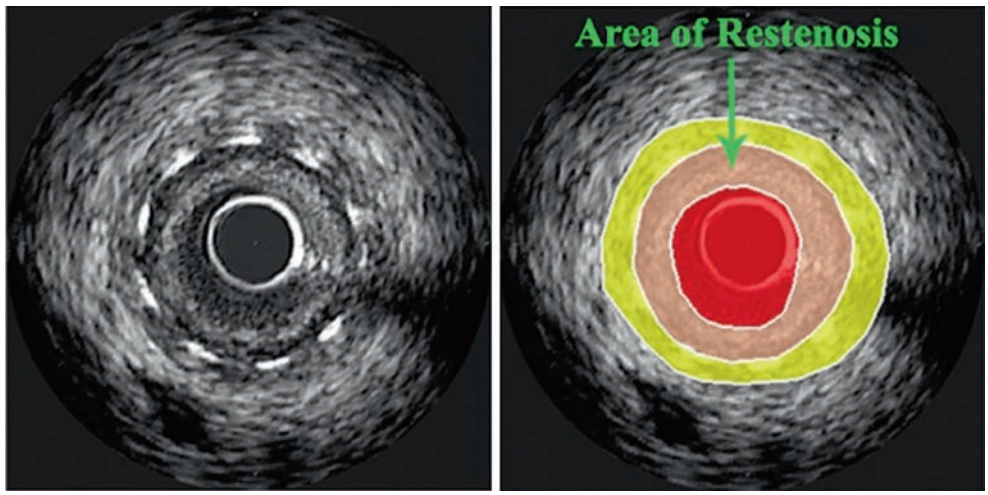

Fig. 9.4. Restenosis: In-stent restenosis is characterized by the proliferation of neointimal tissue inside the stent struts, as demonstrated in this IVUS image

intensive anticoagulation. Seminal IVUS observations demonstrated that low-pressure stent deployment resulted in inadequate stent expansion and apposition of the struts to the vessel wall, both factors increasing the risk of acute thrombosis.[28] Subsequent studies revealed that high inflation pressures could be applied in a safe manner without the use of ultrasound, promoting acceptable stent expansion and strut apposition[29,30] (Fig. 9.3). This practice was associated with lowering the risk of thrombosis and the need for intense anticoagulation, improving clinical outcomes. As IVUS demonstrated that high inflation pressures could be safely employed for stent deployment, the routine use of ultrasonic guidance in the majority of interventional procedures was no longer required.

Neointimal proliferation within stents promotes late lumen loss and restenosis (Fig. 9.4). The detection of inadequate stent expansion on ultrasound has been reported to predict subsequent restenosis.[31] IVUS imaging has provided important insights into the development of neointimal proliferation within stents and has guided the development of strategies to prevent its formation. Coronary ultrasound demonstrated that application of intracoronary radiation had a profound inhibitory effect on the development of neointimal proliferation.[8] IVUS studies assisted in the definition of optimal radiation dose and location of delivery to result in the most effective prevention of restenosis.

The development of drug-eluting stents, coated with antiproliferative and immunosuppressive agents, has had a substantial impact on restenosis rates. Their widespread use has limited the role of radiation therapy to a small number of resistant cases. Clinical trials comparing the efficacy of various drug-eluting stents have employed IVUS to monitor for the incidence and extent of structural change within the stented region.[32] However, increasing use has highlighted a significant association between stent underexpansion and subsequent thrombosis within these devices.[33] The ability of guidance with IVUS has the potential to enable the use of larger diameter stents and higher inflation pressures. In fact, achieving a postprocedure minimum lumen area of 5.0 mm^2 is the most significant predictor of a decreased prospective incidence of developing angiographic restenosis, in patients receiving sirolimus-coated stents.[34] While IVUS helped define the optimal use of a series of interventional approaches, it is likely that with ongoing problems of restenosis and thrombosis within stents that they are likely to be used in an increasing manner, in order to achieve more effective management of symptomatic lesions.

