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INVASIVE IMAGING

Coronary intravascular ultrasound: a closer view

E Murat Tuzcu, Ozgur Bayturan, Samir Kapadia

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Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio, USA

Correspondence to
Professor E Murat Tuzcu, Department of Cardiovascular Medicine, Heart & Vascular Institute, Desk J-23, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA; tuzcue@ccf.org

Intravascular ultrasound (IVUS) is an invasive tomographic imaging modality, providing images of coronary arteries and other blood vessels. Over the last 20 years IVUS has evolved into an excellent adjunct to coronary angiography. Although coronary angiography continues to be the standard tool to assess the coronary artery lumen, angiography does not supply direct information about the plaque and vessel wall. IVUS provides complementary diagnostic information about the artery wall which cannot be obtained by angiography alone.

PHYSICS AND EQUIPMENT

IVUS systems contain a special transducer mounted catheter and an electronics console to reconstruct the image. The ultrasound signal is produced in the transducer by passing an electrical current through the piezoelectric (pressure-electric) crystalline material (usually ceramic) that expands and contracts when electrically excited. After reflection from tissue, part of the ultrasound energy returns to the transducer and is converted into the image. High ultrasound frequencies (20–40 MHz) are employed resulting in an axial resolution in the range of 80–150 μm and lateral resolution of 200–250 μm.[1]

Catheter technology

Currently available monorail rapid exchange intracoronary ultrasound catheters have an outer diameter of between 2.6–3.5 French (0.87–1.17 mm diameter) which can be advanced through a 6 French guide catheter. Two transducer designs are commonly used: the mechanically rotating transducer and the electronically switched phased array system.

Mechanical systems consist of a drive cable to rotate a single transducer at the catheter tip at 1800 rpm (30 revolutions per second), sweeping an ultrasound beam perpendicular to the catheter. At approximately 1° increments, the transducer sends and receives ultrasound signals. In mechanical catheter systems, the imaging transducer is inside a protective sheath, through which the imaging catheter is advanced and pulled back.

Electronic systems, also referred to as the solid state IVUS system, have multiple transducer elements (up to 64) arranged in an annular array rather than a single rotating transducer. The transducers are activated sequentially to generate the image.

Mechanical and electronic system design improvements have resulted in equivalent tracking, flexibility and comparable image quality.

Imaging console

The imaging console includes components and software necessary to convert the IVUS signal to the image shown on the monitor and recording devices. Imaging studies are recorded digitally for archiving.

EXAMINATION TECHNIQUE

Standard coronary interventional techniques and equipment (guiding catheter and 0.014 inch angioplasty guidewire) are used for catheter delivery for intracoronary ultrasound examination. Intravenous heparin and glyceryl trinitrate (nitroglycerin) are routinely administered before imaging, and the IVUS catheter is placed distal to the segment of interest. Subsequently the operator retracts the transducer, either manually or with a motorised pullback device. During pullback, images are obtained and recorded digitally for analysis. Motorised pullback devices allow withdrawal at a constant speed (between 0.25–1 mm/s; most frequently 0.5 mm/s) which is essential in serial studies.

CORONARY ULTRASOUND SAFETY

Intracoronary ultrasound safety is well documented. Major complications, including dissection or vessel closure, are rare (<0.5%). The most frequently reported complication is transient coronary spasm (occurring in 1–3% of examinations), which responds to intracoronary glyceryl trinitrate.[w1] In transplant patients, examination of vessels previously imaged by IVUS compared with non-instrumented vessels showed no acceleration in the progression of allograft vasculopathy at 1 year follow-up.[w2] Despite this favourable safety profile, selective coronary instrumentation carries a potential risk of significant vessel injury and should only be performed by operators experienced in coronary interventional procedures.

DISPLAY MODES

Three display modes are currently available. The standard IVUS system display is comprised of cross-sectional tomographic views. These single cut cross-sectional images are limited by spatial orientation and cannot provide information regarding the length and distribution of plaque. Longitudinal imaging (L mode) is the second display mode in which computerised image reconstruction techniques present a series of evenly spaced IVUS images along a single cut plane to approximate the

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longitudinal appearance of the artery.[w3] Motorised transducer pullback and digital storage of cross-sectional images are necessary for L mode. There are major limitations of the L mode display, including the obligate straight reconstruction of the artery and display of only a single cut plane. Movement of the vessel and IVUS catheter results in a 'saw-tooth' appearance from motion artefacts. ECG triggered image acquisition may eliminate some of these artefacts.

