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Review Articles

Clinical application and image interpretation in intracoronary ultrasound

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Introduction

Miniaturized flexible ultrasound catheters provide detailed information on the vessel wall. They are an additional diagnostic evaluation technique, partly in the realm of coronary interventions in patients with coronary artery disease. Fluoroscopy and angiographic road-mapping are indispensable elements of the intracoronary ultrasound examination and of the therapeutic procedure. Thus intracoronary ultrasound should not be considered an alternative to angiography but rather a complementary diagnostic technique. The clinical advantages deriving from the use of intracoronary ultrasound have not yet been established in randomized trials. However, there is increasing evidence from large prospective studies that ultrasound guidance improves the results of catheter-based intracoronary interventions in terms of immediate lumen enlargement, reduced procedure-related complications and long-term restenosis. Although intracoronary ultrasound has become a routinely applied diagnostic technique in interventional cardiology, no attempts have been made to standardize the examination procedure, the definitions and the format of reporting qualitative and quantitative data.

The aim of this article is to propose guidelines for the acquisition, classification and analysis of intracoronary ultrasound images and to recommend indications for clinical application of intracoronary ultrasound based on recent experience.

Key Words: Intracoronary ultrasound, percutaneous transluminal balloon angioplasty, directional and rotational atherectomy, coronary stents.

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Part I: Image acquisition

To acquire intracoronary ultrasound images requires the intracoronary insertion of a dedicated catheter probe. The cardiologist performing intracoronary ultrasound should be familiar with the selection and positioning of guiding catheters, the steering and positioning of guidewires, and the handling of possible complications such as guidewire loop formation, spasm, and dissections[1–3]. Intracoronary ultrasound studies should, therefore, only be performed by, or under direct supervision of, experienced interventional cardiologists.

Selection and positioning of guiding catheters

Ultrasound catheters currently available for intracoronary application have an outer diameter of between 2·9 and 3·5 French at the distal end. Although mechanical catheters are smaller at the distal end (2·9 and 3·2 French models are available), their diameter increases to 5 French in the shaft. Therefore, 7 French large lumen guiding catheters are required and 8 French guiding catheters are preferred to facilitate positioning of intracoronary ultrasound probes. Intermittent injection of contrast medium also facilitates positioning and reduces the risk of non-uniform rotation. Electronic catheters, although slightly larger in diameter at the distal end, maintain the same size along the entire catheter length, allowing insertion through large lumen 6Fr guiding catheters.

Steering and positioning of intracoronary ultrasound catheters

Although the handling of intracoronary ultrasound probes is similar to the handling of over-the-wire or

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Table 1 Guidelines for image acquisition

(1)	Before insertion of the intracoronary ultrasound catheter
	Inject intracoronary nitroglycerine (0·1–0·3 mg) or isosorbide dinitrate 1–3 mg to prevent spasm and induce maximal vasodilatation.
	Inspect and prepare the catheter (flush carefully if mechanical); connect to ultrasound console or motor unit; test the catheter.
	Subtract the ring-down artifact with catheter not in contact with the vessel wall (electronic transducers):
(2)	During insertion of the intracoronary ultrasound catheter
	During insertion, set the rotation of the images to a predefined standard (i.e., place origin of the circumflex at 9 o'clock when imaging the left anterior descending).
	Insert the catheter distal to the stenosis or the segment under investigation under fluoroscopy (attention must be paid to wire looping for short monorail catheters); for common sheath design remove guide wire up to proximal marker and insert imaging cable;
	Optimize image quality (gain and zoom setting);
	Start recording on super-VHS videotape and check that the entire examination is recorded and that demographic and procedural data have been annotated;
	Indicate when the pull-back is started (written or voice annotation, possibly showing the position of the tip of the ultrasound catheter with fluoroscopy before starting the pull-back):
	Start the pull-back, using a motorized pull-back device operating at constant speed (0·25, 0·50 or 1·0 mm . s^{-1});
	Continue voice comment or annotate positions without interrupting the pull-back until the ultrasound catheter is withdrawn into the guiding catheter;
(3)	After insertion of the intracoronary ultrasound catheter
	Reassess the cross-sections of interest reviewing the videotape or the longitudinal view generated after on-line three-dimensional reconstruction and perform area/diameter measurements of target stenosis and reference;
	Reinsert the ultrasound probe only if doubts in the image interpretation remain (use contrast or saline to better delineate the lumen, if necessary);
	Before new insertions, inspect and flush carefully the ultrasound catheter and test it again.

monorail PTCA catheters, additional caution is required. A stable guiding catheter position is desirable since intracoronary ultrasound catheters still have less trackability and a larger profile than most balloon catheters. The short monorail catheters are prone to prolapse, so that the tip of the guidewire must be placed distal in the target vessel and the intracoronary ultrasound catheter should never be advanced over the floppy end of the guidewire. For negotiating tortuous vessels, long monorail or over-the-wire intracoronary ultrasound catheters should be selected.

Damage to the vessel wall from modern flexible intracoronary ultrasound catheters is rare, but to avoid damage the catheters should not be advanced to the smallest distal coronary vessels and caution must be used in crossing stents immediately after deployment. Intracoronary ultrasound catheters are larger and have less tapering than PTCA balloons, so that disruption of fragile coil stents can be induced by forceful pushing of the intracoronary ultrasound catheter. Occasionally, adjusting the guiding catheter and guidewire position to obtain a more central orientation of the intracoronary ultrasound catheter facilitates crossing of the stented segment.

Intracoronary ultrasound examination

A standard operating procedure is essential for both interpreting and reviewing the intracoronary ultrasound examination (Table 1). For mechanical systems, careful preparation of the catheter with generous forceful flushing is required to remove air bubbles around the transducer. The catheter should always be handled carefully, avoiding twists or kinks, especially during rotation of the ultrasound crystal. For electronic systems, the registration of an ultrasound image while the catheter is not in contact with the vessel wall is also required to subtract the ring-down artifact. The best results are obtained when the registration of the image is performed in the aorta, disengaging the guiding catheter from the coronary ostium. Before starting the insertion, demographic data and annotations of the type of vessel examined and intervention performed should be entered using the alpha-numeric keyboard available in all ultrasound machines. Optimization of the machine setting should be controlled during insertion and checked again before starting the pull-back. Inexperienced operators often tend to reduce the near gain to eliminate artifacts or excessive backscatter from blood. If the near field signals are almost extinguished, however, soft plaques around the catheter can be missed.

An intravenous injection of 5000 to 10 000 units heparin and an intracoronary bolus of 100–300 μg nitroglycerine or 1–3 mg isosorbide dinitrate should be administered before the intracoronary ultrasound study. The role of aspirin and other antiplatelet agents in preventing thrombotic complications during intracoronary ultrasound is not clear at present. The insertion of the intracoronary ultrasound catheter should be

gentle but continuous and rapid, avoiding stopping or withdrawal of the catheter to examine, compare or measure specific sites (stenosis, reference segments, etc). The Stanford Group has suggested that before entering the left anterior descending or left circumflex artery from the left main coronary artery, the image should be electronically rotated so that, entering the left anterior descending, the circumflex is coming off at 9 o'clock and, entering the circumflex, the left anterior descending is positioned at 3 o'clock. With this orientation, during insertion into the left anterior descending the diagonal branches will come off to the left, between 8 and 12 o'clock, and the septal branches will come off at the bottom (between 2 and 8 o'clock). In the circumflex, the obtuse marginal branches will come off between 12 and 6 o'clock. For the right coronary, the orientation is done with the first right ventricular marginal branch, which should be rotated to the 9 o'clock position. Although not essential for intracoronary ultrasound interpretation, the consistent use of this rotational orientation in serial intracoronary ultrasound examinations facilitates the comparison of corresponding cross-sections before and after interventions, especially when selective plaque removal with DCA is performed.

When the intracoronary ultrasound catheter has been inserted distally to the segment of interest, a continuous pull-back should be started. The use of a motorized pull-back device at constant speed (most frequently $0{\cdot}5\ mm\ .\ s^{-1}$) is highly recommended to increase reproducibility and allow precise measurements of vessel length. For mechanical systems, recent advances in catheter design allow the withdrawal only of the imaging cable within an external sheath, minimizing the risk of malrotation or uneven speed during pull-back from friction of the catheter shaft against the vessel wall. The position from which the pull-back was started, and all the relevant sites explored, should be indicated by the operator using a voice comment or written annotation on tape and showing, when possible, the corresponding fluoroscopic position of the ultrasonic catheter on a split-screen. Side-branches, well visualized with both angiography and ultrasound, are clear landmarks that facilitate interpretation and comparison of sequential examinations. Furthermore, the distance from a side-branch can be used as a precise method to identify the same arterial site in serial intracoronary ultrasound examinations (i.e. before and after interventions) when a fixed speed is used for the pull-back.

Electrocardiographic triggering of the pull-back using a step-motor has also been proposed to obtain smoother contours during three-dimensional reconstruction and increase the accuracy of the measurement[1].

Safety of intracoronary ultrasound and handling of complications

Guidewire looping

The relatively short monorail tip of some intracoronary ultrasound catheters easily bends or kinks, especially in tortuous segments (sheperd's crook origin of the right coronary artery or acute origin of the left circumflex from the left main coronary artery). If a wire loop is present proximal to its insertion in the intracoronary ultrasound catheter, the intracoronary ultrasound probe and guiding catheter should be simultaneously removed.

Spasm

Spasm during intracoronary ultrasound can occur during purely diagnostic procedures, such as after heart transplantation, and was reported in approximately 3% of patients in a large multicentre survey including more than 2000 intracoronary ultrasound examinations[1]. In case of spasm, one or more intracoronary boluses of nitrates should be given followed, if necessary, by a slow intracoronary injection of 1–1·5 mg verapamil[2,3]. If the spasm is located distal to the intracoronary ultrasound probe, the probe should be removed carefully, and not pulled out forcefully, as this will cause additional intimal damage.