Evaluating the Impact of Medical Therapies on Plaque Progression

Visualization of the entire artery wall thickness permits accurate quantitation of atheroma burden. The leading edges of the lumen and EEM can be defined by manual planimetry or automatic edge detection software packages (Fig. 9.1), in accordance with consensus guidelines for acquisition and analysis of IVUS images by the American College of Cardiology and European Society of Cardiology.[35] Given that the medial layer of the artery wall has a negligible thickness (less than 500 μm) the area between these leading edges is conventionally regarded to be atherosclerotic plaque.

$$\text{Plaque area} = \text{EEM area} - \text{Lumen area}$$

The ability to continuously acquire images during catheter withdrawal generates a series of consecutive cross-sectional images. A pullback rate of 0.5 mm s^{-1} results in a spatial separation of 1 mm between every 60th. Summation of plaque areas in images spaced 1-mm apart permits calculation of the total atheroma volume (Fig. 9.5).

$$\text{Total Atheroma Volume}\,(\text{mm}^3) = \sum(\text{EEM}_{\text{area}} - \text{Lumen}_{\text{area}})$$

The ability to evaluate the same arterial segment at different time points provides an important opportunity to evaluate factors that influence the natural history of plaque progression. Given that atherosclerosis is a systemic and not focal process, determination of atheroma volume provides a significant advantage compared with investigations at a single site. This is further supported by the difficulty in precisely matching a single site at two different time points. In contrast, segments that are defined by the fixed, anatomic location of arterial side branches can be precisely matched, allowing for accurate comparisons (Figs. 9.6 and 9.7).

Differences in the length of segment evaluated in subjects participating in clinical trials will have a profound impact on

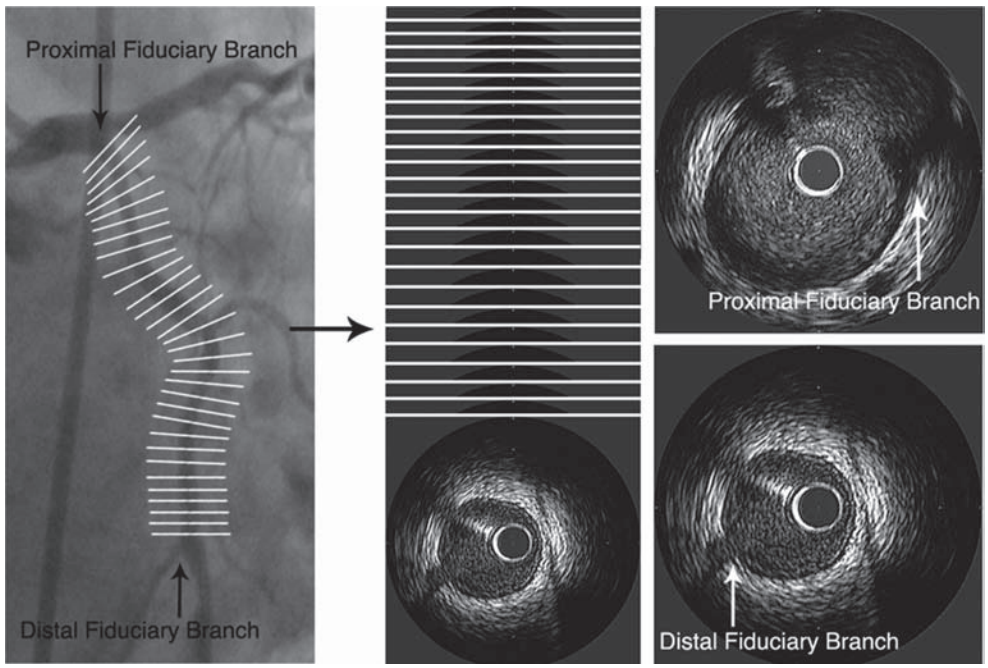

Fig. 9.5. Volumetric Analysis: Multiple IVUS images are generated during pullback. Fixed anatomic fiduciary points, such as side branches, define the segment of interest. Volumetric extent of atheroma (and other measures) can then be calculated by summating plaque areas in equally spaced individual images within the segment of interest. The fiduciary points, as seen in the IVUS pullback images, are shown on the right

