Intravascular ultrasound: questions and answers

İntravasküler ultrason: Sorular ve cevaplar

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ABSTRACT

Coronary angiography is the gold standard for the detection of coronary artery disease, but it only gives information about the lumen of the coronary arteries. Intravascular ultrasound (IVUS) has provided a new perspective for imaging the coronary arteries. It allows assessment of not only the lumen but also the vessel wall and atherosclerotic plaque. In this article, we review the technique, measurements and current applications of IVUS imaging of the coronaries in a question-answer format. *(Anadolu Kardiyol Derg 2007; 7: 169-78)*

Key words: Intravascular ultrasound, coronary artery disease, atherosclerosis

ÖZET

Koroner arter hastalığının saptanmasında koroner anjiyografi altın standarttır. Fakat koroner anjiyografi sadece koroner arterlerin lümeni hakkında bilgi vermektedir. İntravasküler ultrason (IVUS) koroner arterlerin görüntülenmesinde yeni bir bakış açısı sağlamıştır. İntravasküler ultrason sadece lümenin değil damar duvarı ve aterosklerotik plağın da değerlendirilmesine olanak sağlamaktadır. Bu makalede, koroner arterlerin İVUS ile görüntülenme tekniği, kullanılan ölçümler ve güncel İVUS uygulamaları soru-cevap şeklinde gözden geçirilmiştir. *(Anadolu Kardiyol Derg 2007; 7: 169-78)*

Anahtar kelimeler: İntravasküler ultrason, koroner arter hastalığı, ateroskleroz

Introduction

Coronary angiography is the main imaging technique for the diagnosis of obstructive coronary artery disease (CAD). However, it has limitations for the assessment of atherosclerosis. It only provides a silhouette of the coronary artery lumen and does not show the coronary artery wall. Therefore, imaging techniques allowing direct visualization of the vessel wall are needed for complete characterization of coronary atherosclerosis.

Intravascular ultrasound (IVUS) is an invasive imaging technique that is complementary to coronary angiography. By IVUS, the lumen, the vessel wall and the atherosclerotic process within the wall are assessed simultaneously (1-3). Expert consensus documents prepared by the American College of Cardiology and the European Society of Cardiology have set the standards for the methodology and terminology used in IVUS imaging (2,3).

What are the physical principles?

As with other imaging techniques that use ultrasound, an electrical current is passed through a piezoelectric crystalline material. This material produces sound waves by expanding and contracting after electrical stimulation. Sound waves reflect from various tissue planes and are received by the transducer. The image is constructed from the electrical impulse created by the transducer. Ultrasound frequencies of 20-50 MHz are used in IVUS imaging (2,3).

What is the necessary hardware?

Catheter and transducer: Catheter sizes range between 2.6 and 3.5 French (F), compatible with a 6F guiding catheter. Two different transducer systems are available. Mechanical systems include a single rotating transducer that is mounted on a cable. The rotating transducer can be freely moved inside an echolucent sheath at the distal tip of the IVUS catheter (2). Phased array systems include multiple imaging elements that are sequentially activated in a circular way to obtain images (2).

Pullback device: The transducer can be advanced or pulled back manually. Alternatively, an automatic motorized pullback device that draws the catheter at a fixed speed can be used for more precise measurements. The speed of the automatic pullback ranges between 0.25 and 1.0 mm/s (2,3).

Console: It is composed of a hardware and software for image reconstruction, recording devices and a monitor. For storage, videotapes or CD-ROMs are used.

What is the examination technique?

Following anticoagulation with intravenous heparin (5000 to 10000 units), 100 to 300 µg of intracoronary nitroglycerin is given to

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maximally dilate the arteries and to prevent spasm. A 0.014 inch guide-wire is placed into the target artery. Then IVUS catheter is placed distal to the area of interest or as distal as safely possible.

