Intravascular Ultrasound in Graft

46

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Abstract

Intravascular ultrasound (IVUS) is the generic name for any ultrasound technology used in vivo within the blood vessels. IVUS has been recognized as a sensitive tool to assess the anatomy of the epicardial coronary arteries, including intimal and adventitial wall thickness. The procedure is performed at the time of the routinely schedule angiogram and has been demonstrated to be safe and have reproducible findings. Although quantitative coronary angiography has been used to assess late lumen loss, IVUS provides more detailed and reliable information on the extent and distribution of intimal tissue, the presence of stent under expansion, and vascular remodeling after coronary artery bypass surgery. IVUS could be usefully to analyze both arterial and vein grafts, including radial grafts and to monitoring graft failure.

Keywords

Intravascular ultrasound (IVUS) • Coronary artery bypass grafting (CABG) • Epicardial coronary arteries • Lumen • Wall thickness • Spectral analysis • Virtual histology intravascular ultrasound (VH-IVUS)

Introduction

Coronary heart disease (CHD) remains a leading cause of morbidity and mortality [1, 2]. Approximately 350,000 coronary artery bypass grafting (CABG) surgeries are performed annually in the United States [3]. The choice between percutaneous coronary intervention (PCI) and CABG should be made by the Heart Team, and be based on the extent of coronary artery disease (CAD), expected completeness of revascularization, associated valvular disease, and the presence of comorbidities [4]. The increasing prevalence of CAD and the costs of revascularization have resulted in heightened interest regarding the appropriate use of coronary revascularization, which can improve patients' clinical outcomes [5].

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In the 1980s, the potential value of epicardial ultrasound for the quantitative assessment of coronary artery luminal and wall dimensions had been demonstrated, as well as for coronary anastomosis visualizations. Recently, intravascular ultrasound (IVUS) also shows itself to be a promising method to determine vessels' dimensions [6], and could help both the choice of medical therapies and the follow-up after surgeries.

Intravascular Ultrasound Technology

IVUS is the generic name for any ultrasound technology used in vivo within the blood vessels. More specifically, intracoronary ultrasound enables imaging of the epicardial coronary arteries from within the lumen, including intimal and adventitial wall thickness [7, 8]. IVUS is particularly suitable because it is readily available and because of its relatively high image resolution, accurate and reproducible mea-

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surements, ability to detect mild, angiographically silent atherosclerotic disease that can be a precursor of future coronary events, and suitability for serial (baseline and follow-up) imaging and analysis [2]. IVUS cannot predict which segments will change most (or least) or even which segments will progress or regress, other than the fact that calcified segments change the least. Despite its limitations, invasive imaging with IVUS remains the gold standard [2].

The equipment for performing IVUS consists of a percutaneous transducer catheter and a console for reconstructing images of the arterial wall, nature of atherosclerotic plaques, and the vessel lumen [1, 7, 8]. An IVUS system consists of a catheter mounted with a miniature transducer at the tip and a console for processing the data and displaying the images. The transducer may be mechanical, consisting of a single rotating transducer driven by a flexible drive cable, or it may be electronic, consisting of a set of transducing crystals arranged circularly [1].

IVUS of a coronary artery is performed in a catheterization laboratory. The IVUS catheter is inserted into an artery in the groin area, and it is navigated to a coronary artery. The catheter is usually positioned distally to the lesion, stent, or graft, and withdrawn at a constant speed; it is made manually or with an automatic mechanical pullback device. The miniature transducer produces high-frequency sound waves differently because of differences in density. The reflected ultrasound waves are processed electronically to reconstruct black-and-white images displayed on a monitor. The films resulting from the IVUS performed in patients are stored in a DVD, DICOM format. The cardiologists may interpret these images online or offline, with specific software, to assess the images resulting from the exams [1, 9]. Medical ultrasound images are produced by passing an electrical current through a piezoelectric (pressure-electric) crystalline material (usually ceramic) that expands and contracts to produce sound waves when electrically excited. After reflection from tissue, part of the ultrasound energy returns to the transducer, which produces an electrical impulse that is converted into the image [10]. As an ultrasound pulse encounters a boundary between two tissues—fat and muscle, for instance—the beam will be partially transmitted. The degree of reflection depends on the difference between the mechanical impedance of the two materials (for example, the imaging of higher calcification structures is associated with acoustic shadowing) [10].