After the intracoronary ultrasound study, the patient with spasm should be monitored carefully. A final contrast injection following removal of all intracoronary ultrasound hardware and the guidewire is recommended to document the integrity of the vessel wall in all cases.

Dissections and acute closure

Coronary artery dissections and acute closure are a rare, but severe potential intracoronary ultrasound complication with an incidence of 0·4% of all patients studied[1,4]. These complications are very rare after diagnostic intracoronary ultrasound studies, particularly in patients with mild or stable disease and mainly occur during therapeutic procedures, when it is often difficult to decide whether the complication is related to the intervention or to the intracoronary ultrasound examination. The handling of such a complication should be the same as recommended in patients with symptomatic dissections after invasive procedures (new balloon inflation with standard or perfusion balloons, stent implantation, bypass surgery or medical treatment alone, depending on the severity of the dissection and on the clinical condition of the patient)[2].

Part II: Image interpretation

Normal arterial morphology

The ultrasound appearance of normal human arteries in vitro and in vivo has been studied extensively[5–10]. In the normal intima, a superficial layer of endothelial cells covers a very thin subendothelial layer of connective tissue and smooth muscle cells. Its thickness increases with age, from a single cell layer at birth, to a mean of 60 μ from infancy to 5 years and reaches 220 μ at

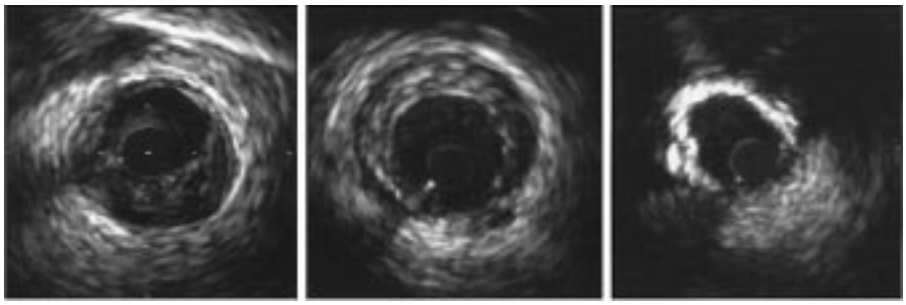


Figure 1 **Three examples of homogeneous plaques with a predominant soft (left panel), fibrous (central panel) and calcific composition (right panel, 270 degrees calcium arc).**

30 years and 250 μ at 40 years[11]. Further adaptive, physiological thickening of the intima occurs at points where wall tension is increased, such as at arterial bifurcations and on the outer parts of bends, and may be either eccentric or diffuse[12]. Diffuse intimal thickening is common in older patients, and is a process which is histologically distinct from atherosclerosis[13].

The muscular media of coronary arteries is predominantly composed of smooth muscle cells with smaller amounts of collagen, elastic tissue and proteoglycans. Fibrous degeneration of the media, particularly of the inner third, is not uncommon in elderly patients or in patients with concomitant atherosclerotic disease[14,15]. The thickness of the media ranges from 125 μ to 350 μ (mean 200 μ) but medial thinning occurs in the presence of atherosclerotic disease[16].

The adventitia is composed of loose collagen and elastic tissue that merges with the surrounding peri-adventitial tissue and is 300–500 μ thick. Two sheets of elastic tissue separate the media from the intima (internal elastic lamina) and the adventitia (external elastic membrane).

The sudden change in acoustic impedance between adjacent tissue plays a particularly important role in the determination of the characteristics of the ultrasound image of the vessel wall[17,18]. The leading edge of the intima and of the adventitia are two strong acoustic interfaces well visualized with ultrasound in most instances. Although the internal elastic lamina is composed of strong echogenic elastic tissue, fibrous changes in the inner third of the media decrease the difference in acoustic impedance between these adjacent layers, making clear delineation of the internal elastic lamina and of the inner border of the media rare[19] thus precluding reliable estimation of the media thickness. Therefore, only two layers are normally distinguished with intracoronary ultrasound, an internal wall layer often described as intima or intimal plaque which should be more correctly defined 'intima-media complex' and an external or adventitial layer. The absence of an acoustic interface between the adventitia and the surrounding peri-adventitial tissue precludes the identification of the adventitia as a discrete, quantifiable entity.

Atherosclerotic lesions

Atherosclerotic plaque has been studied extensively with intracoronary ultrasound in vitro and in vivo, both in peripheral and in coronary arteries[8,9,15,20–23]. Early changes that occur in the development of atherosclerosis, such as fatty streaks or duplication or fragmentation of the inner elastic lamina, do not change the ultrasonic appearance of the vessel wall and cannot be visualized with intracoronary ultrasound as long as they remain below the threshold of resolution of intracoronary ultrasound.

With further progression of atherosclerosis an increase in intimal thickness can be detected in the ultrasound image. In advanced atherosclerosis, three basic types of lesion are distinguished: (1) highly cellular fibromuscular lesions or lesions with diffuse lipid infiltration which have a low echoreflectivity; (2) dense fibrous lesions which produce bright, heterogeneous and sometimes speckled echoes, with an echoreflectivity equal or superior to the echoreflectivity of the adventitia; (3) calcified lesions which produce intensely bright reflections with acoustic shadowing (Fig. 1). Occasionally, areas of diffuse lipid deposition and necrotic degeneration appear as dark areas (low echodensity), often located within fibrous areas or covered by a fibrous cap[5,15,22,23]. Small deposits, however, can be missed due to the limited resolution and dynamic range of the currently available ultrasound systems. Dissections (false lumen) or broad echolucent areas between the intima and the adventitia due to attenuation of the ultrasound signal by thickened fibrous intimal plaques are also often misinterpreted as lipids.

Thrombus appears as a bright heterogeneous speckling reflection which cannot reliably be distinguished from other types of plaques. Intraluminal masses having these ultrasound characteristics or the

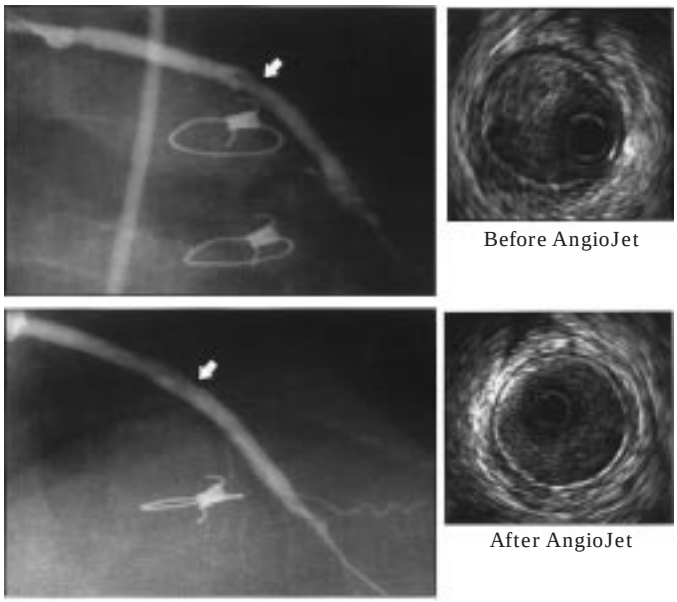


Figure 2 **Upper panels: soft protruding mass between 9 and 12 o'clock, at the site of a moderate reduction in lumen opacity with angiography in the mid-segment of a degenerated saphenous vein graft. Note the almost complete disappearance of this structure in the corresponding cross-section (equidistant from the anastomosis with the left anterior descending coronary artery during a repeated examination using motorized pull-back) when a new device designed for thrombus removal is applied (Angiojet, Possis Medical, Minneapolis, MN), indirectly confirming the thrombotic nature of this structure.**

presence of multiple channels within the plaque communicating with the lumen are highly suggestive of thrombi (Fig. 2). Sometimes mural thrombi generate linear echoes within a thickened intima which represents an acoustic interface between thrombus and underlying intima (wall layering)[24].

Qualitative classification

Normal artery/mild intimal thickening

The presence of a homogeneous vessel wall or of a thin intima is a rare finding in the intracoronary ultrasound population. Since mild intimal thickening is part of the ageing process of the arterial system and does not induce lumen narrowing, a thickness of the intima-media complex smaller than 0·3 mm is often suggested as an empirical arbitrary cut-off to distinguish between atherosclerotic plaque and mild 'physiological' intimal thickening (Table 2(a)). It should be stressed that a thin or minimally thickened intimal layer does not automatically indicate that a vessel wall is normal in terms of reactivity to vasoactive stimuli. Angiographic studies have shown that angiographically smooth and normal segments may have an abnormal response to vasoactive stimuli in patients with coronary artery disease or risk factors for coronary artery disease[25,26]. Ultrasound can detect atherosclerotic lesions in arterial segments that appear normal on angiography, and recent studies have shown that abnormal vasoconstrictive responses occur more frequently and are more severe in segments showing diffuse plaque accumulation with ultrasound[27,28].