Advanced computer rendering techniques allow the third display mode, three dimensional (3D) reconstruction of IVUS data.[w4] However, true 3D techniques require registration of the catheter path during pullback. These 3D methods are not yet included in clinical systems but are an exciting research area.

NORMAL ARTERIAL ANATOMY BY IVUS

A standard IVUS image consists of three main components: catheter, lumen, and arterial wall. The lumen exhibits a characteristic echogenicity pattern, observed as finely textured, swirling echoes that arise from acoustic reflections from circulating blood elements. This blood 'speckle' assists in image interpretation; it helps to differentiate the lumen and the vessel wall and confirm communication between a dissection plane and the lumen. An ultrasound reflection occurs at a given interface if there is an abrupt change of acoustic impedance. In coronary arteries, two strong acoustic interfaces are visualised by ultrasound, the leading edge of the intima and the external elastic membrane (EEM), which is located at the media–adventitia interface (figure 1). The outer adventitia border is indistinct, merging into the surrounding tissues. The echo-dense intima and adventitia with a sonolucent medial layer often give the wall a trilaminar appearance. However, the IVUS appearance of young, morphologically normal coronary artery wall appears as monolayer because of very thin intima. The normal value for intimal thickness by IVUS was shown to be <0.3 mm in young hearts (age <40 years) and <0.5 mm in older hearts (age >40 years).[2] Most investigators use 0.25–0.50 mm as the upper limit of normal.

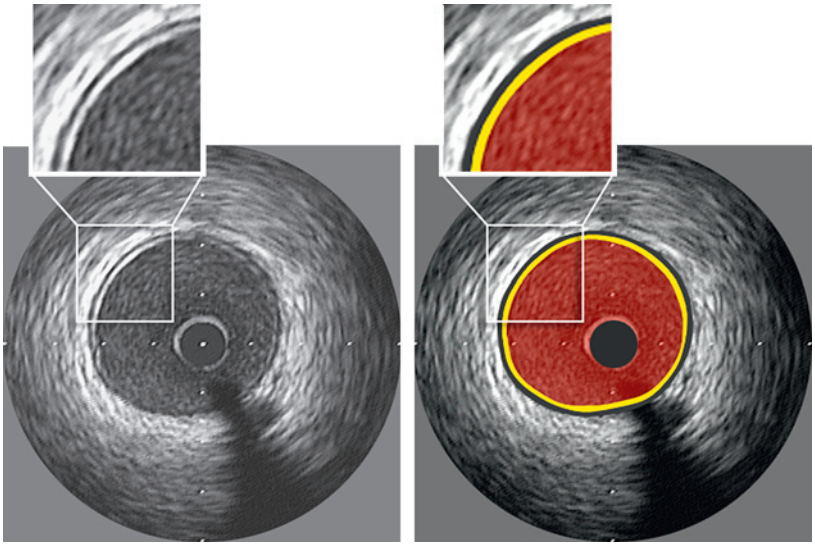

Figure 1 Normal coronary artery anatomy by intravascular ultrasound. Yellow colour represents intima; black colour represents media; red colour represents blood filled lumen.

INSIDE THE CORONARY ARTERIES

One striking observation from IVUS is that the severity and extent of the atherosclerosis within the coronary artery wall is much greater than what is revealed by the angiogram.[w5] This phenomenon is a consequence of the diffuse nature of atherosclerosis and adaptive enlargement of the EEM (remodelling).

Arterial remodelling

The term arterial remodelling refers to changes in EEM area that occur over time during development of atherosclerosis. The magnitude and direction of remodelling is frequently expressed as lesion EEM cross sectional area (CSA)/reference EEM CSA (reference is a least diseased site within a distance of 10 mm from the lesion site). Expansive and constrictive remodelling is defined as a lesion EEM area that is larger or smaller than the reference EEM area. Expansive remodelling helps to explain the discrepancy between angiography and ultrasound. Interestingly, culprit lesions in acute coronary syndromes are associated with expansive remodelling.[3] Subsequent IVUS studies have demonstrated the flip side of this phenomenon—constrictive remodelling or arterial shrinkage which is more frequent in stable CAD.[4 5] It has been shown that constrictive remodelling also contributes to restenosis after plain balloon angioplasty. Another way of looking at remodelling is through serial studies. Observation of size changes in a given arterial segment represents remodelling.