IVUS provides a topographic 360° sagittal scan of the vessel [11], and these tomographic images (or 3-dimensional images, depending on the system) allow characterization of the arterial lumen dimension (including in regions difficult to access): vessel luminal and total areas; plaque area; and presence of coronary calcifications, dissection, plaque rupture, and thrombosis [1, 7–9]. IVUS minimum lumen cross-section area (CSA) can be a major anatomic predictor of events. In patients with a minimum lumen CSA of more than 4.0 mm^2, the event rate has been especially low [12, 13]. The presence of intimal thickening detected by IVUS also provides prognostic information regarding patient mortality and future cardiac events [14].

IVUS uses a miniaturized ultrasound transducer mounted on the tip of a catheter. In principle, IVUS is based on the emission, attenuation, and backscattering of ultrasonic waves that are converted to electrical signals and then processed as an image. Recently new intravascular imaging techniques with other energy sources (e.g., light) have been introduced [15].

The envelope (amplitude) of the radiofrequency signal is used to form the grayscale IVUS image. In recent years, information derived from the spectral analysis of IVUS backscattered data has been added to grayscale reconstructions to obtain a more detailed characterization of plaque morphology as a color-coded map [15]. The IVUS image quality can be described by two factors: spatial resolution (the ability to discriminate small objects) and contrast resolution (the distribution of the grayscale of the reflective signal; it is referred to as dynamic range). The image has two principal directions: axial (parallel to the beam) and lateral (perpendicular to both the beam and the catheter). For a 20–45 MHz IVUS transducer, the typical resolution is 70–200 mm axial resolution, with 5 mm penetration, and 200–250 μm laterally [10, 16]. Grayscale IVUS allows robust quantitative measurements including lumen, vessel, and plaque area; qualitative assessment of lesions preintervention; and quantitative assessment and complications of lesions postintervention; however, it has poor sensitivity for detection of lipid-rich plaque (67 %) [16].

Blood speckle with 40 MHz ultrasound can cause confusion when identifying the lumen-tissue border or detecting in-stent neointimal tissue, etc.; but it is easily solved by saline (negative contrast) injection through the guiding catheter. Standard grayscale IVUS is limited, in part, because it uses only reflected ultrasound amplitude to formulate the image and requires significant postprocessing [16]. In an effort to improve plaque characterization, spectral analysis (VH-IVUS) combines frequency and amplitude analysis and uses an algorithm developed from known tissue types to detect fibrous plaque, fibrofatty plaque, necrotic core (NC), and dense calcium. These are represented as green, light green, red, and white, respectively. Thus, VH-IVUS provides additional information by offering an accurate assessment of plaque composition on top of the 3-dimensional anatomical assessment provided by grayscale IVUS [17]. Reported sensitivity and specificity of VH-IVUS are 91.7 and 96.6 % for identification of the lipid-rich NC. VH-IVUS cannot detect thrombus formation (in fact, thrombus appears as either fibrotic or fibrofatty plaque depending on the age of the thrombus) and has not been validated for assessment of stent metal or intimal hyperplasia [16].

