Intravascular Ultrasound
Novel Pathophysiological Insights and Current Clinical Applications
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Abstract—Intravascular ultrasound (IVUS) is a valuable adjunct to angiography, providing new insights in the diagnosis of and therapy for coronary disease. Angiography depicts only a 2D silhouette of the lumen, whereas IVUS allows tomographic assessment of lumen area, plaque size, distribution, and composition. The safety of IVUS is well documented, and the assessment of luminal dimensions represents an important application of this modality. Comparative studies show the greatest disparities between angiography and ultrasound after mechanical interventions. In young subjects, normal intimal thickness is typically \( \approx 0.15 \) mm. With IVUS, lipid-laden lesions appear hypoechoic, fibromuscular lesions generate low-intensity echoes, and fibrous or calcified tissues are echogenic. Calcium obscures the underlying wall (acoustic shadowing). The extent and severity of disease by angiography and ultrasound are frequently discrepant. Arterial remodeling refers to changes in vascular dimensions during the development of atherosclerosis. At diseased sites, the external elastic membrane may actually shrink in size, contributing to luminal stenosis. The interpretation of IVUS relies on simple visual inspection of acoustic reflections to determine plaque composition. However, different tissue components may look quite similar, and artifacts may adversely affect ultrasound images. IVUS commonly detects occult disease in angiographically “normal” sites. In ambiguous lesions, ultrasound permits lesion quantification, particularly for left main coronary disease. IVUS has emerged as the optimal method for the detection of transplant vasculopathy. An important potential application of ultrasound is the identification of atheromas at risk of rupture. The mechanisms of action of interventional devices have been elucidated using IVUS, and ultrasound is used by some operators to select the most suitable interventional device. IVUS-derived residual plaque burden is the most useful predictor of clinical outcome. In restenosis after balloon angioplasty, negative remodeling is a major mechanism of late lumen loss. IVUS is not routinely used for stent optimization, and there is no consensus regarding optimal procedural end points. Ultrasound has proven useful in evaluating brachytherapy. New and emerging applications for IVUS are continuing to evolve, particularly in atherosclerosis regression-progression trials. (Circulation. 2001;103:604-616.)

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Rationale for Ultrasound Imaging

Limitations of Angiography
Although angiography has endured for >40 years as the predominant method used to define coronary anatomy, many studies have challenged the accuracy and reproducibility of this technique. The visual interpretation of angiograms exhibits significant observer variability and correlates poorly with post-mortem examination. Angiography depicts arteries as a planar silhouette of the contrast-filled lumen. Any arbitrary angiographic projection can misrepresent the true extent of luminal narrowing. Mechanical interventions may increase luminal irregularity, impairing the accuracy of angiography. An assessment of lesion severity requires the measurement of luminal diameter within the lesion and an uninvolved “normal” segment. However, necropsy studies demonstrate that disease is usually diffuse, with no truly normal segment. Angiography is also confounded by outward
remodeling of the vessel wall, which may conceal early atherosclerosis. Although remodeled lesions may not restrict blood flow, retrospective studies demonstrate that nonobstructive lesions represent the most common substrate for acute coronary syndromes.

**Advantages of Ultrasound**

Several characteristics inherent to ultrasound imaging offer potential advantages in the evaluation of coronary disease. The tomographic orientation of ultrasound enables a visualization of the full circumference of the vessel wall, not just two surfaces. Angiographic vessel or stenosis sizing requires calibration to correct for radiographic magnification. However, ultrasound devices use an electronically generated scale, with measurements performed using direct planimetry. The tomographic perspective of ultrasound enables an assessment of vessels that are difficult to image by angiography, including diffusely diseased segments, ostial or bifurcation stenoses, eccentric plaques, and angiographically foreshortened vessels. Finally, the penetrating nature of ultrasound provides unique images of the atherosclerotic plaque, not merely the lumen.

**Equipment and Technique**

**Ultrasound Catheters**

The equipment required to perform intracoronary ultrasound consists of 2 major components, a catheter incorporating a miniaturized transducer and a console containing the electronics necessary to reconstruct the image. High ultrasound frequencies are used, typically centered at 20 to 50 MHz and providing excellent theoretical resolution. At 30 MHz, the wavelength is 50 μm, yielding a practical axial resolution of \( \approx 150 \) μm. Determinants of lateral resolution are more complicated and depend on imaging depth, which average 250 μm at typical coronary diameters. Current catheters range from 2.6 and 3.5 French (0.87 to 1.17 mm) and can be placed through a 6-French guiding catheter.