Atherosclerotic disease

Severity of intimal thickening

The maximal thickness of the intima-media complex or, more appropriately, the percentage of the total vessel area occupied by plaque, are the most common quantitative indices used to define the severity of atherosclerotic involvement. Atherosclerotic lesions may be present in segments which are angiographically normal because compensatory total vessel enlargement in the early phases of atherosclerosis tends to keep the lumen constant[29[. Lumen reduction does not occur, according to these pathology studies, until the plaque occupies more than 40% of the total cross-sectional vessel area. However, atherosclerotic lesions occupying less than 20% and 40% of the total vessel area can still be considered as lesions with a minimal and moderate atherosclerotic burden, respectively (Table 2(a)). Above this threshold (plaque area greater than 40% of the total vessel area), atherosclerotic lesions may reduce the lumen area and can be classified as lesions with a large

Table 2(a) Atherosclerotic burden

Normal intima	Single layer appearance or three layer appearance with intimal thickness <0·3 mm
Minimal atherosclerotic burden	≤20% of VA occupied by plaque
Moderate atherosclerotic burden	>20%, ≤40% of VA occupied by plaque
Large atherosclerotic burden	>40%, ≤60% of VA occupied by plaque
Massive atherosclerotic burden	>60% of VA occupied by plaque

VA = total vessel area

Table 2(b) Qualitative ultrasound definitions

Plaque components Echographic characteristics	Histology
Echoreflectivity < than adventitia	Fibrocellular tissue, thrombus
Echoreflectivity ≥ than adventitia	Dense fibrous tissue
High echoreflectivity + shadowing	Calcium

Plaque characteristics	Homogeneous*		Mixed†
Soft Low echoreflective	Fibrous High echoreflective	Calcific‡ High echoreflective with shadowing	Soft/fibrous Soft/calcific Fibrocalcific

*>80% area constituted by the same plaque components; no calcium or focal calcium deposits (arc of calcium <10 degrees)
†presence of multiple plaque components not matching the 80% criterion of prevalence
‡total calcific arc greater than 180 degrees.

Table 2(c) Wall disruptions

Rupture	Radial tear, perpendicular to the vessel wall
Dissection	Longitudinal tear, parallel to the vessel wall
Characteristics to be specified	
Location	Proximal, distal, at target stenosis
Axial length	in mm
Circumferential extension	Arc in hours or degrees
Maximal depth	
Partial	Plaque between tear and adventitia
Complete	Full thickness tear extending through the plaque to the adventitia

or massive atherosclerotic burden. Although many ultrasound studies have confirmed the pathology studies of Glagov *et al.*[30–33], a reduction of the total vessel area in the stenotic segment has been described in restenotic lesions and in primary lesions (reversed Glagov effect)[34–36]. These observations suggest that caution must be taken in the evaluation of the functional severity of an atherosclerotic lesion based on intracoronary ultrasound measurements of plaque area.

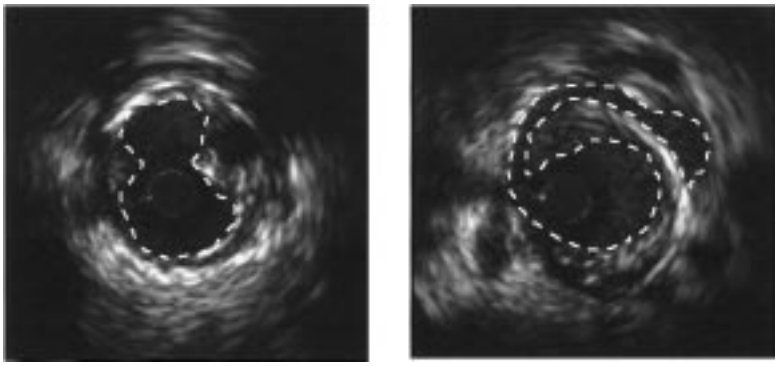
Plaque eccentricity

This feature is based on either the presence of a non-thickened portion of the arterial circumference (disease-free wall), or on a low ratio of the thinnest and the thickest part of the circumference (eccentricity index). A plaque is often defined as eccentric in the presence of an eccentricity index smaller than 0·5.

Eccentric plaques are not uncommonly seen on intracoronary ultrasound despite the angiographic appearance of concentric narrowing[37]. Conversely, angiographically eccentric plaques rarely have a segment of completely normal vessel wall (intima-medial thickness smaller than 0·3 mm). Both these observations are relevant to guide selective plaque removal interventions.

Plaque composition

The echointensity of the different plaque components in the image changes according to the system settings and



Plaque fracture Wall dissection

Figure 3 **Two examples of plaque changes after PTCA. Left panel: plaque fracture, characterized by a plaque tear in a radial direction with the neo-lumen widely communicating with the original lumen; right panel: wall dissection, characterized by a tear in a tangential direction and a small communication with the central original (true) lumen. The dotted line indicate the lumen contours.**

ultrasound system used. In order to define a standard intensity which takes into account this variability, the echointensity of the intima can be compared to the echointensity of the adventitia[38]. Thus intimal thickening with less echointensity than the adventitia is often indicated as 'soft' material, whereas 'hard' plaques are characterized by equal or greater intensity than the adventitia. Low and high echoreflectivity should be preferred to common denominations such as soft and hard since these common terms are not indicators of the mechanical characteristics of the plaque. Intracoronary ultrasound definitions of soft plaque are misleading as many plaques classified as soft will show high resistance to dilatation[39].

The presence of acoustic shadowing and reverberations are specific landmarks of the presence of calcification. With the exception of multiple scattered microcalcification, ultrasound can be considered highly specific and sensitive for the detection of calcium in a plaque. Extremely bright echoes can be induced by densely fibrotic plaques and the extreme attenuation of the echo-signal can be misinterpreted as shadowing. The abrupt disappearance of echoes and the presence of duplicate echoes can be used to distinguish attenuation from true shadowing. Because of the importance of calcium for the selection of coronary interventional devices, it is important to define: (a) the presence of single or multiple calcium deposits; (b) their depth ('superficial', defined as no tissue between the calcium deposit and the lumen and 'deep', defined as all other depths), (c) their circumferential extent, measured in degrees or hours, or defined semi-quantitatively as calcium occupying less/more of 1, 2 or 3 quadrants of the vessel; (d) their axial distribution (length in mm).

Histologically, atherosclerotic plaques are rarely homogeneous and contain a mixture of plaque components with different echoreflectivity. Using the classification proposed in Table 2(b), most of the atherosclerotic plaques are described as mixed and the majority of the homogeneous plaques are described as soft or calcific. Although a group of investigators found a larger prevalence of soft plaques in unstable lesions, they were unable to define features that were truly pathognomic of unstable angina[38]. Using this classification, no differences in composition of the culprit lesion were observed between patients with stable and unstable syndromes, despite the confirmation with angioscopy of large differences in terms of superficial plaque disruption and thrombosis[40].

These limitations and the relatively large inter-observer variability of this qualitative classification suggest the need of quantitative techniques for analysis of the ultrasound characteristics of plaque components (densitometry[41], computer assisted gray level texture analysis[42] or, more promisingly, backscatter analysis).

Plaque disruption

With improvements in image quality and increased operator experience, spontaneous plaque ruptures or fissures are increasingly observed, mainly in unstable ischaemic syndromes[43]. These ultrasound observations have clarified the pathological changes underlying many of the angiographic 'pseudoaneurysms' by showing the presence of niches within the atherosclerotic plaque likely due to emptying of the lipid-rich necrotic plaque core into the lumen.

Wall rupture or dissection are frequently the consequence of percutaneous interventions directed to enlarge the arterial lumen and displace or remove the plaque. Two main types of wall disruptions should be considered (Fig. 3, Table 2(c)). Rupture of the vessel wall is defined as a radial tear, i.e. perpendicular to the vessel wall layers. The troughs produced by atherectomy devices, that may be classified as a specific type of wall rupture, are more readily appreciated when the matched pre-interventional images are available for comparison.

Dissection of the vessel wall is defined as tear parallel to the vessel wall. The diagnosis of wall dissection or fracture is based on the visualization of blood flow in the newly created lumen, if necessary confirmed by saline or contrast injection. Pulsatility of an echolucent area within or behind a plaque is also suggestive of a false lumen. The following characteristics of disruptions must be noted: (1) location relative to the narrowest point (proximal, distal or at the narrowest point); (2) axial length if a motorized pullback is available; (3) circumferential arc in hours, measured in the cross-section with the largest circumferential extension of the dissection; (4) maximal depth, classified as partial (some plaque remaining intact between the rupture and the underlying adventitia) or complete (extending through the plaque up to the adventitia).

A peculiar type of dissection is the superficial intimal flap, characterized by a slight, thickening of the dissected intima (<0·20 mm), but still very visible because of its great motility.

Various classifications of the effects of coronary interventions have been proposed, combining the presence and axial/circumferential extent of wall disruption[44,45]. The advantage of using these complex classifications over the more descriptive approach proposed above is questionable, especially in the absence of a clear predictive value in terms of risk of acute complications and late restenosis.

Quantitative assessment

Normal range of coronary artery dimensions

The normal range of coronary artery diameters in adults has been established in autopsy studies[14]. The left main coronary artery ranges between 2·5 and 5·5 mm (mean 4·0 mm); the proximal left anterior descending artery between 2·0 and 5·0 mm (mean 3·6 mm); the proximal left circumflex artery between 1·5 and 5·5 mm (mean 3·0 mm) and the right coronary artery between 1·5 and 5·5 mm (mean 3·2 mm). These measurements are larger than the angiographic measurements of corresponding segments in apparently normal coronary arteries, especially in older patients, but were confirmed by ultrasonic measurements in arteries with no plaque[46]. The left anterior descending and left circumflex arteries taper along their length, but the calibre of the right coronary artery remains constant up to the crux cordis[47].

Calibration and ultrasound artefacts

Unlike quantitative coronary angiography, intracoronary ultrasound quantitation does not require routine calibration. The accuracy of measurement depends on the incorporation of the correct offset and estimated average speed of sound in blood and vascular tissue into the scan-converting algorithm. However, correct system calibration should not be taken for granted, and must be confirmed in in-vitro phantoms prior to the use of a new scanner.

Catheter malalignment

Non-coaxial alignment of the transducer within the artery results in an epilliptic rather than circular cross-sectional imaging plane, leading to overestimation of both areas and diameters. In a comparative study of intracoronary ultrasound and quantitative coronary angiography in normal arteries, no significant inaccuracy was caused by non-axial alignment of the catheter. This was probably because the small size of the coronary artery lumen relative to the length of the intracoronary segment of the imaging catheter prevents significant malalignment[48]. Nevertheless, this potential source of error should be considered in aorta-ostial lesions, in tortuous segments, in large or ectatic vessels, and when measuring close to acute bends.