Motorized transducer pullback allows steady withdrawal of the catheter, providing equidistant images for volumetric calculations. It is particularly important in serial studies because obtained images are reproducible, thus allowing comparative volumetric calculations (4). Manual transducer pullback allows to pause the catheter at specific locations. This gives an advantage of focusing for a long time on specific lesion characteristics. However, pulling the transducer rapidly or irregularly may result in missing an important pathology (4).

What are the display modes?

With 2-dimensional IVUS imaging, only cross-sectional images of the coronary artery are displayed. However, information about length and distribution of the lesions can not be obtained with this display method. Alternatively, in L (longitudinal)-mode imaging, longitudinal appearance of the artery along a single cut plane is displayed by image reconstruction techniques (2) (Fig. 1). The vessel size changes with each cardiac cycle and this causes a characteristic 'sawtooth' appearance.

By advanced computer techniques, three-dimensional imaging can also be performed (5-7). Since tissue interfaces may be located arbitrarily by current systems, there may be errors in the determination of the real boundaries.

Vessel wall morphology and plaque components can be analysed objectively and reproducibly by the integrated radiofrequency analysis, elastography and backscatter analysis, which are more advanced techniques for interpretation of ultrasound signals (8-10). Currently, the clinical merits of these novel tissue characterization techniques are under investigation (Fig. 2).

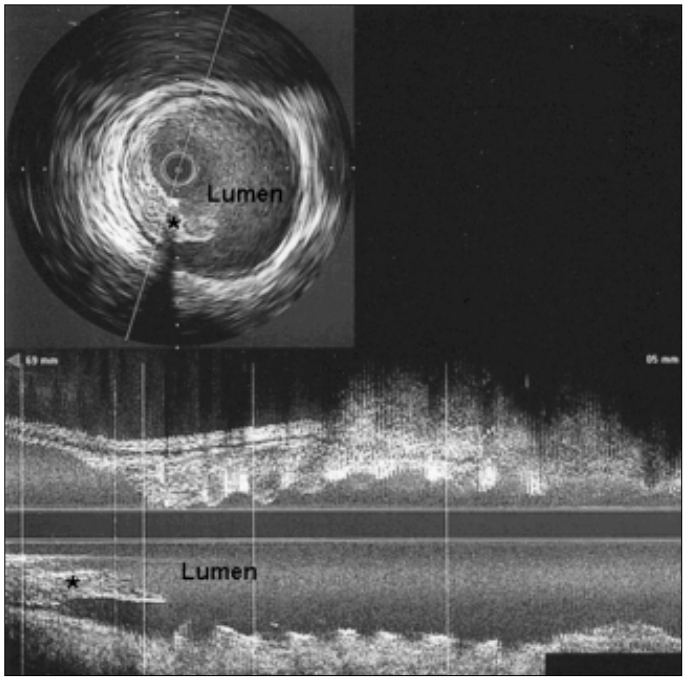

Figure 1. Two-dimensional display modes of IVUS. Cross-sectional imaging (top) and longitudinal (L)-mode imaging (bottom). Asterisk shows the ruptured atherosclerotic plaque

IVUS- intravascular ultrasound

Which structures are seen during IVUS imaging of a normal coronary artery?

The catheter is usually located near to the center of the vessel and the lumen, vessel wall and adjacent structures are around the catheter. In the coronary artery, there are 2 tissue interfaces that give strong ultrasound reflection. These are the lumen-intima border and the external elastic membrane (EEM) border (Fig. 3) (11,12). The outer edges of intima and adventitia are not easily defined. Side branches, cardiac veins and pericardium are the adjacent structures and they are used as markers for matching images at serial studies.

What are the image artifacts?

Intravascular ultrasound image quality is affected negatively by artifacts. Detailed information about them is beyond the scope of this review but namely these are guide-wire artifact, ring-down, digital subtraction, slow flow, heart and catheter motion artifact, catheter obliquity and calcium shadow (13). Non-uniform rotational distortion is particularly important in mechanical systems.

What are the IVUS measurements?