Two different approaches to transducer design have emerged: mechanically rotated devices and multielement electronic arrays. Mechanical probes use a drive cable to rotate a single piezoelectric transducer at 1800 rpm, yielding 30 images per second. In electronic systems, multiple transducer elements (currently up to 64) in an annular array are activated sequentially to generate the image. Multielement designs typically result in catheters that are easier to set up and use, whereas mechanical probes have traditionally offered superior image quality, although these differences have narrowed in recent years. Imaging studies are usually recorded on videotape, although one system permits digital recording of \( \geq 60 \) seconds with permanent archiving on a recordable CD-ROM.

**Examination Technique**

Standard techniques for intracoronary catheter delivery are used for intravascular examination. Heparin and intracoronary nitroglycerin are routinely administered, and the coronary artery is subselectively cannulated. The operator advances or retracts the imaging device over the wire, recording images on videotape or CD for subsequent analysis. Many centers use a motorized pullback device to withdraw the catheter at a constant speed (between 0.25 and 1 mm/s; most frequently, 0.5 mm/s). However, a single pullback, even when controlled by a motor, may be insufficient for a complete diagnostic examination. Side branches visualized by angiography or ultrasound are useful landmarks to facilitate interpretation and comparisons in sequential examinations.

**Safety of Coronary Ultrasound**

The safety of intracoronary ultrasound is well documented.\textsuperscript{15,16} Studies report complication rates varying from 1% to 3%; the complication most frequently reported is transient spasm, which responds rapidly to intracoronary nitroglycerin. The major complication rate (dissection or vessel closure) is <0.5%. Nearly all major complications occur in patients undergoing intervention rather than diagnostic imaging. Examination of vessels previously imaged by IVUS compared with noninstrumented vessels shows no accelerated progression of atheroma at 1 year of follow-up. Despite the favorable safety profile, subselective coronary instrumentation always carries a potential risk of vessel injury. Accordingly, only operators experienced in intracoronary catheter manipulation should perform intravascular imaging.

**Image Interpretation and Measurements**

**Lumen Appearance and Measurements**

At frequencies >20 to 25 MHz, flowing blood exhibits a characteristic pattern of echogenicity, observed as finely textured echoes moving in a swirling pattern (Figure 1). Blood “speckle” can assist image interpretation; for example, it can help confirm the communication between a dissection plane and the lumen. The pattern of blood echogenicity depends on blood flow velocity; it shows increased intensity and a more coarse texture when flow is reduced. Blood speckle is also more prominent at higher imaging frequencies, which may interfere with delineation of the blood-tissue interface. This phenomenon has so far limited IVUS imaging devices to frequencies \(<\)40 to 45 MHz, although automatic methods of blood noise reduction may substantially reduce the problem in the future.

Assessment of luminal dimensions affects many therapeutic decisions and represents an important application for IVUS. Lumen area is determined by planimetry of the leading edge of the blood-intima acoustic interface. Because of the speckled nature of ultrasound, individual video frames may not contain a continuous intimal leading edge. Accordingly, a review of moving images is routinely performed to assist edge detection by “filling-in” a discontinuous border. Comparisons of ultrasound luminal measurements with angiography usually show a close correlation for vessels without atherosclerosis. However, for diseased arteries, investigators report only a moderate correlation \((r=0.7 \text{ to } 0.8)\) and a standard error \(>0.5 \text{ mm}\).\textsuperscript{3,5,17}

Comparative studies show the greatest disparities between angiography and ultrasound after mechanical interventions.\textsuperscript{18} In this setting, the shape of the lumen may be extremely complex, with plaque fissures or deep wall dissections.\textsuperscript{14,18} Accordingly, the reduced correlation between IVUS and angiography is probably explained by an irregular, noncircular cross-sectional profile, which cannot be adequately depicted by angiography.\textsuperscript{13}
Extraluminal channels contribute little to blood flow, raising the question of whether such structures should be included in tracing the luminal contour. A commonly applied approach distinguishes the true lumen area from the “dissection area.” Lumen eccentricity is often reported using a variety of indices that compare minimal and maximal lumen dimensions.