Calcification

Ultrasound imaging is more sensitive than fluoroscopy for coronary calcification detection.[w6] The significance of coronary calcification is complex, and its relation to plaque stability is unclear. Large calcifications may be associated with lesion stability. In contrast, microcalcifications are frequently found in lipid-rich necrotic core areas of unstable plaques, and may not be well reflected in IVUS images.[6 w7]

Plaque rupture and ulceration

Rupture or superficial erosion of vulnerable coronary plaques with subsequent thrombosis represents the principal pathophysiology underlying most acute coronary syndromes. Plaque rupture or ulceration is defined by IVUS as a cavity in the vessel wall, with disruption of the intima, and blood flow within the plaque cavity.

Thrombus

The ultrasound appearance of a thrombus may be relatively echolucent or have a more variable

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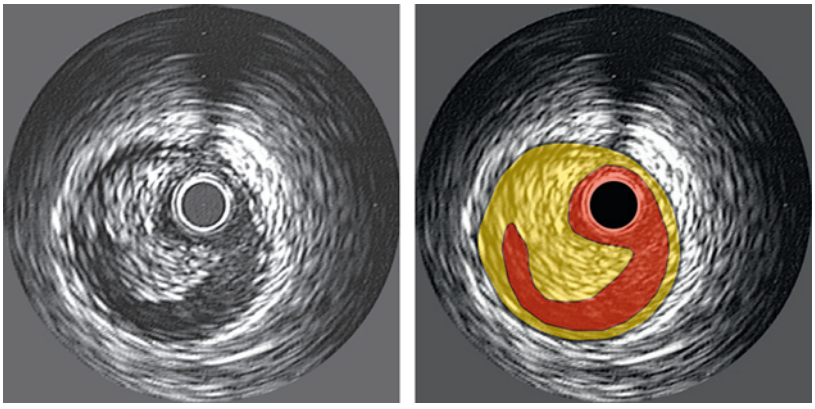

Figure 2 A plaque site with dissection.

echogenicity with speckling scintillation. Blood flow in microchannels may also be apparent within some thrombi. However, in vitro studies have revealed limitations of IVUS in the diagnosis of thrombi (sensitivity of 57% and specificity of 91%), considerably inferior to angioscopy.[7] Differentiating thrombi from echolucent plaque, loose connective tissue, and slow flowing or stagnant blood may be difficult.

Coronary dissection

IVUS is a sensitive tool to detect coronary dissections which have typical characteristics of false lumen, intimal flap, or a second blood filled channel with stagnant flow. Injection of contrast medium generally shows a connection between the true and false lumen (figure 2).

Intimal hyperplasia

Recent studies suggest that both cell proliferation and enhanced extracellular matrix accumulation contribute to in-stent restenosis.[8] The intimal hyperplastic tissue of early in-stent restenosis often has a very low echogenicity, at times less echogenic than the blood speckle in the lumen. The intimal hyperplasia of late in-stent restenosis often appears more echogenic.

Coronary venous bypass grafts

The bypass graft wall is free from the surrounding tissue and has no side branches. In situ vein grafts do not have an EEM. However, vein grafts typically undergo 'arterialisation', with morphologic changes that include intimal fibrotic thickening, medial hypertrophy, and lipid deposition.

Aneurysm

IVUS imaging can be useful in examining the ectatic segments found by angiography. Clinical aneurysm definitions require that the EEM and lumen diameter should be at least 50% larger than the proximal reference segment. In addition IVUS can discriminate between a true aneurysm and a pseudoaneurysm.

Angiographically hazy lesions

Persistent haziness refers to the non-homogenous density or ground-glass appearance on an angiogram. Coronary lesions are frequently more complex and markedly distorted than they appear by contrast filled luminal angiography. Those hazy lesions can represent a broad morphological spectrum including calcium, spontaneous dissections, thrombus, and large plaque burden with expansive remodelling which could be tighter than its angiographic appearance.[9] Hazy appearance after stent placement may be a challenge to decipher by angiography alone. Therefore, IVUS can be an enormously helpful tool in this regard.

Haematoma

An intramural haematoma is defined as an accumulation of blood within the adventitial space, displacing the internal elastic membrane inward and the EEM outward. It is characterised by a homogeneous appearance of relatively dark spaces in adventitial tissue.