Because the IVUS catheter provides a sonar image of intimal and medial thickness, IVUS is more sensitive than coronary angiography, which only outlines the lumen with contrast dye. Whereas angiography depicts only a 2-dimensional lumen silhouette, IVUS allows tomographic assessment of lumen area, plaque size, and lesion distribution [18]. The coronary angiogram may appear normal, whereas IVUS could reveal significant amounts of atherosclerosis (or intimal thickening). IVUS is a valuable adjunct to angiography, providing further insights into both diagnosis and therapy, including stent implantation [7, 11, 15, 18–21]. IVUS could detect calcification twice as often as angiography and it is more sensitive at detecting significant left main coronary artery stenosis than angiography alone, peculiarly when the angiography showed ambiguous or inconclusive left main coronary artery disease [13]. There is a dissociation between angiography (or "lumenography"), the true extent of plaque burden, and correspondence with a physiological significance of coronary arterial stenosis [19, 22]. Contrary to findings upon angiography, IVUS identifies the diffuse nature of atherosclerosis involving not only the parent (left main coronary artery [LMCA]) segment, but also both flow dividers (left anterior descending [LAD] or left circumflex [LCX]). On IVUS, the independent predictors of LMCA segment calcification were found to be related to prior CABG, increasing age, Caucasian race, and bifurcation location [22]. IVUS cannot fully assess the physiological significance of lesions (in deciding if a coronary lesion needs intervention); therefore, operators may have to use additional techniques to evaluate physiological stenosis, especially in non-left main disease lesions and small coronary arteries (less than 3 mm minimal lumen diameter). Fractional flow reserve (FFR) and IVUS are often used in complementary modalities during an intervention to evaluate different aspects of coronary atherosclerosis disease and to help decide on the best approach for disease management. Intravascular diagnostic techniques are quickly evolving, and differences in their learning curves and the skill with which they are employed can potentially influence outcomes [23].

When we analyzed procedure time, additional costs, and safety, there is little international information. Intravascular ultrasound appears to be a safe tool when used in coronary interventions. Periprocedural complications associated with the use of IVUS in coronary interventions ranged from 0.5 % in the largest study of 4 %. Coronary rupture was reported as well as other complications including prolonged spasms of the artery after stenting, dissection, and femoral aneurysm [1]. An assessment of the predictors of grade III coronary perforation showed that this adverse event was associated with complex coronary lesions (type B2 or C lesions), coronary occlusions, and the use of rotablation or IVUS during the procedure. Notably, IVUS is more likely to be used in complex lesions or for those patients in which PCI is complicated [24]. This procedure is performed at the time of the routinely schedule angiogram and has been demonstrated to be safe with reproducible findings [7, 25]. IVUS guidance quite conceivably could increase the procedure time that would lead to a reduction in patient throughput or the need to add new facilities. The former option increases waiting times and could increase the rate of adverse events, while in the latter the associated costs must be included in the procedure analysis [8]. If all CABG procedures were billed at the emergency rate, the cost difference in favor of the IVUS branch would reduce by £2 [8]. However, the additional IVUS costs are still an important limiting factor for IVUS utilization by health services around the world.

The Clinical Uses of IVUS in Native Arteries

Among the clinical uses of IVUS, the most frequently requested was the analysis of plaque morphologies (Table 46.1). Plaque composition may be an important contributing factor in the occurrence and extent of distal embolization [17]. Because the percentage of atheroma volume is calculated as plaque and media volume divided by external elastic membrane volume, it can also be influenced by remodeling. Positive remodeling (an increase in external elastic membrane volume) could reduce the percentage of atheroma volume with no absolute change in plaque mass, and negative remodeling (or an increase in vessel tone) would decrease external elastic membrane volume to increase the percentage of atheroma volume with no absolute change in plaque mass. Thus, an inward shift of the remodeling pattern may be considered a sign of plaque stabilization [2]. Virtual histology intravascular ultrasound (VH-IVUS) is a widely available technique allowing real-time determination of plaque composition in vivo using radiofrequency analysis of the backscattered ultrasound signal [17].

IVUS has an important use at coronary artery disease diagnosis. The majority of acute coronary syndromes (ACS) are caused by coronary plaque rupture at the site of a thin-cap fibroatheroma (TCFA) with subsequent local thrombosis [18, 26]. Postmortem pathological examinations showed that 60–70 % of the culprit lesions for ACS demonstrated plaque rupture. Several IVUS studies revealed the presence of plaque rupture in 14–66 % of the culprit lesions from patients with ACS in vivo. Moreover, recent three-vessel IVUS studies have also revealed that plaque rupture may be present not only in the culprit lesion but also in nonculprit lesions. IVUS images revealed the presence of plaque rupture in 42 % of the patients with iliofemoral arterial disease [27]. The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study was the first multicenter, natural history study that employed angiography along with grayscale and radiofrequency VH-IVUS to