Normal Arterial Appearance
Studies performed in vivo or using excised, pressure-distended vessels have characterized the appearance of normal coronary arteries. An ultrasound reflection is generated at a tissue interface if there is an abrupt change in acoustic impedance. In the normal artery, 2 such interfaces are usually observed, one at the border between blood and the leading edge of the intima and a second at the external elastic membrane (EEM), which is located at the media-adventitia border (Figure 1). The tunica media is relatively sonolucent and, in good-quality images, it can be visualized as a distinct, relatively sonolucent layer. The trailing edge of the intima is poorly defined and cannot be used reliably for measurements. The outer border of the adventitia is also indistinct, merging imperceptibly into the surrounding tissues. In normal arteries, the intima is thin, consisting mostly of endothelial cells and connective tissue, with a relatively small difference in impedance from blood. In 30% to 50% of normal coronary arteries, the thin intima reflects ultrasound poorly, so it is not visualized as a separate layer. This finding has led some observers to propose that a trilaminar wall represents evidence of early atherosclerosis. In young subjects, the reported normal value for intimal thickness is typically 0.15 ± 0.07 mm. Most investigators use 0.25 to 0.50 mm as the upper limit of normal.

Characterization of Atherosclerosis
Ultrasound provides a unique method for studying the morphology of atherosclerosis in vivo. Studies have compared the ultrasound appearance of plaques to histology in freshly explanted human arteries. Lipid-laden lesions appear hypoechoic, fibromuscular lesions generate low-intensity or “soft” echoes, and fibrous or calcified tissues are relatively echogenic. Lipid-laden or fibromuscular lesions may exhibit a prominent echogenic fibrous cap, although most fibrous caps are too thin to be resolved by IVUS. Calcium obstructs ultrasound penetration, obscuring the underlying vessel wall (acoustic shadowing; Figure 2). The angle subtended by the calcified arc is often used to quantify the severity of calcification. Ultrasound imaging has shown significantly higher sensitivity than fluoroscopy in the detection of coronary calcification. Target lesion calcification is detected by ultrasound in 70% to 80% of patients undergoing intervention, whereas fluoroscopy detects calcium in 10% to 35%. The arc of calcium measured by ultrasound is usually greater in patients with angiographically visible calcification.

Figure 1. Normal anatomy by IVUS. In magnified image (right), thin intimal leading edge is highlighted by arrows. Scale is 1 mm between markers.

Figure 2. Atheroma morphology by IVUS. Soft (left), mixed fibrous and calcified (center), and heavily calcified atheromas (right) are illustrated.
Atheroma Measurements

Ultrasound atheroma measurements are obtained from leading edge to leading edge, a standard approach that has been validated in echocardiography. Atheroma area is determined by planimetry of the intimal leading edge and EEM, thereby including the media in measurements. The rationale for this convention arises from several phenomena. First, the media is not always distinguished as a sonolucent layer, whereas the EEM represents a reliable boundary. Second, the location of the trailing edge of the intima is confounded by the spread of the ultrasound signal into the media (called blooming). Atheroma area measurements performed in this fashion correlate closely with histology. However, calcium-induced acoustic shadowing can obscure a large portion of the EEM, requiring interpolation with a reduction in accuracy. In the literature, the vague term “vessel area” is sometimes substituted for “EEM area.”

The percentage of the EEM area occupied by atheroma is often calculated, and this parameter is often referred to as “percent area stenosis,” “plaque area stenosis” or, simply, “plaque burden.” It should be realized, however, that this measurement is not equivalent to angiographic percent stenosis, which represents an expression of luminal narrowing at the lesion relative to a reference segment. Some laboratories routinely measure maximum atheroma thickness, which is defined as the longest distance between the intimal leading edge and the EEM. The difference between maximum and minimum thickness represents a measure of plaque eccentricity. The circumferential extent of disease is also commonly classified by determining whether abnormal intimal thickening is present throughout the 360° arterial circumference. The longitudinal extent of disease is also commonly reported; it is defined as “diffuse” if the intimal thickness is abnormal at every site within the segment.

Discrepancies With Angiography

The extent and severity of disease by angiography and ultrasound are frequently discrepant. The percentage of stenosis determined by ultrasound is usually substantially greater than that determined by angiography. This phenomenon is a consequence of 2 major factors, the diffuse nature of atherosclerosis affecting the angiographically “normal reference sites” and adaptive enlargement of the EEM, which maintains a constant lumen during early atherosclerosis (Figure 3). Studies have demonstrated a significant discordance between angiography and ultrasound in assessing plaque distribution, highlighting the inaccuracy inherent in determining plaque location from a projected 2D silhouette of the lumen. IVUS demonstrates that the majority of plaques are eccentrically located, a phenomenon with important implications for guiding coronary interventions, particularly for selective plaque removal techniques such as directional atherectomy.