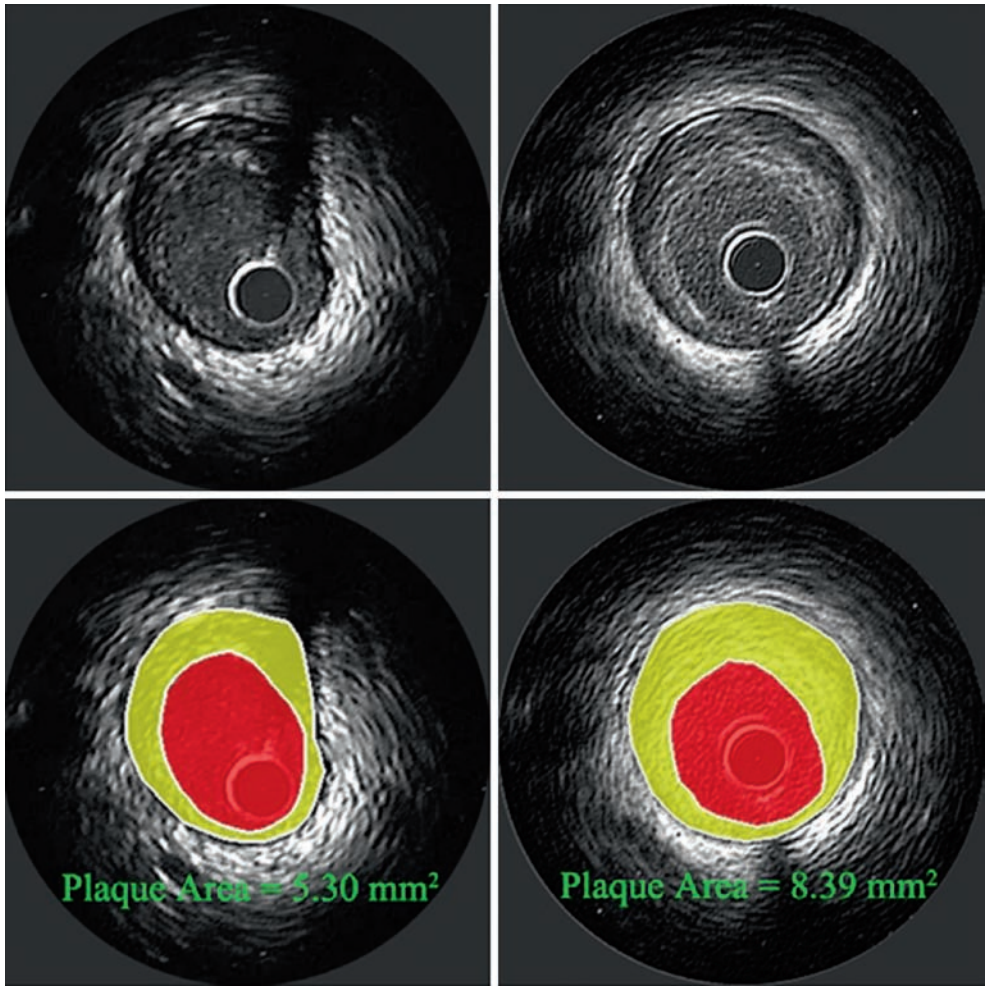

FIG. 9.6. Plaque Progression: Matched IVUS images demonstrating an increase in plaque area from baseline (*left*) to follow-up (*right*)

the calculated atheroma volume. To control for the heterogeneity in segment length, atheroma volume is adjusted, or normalized, by multiplication of the mean plaque area within a segment by the median number of evaluable images for the entire study cohort.

$$\text{Normalized TAV}\,(\text{mm}^3) = \frac{\sum(\text{EEM}_{\text{area}} - \text{Lumen}_{\text{area}})}{\text{Number of Frames per Patient} \times \text{Median Number Frames for all Patients}}$$

The extent of atherosclerosis can also be calculated as the percent atheroma volume (PAV), which defines the amount of atheroma as a proportion of the volume occupied by the entire arterial wall.