Table 46.1 The clinical uses of IVUS

1. Definition of coronary atherosclerosis: vessel lumen, vessel total area, plaque morphology, presence of calcification, thrombosis or plaque rupture
2. Virtual-histology coronary analysis
3. Definition of silent atherosclerosis: when angiography was ambiguous or indeterminate lesion severity
4. Definition of peripheral artery atherosclerosis
5. Differentiation between atherosclerosis disease and artery dissection
6. Helping the treatment decision at a stable coronary acute disease
7. Helping the treatment decision at a chronic total coronary occlusion
8. Definition of the cause and morphology of a spontaneous artery dissection
9. Guiding stent implantation at a percutaneous coronary intervention, and analyzes the presence of stent restenosis or thrombosis at the outcome follow-up
10. Analyzing vascular remodeling after CABG or heart transplantation
11. Definition of rupture or failure of CABG
12. Definition of cardiac allograft disease

relate site-specific quantitative and qualitative measures of coronary disease to major adverse cardiac events at 3 years. The current analysis from the prospective PROSPECT study has demonstrated the proximal predominance of large plaques in the LAD (left anterior descending coronary artery) and LCX (left circumflex coronary artery), the diffuse nature of such plaques in the RCA (right coronary artery), and the relative paucity of high-risk plaque in the LMCA (left main coronary artery) [18, 26, 28]. The VIVA study reported an association between VH-IVUS-identified thin-capped fibroatheroma and major adverse cardiovascular events, and also reported an association with biomarkers that confer increased cardiovascular risk, such as serum cytokines or shortened leukocyte telomere length (DNA-based cardiovascular risk predictors) [29]. Even in no clearly clinical evaluations of ACS, IVUS could provide explanations. For example, the notion that women have "normal" coronary arteries should be reconsidered in light of the IVUS sub-study within the Women's Ischemia Syndrome Evaluation (WISE) showing that, among the sample of 100 such women, almost 80 % had definite coronary atherosclerosis that was concealed by positive remodeling [30].

The use of IVUS has been broadly investigated also in stable coronary acute disease with many different subsets of lesions. IVUS is an imaging diagnostic tool and does not provide assessment of the functional severity of a stenosis. Previously accepted cut-off limits of 3.5 or 4.0 mm^2 for major epicardial artery stenosis and 6.0 mm^2 for left main stenosis have been shown to be unreliable and poorly correlated with fractional flow reserve (FFR). Somewhat better results are obtained when the absolute IVUS measurements are corrected for the reference vessel size. Once the indication to treatment is established, when more information is needed, IVUS is far superior to FFR because it provides an anatomical characterization of the lesion in terms of vessel size and plaque composition, and can control stent expansion and strut apposition [30].

IVUS could be useful for investigating peripheral artery disease (PAD). In one study with 126 patients with peripheral artery disease of the iliofemoral territory, after the diagnostic angiography, IVUS imaging was performed at baseline and repeated after percutaneous transluminal angioplasty. IVUS imaging revealed the presence of plaque rupture in 42 % of the patients with iliofemoral arterial disease [27].

At chronic total coronary occlusion, bilateral angiography and intravascular ultrasound imaging can be helpful as well for special techniques such as guide anchoring, various retrograde approaches, and specific wiring manipulation techniques [18].

IVUS guidance during stent implantation is well-established in the international literature. IVUS evaluation before the stenting procedure cannot only measure the degree of stenosis, plaque involvement, and anatomic configuration (with delineation of major side branches) [31]. In this review, the authors suggested that IVUS and FFR guidance during drug-eluting stent (DES) implantation has the potential to influence treatment strategy and reduce both DES thrombosis and repeat revascularization [32]. Conversely, the increased hemodynamic assessment of coronary lesions using FFR and anatomic assessment using IVUS could have contributed to the decrease in PCI [33]. In another study, based on the MAIN-COMPARE study, the authors investigated patients with unprotected left main coronary artery (LMCA) stenosis who underwent either CABG surgery or PCI, and they compared long-term outcomes of IVUS-guided stenting and conventional angiography-guided stenting. They founded that long-term mortality after unprotected LMCA stenting was reduced by IVUS guidance as compared with conventional angiography guidance [34].