Arterial Remodeling

The term arterial remodeling refers to changes in vascular dimensions during the development of atherosclerosis (Figure 4). This phenomenon was initially described from necropsy specimens by Glagov et al., who reported a positive correlation between EEM and atheroma area. At lesions with a stenosis <40%, an increase in arterial size “overcompensated” for plaque accumulation, resulting in an increase in lumen area. At advanced lesions, remodeling was less evident and lumen size was reduced. The authors hypothesized that this phenomenon represented a compensatory mechanism to preserve lumen size. IVUS provides cross-sectional areas of the lumen, atheroma, and EEM, allowing the in vivo study of remodeling. Ultrasound studies show a correlation between EEM and plaque area and confirm overcompensation in early disease. Although the exact mechanism of remodeling remains uncertain, this phenomenon helps explain the underestimation of the disease severity by angiography and may influence the assessment of the true vessel size in guiding coronary interventions.
IVUS studies have demonstrated a new dimension to arterial remodeling: negative remodeling or arterial shrinkage\textsuperscript{31,32} (Figure 5). At diseased sites, the EEM may actually shrink in size, contributing to luminal stenosis. However, it is important to realize that when remodeling is defined by comparing lesion to reference EEM areas, there is an inherent assumption that the reference EEM area represents the original vessel size. Studies of atherosclerotic coronary arteries demonstrate that angiographic reference segments are invariably diseased by ultrasound. Therefore, these reference segments are probably remodeled and may not provide an accurate measure of vessel size. Recently, negative remodeling has been implicated in restenosis after mechanical intervention\textsuperscript{33,34}.

Recent and intriguing IVUS studies have examined the relationship between remodeling and clinical presentation in patients with coronary artery disease\textsuperscript{35}. In unstable patients, both EEM and plaque areas were significantly larger than the corresponding measurements in stable patients. Positive remodeling seems to be significantly more prevalent in the unstable group and negative remodeling more prevalent in the stable group.

Figure 4. Example of coronary remodeling. Left, Angiogram is completely normal. However, 2 sites in left anterior artery (arrows) show a varying extent of atherosclerosis by IVUS. More distal site (top right) has little disease, but more proximal site (bottom right) has a large crescentic atheroma. The lumen size at both sites is similar because of remodeling, resulting in a false-negative angiogram.

Figure 5. Example of stenosis with negative remodeling. A distal reference segment (gray arrow on left) has EEM area of 16.4 mm\textsuperscript{2} (middle panels). Stenosis (black arrow on left; right panels) has EEM area of 13.9 mm\textsuperscript{2}, demonstrating that it is partly due to negative remodeling.
Limitations of IVUS
Although contemporary ultrasound devices produce remarkably detailed views of the vessel wall, interpretation must rely on simple visual inspection of acoustic reflections to determine plaque composition. The echogenicity and texture of different tissue components may exhibit comparable acoustic properties and therefore appear quite similar. A sonoluent luminal mass of tissue may represent intracoronary thrombus, while a nearly identical appearance may result from an atheroma with a high lipid content. Thus, IVUS is accurate in determining the thickness and echogenicity of vessel wall structures, but it is not consistently able to provide actual histology. Validated methods do not yet exist for objective or automated classification of atheromatous lesions. Although promising, radiofrequency analysis is not yet reliable enough for routine clinical applications.

Artifacts may adversely affect ultrasound images, including “ring-down” artifacts produced by acoustic oscillations in the piezoelectric transducer that obscure the near field, resulting in an acoustic catheter size larger than its physical size. Geometric distortion can result from imaging in an oblique plane (not perpendicular to the long axis of the vessel). An important artifact, “non-uniform rotational distortion,” arises from uneven drag on the drive cable of the mechanical style catheters, resulting in cyclical oscillations in rotational speed, observed as visible distortion of the image. The physical size of ultrasound catheters (currently ~1.0 mm) constitutes an important limitation in imaging severe stenoses.

Diagnostic Applications

Angiographically Normal Coronary Vessels
Angiographically normal coronary arteries are encountered in ~10% to 15% of patients undergoing catheterization for suspected coronary disease. IVUS commonly detects occult disease in these patients. However, no short- or long-term studies have determined whether disease detected exclusively by ultrasound portends a worse prognosis than “true normal” angiography. If any luminal irregularity is present by angiography, ultrasound will usually demonstrate disease at most other examined sites. The prevalence of disease at angiographically normal sites confirms the finding, previously reported from necropsy studies, that coronary disease is usually diffuse, not focal, and that angiography frequently underestimates disease burden.