Lumen measurements: After determination of the lumen-intima border, the following measurements are performed.

• Lumen cross-sectional area (CSA): the area bounded by the lumen-intima border (Fig. 4).

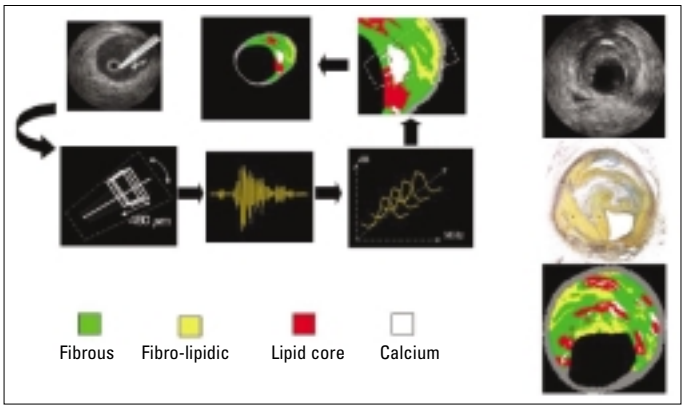

Figure 2. Tissue characterization by IVUS. Plaque components are assigned color codes and tissue maps are constructed (From Sipahi I, Ziada KM, Kapadia S, Nissen SE. An approach to coronary imaging with IVUS. In: Holmes DR Jr, Ellis SG, editors. Strategic Approaches In Coronary Intervention, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 67, with permission)

IVUS- intravascular ultrasound

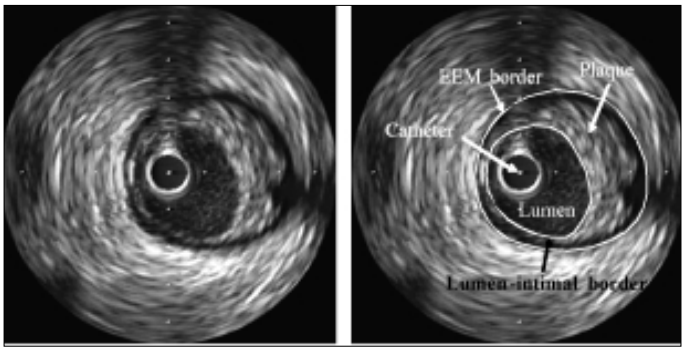

Figure 3. Structures seen during IVUS imaging

EEM- external elastic membrane, IVUS- intravascular ultrasound

• Minimum lumen diameter: the shortest diameter through the center of lumen.

• Maximum lumen diameter: the longest diameter through the center of lumen.

• Lumen eccentricity: 100% x [(maximum lumen diameter-minimum lumen diameter)/maximum lumen diameter].

• Lumen area stenosis: (reference lumen CSA-minimum lumen CSA)/reference lumen CSA. The reference segment may be proximal, distal, largest or average of proximal and distal. This calculation is similar to the calculation of angiographic stenosis.

EEM measurements: After determination of the EEM, the following measurements are performed.

• EEM CSA: the area bounded by the EEM (Fig. 4).

• Minimum EEM diameter: the shortest diameter through the center of EEM CSA.

• Maximum EEM diameter: the longest diameter through the center of EEM CSA.

Large side branches, signal dropout behind stent struts and acoustic shadowing due to extensive calcification can cause difficulty in these measurements. If circumferential extent of the acoustic shadowing is less than 90°, the EEM CSA is usually extrapolated from the closest identifiable EEM. The EEM extrapolation can also be performed in case of side branches. However, these extrapolations decrease reproducibility and accuracy of the measurements (13).

Plaque (atheroma) measurements:

• Plaque CSA: EEM CSA-lumen CSA (Fig. 4)

• Minimum plaque thickness: the shortest distance from the lumen-intimal border to the EEM along any line passing through the center of lumen.

• Maximum plaque thickness: the longest distance from the lumen-intimal border to the EEM along any line passing through the center of lumen.