Non-uniform rotation

Image distortion may occur as a result of rotation angle artefacts induced by non-uniform rotation of the drive shaft in mechanical imaging catheters. When non-uniform rotation is obvious visually the degree of distortion may be significant and measurements are not reliable.

Systolo-diastolic changes

The lumen area varies in relation to changes in distending pressure during the cardiac cycle. The maximum area is present in mid-systole and the minimum area in late diastole except in the presence of a 'tunnelled' artery which runs under a muscle bridge causing systolic external compression of the artery[49]. The pulsatile variation in lumen area of normal coronary arteries is on average 8% in native coronary arteries, whereas in the presence of plaque this variation is reduced depending upon the thickness, eccentricity and composition of the plaque[50]. By convention, the end-diastolic frames of angiograms are used quantitatively when cardiac motion and contrast streaming are at a minimum. A number of arguments can be made for employing the opposite strategy and measuring the intracoronary ultrasound images at end-systole. The maximum lumen dimensions during the cardiac cycle are clinically the more relevant measurements for the purpose of sizing percutaneous interventional devices and the movement of the ultrasound catheter within the artery is minimal at end-systole, making the ultrasound image more easily interpretable and the area measurements more reliable and reproducible. Furthermore, after interventions the minimum lumen area may vary considerably during the cardiac cycle as tissue flaps move to-and-fro into the lumen. The most practical approach is to measure lumen dimensions in systole, when the size of any false lumen is minimized by the maximal distending pressure during the cardiac cycle.

Table 3 Intracoronary ultrasound measurements of common use

Measurement	Abbreviation/ units of measurement	Comments
Lumen area	LA, mm^2	
Total vessel area	VA, mm^2	Area inside leading edge brighter adventitia; do not trace if >90 degrees of vessel circumference not visible (shadowing or attenuation)
Plaque area	PA, mm^2	Area included between the two contours indicated above (VA minus LA)
Percent plaque area	% PA, %	Percentage of VA occupied by plaque, calculated as $(VA - LA)/VA \times 100$
Max lumen diameter	MaxLD, mm	
Min lumen diameter	MinLD, mm	
Mean lumen diameter	MeanLD, mm	Calculated as: $(\sqrt{LA}/\pi) \times 2$
Lumen symmetry index	MinD/MaxD	1 indicates circular lumen, <1 indicates increasing elliptical lumen shape
Max plaque thickness	MaxPT, mm	
Min plaque thickness	MinPT mm	
Plaque eccentric. index	Min/max PT	1 indicates concentric plaque, <1 indicates increasing plaque eccentricity

Area measurements

Table 3 summarizes the most frequently used measurements with intracoronary ultrasound. All measurements (diameters and areas) should be performed in the stenosis at the site of the minimum lumen area and in the reference segments, proximal and distal to the stenosis. While the stenosis location is unequivocal, the position of the reference cross-section is highly subjective. Specific indications (5 mm from both ends of the stented segment) have been proposed for stent implantation but recommendations are more difficult for other types of interventions.

Lumen area

The lumen area is measured by tracing the leading edge of the circumferential blood/intima interface signals. Edge detection may be facilitated on the real-time images by observing the dynamic alteration in speckle pattern characteristic of flowing blood compared to the more static pattern of adjacent tissue. A bolus injection of contrast dye or saline (at body temperature) into the vessel temporarily clears the bright blood signals and facilitates edge detection. These images should not be used for quantitative assessment because of the different propagation speed of sound waves in water or contrast and in blood.

The complex morphology of the lumen after coronary interventions, and especially after balloon angioplasty, raises questions concerning the appropriateness of also considering small fissures behind plaque as part of the vessel lumen, since their functional importance for blood passage is questionable and unpredictable. A commonly applied solution in the presence of extensive wall disruption is to distinguish between the 'true' lumen area (in general the lumen in which the ultrasound catheter is positioned), and the 'dissection area', separated from the true lumen by the dissection flap. This distinction, straightforward in the example of Fig. 3, can become very subjective when a broader junction between true lumen and dissection lumen is present.

Total vessel area

As the adventitia imperceptibly merges with the surrounding perivascular tissue, for the purpose of intracoronary ultrasound measurements the total cross-sectional area of the vessel is taken to mean the area enclosed by the outermost definable interface, i.e. the well delimited interface between the media and adventitia coinciding with the position of the external elastic lamina. This is also referred to as the external elastic lamina area. Measurement of the area within the internal elastic lamina theoretically allows the calculation of true plaque or intimal area, but, as previously discussed, the internal elastic lamina is not well delineated in most cases. Vessel area cannot be measured when calcium-induced acoustic shadowing obscures more than 90 degrees of the vessel circumference. When lesser degrees of shadowing are present, the vessel border is extrapolated from the closest identifiable segments of the media/adventitia interface. The variable degree of acoustic shadowing cast by the stent struts and the blurring of the vessel layers deep to the stent may also give rise to difficulties in quantitating the vessel area.

Plaque area

The plaque area should be more accurately termed the 'plaque + media' area and is calculated as the difference between the total vessel area and the lumen area. As this measurement is derived from the vessel and lumen areas problems applicable to total vessel and lumen area

measurement are also applicable to the measurement of plaque area. In the case of plaque dissection, it has been proposed that the plaque area between true lumen and dissection lumen be planimetered as a means of quantitatively expressing the severity of coronary dissections (dissection arm).

Percentage plaque area

The percentage of the vessel area occupied by plaque is calculated using the formula: (total vessel area − lumen area)/vessel area × 100. This parameter has been referred to as 'percent plaque area', or 'percent plaque burden', 'percent cross-sectional area narrowing or stenosis or obstruction'. As the last terms are also used to describe the ratio of the lumen area at the site of stenosis relative to the lumen area in the reference segment they must be avoided. A number of investigators have taken the opposite approach and calculated the proportion of the vessel area occupied by the lumen, termed the percentage lumen cross-sectional area.

Measurement of the plaque burden relates to histological practice, and is therefore recommended. A simple but noteworthy distinction must be made between intracoronary ultrasound percent plaque area and angiographically assessed percent stenosis. Compensatory vessel expansion and disease in the proximal 'reference' segment accounts for the poor correlation noted between intracoronary ultrasound and angiographic percent stenosis with, in general, intracoronary ultrasound percent stenosis more severe than angiographic percent stenosis[9,10].

Intracoronary ultrasound derived diameters

Lumen diameter measurements remain central in everyday clinical practice, as the appropriate size of interventional devices is chosen on the basis of the estimated diameter of the reference segments adjacent to a stenosis. In addition, the severity of a stenosis and the outcome of coronary interventions continue to be routinely evaluated in terms of the percentage diameter stenosis of the vessel.

With intracoronary ultrasound, direct measurement of maximum and minimum diameter is the most widely applied method. Whereas the maximum lumen diameter is usually readily identified, selection of the minimum diameter may be difficult in cases in which the borders of the lumen are irregular and incorporate sections that protrude into the lumen. The minimum diameter is normally drawn as the smallest diameter in any direction passing through the mid-point of the maximum diameter.

The ratio between the maximum and minimum lumen diameter can be used to define the symmetry of the lumen, with ratios lower than 1·0 indicating increasing lumen asymmetry. The mean diameter can also be derived from the lumen area assuming a circular area. Once the lumen boundary has been traced, automated methods can determine the maximum and the minimum diameter through the geometric centre of the lumen.

Part III: Clinical applications

Angiographically normal coronary arteries

Normal angiograms are present in 10%–15% of patients undergoing coronary angiography because of suspected coronary artery disease. Plaque formation can often be demonstrated with intracoronary ultrasound in these patients. Erbel *et al*. observed atherosclerotic changes in 21/44 patients (48%) with suspected coronary artery disease and a normal coronary angiogram[51]. If functional parameters are also considered (coronary flow reserve and endothelium-mediated vasodilatory response) only 36% of patients were confirmed to be fully normal.

These findings suggest a revision and a new classification for patients with syndrome X or chest pain without significant angiographic changes. Before recommending a routine intracoronary ultrasound assessment in these patients, however, it is necessary to demonstrate the clinical relevance of these findings and in particular differences in prognosis in patients with and without intracoronary ultrasound-detectable atherosclerotic changes.

Intracoronary ultrasound can also be used to evaluate other vessel abnormalities such as myocardial bridging[49], spontaneous coronary dissection[52] and contrast inhomogeneties within the vessel lumen.

Evaluation of intermediate stenoses and ambiguous lesions

Suboptimal angiographic visualization impairs accurate assessment of stenosis severity. Ostial stenoses, at the origin of the left and right coronary arteries from the aorta, at the bifurcation of the left main coronary artery or at the origin of large side branches, especially in the proximal left anterior descending coronary artery, are often poorly visualized because of guiding catheter wedging, vessel overlap or foreshortening. Out-of-plane projections do not always solve the problem.

Occasionally, insufficient quality of the angiogram results from extreme obesity, emphysema or chest deformities. Extreme lumen eccentricity (slit-like orifices) are certainly more rare than estimated from pathology studies in non-pressurized arteries. However, a discrepancy between measurements in orthogonal projections (lesions significant in one projection and moderate in another projection) is not rare in clinical practice and complicates clinical decision-making. Intracoronary ultrasound does not suffer from these limitations and measurements of lumen cross-sectional area in lumens of non-circular morphology are straightforward. It is common experience that ultrasound can often solve the problem of angiographically intermediate or ambiguous lesions by showing obviously normal or severely diseased vessels.

In two large prospective series, in more than 20% of the examinations before coronary interventions,

intracoronary ultrasound changed the management strategy (treatment of angiographically non-significant lesions after intracoronary ultrasound examination and vice-versa)[53,54]. In both studies, however, the selection of the patients scheduled for an intracoronary ultrasound examination before intervention may have resulted in an overestimation of the real impact of ultrasound for clinical decision making. Furthermore, the criteria used to define the severity of the stenosis with ultrasound were not objectively defined.