Angiographically Indeterminate Lesions
Despite improvements in x-ray equipment, angiographers still commonly encounter lesions that elude accurate characterization, despite thorough examination using multiple radiographic projections. In ostial and bifurcation lesions, the stenosis may be obscured by overlapping contrast-filled structures. Intermediate stenoses (angiographic severity ranging from 40% to 75%) are particularly problematic in patients whose symptomatic status is difficult to assess. In ambiguous lesions, ultrasound provides a tomographic perspective, independent of the radiographic projection, that often permits lesion quantification. In 2 large prospective series, intracoronary ultrasound changed the management strategy (primarily decisions to perform or defer interventions or choice of interventional device) in ~20% of examinations performed immediately before coronary intervention. In both studies, however, the selection of patients for ultrasound may have resulted in an overestimation of the true impact of intravascular imaging on clinical decision-making.

Left Main Coronary Disease
Assessment of left main coronary disease by angiography represents a particularly difficult clinical problem. Three major anatomic factors impair angiographic left main evaluation. Aortic cusp opacification or “streaming” of contrast may obscure the ostium, the short length of the vessel may leave no normal segment for comparison, and the distal left main artery may be concealed by bifurcation or trifurcation. Ultrasound can help overcome these confounding factors. The ultrasound transducer is placed distal to the left main vessel, and a slow pullback to the aorta is performed with the guiding catheter disengaged. There is no consensus regarding the cross-sectional area at which the left main obstruction is considered critical. However, a stenosis area >50% or an absolute area <9 mm² have been proposed as criteria for left main stenosis severity requiring revascularization.

Transplant Coronary Artery Disease
Coronary disease represents the major cause of death in the first year after transplantation. This disease is often clinically silent because the heart is denervated and ischemia by functional testing does not usually occur until the disease is advanced. Although angiography has been performed annually for surveillance, the diffuse nature of the disease often impairs detection. IVUS has emerged as the optimal method for early detection. Disease by angiography is present in 10% to 20% of patients at 1 year and ~50% by 5 years. The prevalence of arteriopathy detected by ultrasound is much higher; abnormal intimal thickening is seen by IVUS in 50% of patients by 1 year. The definition of abnormal intimal thickness is controversial because the categorical classification of a continuous variable, intimal thickness, into normal or abnormal is inherently arbitrary. Most ultrasound studies define the threshold for transplant vasculopathy as an intimal thickness >0.5 mm.

Despite the young donor age, conventional atherosclerosis was detected in 56% of patients at a mean donor age of 32 years. However, the natural history of donor lesions after transplantation is largely unknown. In the first year after transplantation, progression of donor disease occurred in 42% of patients. A case report documenting regression of donor lesions has also been published. Ultrasound studies have demonstrated an association between the severity of disease by ultrasound and clinical outcome, with an increased incidence of death, myocardial infarction or retransplantation in those with more severe disease. Rapidly progressive intimal thickening (≥0.5 mm increase) in the first year after transplantation has major negative prognostic significance. Intravascular imaging has been used to evaluate therapies for transplant vasculopathy, including statin drugs, ACE inhibitors, and calcium blockers.
Unstable Plaque and Thrombi

An important potential application of intracoronary ultrasound is the identification of atheromas at risk of rupture. Acute coronary syndromes frequently develop in territories with minimally diseased vessels rather than high-grade stenoses.53 The histology of unstable plaques usually reveals a lipid-laden atheroma with a thin fibrous cap (Figure 6). Preliminary ultrasound reports have associated echolucent, presumably lipid-laden, plaques with acute coronary syndromes.54 Positive remodeling has also been associated with an unstable clinical presentation54 (Figure 7). Intraluminal thrombi at ruptured or fissured plaques are considered the hallmark of acute coronary syndromes. Small studies have attempted to define the ultrasound appearance of thrombi.55,56 However, IVUS is still unreliable in differentiating acute thrombi from echolucent plaques because of the similar echogenicity and texture of lipid-laden tissue, loose connective tissue, and stagnant blood. Ultrasound is less reliable than angioscopy for the diagnosis of thrombi in vitro.57 Radiofrequency analysis has shown some promise in differentiating between thrombus and atheroma.58

Interventional Applications

A number of new devices have been added to the interventional armamentarium over the last decade. The mechanisms of action of these devices and their interaction with different plaque morphologies have been largely elucidated using IVUS. Although IVUS has played a pivotal role in understanding the effects of interventional devices, the precise clinical role for ultrasound during intervention has, for the most part, not been well defined in large-scale clinical trials.