• Plaque burden: plaque CSA/EEM CSA

• Plaque eccentricity: 100% x [(maximum plaque thickness-minimum plaque thickness)/maximum plaque thickness]

The true histologic plaque area can not be determined because the internal elastic membrane is not well defined by IVUS (14). Therefore, the plaque area is calculated by subtracting the lumen CSA from the EEM CSA. This value includes the media area in addition to the plaque area (2,3). Plaque plus media measurements correlate closely with plaque areas measured by histological methods (11,15).

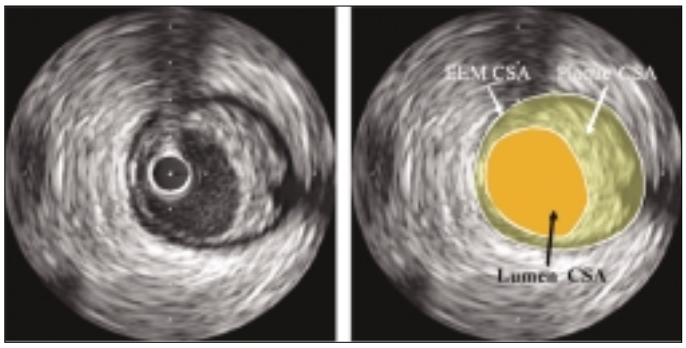

Figure 4. Some measurements performed during IVUS imaging

CSA- cross-sectional area, EEM- external elastic membrane, IVUS- intravascular ultrasound

Stent measurements:

• Stent CSA: the area bordered by the stent struts.

• Minimum stent diameter: shortest diameter through the center of stent.

• Maximum stent diameter: longest diameter through the center of stent.

• Stent expansion: obtained by comparison of the minimum stent CSA with the reference area. The reference segment may be proximal, distal, largest or average of proximal and distal.

• Stent symmetry: 100 x [(maximum stent diameter-minimum stent diameter)/maximum stent diameter].

• Strut apposition: Contact of the stent struts to the vessel wall is evaluated by searching for space between the struts and vessel wall (16). It can be done by injecting saline or radiographic contrast via the guiding catheter and then observing presence or absence of flow behind the struts.

Stent struts are seen as echogenic points or arcs along the vessel wall due to their various reflective characteristics. Signal dropout behind the stent struts may confound the IVUS measurements. 'Black hole' which is an intraluminal tissue with a homogenous echolucent appearance on IVUS may be seen after implantation of drug-eluting stents (DES) especially following intracoronary brachytherapy (17).

Remodeling measurements: The change in EEM area in response to the development of atherosclerotic plaque is called as arterial remodeling (18).

• Remodeling index: lesion EEM CSA/reference EEM CSA

When the lesion site is compared with proximal reference, expansive (positive) remodeling is defined as a ratio of >1.05 and constrictive (negative) remodeling is defined as a ratio of <0.95 (19,20). Other definitions for direction and extent of remodeling were also published (21,22).

Calcium measurements: Coronary calcium is detected with high sensitivity by IVUS (23). Calcium deposits are seen as bright echogenic structures. Calcium is a barrier to the penetration of ultrasound signal and causes characteristic 'acoustic shadowing'. Oscillation of ultrasound signal between calcium and the transducer causes 'reverberations' which appear as multiple reflections.

• Superficial calcium: the leading edge of the acoustic shadowing is within the superficial half of plaque thickness.

• Deep calcium: the leading edge of the acoustic shadowing is within the deep half of plaque thickness.

• Calcium arc: measured in degrees by an electronic protractor.

Length measurements: Length measurements can be obtained if motorized transducer pullback is used. Length of a segment of interest is equal to the number of seconds multiplied by the pullback speed.

Volumetric measurements: Distal and proximal fiduciary points identified by constant landmarks such as side-branches serve as starting and stopping points of imaging. When side branches are not available, pericardium and cardiac veins are also used as points of reference. Images are obtained by motorized transducer pullback (24). Plaque cross-sectional areas of images representing 1 millimeter equidistant segments are measured. Plaque volume is equal to average plaque CSA multiplied by distance between first and last images (Fig. 5).