$$\text{Percent Atheroma Volume} = \frac{\sum(\text{EEM}_{\text{area}} - \text{Lumen}_{\text{area}})}{\sum \text{EEM}_{\text{area}}} \times 100$$

The lower variability in PAV measurements permits the use of smaller sample sizes and has become the primary end point in many studies that assess the impact of medical therapies on plaque progression. A number of additional measures are obtained at the time of analysis. These include maximum and minimum plaque thickness and the degree of plaque calcification. Serial measurements of each of these parameters have been performed in a number of studies that evaluate the impact of medical therapies that target established atherosclerotic risk factors and novel pathologic targets within the artery wall.

Lowering Low-Density Lipoprotein Cholesterol

While lowering levels of low-density lipoprotein cholesterol (LDL-C) with statins reduces event rates in placebo-controlled trials,[36–38] their optimal use in clinical practice remains uncertain. In particular, considerable debate has focused on whether intensive lowering of LDL-C results in incremental benefit. The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)[39] trial compared the effects of a

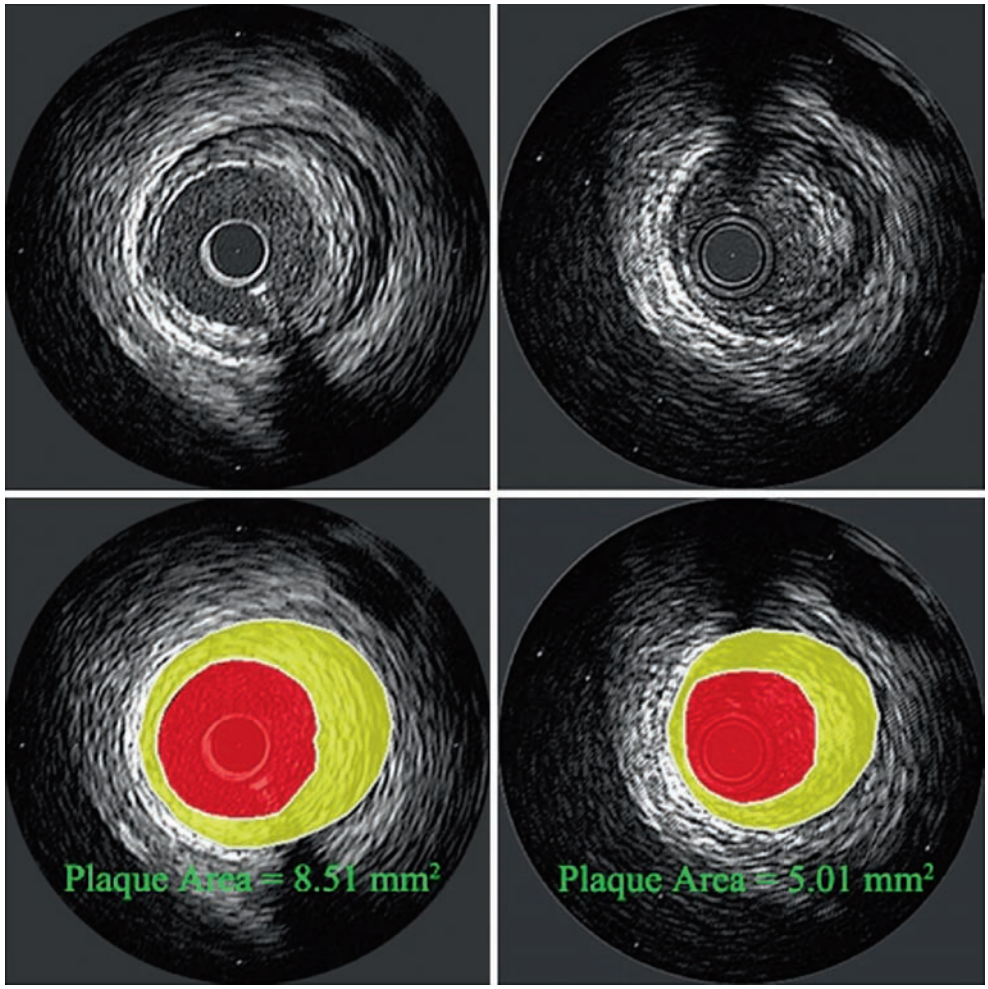

Fig. 9.7. Regression: Matched IVUS images demonstrating a decrease in plaque area from baseline (*left*) to follow-up (*right*)