In most instances, intracoronary ultrasound may help to solve the clinical dilemma proposed by angiographically ambiguous or intermediate stenoses on a purely visual analysis of the angiogram. In particular, the minimal lumen diameter derived from intracoronary ultrasound area measurement is well correlated with physiological parameters such as measurements of coronary flow (Kern *et al*., personal communication). Not infrequently, however, the analysis of the severity of intermediate stenoses in the catheterization laboratory requires functional investigations such as intracoronary Doppler and post-stenotic pressure measurements.

Coronary artery disease after heart transplantation

Accelerated transplant coronary artery disease represents the most important cause of morbidity and mortality in cardiac transplant recipients beyond the first year after transplantation[55–57]. Because cardiac allografts are functionally denervated, major clinical events due to advanced coronary atherosclerosis, including myocardial infarction, congestive heart failure, and sudden death, usually occur without prodromal angina. Thus, repeated coronary angiography is performed for surveillance of coronary artery disease progression[58].

The pathology of transient vasculopathy is distinctive in that it initially consists of concentric intimal proliferation throughout the coronary tree which then progresses to diffuse arterial obliteration. This is characterized angiographically by longitudinal narrowing of the arteries with pruning of distal vessels[58]. The limitations of standard coronary arteriography to accurately measure the severity of transplant coronary artery disease has been highlighted by angiographic–pathology correlation studies[59].

Intracoronary ultrasound is an effective and reproducible method of measuring intimal proliferation in cardiac transplant recipients. One or more years after cardiac transplantation the majority of patients have intracoronary ultrasound evidence of silent intimal thickening not apparent by angiography[60,61]. Intracoronary ultrasound offers early detection and quantitation of transplant coronary disease, and provides characterization of vessel wall morphology. The studies performed in patients early after transplantation serve as a reference for the ultrasound appearance of young, morphologically normal coronary arteries[62]. A subset of these patients, however, studied early after cardiac transplantation, has provided ultrasound evidence of donor-related atherosclerotic changes.

The ultrasound images obtained in patients a year or more after transplantation show a broad spectrum of morphological abnormalities and a high incidence of angiographically silent intimal thickening[60,62,63]. Furthermore, in contrast with the histological paradigm of coronary artery disease after heart transplant, focal lesions are often observed[63,64].

Preliminary longitudinal studies comparing the sensitivity of intracoronary ultrasound to coronary angiography for detecting and monitoring progression of atherosclerotic disease have shown that progression of intimal proliferation identified with intracoronary ultrasound in cardiac transplant recipients, occurs in approximately 40% of the serially studied sites[65]. It has been seen that intimal proliferation occurs mostly during the first 2 years after transplantation, whereas calcification of plaques occurs only later in the process[61,66]. The presence of a mean intimal thickness greater or equal to 0·3 mm was shown to be an independent predictor of overall and cardiac survival as well as of freedom from retransplantation[67].

Identification of factors predisposing to intimal proliferation is an important contribution to the understanding of the pathogenesis of transplant vasculopathy and to develop preventive and therapeutic strategies. Recent studies have correlated multiple immunological and metabolic factors with intimal thickness by univariate analysis, suggesting a multifactorial aetiology for transplant vasculopathy[68].

Guidance during interventions

Table 4 summarizes the indications for intracoronary ultrasound in association with coronary interventions.

Lesion assessment before coronary interventions: selection of treatment

The intracoronary ultrasound examination offers potential advantages over angiography for deciding which specific treatment modality is most appropriate for a given lesion. Despite the extreme miniaturization of the ultrasound catheters, before interventions the probe occludes the lesion in most cases, precluding a prolonged assessment because of the rapid development of symptoms and signs of myocardial ischaemia and complicating the image interpretation because of blood stagnation.

Since the ultrasound catheter must be advanced into the lesion, in the examination of ostial stenoses of the two main coronary arteries particular attention must be paid to avoid the complications of the severe ischaemia induced by the partial or complete occlusion of flow.

Despite these limitations, the additional information provided by ultrasound on lesion composition, eccentricity and length modified the treatment strategy

Table 4 Intracoronary ultrasound: clinical applications

	Main advantage intracoronary ultrasound	Score
Angiographically normal artery	Improved diagnostic accuracy (early atherosclerotic changes, spontaneous dissection, muscular bridge, etc)	+
Ambiguous and intermediate lesion	Improved lumen visualization and measurement	+ +
Post-transplant coronary arteriography	Detection of angiographically silent intimal thickening; prognostic definition of the group at risk of developing coronary arteriopathy	+ +
Guidance of interventions	PTCA: selection of balloon diameter; identification of pseudo-successful results and presence/severity of wall dissections;	+ +
	HSRCA: definition pre-intervention of the lesions most suitable (diffuse subendothelial calcification);	+ +
	DCA: exclusion of lesions not suitable; selection of cut direction; direct assessment of the adequacy of plaque removal and identification of adventitial cuts;	+ +
	STENT: completeness of apposition; detection of residual narrowing or proximal/distal stenoses or dissections requiring further treatment	+ + +

DCA = directional coronary atherectomy; HSRCA = high speed rotational coronary atherectomy; ICUS = intracoronary ultrasound; PTCA = percutaneous transluminal coronary balloon angioplasty, STENT = coronary stenting.
Clinical usefulness score: + = can be helpful but application not well established; + + = weight of evidence in favour of usefulness; + + + = application recommended in selected patient groups.

in almost 20% of the cases in the large experience of the Washington Heart Center[54]. Intracoronary ultrasound made an even greater impact on clinical decision making, as reported by Lee *et al*. They showed that increased confidence with the technique and the increased experience of the operators in the interpretation of the images led to a progressive increase over time of decisions based on intracoronary ultrasound findings[53].

Calcium Presence, depth and circumferential extent of the calcification is of great importance for selecting the type of interventional device and for estimating the risk of complications. Fluoroscopy detects calcium deposits which occupy more than 180 degrees of the vessel circumference with insufficient sensitivity (60%) and is completely unreliable in the presence of smaller calcium deposits[69,70]. In 1155 coronary lesions examined with intracoronary ultrasound, Mintz *et al*.[69] detected lesion calcium in 73% of the lesions (38% by angiography), showing that calcium is more often subendothelial (72%) and located at the maximal thickness of the plaque. Subendothelial calcium is an important factor limiting tissue retrieval and increasing the incidence of procedural complications after directional atherectomy[71–73]. The presence and circumferential extent of calcium is also predictive of the development of dissection or fracture after PTCA, almost always present when the arc of vessel calcium is greater than 90 degrees[74,75]. Dissections frequently occur at the junction between soft tissue and calcium due to the different stress modulus of these two plaque components[76,77].

Rotational ablation can successfully remove subendothelial calcium and create a smooth channel which can be further enlarged with balloon angioplasty, directional atherectomy, or stent implantation[78,79]. There is general agreement among operators from high volume centres used to perform routine pre-intervention intracoronary ultrasound, that rotational atherectomy is indicated in the presence of an area of superficial calcium greater than 180 degrees in multiple cross-sections along the stenotic segment. Although the removal of plaque calcification with excimer laser is more difficult, shattering of the calcific deposits was observed with ultrasound, facilitating the subsequent angioplasty[80].

Plaque eccentricity Lesion eccentricity and location of maximal plaque accumulation is another element of great importance to guide the interventional procedure, which is only indirectly assessed with angiography. With a direct measurement of the maximal and minimal plaque thickness, eccentricity is recognized much more frequently than appreciated from the angiographic appearance[9,37,81]. For highly eccentric plaques, in the absence of subendothelial calcium, directional atherectomy appears a logical choice, but the advantage of this procedure over balloon angioplasty and stenting in this setting remains to be confirmed. In eccentric plaques, the origin of side-branches from the diseased part of the vessel wall is an element predictive of occlusion after balloon dilatation or stent implantation.

Diffuse atherosclerotic disease in vein grafts Degenerated vein grafts are a challenge for the interventionalist since

percutaneous treatment can avoid the increased risk of surgical reintervention but the immediate complications (distal emboli, myocardial infarction) and the long-term restenosis are both high in this setting. Vein grafts, as native coronary arteries, undergo a process of remodelling and compensatory enlargement which leads to an underestimation of the diffuseness of the disease with angiography[82]. Intracoronary ultrasound examination leads to extension of treatment to longer graft segments, treatment of lesions at high risk of rapid progression at the medium term and to referral of patients to surgery in the presence of diffuse vein degeneration with friable plaque (low echoreflectivity with irregular borders)[54]. Various types of interventions (PTCA, extraction, directional or laser atherectomy) can also be guided with intracoronary ultrasound[83]. This is particularly useful for appropriate sizing of stents in these large conduits, with only 9% of the stents optimally expanded with angiography matching the reference cross-sectional area[84].

Type of vessel remodelling As discussed in the previous sections, lumen reduction can be induced either by plaque accumulation that has exceeded the capacity of the vessel to remodel, or by failure to remodel in the presence of a small or moderate plaque burden. These two conditions cannot be recognized by angiography but are readily distinguished with ultrasound and may require a different therapeutic approach. Pasterkamp *et al*. observed a difference in the mechanism of lumen enlargement after balloon angioplasty in these two types of lesions, with a similar final increase in lumen area after balloon angioplasty[35]. Although other studies are needed to establish the optimal treatment for these two lesion types, it is conceivable that stenoses due to negative remodelling might mainly require expansion of the total vessel area, possibly using a stent to avoid acute or chronic vessel recoil, while in lesions with a large plaque burden partial plaque removal would facilitate the lumen expansion with adjunctive balloon dilatation or stent implantation.