Preinterventional Imaging

Ultrasound is used by some operators to select the device most suitable for a specific patient or lesion. The process of device selection depends on several factors, most commonly measurements of atheroma severity, plaque distribution, depth and extent of calcification, and the presence of thrombi or dissections. Single-center studies have reported that ultrasound imaging frequently influences the operators’ appreciation of target lesion severity, morphology, and the optimal approach to therapy.40 However, in these studies, patients were not randomized, allowing for bias in the selection of...
Guidance for Angioplasty and Atherectomy

In the early 1990s, studies were initiated to determine whether intravascular imaging could predict clinical and angiographic outcome after intervention. The goal of these investigations was to determine whether some morphological features, such as the presence or extent of dissection, or morphometric features (e.g., lumen size or plaque burden) were related to restenosis. The first multicenter trial, Post-IntraCoronary Treatment Ultrasound Result Evaluation (PITURE), showed no statistically significant predictors of outcome in a relatively small cohort (250 patients) using early generation equipment. Single-center studies, however, identified residual plaque burden as an independent predictor of outcome in multivariable analysis. To examine this issue more completely, phase II of the Guidance by Ultrasound Imaging for Decision Endpoints (GUIDE) trial enrolled 524 patients undergoing angioplasty and/or atherectomy. Among the angiographic and ultrasound variables, ultrasound-derived residual percent plaque burden was the most powerful predictor of clinical outcome, with a risk ratio of 1.7. However, the long-term clinical impact of differences in angiographic result has not been established.

The first trial to directly address the outcome of ultrasound guidance of balloon angioplasty was the Clinical Outcomes With Ultrasound Trial (CLOUT), in which IVUS imaging was performed after obtaining a satisfactory angiographic result. If vessel remodeling at the lesion or involvement of the reference segment was apparent on ultrasound, a larger balloon size was used. After IVUS, the balloon-to-artery ratio increased from 1.12 to 1.30, resulting in an increase in angiographic minimal lumen diameter from 1.95 to 2.21 mm. Several subsequent studies addressed the clinical outcome of IVUS-guided balloon sizing. In 2 single-center, nonrandomized studies of aggressive balloon sizing (based on the media-to-media dimension determined by IVUS), rates of major events and revascularization were similar to stenting. In these studies, stents were used as a backup strategy if aggressive angioplasty resulted in dissection (a strategy that has been called provisional stenting).

Although balloon angioplasty has been available for many years, the mechanisms of lumen gain have been difficult to elucidate using angiography. Ultrasound demonstrates plaque fracture and arterial wall dissection much more often than angiography, with some form of disruption seen in between 50% and 75% of cases. Vessel wall stretching represents another potential mechanism of lumen gain; this is most evident when the angioplasty is performed on soft echolucent plaques (Figure 8). Plaque compression was originally suggested as a mechanism for lumen gain. However, recent in vivo ultrasound studies have disproved any significant contribution of compression, demonstrating “axial redistribution” rather than compression of the plaque at angioplasty sites.

In the setting of directional coronary atherectomy, IVUS can facilitate lesion selection, demonstrating the presence of significant calcification, which is an important predictor of procedural failure. In particular, ultrasound imaging can identify superficial calcium, which is associated with poor tissue retrieval. The most striking finding from IVUS studies of directional atherectomy is the substantial residual plaque burden after an atherectomy in which the angiographic result seems to be good. Several studies have addressed the issue of more aggressive plaque removal on the basis of ultrasound imaging. In the Optimal Atherectomy Restenosis Study (OARS), ultrasound guidance yielded a target lesion revascularization rate of 17.8% and an angiographic restenosis rate of 28.9% at 6 months. However, these results failed to reach statistical significance compared with balloon angioplasty with stent backup. In the Adjunctive Balloon Angioplasty After Coronary Atherectomy Study (ABACAS), ultrasound-guided atherectomy provided a trend to lower restenosis rates than angioplasty (23.6% versus 19.6%), but this trend did not achieve statistical significance. In contrast, the Stent versus Directional Coronary Atherectomy Randomized Trial (START) demonstrated a significant reduction in restenosis in a group receiving aggressive IVUS-guided atherectomy (16%) compared with stenting (33%).