IVUS MEASUREMENTS

Quantitative IVUS measurements are typically derived from planimetric calculations. Lumen–intima and the EEM borders are traced manually or by operator corrected automation for computerised calculations of distance and area measurements. All measurements are performed relative to the centre of the lumen, rather than relative to the centre of the IVUS catheter. Lumen CSA is the area bounded by the luminal border. Minimum and maximum lumen diameters are the shortest and longest diameters through the centre of the lumen. Lumen eccentricity is calculated as: 100×[maximum lumen diameter−minimum lumen diameter]/maximum lumen diameter. Lumen area stenosis is calculated as: [reference lumen CSA−minimum lumen CSA]/reference lumen CSA. This measurement is similar to the angiographic percentage stenosis. After delineation of the EEM, the area bounded by the EEM border refers to the EEM CSA. Comparison of luminal measurements between IVUS and angiography usually shows a close correlation for vessels without atherosclerosis. However, for diseased arteries, only a moderate correlation has been reported.[w8]

Plaque area measurements are derived by subtracting the lumen area from EEM area (EEM CSA−lumen CSA). This approach results in a slight overestimation of atheroma area (in comparison to histology) which includes the media. Maximum and minimal plaque thickness, plaque eccentricity (100×[maximum plaque thickness−minimum plaque thickness]/maximum plaque thickness), and plaque burden (plaque CSA/EEM CSA) are the complimentary parameters regarding the extent of atherosclerotic plaque measurements.

IVUS RESEARCH APPLICATIONS

Volumetric IVUS analysis has been used in studies to monitor the rate of atheroma progression/regression as an efficacy measure in clinical trials of emerging atherosclerosis therapies, assessing new interventional approaches for the prevention and treatment of in-stent restenosis, and development

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of pharmacological agents for prevention of transplant vasculopathy (supplementary table 1, part A).

Monitoring progression of atherosclerosis

Precise quantitation of the extent of atheroma within an arterial segment at different time points using serial IVUS provides a unique opportunity to investigate the factors that influence the natural history of atheroma progression.

Serial IVUS studies evaluating the impact of high dose statins and various statin agents have been reported.[10 w9–w11] Small serial studies suggested that drug treatment raising high density lipoprotein cholesterol can lead to shrinkage of atheroma in a relatively short time.[w12 w13] Another study which investigated the effect of antihypertensive therapy in patients with coronary artery disease (CAD), who were considered to be normotensive, showed less atheroma progression compared to placebo.[w14] Other targets for progression/regression trials included insulin sensitising, and anti-obesity agents. Some adequately powered serial IVUS studies were done to evaluate the efficacy of acyl: cholesterol acyltransferase (ACAT)[w15] and cholesteryl ester transfer protein (CTEP) inhibitors.[w16] They showed no treatment benefit. In some instances, a negative result in a pilot IVUS study may lead to rethinking of a larger study design. The prognostic role of plaque burden has been studied by IVUS clinical trials that examined the relationship between plaque burden and future cardiovascular events. In a study of 107 patients with angiographically insignificant coronary atherosclerosis, left main CAD detected by IVUS was significantly associated with future coronary events.[w17]