For further details of the IVUS measurements, the readers are urged to examine the expert consensus documents by the American College of Cardiology and the European Society of Cardiology (2,3).

Which lesion morphologies are seen?

Intravascular ultrasound images are products of sophisticated postprocessing procedures in the scanner. Although plaque appearance is classified according to gray scale characteristics, comparative studies demonstrated inaccuracies in plaque characterization by IVUS. Thus, the following definitions should be used as echocardiographic not histologic definitions.

Echolucent plaques: High lipid content and cellularity are usually but not always the reason of echolucency of these plaques (25). Most of them are composed of minimal collagen and elastin. They sometimes have an echogenic structure at their luminal side which may correspond to a thick fibrous cap. However, spatial resolution of IVUS (about 150 μm) does not allow accurate measurements of the fibrous cap (26).

Calcified plaques: Bright echogenic calcium deposits in the plaques obstruct penetration of ultrasound signal. This phenomenon causes characteristic 'acoustic shadowing'.

Echodense plaques: Their echogenicity is usually due to fibrosis and is between that of echolucent and calcific plaques. If heavy fibrosis is present, this may cause signal attenuation as the calcified plaques (13). Most of the atherosclerotic plaques are either mixed or echodense.

Vulnerable plaques: Rupture of the vulnerable plaques is the cause of the most acute coronary syndromes (27). These plaques are also called as unstable plaques or high-risk lesions. Currently a reliable and consistent technique to detect vulnerable plaques before rupture is not available. Studies by conventional IVUS provided some clues. There is a close association between the echolucent plaques and acute coronary syndromes (28, 29). Expansive (positive) remodeling is frequently observed in the culprit lesions of patients with acute coronary syndromes (19, 30). Fibrotic changes are usually present in the lesions with constrictive (negative) remodeling and this may increase the plaque stability (31).

Ruptured plaques: These plaques have variable morphologies. Ulceration, fissuring or erosion of the plaque surface are commonly seen in the setting of acute coronary syndromes.

Thrombus: Diagnosis of the acute thrombus is difficult by IVUS because it has similar echogenicity with the stagnant blood and echolucent plaques (32). Differentiation from the stagnant blood can be done by injecting radiographic contrast or saline. The stagnant blood, but not the thrombus is dispersed after the injection.

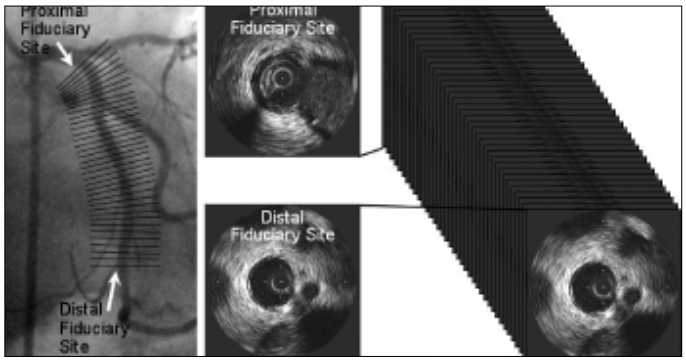

Figure 5. Volumetric IVUS measurements are performed starting at a distal fiduciary point and ending at a proximal fiduciary point. After motorized pullback, mean atheroma area multiplied by the analyzed segment length gives the atheroma volume (From Sipahi I, Ziada KM, Kapadia S, Nissen SE. An approach to coronary imaging with IVUS. In: Holmes DR Jr, Ellis SG, editors. Strategic Approaches In Coronary Intervention. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 66, with permission)

IVUS- intravascular ultrasound

Intimal hyperplasia: It is seen at in-stent restenosis by a mechanism of cell proliferation and extracellular matrix accumulation (33). Early in-stent restenosis has a low echogenicity. Late in-stent restenosis is usually more echogenic.