IVUS imaging in the context of high-speed rotational atherectomy has confirmed the principle of differential cutting (selective removal of less compliant plaque material, most notably calcium) As in the case of directional atherectomy, IVUS demonstrates a large residual plaque burden after rotablation. Measurement of the true vessel size by ultrasound may allow safe use of larger burrs, with a greater lumen gain and less residual plaque burden.
Mechanisms of Restenosis
For the first 15 years of interventional cardiology, investigators believed that the predominant mechanism of restenosis after angioplasty and atherectomy was intimal proliferation. Ultrasound studies in the peripheral vessels by Pasterkamp and colleagues presented the first indication that negative remodeling, or localized shrinkage of the vessel, was a major mechanism of late lumen loss. Mintz et al studied 212 native coronary arteries in patients undergoing repeat catheterization for recurrent symptoms or research protocols after coronary interventions. At follow-up, there was a decrease in EEM area and an increase in plaque area at the target lesion. Interestingly, >70% of lumen loss was attributable to the decrease in EEM area, whereas the neointimal area accounted for only 23% of the loss. Moreover, the change in lumen area correlated more strongly with the change in EEM area than with the change in plaque area. For lesions with an increase in EEM area at follow-up (47% of segments studied), there was no change or an actual gain in lumen area and a reduction in angiographic restenosis (26% versus 62%; \( P < 0.0001 \)).

These observations have provided a key insight into the reduction of restenosis observed with stenting. Unlike the restenotic response to angioplasty or atherectomy, which is a mixture of arterial remodeling and neointimal growth, stent restenosis is primarily due to neointimal proliferation. In serial ultrasound studies, late lumen loss correlated strongly with the degree of in-stent neointimal growth (\( r = 0.98 \)). The amount of intimal proliferation has been shown to correlate with the pre-stent plaque burden. In a serial study using IVUS of stented coronary segments, no significant change occurred in the area bound by stent struts, indicating that stents can resist the arterial remodeling process. This phenomenon, combined with the greater initial lumen expansion accomplished with stenting, results in a lower net restenosis rate than that with angioplasty or atherectomy.

Guidance for Stenting
In part because of this reduction in restenosis, use of stents for percutaneous revascularization has increased exponentially over the last 10 years. More refined stents and developments in adjuvant pharmacological therapy have improved both short- and long-term results. IVUS imaging has played a pivotal role in understanding and optimizing the benefits of stent therapy.

During the initial clinical experience with stent implantation, acute thrombosis was the most feared complication, limiting application to a relatively narrow subset of patients and leading to the routine use of warfarin. The pioneering observations of Columbo et al., based on IVUS, dramatically changed clinical practice. These investigators demonstrated that deployment with conventional balloon pressures resulted in a high incidence of incomplete expansion and apposition. In a pivotal series, these investigators used ultrasound imaging to guide high-pressure dilatation, achieving full expansion and complete stent apposition in 96% of 359 consecutive but nonrandomized patients (Figure 9). Patients with optimal expansion received antiplatelet therapy using aspirin and ticlopidine but no warfarin. These technical modifications resulted in outstanding clinical outcomes. The incidence of acute and subacute stent thrombosis was <1%, and target vessel revascularization for symptomatic restenosis at 6 months was 13%.

The concept of high-pressure stent implantation disseminated quickly, and larger trials demonstrated the safety of stent implantation using high pressures and antiplatelet therapy alone (without IVUS guidance). Consistent with these later trials, IVUS is not routinely used for stent optimization today, although there is great variability in its application from center to center, and conflicting evidence exists concerning the impact of IVUS on long-term freedom from restenosis. In a retrospective analysis of 315 lesions treated by high-pressure stenting, additional ultrasound-triggered inflations improved in-stent lumen area by >25% in 83 lesions (26%). Because in-stent restenosis is determined by the degree of intimal hyperplasia, it is a reasonable hypothesis that larger lumens should translate into lower rates of clinically significant restenosis.

Four multicenter trials have directly addressed the question of whether the increased lumen areas resulting from ultrasound guidance actually lead to a significant reduction in restenosis. In the nonrandomized Can Routine Ultrasound Influence Stent Expansion (CRUISE) study, 8 centers were assigned to ultrasound and 10 centers to angiographic guidance with a blinded ultrasound examination at the end of the procedure. The ultrasound-guided group achieved a 0.9 mm larger stent area, which translated into a 38% lower rate of target vessel revascu-

Figure 9. Fully deployed and incompletely deployed stents. In left panel, all stent struts are fully in contact with vessel wall, whereas in right panel, several struts are incompletely apposed (black arrows).
Several groups have demonstrated that the degree of in-stent neointimal hyperplasia is independent of the achieved stent lumen size.88 This explains the higher restenosis rates in smaller vessels and inadequately expanded stents, in which the acute lumen gain is not adequate to accommodate for tissue proliferation, resulting in significant late loss and restenosis. A target minimal stent area is applied in some laboratories as a shorthand criterion for identifying an optimal result (although, of course, the threshold will actually vary with the size of the vessel). Some laboratories aim at reaching a lumen symmetry index >0.7, determined as the minor in-stent diameter divided by the major diameter. Other investigators have advocated more extensive stenting to cover reference segment disease or dissections detected by IVUS. Interestingly, the expansion, apposition, and symmetry end points are not achieved in most cases.