moderate (pravastatin 40 mg) and intensive lipid-lowering (atorvastatin 80 mg) strategy in 502 patients with angiographic CAD and LDL-C between 125 and 210 mg dL^{-1}. The mean LDL-C levels were reduced to 110 and 79 mg dL^{-1} in the pravastatin- and atorvastatin-treated groups, respectively. After 18 months of therapy, serial IVUS measurements demonstrated no significant change in atheroma volume (−0.4%) compared with baseline in atorvastatin-treated patients, while there was evidence of disease progression in the pravastatin group (+2.7% change in total atheroma volume). The direct relationship between LDL-C lowering and rate of plaque progression suggested that intensively lowering levels of LDL-C could halt the natural history of atheroma progression.

Subsequent analysis revealed that pravastatin-treated patients required an additional 30 mg dL^{-1} lowering of LDL-C to achieve the same impact on plaque progression. This suggested that factors, in addition to differences in LDL-C lowering, contributed to the observed benefit of high-dose atorvastatin. The finding of greater reductions in levels of the inflammatory marker C-reactive protein (CRP) with atorvastatin and a direct relationship between changes in CRP and atheroma volume suggest that anti-inflammatory properties of statins may contribute to their benefit.[40] These findings correlate well with the results of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT) study,[41] which demonstrated a beneficial impact of atorvastatin 80 mg compared to pravastatin 40 mg on clinical events in patients with acute coronary syndromes. Furthermore, it was reported that patients who achieved the greatest lowering of both LDL-C and CRP demonstrated the lowest number of clinical events and rate of plaque progression. The National Cholesterol Education Program subsequently included an optional treatment goal of 70 mg dL^{-1} for management of high-risk patients.

A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID)[42] investigated the impact of lowering LDL-C to very low levels. 349 patients with angiographic CAD were treated with rosuvastatin 40 mg for 24 months, resulting in lowering of LDL-C by 53.2% to 60.8 mg dL^{-1} and raising

high-density lipoprotein cholesterol (HDL-C) levels by 14.7% to 49 mg dL^{-1}. These changes were associated with significant reductions in all measures of atheroma burden, consistent with regression. Statistically significant reductions in atheroma burden were only observed in patients who achieved LDL-C levels less than 70 mg dL^{-1}. This result supported the concept that lowering LDL-C levels to very low levels with statin monotherapy could reverse plaque accumulation within the coronary arteries. These findings also support early reports of regression in response to statin therapy in small cohorts of subjects.

Promoting the Biological Activity of HDL

The protective role of HDL in atherosclerosis has been consistently demonstrated in epidemiological and animal studies.[43–45] The finding that current therapies raise HDL-C levels by modest degrees has stimulated the search to develop new strategies to promote HDL function. IVUS has recently been employed in clinical trials that have evaluated the potential efficacy of experimental agents that can be administered either by intravenous infusion or chronic oral therapy.

Carriers of the mutant apolipoprotein A-I Milano (AIM) have low levels of HDL-C, but are protected from atherosclerotic cardiovascular disease. Administration of AIM in animal models has a substantial impact on atherosclerotic lesion formation. A small clinical trial was subsequently performed to assess the impact of infusing AIM in humans.[46] 47 patients, within 2 weeks of an acute coronary syndrome, received weekly intravenous infusions of saline or low (15 mg kg^{-1}) or high (45 mg kg^{-1}) doses of reconstituted HDL particles containing AIM and phospholipids (ETC-216) weekly for 5 weeks. IVUS performed within 2 weeks of the final infusion revealed regression of coronary atherosclerosis in patients receiving either dose of ETC-216. The rapid regression observed is consistent with the observation that lipid-depleted forms of HDL are efficient promoters of cholesterol efflux. The recent report from the Effect of rHDL on Atherosclerosis – Safety and Efficacy (ERASE) study[47] that infusing reconstituted HDL particles containing wild-type apoA-I promotes plaque regression provides further support for the concept that infusing HDL may be of clinical utility in the management of patients with acute ischemic syndromes. The impact of these therapies on clinical outcome remains to be defined in large-scale clinical trials.