Intracoronary ultrasound during balloon angioplasty Modifications of the dilatation strategy based on intracoronary ultrasound results include changes in balloon size and inflation pressure. Occasionally a lesion length greater than that expected from the angiographic image may suggest the use of a long balloon. Diffuse lesion calcification certainly requires higher inflation pressures and carries a higher risk of dissection[73–75,86], but the length and circumferential extent of calcification at which the risk of an unsatisfactory result after plain balloon angioplasty is so high as to prompt the use of alternative techniques such as rotational atherectomy is not yet defined[85,86]. Plaque area reduction is the major cause of lumen gain in unstable angina and acute myocardial infarction suggesting that compression, redistribution or dislodgement of mural thrombus occurs in acute coronary syndromes[24,86]. With intracoronary ultrasound the selection of the balloon size can be based on measurements of the total diameter of the vessel. The CLOUT Study Group has proposed upsizing the diameter of the balloon based on the calculation of the mid-wall diameter and has reported initial favourable results in terms of increase in lumen area without a higher incidence of complications[87]. The efficacy of this strategy has been confirmed in a recent preliminary report, showing a large lumen gain and low target lesion revascularization (17%) using a balloon diameter equal to the total vessel diameter and high pressure dilatation[88].

The most important information obtained with intracoronary ultrasound concerns the results of the procedure. After angioplasty, intracoronary ultrasound can detect circumferential and longitudinal extension of plaque fracture or dissection[44,45,89] (Fig. 3). Although the angiographic presence of dissections increases the risk of in-hospital complications after angioplasty, they occur in only 5% of the stenoses with angiographic signs of dissection after balloon angioplasty. Intracoronary ultrasound has the potential to more accurately detect dissections at risk which require immediate further treatment. Although depth and circumferential extension of the dissection appear the most relevant parameters to be considered, firm intracoronary ultrasound predictors of complications have not yet been established and probably require the integration of longitudinal and circumferential measurements with three-dimensional intracoronary ultrasound[90].

Since the angiographic parameters, including quantitative angiographic measurements are poor predictors of the long-term result after balloon angioplasty[91,92], the best application of intracoronary ultrasound after balloon angioplasty is the detection of lesions at high-risk of development of restenosis at the time of the initial procedure. This would allow the operator immediately to perform further interventions to improve long-term outcome. Preliminary studies have shown conflicting data concerning the factors predictive of restenosis after balloon angioplasty, indicating that absence of plaque fracture or conversely large dissections are prognostic markers of restenosis[44,93].

In 200 patients studied with intracoronary ultrasound after the final balloon inflation in the PICTURE study (Post Intra-Coronary Treatment Ultrasound Restenosis Evaluation)[94], no correlation was found between ultrasonically identified lesion composition, fracture or dissection after dilatation and quantitative measurements of the lumen and plaque after intervention and clinical and angiographic results. More encouraging results have been reported by Mintz *et al*. who have studied lesions after transcatheter interventions and tested the predictive value of multiple angiographic and ultrasonic parameters for restenosis[95]. With multivariate analysis, these authors found that the residual plaque burden measured with intracoronary ultrasound was an independent predictor of restenosis. Plotting the residual plaque burden vs the probability of restenosis at 6 months, a curvilinear relationship was observed, with restenosis occurring in more than 50% of the lesions with more than 70% residual plaque burden immediately

after intervention[96]. The GUIDE II trial (Guidance by Ultrasound Imaging for Decision Endpoints) is a multicentre study assessing the factors predictive of restenosis after balloon angioplasty and directional atherectomy based on a final intracoronary ultrasound examination with the operator blinded to the intracoronary ultrasound results[97]. The first interim analysis performed without discriminating between balloon angioplasty and directional coronary atherectomy has shown that two intracoronary ultrasound parameters were predictive of long-term recurrence of symptoms: residual plaque burden and luminal cross-sectional area after intervention. Similar intracoronary ultrasound parameters (residual plaque burden and minimal luminal diameter measured by intracoronary ultrasound but not by angiography) were found to be predictive of restenosis after PTCA in a large single-centre study including 89 patients[98].

The final analysis of these trials will show whether intracoronary ultrasound provides sensitive and specific predictors of restenosis after balloon angioplasty, justifying its more widespread application during PTCA. There is little doubt, however, that intracoronary ultrasound unmasks pseudosuccessful angiographic results in which the lumen area increase is only due to circumferential dissections filled with contrast. Diffuse haziness or intraluminal defects in the treated segment are suggestive of the presence of these suboptimal results which are likely to be associated with a high risk of persistence or recurrence of symptoms. In these selected cases, especially in large vessels, it is the routine practice of many centres to use intracoronary ultrasound to confirm the need for further interventions.

Directional atherectomy

The direct visualization of the quadrants of maximal plaque accumulation has great potential for guidance of interventions directed to selective plaque removal. Unfortunately, until now combined ultrasound–atherectomy devices are not in current clinical use and only prototypes have been tested, providing images limited to the quadrant towards which the cutter is oriented[99].

The orientation of the atherectomy cutter based on images obtained in a separate preliminary insertion of the ultrasound catheter is cumbersome. An angiographically visible side-branch close to the lesion must be identified and the arc between this branch and the radiant of maximal plaque accumulation defined. Afterwards, using angiography the cutter is positioned pointing to the side-branch identified and appropriate rotation of the cutting catheter is performed[100]. More recently, a technique which allows both a proper orientation of the atherectomy cutter and a complete plaque removal has been proposed[101]. The initial 'reference cut' is performed based on the angiographic image and then imaged by intracoronary ultrasound. The orientation of the cutter is maintained within the hemisphere of the 'reference cut' until complete plaque removal has been achieved. If necessary (concentric plaques), the cutter is then turned 180 degrees from its initial position and cutting is performed until also the opposite hemisphere is appropriately treated. During atherectomy, serial ultrasound examinations are performed: before intervention to confirm the appropriateness of the indication (absent or deep calcification, short stenosis, ideally soft plaques); between subsequent atherectomy passes to assess the completeness of plaque removal and avoid deep cuts in the periadventitial tissue; after atherectomy to determine the need and effect of adjunctive balloon dilatation or stent implantation to be used to tackle the flaps and smooth the irregular wall contours often induced by the atherectomy cuts. It is common experience that the use of intracoronary ultrasound during atherectomy results in a more aggressive strategy and leads to greater plaque removal and a larger lumen diameter[102]. These experiences suggest that intracoronary ultrasound helps to overcome some of the limitations of the angiographically-guided directional atherectomy, reflected by its inability to provide a clinically relevant reduction in restenosis as documented in randomized multicentre comparisons with balloon dilatation[103,104]. The results of the OARS trial (Optimal Atherectomy Restenosis Study)[105] confirm the possibility of achieving an improved immediate result (residual angiographic diameter stenosis $8 \pm 11\%$) and a high procedural success with aggressive ultrasound guided atherectomy. Despite these 'stent-like' immediate results, however, the angiographic restenosis rate was 29%, with subsequent target vessel revascularization or major ischaemic cardiac events in 20% of the patients. More encouraging are the results reported in a Japanese multicenter trial (ABACAS) showing that plaque removal, more complete than in the OARS trial, (45% vs 57% residual plaque burden) results in a reduction in angiographic restenosis rate (21%)[106].

Stent implantation

Serial intracoronary ultrasound examinations have shown, with slight differences among the different investigators[36,107–110], that a late reduction in total vessel area (chronic negative remodelling) is an important mechanism of restenosis after PTCA and DCA. These observations explain why coronary stenting is able to reduce the restenosis rate in comparison with PTCA[111,112]. In these large multicentre trials, however, stent implantation was associated with a high incidence of subacute thrombosis, especially for implantation as bail-out after PTCA.

Intracoronary ultrasound had an essential role in developing an optimal strategy for stent deployment. The demonstration that incomplete apposition of the stent struts to the vessel wall, residual lumen narrowing or irregular eccentric lumen in the stented segment were still present in 88% of the cases with an optimal angiographic result suggested that the poor technique of implantation rather than the inherent stent thrombogenicity was responsible[113] (Fig. 4). This prompted operators to develop a more aggressive stent implantation strategy based on high-pressure balloon dilatation inside the stent[114–117].