Other lesions: True and pseudoaneurysms can be differentiated. At the true aneurysms, all vessel wall layers expand at the lesion site. The pseudoaneurysms are usually observed after the interventions and are caused by interruption in the continuity of the EEM.

What are the applications of IVUS?

The American College of Cardiology (ACC) and American Heart Association (AHA) recommendations for coronary IVUS have been summarized in Table 1 (34).

Angiographically ambiguous lesions: Presence and degree of severity of an atherosclerotic lesion may be uncertain despite multiple different projections. IVUS is useful in the catheterization laboratory when angiography alone can not clarify the coronary anatomy or the status after percutaneous coronary intervention adequately. Some of these circumstances are listed below;

- Lesions with borderline stenotic diameter of 40% to 70%,
- Borderline left main coronary artery lesions (particularly ostial and distal) (Fig. 6),
- Hazy lesions,
- Ostial lesions,
- Bifurcation lesions,
- Overlapping vessels,
- Lesions with spasm,
- Aneurysmal lesions.

These lesions can be examined and additional information can be obtained by IVUS (35-37). It was reported that a minimum lumen diameter of <1.8 mm, a minimum lumen CSA of <4 mm^2 and a plaque burden of >70% were the indicators of hemodynamical significance in the non-left main coronary artery (LMCA) lesions (38). The event rate on follow-up was low in the non-LMCA lesions with the minimum lumen CSA of ≥4 mm^2 (39). In the case of LMCA lesions, a minimum lumen diameter of <2.8 mm and a minimum lumen CSA of <5.9 mm^2 have been found to be associated with the hemodynamical significance by fractional flow reserve (40). A minimum lumen diameter of 3 mm was found to be a threshold value for the prediction of cardiac events in the LMCA lesions (41).

Identification of transplant vasculopathy: Transplant vasculopathy (TV) starts with intimal thickening that can not be detected by coronary angiography (42). It has been shown that serial IVUS analysis after the cardiac transplantation is a safe procedure for the identification and follow-up of the TV (43). Recent reports concluded that increase in the intimal thickness of ≥0.5 mm within the 1st year after the transplantation is a strong predictor of mortality, myocardial infarction and angiographic abnormalities (44, 45).

Differentiation of TV from the donor transmitted CAD is important (Fig. 7). Although heart donors are usually young and their causes of death are noncardiac, the donor transmitted CAD is observed in nearly 50% of the donor hearts. It was reported that atherosclerotic lesions were present in more than half of the heart donors whose mean age was 32 (46). Although progression

can be seen within the first year of the transplantation in some lesions, it is thought that the donor transmitted CAD does not lead to the development of the TV (46,47).

The effect of different treatment strategies on the TV was evaluated by IVUS. It has been shown that pravastatin, everolimus, diltiazem, vitamins C and E may be beneficial for TV (48-51).

Target lesion assessment before intervention: IVUS is useful in the baseline assessment of the target lesion before a percutaneous coronary intervention. In the pre drug-eluting stents (DES) era, IVUS was frequently used to determine the most suitable interventional device for a particular lesion. In a report of an early experience, the management strategy was found to change in about 40% of the patients if IVUS assessment was used before the intervention (52). Although in the era of DES, IVUS may still be impactful to determine the size and length of the stent. Since diabetic patients usually have a diffuse CAD with angiographically small lumen dimensions, real vessel size can be evaluated by IVUS (53).

During angioplasty and atherectomy: IVUS guided PTCA usually leads to the utilization of larger balloons (54, 55). Greater lumen gain can be obtained by this way, but long-term effect of this technique was not documented. Even though the angiographic results are satisfactory, a large residual plaque burden is usually detected by IVUS after atherectomy (56). Intravascular ultrasound was used in order to perform aggressive plaque removal by directional or rotational atherectomy (57-59) (Fig. 8).