While current therapies raise HDL-C levels to a modest degree, emerging evidence suggests that this can have a substantial impact on clinical outcome. In a recent pooled analysis of clinical trials that employed serial assessments by IVUS, the modest elevation of HDL-C levels was found to be an independent predictor of the impact of statin therapy on atheroma progression.[48] In fact, raising HDL-C levels by as little as 7.5%, in addition to intensive lowering of LDL-C, resulted in the greatest degree of plaque regression. This observation further supported the concept that improvements in the functional quality of HDL may be the most important target for new therapies.

Inhibiting cholesteryl ester transfer protein (CETP) has been proposed as a therapeutic strategy to raise HDL-C levels. CETP facilitates the transfer of esterified cholesterol from HDL to LDL particles. Pharmacological inhibitors of CETP have been demonstrated to inhibit lesion formation in animal models and to raise HDL-C levels by greater than 50% in humans.[49] Serial IVUS recently evaluated the impact of CETP inhibition in humans. The Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) study[50] randomized 910 patients with CAD to treatment with either atorvastatin as monotherapy or in combination with 60 mg of torcetrapib daily for 24 months. Atorvastatin was administered at a dose to achieve a LDL-C level less than 100 mg dL^{-1}. Addition of torcetrapib resulted in a 61% increase in HDL-C and 20% decrease in LDL-C. Despite the remarkable effect on plasma lipids, torcetrapib had no effect on the change in PAV. It remains to be determined whether the lack of benefit was due to the formation of dysfunctional forms of HDL, the ability of torcetrapib to raise blood pressure, or some unknown vascular toxicity of the compound. The finding that torcetrapib does not slow progression of coronary atherosclerosis or carotid intimal-medial thickness is consistent with its lack of efficacy in a large clinical trial.[50]

Inhibition of Cholesterol Esterification

Uptake of cholesterol ester by macrophages is the pivotal event in the formation of foam cells, the cellular hallmark of atherosclerotic plaque. In addition to lowering systemic levels of LDL-C, it has been proposed that inhibition of cholesterol esterification may be a therapeutic strategy of potential utility in cardiovascular prevention. Serial IVUS has demonstrated that two pharmacological inhibitors of acyl-coenzyme A:cholesterol acyltransferase (ACAT), a pivotal factor in promoting cholesterol esterification, do not have a beneficial impact on atheroma progression. The Avasimibe and Progression of Lesions on Ultrasound (A-PLUS) study[51] evaluated the impact of the ACAT inhibitor avasimibe compared to placebo on the rate of plaque progression. No significant difference was observed between the treatment groups with regard to the change in atheroma volume. LDL-C levels were higher in avasimibe-treated patients, consistent with its ability to induce cytochrome P450 3A4 and statin metabolism.

The ACAT Intravascular Atherosclerosis Treatment Evaluation (ACTIVATE)[52] study compared the effect of pactimibe, an ACAT inhibitor with no influence on statin metabolism, and placebo on the serial change in atheroma burden after 18 months of treatment. The groups did not differ with regard to the primary end point, the change in PAV. However, greater reductions in atheroma volume throughout the entire segment evaluated and the most diseased 10-mm segment were observed

in placebo-treated patients. This suggested that pactimibe may have a detrimental influence on plaque progression. Accumulation of cytotoxic, intracellular-free cholesterol has been proposed as a potential mechanism that may contribute to the detrimental effects of pactimibe on plaque accumulation.[53,54]