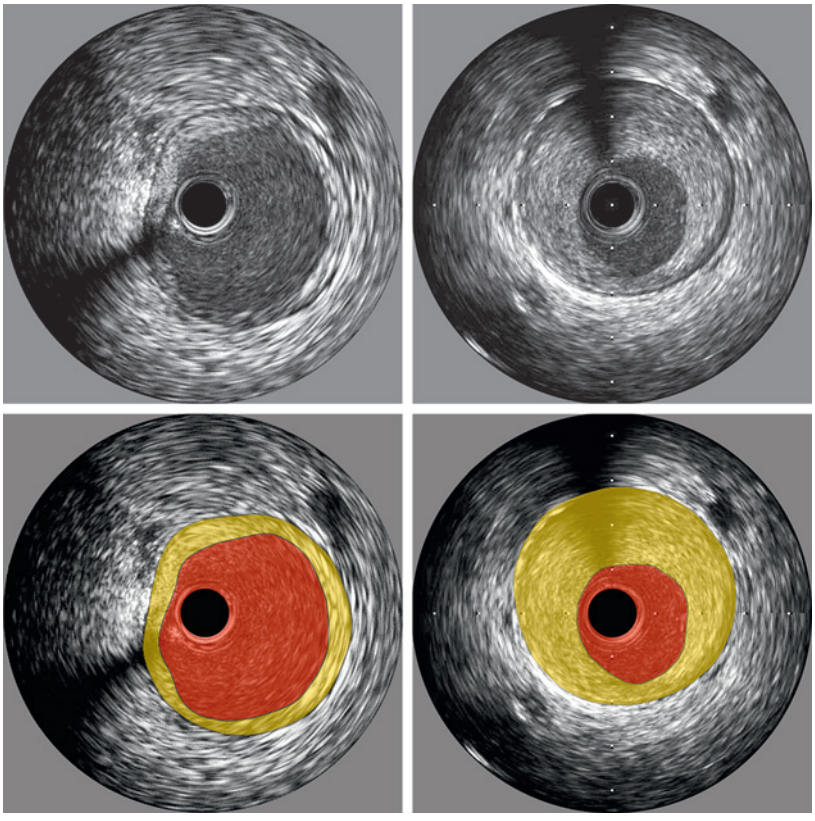

Figure 3 Transplant vasculopathy at the same site in a coronary vessel segment. Serial intravascular ultrasound examination at baseline (left side panel) and 1 year follow-up (right side panel) demonstrates significant plaque development at the first year.

Virtual histology

Greyscale IVUS is able to visualise coronary atherosclerosis in vivo including plaque area, plaque distribution, lesion length, and coronary remodelling, but it is limited in regard to plaque composition analysis. A more detailed diagnosis of plaque composition is enabled by IVUS derived virtual histology (VH). VH-IVUS is based on the spectral analysis of the radiofrequency (RF) ultrasound signals in a frequency domain and displays the reconstructed colour coded tissue map of plaque composition overlaid on greyscale image. Plaque components are grouped into four basic tissue types: fibrous tissue (green), fibro-fatty tissue (light green), necrotic core (red), and dense calcium (white).

In a histopathological validation study, the overall predictive accuracies were 90.4% for fibrous tissue, 92.8% for fibrolipidic, 89.5% necrotic core, and 90.9% for dense calcium.[11] The driving force behind the development of VH-IVUS is the need for more complete information about atherosclerotic plaque composition because plaque stability is related to histological composition. Histopathological studies have demonstrated that the amount of necrotic core and the fibrous cap thickness are critical to plaque stability. Hence, it has been hypothesised that accurate in vivo identification of plaque components may allow the detection of vulnerable atheroma before rupture. In a registry of 473 male patients, the ratio of necrotic core to dense calcification detected by VH-IVUS in diseased coronary segments was related to known risk factors for sudden cardiac death.[w18] Although there are several studies showing correlation between VH-IVUS and pathology, their implications on clinical practice remain uncertain.

ROLE OF IVUS IN CLINICAL PRACTICE

Over the last two decades IVUS has become an integral part of modern catheterisation laboratory practice. Its clinical use includes complimentary diagnostic information when angiography is ambiguous and provides guidance for interventional procedures. The use of IVUS for diagnosis alone is less frequent than its interventional use.

Transplant vasculopathy assessment

Transplant CAD is the leading cause of death beyond the first year after cardiac transplantation, with a reported incidence of 15–20% per year.[w19] Its development is often clinically silent, because the transplanted heart is denervated and ischaemia is usually not detected with functional testing until the disease is advanced (figure 3).[w20] In addition, because of its frequently diffuse and circumferential nature, transplant CAD may be particularly challenging to characterise using angiography alone.

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Necropsy studies have demonstrated that angiography systematically underestimates coronary atherosclerosis in transplant recipients.[w21] IVUS allows assessment of early plaque accumulation before luminal stenosis develops. The silent progression of vasculopathy in transplant recipients is associated with a poor clinical outcome. Two studies demonstrated that rapidly progressive vasculopathy by IVUS, defined as an increase of ≥0.5 mm in intimal thickness within the first year after transplantation, was a powerful predictor of all cause mortality, myocardial infarction, and angiographic abnormalities.[12 w22]

Serial IVUS has also been used as a research tool in studies that assess emerging transplant vasculopathy therapies, including immunosuppressive medications,[w23] statins, and angiotensin converting enzyme (ACE) inhibitors.