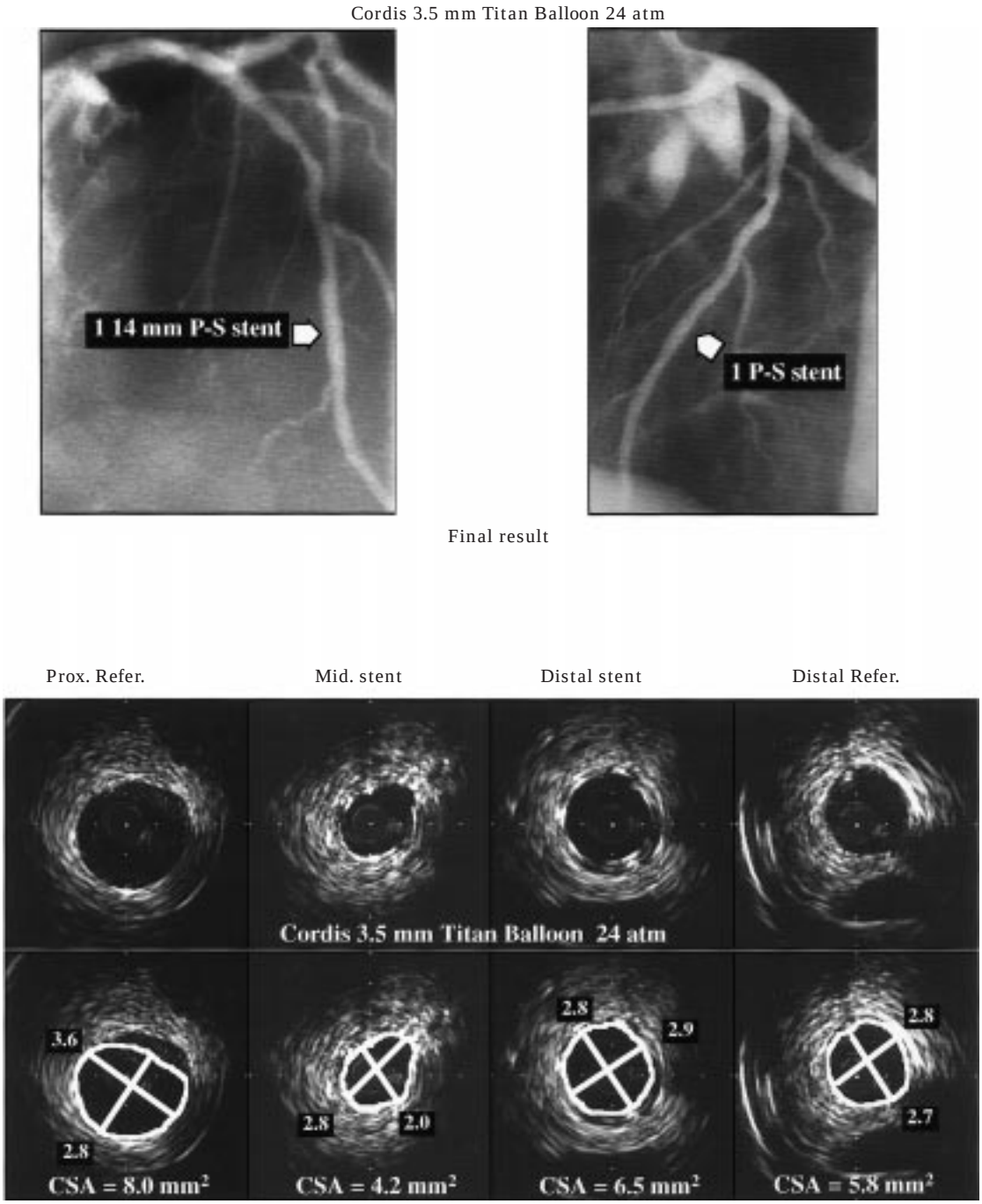


Figure 4 **Upper panel: Optimal angiographic result after implantation of a single Palmaz–Schatz stent in the mid-left anterior descending coronary artery. Lower panels: Despite high pressure balloon dilatation with a large balloon, a segment of incomplete expansion is observed with intracoronary ultrasound within the stent (Mid-stent). CSA = cross-sectional area.**

The guidelines of the Milano group[116] have been modified and simplified by the MUSIC Investigators (Multicenter Ultrasound guided Stent Implantation in the Coronaries) (Table 5). These guidelines are based on a comparison between lumen inside the stent and lumen of the proximal and distal reference segment. Although the strict criteria proposed cannot be achieved in all cases of stent implantation and they do not need to be completely fulfilled to prevent subacute thrombosis, they should be considered as an ideal goal to be reached. With this approach, the low incidence of subacute thrombosis of the Milan experience has been confirmed (personal communication).

Table 5 Guidelines for optimal stent expansion (The MUSIC criteria)

(1)	Complete apposition of the stent over its complete length
(2)	In-stent minimal lumen area greater or equal to 90% of the average reference area or greater or equal to 100% of the lumen area of the reference segment with the smallest lumen area; this criterion is modified (80% average reference area and 90% lumen area of the reference segment with smallest area) if minimal lumen area inside the stent is equal or greater than 9·0 mm^2; In-stent lumen area of proximal stent entrance greater or equal to 90% of proximal reference lumen area;
(3)	Symmetric stent expansion defined by the ratio minimal/maximal lumen diameter greater or equal to 0·7.

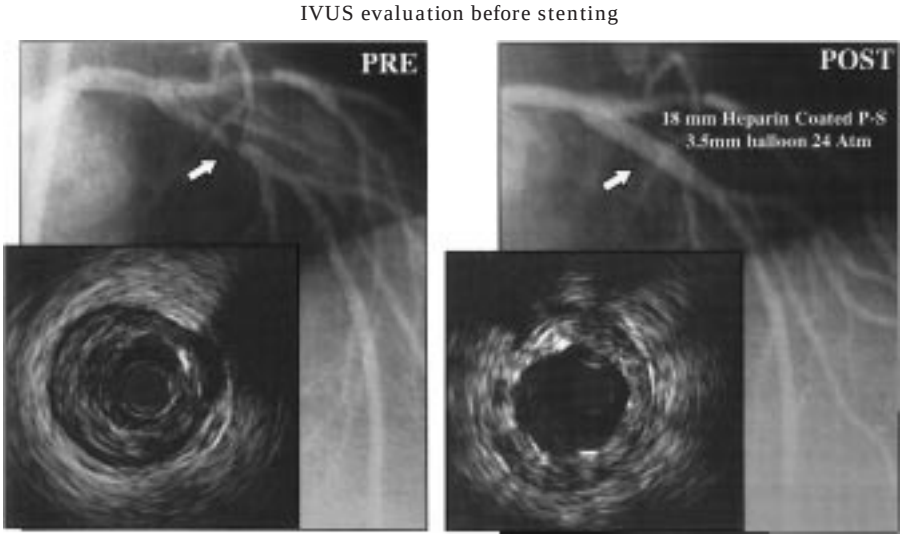
With the consistent use of a strategy of high pressure dilatation but without intracoronary ultrasound guidance, a subacute thrombosis rate of 1·6% has been reported in 1156 patients treated with a combination of aspirin and ticlopidine[118]. The improved diagnostic accuracy of angiography after high pressure dilatation is explained by a recent report showing gross over-estimation of lumen diameter with quantitative angiography when the stent is deployed at low pressure but a progressive improvement in the correlation between intracoronary ultrasound and angiographically measured diameters after high pressure dilatation[119]. Similar conclusions have been reported by the Essen group in a retrospective analysis of the comparison between intracoronary ultrasound and angiography in the early experience (deployment at low pressure) and in the most recent cases treated with high pressure balloon dilatation[120]. Although the subacute thrombosis rate of the French Registry and of other groups not using intracoronary ultrasound guidance for stenting is between 1 and 2%[118,121], these data must be compared to the even lower percentages of subacute thrombosis in centres using intracoronary ultrasound-guided implantation (Columbus Milan 0·9%[117], Cleveland Clinic Registry 0%[122], APLAUSE trial in Washington Heart Center (Anti PLAtelet treatment After Ultrasound Guided Stent Evaluation) 0·4%[123]). These differences, although small, appear clinically relevant, especially if the extreme complexity of the lesions treated in these tertiary referral centres is considered, suggesting that there is a price to pay in terms of additional immediate complications when the intracoronary ultrasound guidance is abandoned. Unfortunately, it will be very difficult to organize a trial sufficiently large to demonstrate statistically the significance of this small difference. In the French Registry small arteries, often corresponding to diffuse disease with ultrasound, bail-out scenting, unstable syndromes and low operator experience were independent predictors of complications and subacute thrombosis[124]. These data suggest that intracoronary ultrasound guidance can be more important and cost-effective in these specific clinical and anatomical conditions. In practice, a possible compromise weighting risk of subacute thrombosis and cost of intracoronary ultrasound might be that intracoronary ultrasound is not applied to elective stent implantation in short discrete stenoses in angiographically normal vessels when an optimal angiographic result is obtained with high pressure dilatation. On the contrary, in complex procedures for long stenoses or dissections, if the implantation of multiple stents is required or when there are still doubts angiographically after high pressure dilatation concerning adequacy of stent expansion and presence of edge lesions, intracoronary ultrasound is recommended. The combination of ultrasound probe and balloon in the same catheter[125] or the immediate assessment of the appropriate and symmetrical expansion of the balloon using an intracoronary ultrasound guidewire[126] are innovative approaches to facilitate the application of intracoronary ultrasound during routine procedures of stent implantation.

Having learned from intracoronary ultrasound how a stent must be implanted to avoid subacute thrombosis, the new challenge is represented by the reduction of restenosis after stenting. Ultrasound can facilitate the optimization of stent expansion since it can help to:

(1) identify the length of the diseased segment to avoid significant residual stenosis or dissection at the edges of the stent after high-pressure balloon dilatation; these axial measurements are highly facilitated using three-dimensional intracoronary ultrasound[127,128];
(2) detect presence and extension of plaque calcification, an important factor limiting stent expansion[129] which can be treated with rotational atherectomy (Fig. 5);
(3) guide selective interventions of plaque removal (DCA) before stent implantation to avoid plaque prolapse or shift and reduce vessel stretch;
(4) guide and confirm the achievement of an optimal lumen gain in the stented segment.