One IVUS study revealed that the plaque with ultrasonic attenuation might be related to deterioration of coronary flow after PCI for acute coronary syndrome. The atherosclerotic plaque with echo signal attenuation (EA) was detected in the culprit plaques of 35.7 % of patients and was more common in patients with ACS than those with stable angina pectoris. Detecting EA in culprit lesions was a strong independent predictor of no reflow after PCI. EA might indicate that a lesion contains high-risk plaque components that are susceptible to distal embolization [35]. Serial IVUS analysis in the HORIZONS-AMI trial showed that attenuated plaques were ubiquitous in culprit lesions in patients with acute myocardial infarction and that these plaques were associated with less intimal hyperplasia and increased lesion-site calcification at follow-up [36]. The 2011 American College of

Table 46.2 The IVUS utilization after coronary artery bypass graft

1. Analysis of vein and artery grafts (including peripheral artery grafts) periprocedures
2. Detection of early failure of graft anastomosis
3. Detection of changes at the native vessel atherosclerosis after surgeries
4. Detection of changes at plaque areas, vessel lumens, or graft lumens after surgeries
5. Detection of early and later graft failure: vessel remodeling, calcification, or thrombosis
6. Follow-up of graft failure

Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) guidelines [37] for PCI state that IVUS is reasonable for the assessment of angiographically indeterminate left main coronary artery disease (class IIa, Level of Evidence B). Clinical outcomes after PCI appear worse in patients with more complex coronary anatomy, in particular those with SYNTAX scores more than 32 [38].

IVUS is useful to differentiate atherosclerotic disease from spontaneous coronary artery dissection in cases of ambiguous coronary angiography and to determine the morphology and the extension of dissection. Moreover, if stent is chosen as a treatment, IVUS is invaluable in confirming correct guide wire placement before the stent (risk of false-lumen stent), stent apposition, symmetry and expansion, and especially to rule out dissection extension. IVUS may not have the resolution power to show the small entry flaps (as it is likely in our case), as opposed to optimal coherence tomography (OCT), which is in turn limited by reduced depth penetration [39].

IVUS could be useful to analyze both arterial and vein grafts, including radial grafts, and it is especially useful for monitoring graft failure (Table 46.2). It is well established that the success of coronary artery bypass grafting (CABG) surgeries are based on high rates of long-term graft patency [40]. Most of the studies where grafts were examined by IVUS had monitored the development of graft failure. After CABG, however, the saphenous vein grafts show a high incidence of accelerated atherosclerosis. An adaptation of the vein graft wall to the arterial circulation with both increased graft size and intimal wall thickening has been demonstrated in previous IVUS studies [40].

Although the cellular and molecular mechanisms underlying vein graft disease have been systematically investigated, the time course and development of this process in patients after coronary bypass has only recently been defined as a consequence of the increased use of IVUS. This results in the detection of diffuse atherosclerotic plaque, compensatory vessel enlargement, and preservation of the luminal diameter even in angiographically normal vessels. IVUS findings in vein grafts also show good correlation with histological findings in clinicopathological studies [41]. The VICTORY study suggested validating the use of IVUS for investigating saphenous vein grafts (SVG) and its model of accelerated atherosclerosis in patients with diabetes [42]. First employed in humans in postmortem studies, it was only with the widespread use of IVUS that its central role in atherosclerosis, post angioplasty restenosis, transplant vasculopathy, and vein graft disease was realized. The early changes seen in the vessel walls in vein grafts are similar to those seen during vessel remodeling in atherosclerotic coronary artery segments. Early vein graft changes can be viewed as adaptive; however, they also predispose the graft to later accelerated graft atherosclerosis. Atheromatous plaque is detected by IVUS as early as 8–10 months post grafting in association with both expansive and constrictive remodeling. IVUS studies have clearly shown that early "adaptive" or pathological changes occur within weeks of grafting and that occlusive atheroma in susceptible individuals occurs within 1 year. The IVUS reproducibly facilitates not only accurate comparisons between groups of patients but also assessment of the effects of intervention on grafts in longitudinal studies. IVUS has significantly contributed to our understanding of vein graft failure. It also serves as the natural tool for the development of clinical strategies that may lead to significant improvements in vein graft patency and more importantly for better long-term quality of life and longevity for patients with coronary artery disease [41].