Blood Pressure-Lowering Therapies

While the role of hypertension in promoting cardiovascular disease is well established, the optimal management of blood pressure in patients with CAD is controversial. Epidemiological observations suggest that cardiovascular risk begins to increase at levels of systolic blood pressure considered to be within the normal range.[55,56] In the Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT)[57] trial, 1991 patients with angiographically documented CAD and diastolic blood pressure less than 100 mm Hg were treated with amlodipine 10 mg daily, enalapril 20 mg daily, or placebo for 24 months. Treatment with amlodipine significantly reduced a combination of cardiovascular clinical events. In a unique study design, 274 patients also underwent serial evaluation of atheroma burden by IVUS. This revealed progression in placebo-treated patients, a trend toward progression with enalapril and no change in atheroma volume with amlodipine. In particular, the findings on imaging complemented the impact of therapy on clinical events. A direct relationship was observed between blood pressure reduction and change in atheroma volume. These findings suggest that blood pressure should be more intensively lowered in patients with CAD.

Monitoring the Impact of Therapies on Transplant Vasculopathy

The use of ultrasonic imaging within the coronary arteries has been employed to evaluate the impact of medical therapies aimed at preventing formation and propagation of transplant vasculopathy. Emerging evidence of the inflammatory events promoting formation of neointimal hyperplasia in the coronary arteries following heart transplantation has stimulated the search to develop immunomodulatory therapies. Serial IVUS monitored the impact of the immunomodulatory and antiproliferative agent, everolimus, in heart transplant recipients.[58] Treatment with everolimus reduced the incidence and progression of vasculopathy compared with standard medical therapy with azathioprine. This beneficial impact on the coronary arterial wall was associated with a reduction in the incidence of clinical events including death, rejection and retransplantation.

Limitations of Intravascular Ultrasound

The invasive nature of IVUS limits its application to patients who require a coronary angiogram for clinical indications. It precludes the opportunity to study the natural history of atherosclerosis in patients without clinical symptoms and to directly translate the impact of medical therapies to the setting of primary prevention. The emerging ability of computed tomography and magnetic resonance imaging to image the artery wall may provide a potential option to study the natural history of atherosclerosis in a noninvasive fashion. As imaging is typically performed within one coronary artery, it is uncertain whether the impact of medical therapies in regression-progression studies is homogenous throughout the coronary arterial tree.

The quality of information obtained is critically dependent on the ability to generate high-resolution images of the vessel wall. Limitations in catheter size preclude ultrasonic imaging in small vessels and at sites of severe luminal stenosis. A number of imaging artifacts impair the ability to directly visualize the entire artery wall. Imaging artifacts are commonly due to the presence of the guidewire, arterial side branches, calcium, bright haloes surrounding the imaging catheter, geometric distortion due to imaging in an oblique plane, and nonuniform rotational distortion due to uneven drag on the catheter resulting in cyclical oscillations and image distortion. Technological advances in catheter profile and ultrasound frequency have made substantial improvements in the ability to consistently acquire high-resolution imaging within the coronary arteries.

IVUS provides a suboptimal characterization of plaque composition to evaluate the natural history of atherosclerosis. The broad distinction between lipidic, fibrotic, and calficic plaque lacks the precision required to assess serial changes in plaque components in response to use of medical therapies. Technological developments permit analysis of the radiofrequency backscatter, providing a tissue map with good correlation with plaque composition on histology. Preliminary studies using this approach have suggested that lowering levels of LDL-C with statins reduces the lipidic and increases the fibrotic components of atherosclerotic plaque.[59]

Another major challenge for clinical trials that employ imaging modalities as surrogate markers of atherosclerosis is to define the relationship between the impact of therapies on the artery wall and clinical outcome. A number of observations suggest complementary effects of interventions on clinical events and the rate of atheroma progression. However, further evidence is required to directly associate atheroma burden and its change with clinical outcome.

Overview

The evolution of IVUS provides the opportunity to directly visualize the arterial wall with high-resolution imaging. This has permitted a greater understanding of the factors influencing the natural history of atherosclerosis and other vasculopathies within the coronary arteries. Its use has played a pivotal role in the development and validation of new medical and interventional approaches to the management of patients with CAD.

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