Angiographically borderline lesion assessment

Angiographically ambiguous lesions include intermediate lesions of uncertain stenotic severity, aneurysmal lesions, ostial stenosis, disease at branching sites, tortuous vessels, left main stem lesions, sites with dissections, sites with focal spasm, sites with plaque rupture, intraluminal filling defects, and angiographically hazy lesions.[9]

Although IVUS is frequently employed to examine lesions of uncertain stenotic severity, specific threshold criteria for intervention derived by IVUS measurements have not been prospectively validated with non-invasive assessments of myocardial ischaemia. On the other hand, functional lesion assessment using pressure wire measurements has been prospectively validated.[13] Some studies have evaluated the concordance of IVUS derived parameters and their haemodynamic significance. It appears that the best IVUS cut-off values for major epicardial coronary arteries (not including left main) that correlate with a fractional flow reserve (FFR) <0.75 are in the range of 3–4 mm^2 minimal lumen area.[13 w24] Although the finding that a minimal lumen area >4 mm^2 is associated with a favourable clinical outcome, its FFR based specificity is low (specificity 56%, sensitivity 92%). The combination of an area stenosis >70% and a minimal lumen diameter <1.8 mm has better sensitivity (100%) and specificity (76%).[14] Taken together, these data still demonstrate that the moderate specificity could lead to many (24%) unnecessary revascularisation procedures for these intermediate lesions. Predictably, a CSA <3.00 mm^2 has a better specificity.

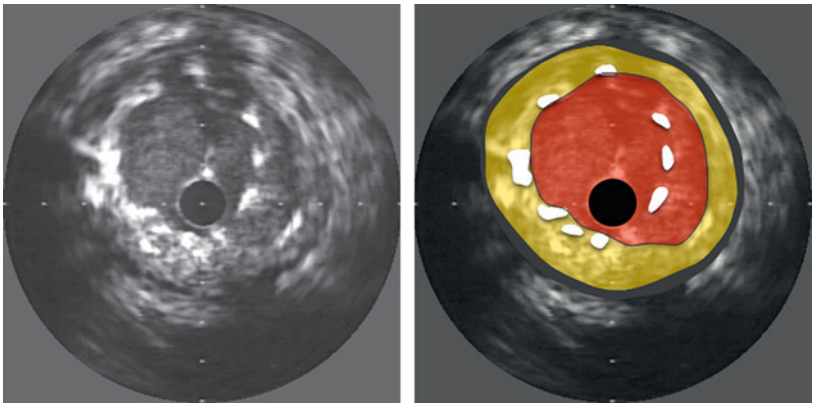

Figure 4 Intravascular ultrasound cross-section at a site with unopposed coronary stent struts.

Left main disease

Assessment of left main coronary artery (LMCA) disease by angiography may be challenging. IVUS can often provide additional information. Although there is no consensus regarding the IVUS threshold for haemodynamically significant LMCA obstruction, in one study minimal luminal area (MLA) >7.5 mm^2 identified a safe cut-off point for deferring revascularisation.[w25] Another study that aimed to correlate IVUS and haemodynamic measurements demonstrated that a minimal lesion diameter of 2.8 mm and MLA of 5.9 mm^2 predicted a haemodynamically significant lesion.[w26] In addition, it is important to obtain the measurements when the catheter is co-axial to the ostial segment of the vessel. An 8 French JL-4 short tip guiding would be a good choice for this purpose. Serial IVUS studies have shown that the rate of plaque growth in the LMCA correlates with traditional risk factors.[15 w27] Patients at greatest risk of cardiovascular events, assessed by the PROCAM, SCORE, and Framingham risk score algorithms, exhibited significantly greater plaque progression between baseline and follow-up (median 14 months). Moreover, a positive linear relationship between the risk of clinical events and plaque progression has been demonstrated.[15]

Importantly, recent IVUS studies have demonstrated non-atherosclerotic ostial LMCA narrowing. This phenomenon has also been called 'reverse tapering' and cannot be differentiated from an ostial atherosclerotic stenosis by angiography alone.[16]

Interventional applications

IVUS has played a pivotal role in understanding the mechanisms of percutaneous coronary intervention (PCI) and in the enhancement of interventional cardiology. IVUS provides incremental value in a number of circumstances in clinical coronary interventions.

Pre-interventional IVUS imaging allows assessment of plaque distribution, ostial involvement, lumen and vessel area and diameters, extent of calcification, and the presence of thrombi or dissections, and can alter strategy and the decision to use a particular device.[w28] Although there are potential benefits of pre-interventional IVUS imaging, one potential problem occurs when advancing the IVUS catheter through tight lesions before intervention.