In addition to evaluating stent expansion and strut apposition, ultrasound imaging may be useful in identifying reference segment disease or dissections that require additional interventions. The presence of significant persistent flow, limiting lesions, or dissections has been linked to a higher likelihood of stent thrombosis.89 Such findings are often angiographically occult, either not detectable at all or appearing as areas of vague haziness.90 The extent of neointimal hyperplasia at the stent margins has been linked to preexisting reference segment disease.91

Several studies have demonstrated the benefits of intravascular imaging before the implantation of coronary stents. In heavily calcified lesions, stenting results in a relatively small and asymmetrical acute lumen gain.92 In ostial lesions, ultrasound can identify whether the lesion involves the “true” ostium or if it spares first 1 or 2 mm. When stents are used to treat dissections, ultrasound often reveals the involvement of a longer vessel segment than appreciated angiographically. This is particularly relevant in cases of bailout stenting for threatened abrupt closure, where a residual dissection in the vicinity of the stent may increase the risk of stent thrombosis.

Percutaneous treatment of stent restenosis is a challenging task. Balloon angioplasty results are satisfactory in focal narrowing but disappointing in diffuse stent restenosis. Ultrasound imaging may prove very helpful in the management of these cases, often revealing that the stent expansion was inadequate at the initial procedure, and proper balloon sizing may lead to an improved lumen area (Figure 10). In adequately expanded stents, ultrasound-guided use of debulking devices such as rotational atherectomy or laser ablation has been advocated. Ultrasound imaging helps determine whether the site of maximum tissue growth has occurred within the stent or in the vicinity of the stent margins.
adjacent reference segment near the stent border. This is particularly valuable with radiolucent stents, where precise angiographic localization is problematic. However, it should be noted that the various approaches suggested for the treatment of stent restenosis have been studied in relatively small numbers of patients. Larger randomized studies are needed to determine the optimal strategy for the treatment of these difficult cases.

**IVUS and Brachytherapy**

Ultrasound has proven useful in clarifying the mechanisms of benefit and refining the techniques in brachytherapy. Ultrasound studies demonstrate that radiation has the potential to inhibit profoundly neointimal proliferation within a stent. In the nonstented segments, studies suggest that radiation initiates a process of vessel expansion (a type of positive remodeling). These effects are strongly influenced by the dose delivered to the media or adventitia, which is dependent on the thickness and composition of the atheroma and the position of the catheter in the lumen. Current research is examining whether an ultrasound image-based dosing algorithm will be required to optimize therapeutic benefit. Ultrasound has already demonstrated the potential for radiation to accelerate restenosis at the edges of the treatment region, where the dosing falls off (“candy wrapper effect”; Figure 11).

**Future Directions**

The use of IVUS in the United States is in a phase of slow growth, with an average of 5% to 8% of coronary interventions currently being performed with IVUS guidance (mostly for stent optimization). IVUS use in Europe is considerably less than that in the United States and, in Japan, use is considerably higher, reflecting differing reimbursement rates and practice patterns. Technical developments in both catheters and systems are continuing with several companies, focusing on catheter deliverability, ease of use, and image quality.

New and creative areas of IVUS-guided therapy are being tested. Ultrasound provides the guidance modality for the so-called PICAB procedure (percutaneous in-situ coronary artery bypass), in which a conduit is created between a proximal coronary vessel and a coronary vein, providing a new source of oxygenated blood to ischemic myocardium. New combined imaging/stent delivery and imaging/atherectomy catheters are under development.

The ability of ultrasound to quantify precisely the extent of intramural atherosclerotic plaque is currently being exploited through a series of regression-progression trials that are currently underway. These include the Reversal of Atherosclerosis with Lipitor (REVERSAL) trial (600 patients), which is comparing 2 lipid-lowering regimens (expected completion, 2002), and the Norvasc for Regression of Manifest Atherosclerotic Lesions (NORMALISE) trial (750 patients), which is comparing amlopidine, enalapril, and placebo (expected completion, 2003). In both studies, IVUS measurements represent the primary end points of the trials. Such studies avoid the inherent limitations of angiographic regression trials and have the potential to define a new standard for the evaluation of drug therapy to limit the progression of atherosclerosis.

**References**


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