Thrombosis and surgical factors are the predominant causes of SVG failure in the first month after implantation. Intimal hyperplasia is thought to be the predominant cause of graft failure from postoperative months 1–12. Venous conduits may exhibit mild intimal or medial fibrosis pre-grafting, but most develop further intimal thickening within 4–6 weeks of arterial anastomosis. In angiographically normal SVG, IVUS and pathological studies have shown a doubling of intimal thickness and total wall thickness by the end of the first postoperative year. Lumen loss after CABG is important, because SVG with smaller lumen diameters are more prone to early graft failure. The authors had identified in occluded SVGs a mean loss of SVG lumen diameter of 9 % between postoperative months 1–12, and a decrease in SVG wall thickness over this time. Lumen loss can result from negative remodeling (loss of total vessel diameter) and/or wall thickening. This study shows that in the first postoperative year, lumen loss in SVG is predominantly caused by negative remodeling, with a mean decrease of total vessel diameter by 0.56 mm, and an unexpected decrease in mean wall thickness of 0.33 mm. The pathophysiology of vascular remodeling is not completely understood, but data suggest that remodeling is initiated by changes in hemodynamic conditions (flow, wall stretch, shear stress) and humoral factors (cytokines, vasoactive substances). These lead to signals that influence cell growth and migration and altered activity of

matrix metalloproteinases. IVUS and pathology studies have described an increase in SVG intimal area and adventitia days to weeks after implantation. The authors postulate that early cellular and extracellular changes mediate increased wall thickness of the first 6 weeks, which then plateaus and, in the absence of atherosclerosis, may regress. The authors suggested that in the absence of atherosclerotic plaque build-up, further but slowed progressive wall thinning may occur after the first year postoperatively [43, 44].

At the CASCADE trial, the authors performed a post hoc analysis by IVUS of 90 grafts at 1 year after CABG. The authors suggested that hypertension, SVG diameter, grafting to the right coronary artery, and low quality of the target vessel correlate with the development of SVG hyperplasia or occlusion by 1 year after CABG, whereas beta-blockers and statins are associated with less SVG disease [45, 46].

The findings in the present study of SVG calcium are significantly different from previous IVUS reports of native artery calcification. Positioned in a new environment (at CABG), SVGs should deteriorate faster than native coronary arteries. Indeed, in the present study, calcium-containing SVGs had an average arterialized age of 10.5 years, whereas native coronary arteries take many decades to exhibit any calcium. Significantly, graft calcification occurred mainly within the wall and not within the plaque, which suggests that SVG calcification is not just a result of lesion formation but also of wall changes associated with arterializations and (passive or active) degeneration. In support of this, the authors hypothesized that the pattern of calcium distribution in SVGs can be explained by hemodynamic changes caused by transferring the vein from high-capacitance and low-pressure conduit to a low-capacitance and high-conduit (like an artery native) [3, 47]. Pathological, angioscopic, and IVUS studies have shown that, similar to native lesions, SVG lesions have a fibrofatty composition with evidence of positive remodeling; in patients with ACS plaques, SVG lesions demonstrate a complex appearance with rupture. A previous IVUS study has demonstrated that rupture SVG plaques occur almost exclusively in old SVGs (more than 12 years), are found more often in patients with ACS, have a complex angiographic appearance, and demonstrate similar IVUS features as rupture plaques in native coronary arteries (e.g., positive remodeling) [48]. The IVUS characteristics of ruptured saphenous vein plaques included positive remodeling, the presence of calcium deposits adjacent to the plaque cavity, and eccentricity. This is similar to quantitative and qualitative IVUS descriptors of ruptured plaques in native coronary arteries: positive remodeling, a high eccentricity index, a plaque cavity that measured 2.8 mm^2 in area and 3.9 mm in length, a 60 % frequency of shoulder-site plaque rupture, and pericavity calcium deposits [49].

In one study that analyzed five radial artery grafts, in four cases that were perfectly patent at angiography, IVUS excluded the presence of atherosclerotic plaques and revealed minimal intimal thickening. In the remaining radial artery, which exhibited some irregularities at angiography, IVUS confirmed the presence of limited atherosclerotic deposits and revealed moderate plaque burden at the site of maximal angiographic narrowing [50].

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