The value of intraprocedural IVUS was validated long ago. Colombo and colleagues demonstrated that high pressure stent deployment[17] by IVUS guidance resulted in better stent expansion and complete apposition (figure 4). This strategy also established the safety and efficacy of dual

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Coronary intravascular ultrasound (IVUS): key points

- Although coronary angiography continues to be the standard tool to assess the coronary artery lumen, as a lumenography method, IVUS provides complementary diagnostic information about the artery wall which cannot be obtained by angiography alone.
- The severity and extent of the atherosclerosis within the coronary artery wall is much greater than revealed by the angiogram. This is a consequence of the diffuse nature of atherosclerosis and adaptive enlargement of the external elastic membrane (remodelling).
- The silent progression of vasculopathy in transplant recipients is associated with a poor clinical outcome. IVUS allows assessment of early plaque accumulation and management of immunosuppressive therapy before luminal stenosis develops.
- IVUS studies have demonstrated that the larger the in-stent lumen area, the lower the restenosis rate.
- Identification of precise morphologic characteristics of ambiguous coronary lesions by IVUS provides valuable information before, during and after intervention. Hence, it is a great adjunctive imaging modality in the catheterisation laboratory.

antiplatelet therapy (aspirin and thienopyridines) instead of anticoagulation with warfarin. Subsequent studies confirmed these findings.[w29 w30] IVUS guided stenting versus angiography alone guided stenting were assessed in case–control studies,[18 w31] randomised studies[w32 w33] and in a meta-analysis.[19] Most of these studies are limited by small sample size and limited follow-up. There was a trend towards a benefit with respect to target lesion revascularisation favouring IVUS guided coronary stent implantation. However, all these randomised trials are underpowered to demonstrate a difference in clinical outcomes between IVUS guided PCI versus angiography guided PCI (supplementary table 1, part B).

IVUS examinations have also played an important role in establishing the mechanisms of in-stent restenosis. Unlike the restenotic response after angioplasty or atherectomy, which is largely driven by constrictive arterial remodelling, with neointimal growth playing a lesser role, in-stent restenosis is primarily due to neointimal hyperplasia.[w34] Studies have demonstrated that the larger the in-stent lumen area, the lower the restenosis rate.[w35]

IVUS and drug eluting stents

A number of studies have demonstrated the superiority of drug eluting stents (DES) to bare metal stents, in that DES reduced restenosis and repeat revascularisation. Although DES inhibit neointimal proliferation, they are not free from restenosis and are limited by stent thrombosis. IVUS has provided valuable insights into understanding that stent under-expansion is the predominant mechanism underlying DES restenosis. A post-deployment minimal stent area of 5 mm^2 predicts increased likelihood of angiographic restenosis.[w36] In some studies, small in-stent minimum CSA and proximal reference segment plaque burden were associated with DES thrombosis.[w36 w37] These data suggest that adequate stent expansion and covering any residual stenosis with a stent of adequate length may be important in preventing DES thrombosis. Although the mechanism of late DES thrombosis is not clear, a recent meta-analysis reported four times higher acquired stent malapposition compared to BMS. Furthermore, this was found to be associated with late and very late stent thrombosis.[20] It appears that a well expanded stent without a gap between the vessel wall and the stent, with no dissection or large atheroma at the edges, is less likely to have thrombosis. The restenosis rate with DES is now <10%, but the clinical usefulness of ultrasound guidance in stent deployment maintains its value. Particularly in small vessels, bifurcation stenting, ostial lesions, long segments, and in left main stenting, ultrasound can provide beneficial guidance.

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► **This groundbreaking study was the first clinical trial to suggest high pressure final balloon dilatation with IVUS guidance could provide adequate stent expansion and that anticoagulation therapy could be safely omitted.**

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► **This important meta-analysis demonstrated that IVUS guided stent implantation has a neutral effect on long term death and non-fatal myocardial infarction compared to an angiographic optimisation. However, it also demonstrated that IVUS guided stenting significantly lowers 6 month angiographic restenosis and target vessel revascularisations.**

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► **This important meta-analysis demonstrated that late acquired stent malapposition in patients with drug eluting stents was four times higher compared with bare metal stents, suggesting that late stent malapposition may play a role in patients who develop late stent thrombosis.**

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E Murat Tuzcu, Ozgur Bayturan and Samir Kapadia

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