Despite the improvement in immediate results, the risk of stent restenosis still remains clinically relevant, with a higher risk in long stenoses and in small vessels[130]. In the Milan experience, despite the high incidence of restenotic lesions, long lesions, small vessels with diffuse disease and total occlusions, the overall angiographic restenosis rate was low (21% using the 50% diameter stenosis criterion at 6 months) and repeated interventions were required in 13% of the patients[116]. In a matched comparison of 346 lesions treated with angiographic guided and ultrasound guided stent implantation, both performed with high-pressure balloon expansion, a 57% reduction in target lesion revascularization was observed in the ultrasound group[131]. A significant increase in post-stent cross-sectional lumen area and a 40% decrease in target lesion revascularization has been recently reported in the ultrasound guided group of the CRUISE trial. Randomized comparative studies (see Table 6) are targeted to a reduction of the restenosis rate in the high-risk group (small

(a)



(b)

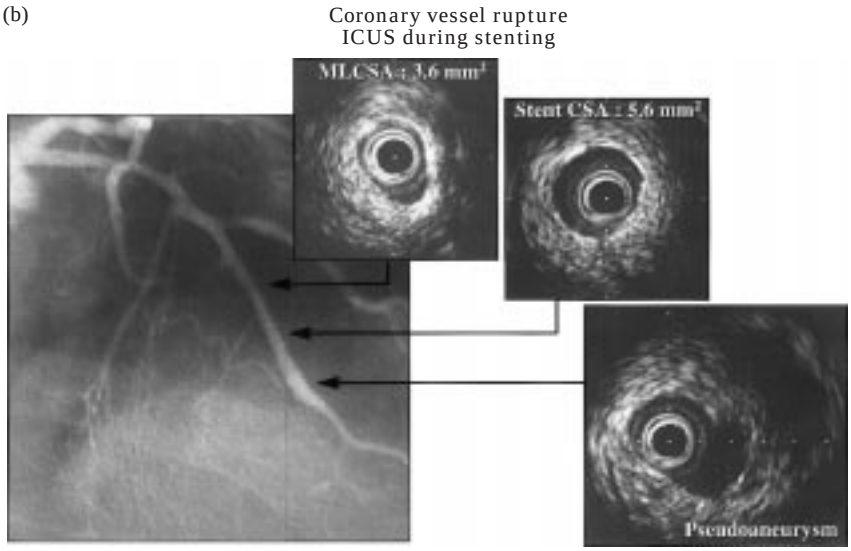


Figure 5 **Importance of plaque composition for stent expansion. (a) Optimal expansion of a Palmaz-Schatz stent in a lesion with a prevalence of echogenically soft plaque material, with subendothelial very low echoreflective plaque between 6 and 12 o'clock suggestive of mural thrombosis. (b) Incomplete expansion of a Gianturco–Roubin type 2 stent at the site of a subendothelial calcification (upper left panel) despite aggressive balloon dilatation resulting in partial vessel rupture (pseudoaneurysm) at the distal end of the stent. CSA = cross-sectional area.**

vessels, long lesions) in which restenosis still represents a major factor limiting the application of percutaneous interventional treatment modalities.

Intracoronary ultrasound will also become the ultimate method to test the efficacy of different strategies of prevention of intimal hyperplasia (local or systemic pharmacological treatment, radioactivity, etc), measuring the volumetric plaque increase inside the stent[133,134]. Ultrasound has shown that the mechanism of restenosis after stent implantation is not a chronic mechanical recoil as in other types of interventions but that intimal hyperplasia or plaque protrusion explain the lumen reduction within the stent[135,136].

Conclusions

Although thousands of patients have successfully undergone intracoronary ultrasound studies for guidance of coronary interventions (Table 6), the absence of randomized studies precludes a definitive identification of role and clinical usefulness of this technique during interventions. Intracoronary ultrasound can be used to solve selected diagnostic problems and is a standard method for in vivo quantification of intimal proliferation in cardiac allograft recipients and to follow progression of coronary disease.

Table 6 Multicentre intracoronary ultrasound studies during coronary interventions

Study	Type of intervention	Patients enrolled (n)	Aim of the study	Results
GUIDE (Phase I)	PTCA/DCA	187	Comparison between angiography and IVUS in target lesion evaluation	Significant discrepancy in the assessment of plaque distribution, composition and morphology.
PICTURE[94]	PTCA	200	IVUS predictors of restenosis	Plaque composition and eccentricity non predictive. Absence of dissection narrowest point and large residual plaque burden positive predictors of angiograhic restenosis
GUIDE (Phase II)[97]	PTCA/DCA	500	IVUS predictors of restenosis	Residual plaque burden and IVUS MLD positive predictors of angiographic restenosis and clinical events
CLOUT (pilot)[87]	PTCA	100	IVUS measurement of target lesion used to upsize the balloon (midwall diameter)	Upsize balloon necessary in 73% of the pts; new dilatations performed without complications and inducing a 40% increase in IVUS lumen area with an angiographic residual DS equal to 18%
SIPS	PTCA/STENT	269	Effect of IVUS guidance on MACE and TLR	Reduction of MACE and TLR (Significant for vessels with reference diameter <3 mm)
SURE[110]	PTCA/DCA	100	Time-course of remodelling after PTCA	Reduction in total vessel area is a late phenomenon occurring between 1 and 6 mths
OARS[105]	DCA	200	Mechanisms of acute lumen gain and restenosis after DCA	Tissue removal contributes 58% of final increase in lumen CSA; the remaining CSA increase is due to an increase in total vessel area (27% during DCA + 15% during additional PTCA). Remodeling contributes 85% of late lumen loss
ABACAS[106]	DCA	200	Aggressive debulking guided by IVUS and adjunctive PTCA for reduction of acute complications and restenosis	Aggressive IVUS guided DCA reduces the residual plaque burden to 45% (42% after adjunctive PTCA). Six months restenosis = 21%
MUSIC	STENT	160	Safety of withdrawing anticoagulation after optimization of stent implantation with IVUS	Subacute thrombosis 0·6%. Restenosis rate: 7%; TLR = 5.7%
STRUT	STENT	178	Frequency of IVUS detected suboptimal expansion/apposition after high pressure stent deployment	48% incomplete stent expansion undetected with angiography; marginal tears frequent (18%)
POST	STENT	22	Retrospective survey of consecutive stent subacute thrombosis with final IVUS evaluation	Strut malapposition and thrombus are present in 47% and 24% cases
CRUISE	STENT	472	Effect of IVUS guidance on 9 month TLR	Reduction of TLR from 14.9% (IVUS documented) to 8.9% (IVUS guided)
AVID	STENT	800	Effect of IVUS guidance on 6–12 month TLR	Pending
OPTICUS	STENT	550	Effect of IVUS guidance on 6 month angiographic restenosis	Pending

ABACAS: Adjunct Balloon Angioplasty Coronary Atherectomy Study; AVID: Angiography vs Ultrasound Directed Coronary Stent Placement; CLOUT: Clinical Outcomes with Ultrasound Trial: CRUISE: Can Routine Ultrasound Influence Stent Expansion; GUIDE: Guidance by Ultrasound Imaging for Decision Endpoints; MACE: Major Adverse Cardiac Events; MUSIC: Multicenter Ultrasound Stenting in Coronary Arteries; OARS: Optimal Atherectomy Restenosis Study; OPTICUS: Optimization with ICUS to Reduce Stent Restenosis; PICTURE: Post-intracoronary Treatment Ultrasound Results Evaluation; POST: Predictors and Outcomes of Subacute Thrombosis; SIPS: Strategy of ICUS Guided PTCA and Stenting Trial; SURE: Serial Ultrasound REstenosis Trial; STRUT: Stent Treatment Region assessed by Ultrasound Tomography; TLR: Target Lesion Revascularization.

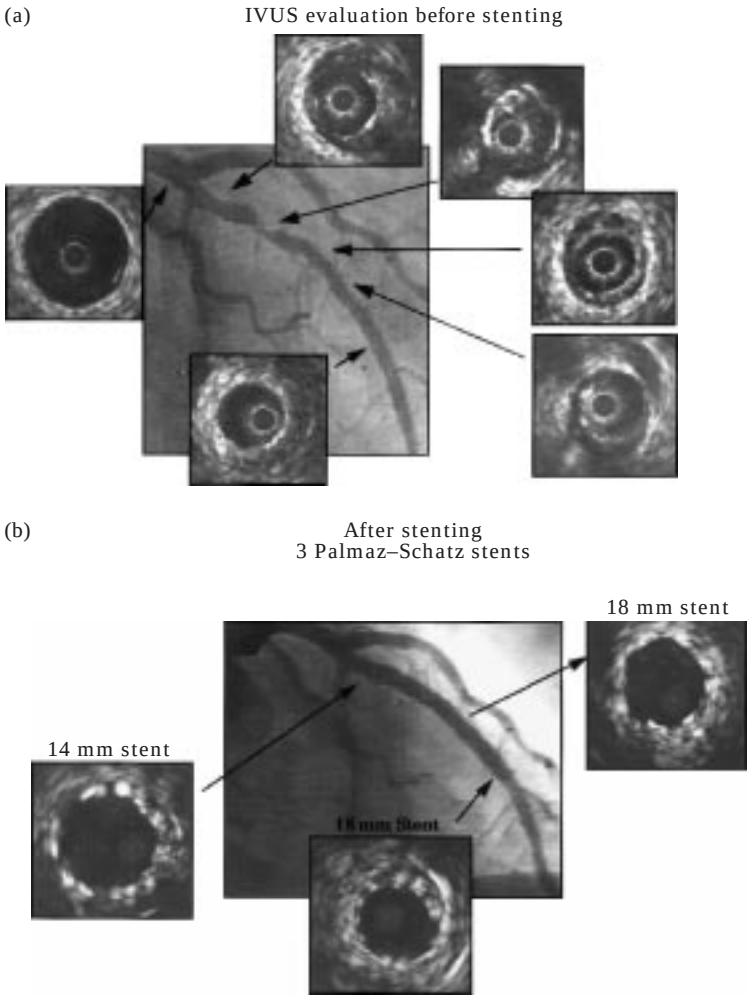


Figure 6 **(a) Multiple cross-sections at different levels along the mid-segment of the left anterior descending coronary artery: note the discrepancy between the short lesion shown with angiography and the diffusely diseased segment observed with ICUS. (b) The intracoronary ultrasound findings allow a complete coverage of the stenotic segment with an optimal angiographic result after high-pressure dilatation, confirmed with ultrasound. CSA = cross-sectional area.**

The importance of intracoronary ultrasound for guidance of ballon selection during PTCA requires further studies and its application is currently limited to the identification of suboptimal results and complications. Intracoronary ultrasound can be used to optimize the results of alternative treatment modalities, guiding selective plaque removal during directional coronary atherectomy and assessing the adequacy of stent expansion. For these indications and in selected subsets of patients, data obtained in experienced intracoronary ultrasound centres suggest that this technique can improve the immediate result of the intervention and reduce in-hospital complications and late restenosis.

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