During stenting: Assessment of stent deployment, particularly strut to vessel wall contact, may be difficult by coronary angiography alone. Inadequate stent expansion and apposition were frequently found by IVUS (16). This finding led to development of the current high pressure implantation techniques (60). With IVUS guidance, complete apposition of the stent struts to the vessel wall can be achieved more frequently. In addition, in-stent minimal lumen area can be maximized by IVUS (61). The effect of IVUS guidance on the clinical end-points has been evaluated in many studies resulting in contradictory results mostly because of underpowered study designs (62-69).

Assessment of restenosis: One of the most important interventional applications of IVUS in the DES era is the assessment of in-stent restenosis. Although the mechanism of restenosis after angioplasty or atherectomy is a combination of neointimal growth and constrictive arterial remodeling, it is mainly due to neointimal growth in the stents (21,70). However, it is not infrequent to find a grossly underdeployed stent as the primary mechanism of restenosis. It was suggested that an in-stent minimal stent area ≥55% of the average reference vessel CSA was the most suitable IVUS criterion to decrease the probability of stent restenosis (61). After implantation of sirolimus-eluting stents in treatment of in-stent restenosis, minimal stent area of <5 mm^2 was a strong predictor of angiographic restenosis in recurrent lesions (71). High-pressure postdilatations, use of large balloons and antiplatelet therapy with aspirin and clopidogrel resulted in a significant reduction in the stent thrombosis (60). However, mechanical factors are still contributing to the stent thrombosis. When patients with stent thrombosis following stent deployment under IVUS guidance were evaluated, 94% of cases demonstrated at least one abnormal IVUS finding (stent underexpansion, malapposition, inflow/outflow disease, dissection, or thrombus) (72).

Table 1. ACC/AHA Recommendations for Coronary Intravascular Ultrasound* (34)

Class I: None

Class IIa:

1. Assessment of the adequacy of deployment of coronary stents, including the extent of stent apposition and determination of the minimum luminal diameter within the stent. (Level of Evidence: B)
2. Determination of the mechanism of stent restenosis (inadequate expansion vs. neointimal proliferation) and to enable selection of appropriate therapy (plaque ablation vs. repeat balloon expansion). (Level of Evidence: B)
3. Evaluation of coronary obstruction at a location difficult to image by angiography in a patient with a suspected flow-limiting stenosis. (Level of Evidence: C)
4. Assessment of a suboptimal angiographic result following PCI. (Level of Evidence: C)
5. Diagnosis and management of coronary disease following cardiac transplantation. (Level of Evidence: C)
6. Establish presence and distribution of coronary calcium in patients for whom adjunctive rotational atherectomy is contemplated. (Level of Evidence: C)
7. Determination of plaque location and circumferential distribution for guidance of directional coronary atherectomy. (Level of Evidence: B)

Class IIb:

1. Determine extent of atherosclerosis in patients with characteristic anginal symptoms and a positive functional study with no focal stenoses or mild CAD on angiography. (Level of Evidence: C)
2. Preinterventional assessment of lesion characteristics and vessel dimensions as a means to select an optimal revascularization device. (Level of Evidence: C)

Class III:

1. When angiographic diagnosis is clear and no interventional treatment is planned. (Level of Evidence: C)

*Class I-Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective. Class II-Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. Class IIa - Weight of evidence/opinion is in favor of usefulness/efficacy. Class IIb - Usefulness/efficacy is less well established by evidence/opinion. Class III-Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective, and in some cases may be harmful. Level of Evidence A-Data derived from multiple randomized clinical trials. Level of Evidence B-Data derived from a single randomized trial or nonrandomized studies. Level of Evidence C-Consensus opinion of experts.

Strategies for reducing the restenosis can be assessed also by IVUS. It has been shown that brachytherapy inhibits neointimal growth within the stent, but it has a potential to augment the restenosis at the borders of the radiation region (73). It was reported that the incidence of neointimal growth was dramatically reduced by the DES (74, 75).

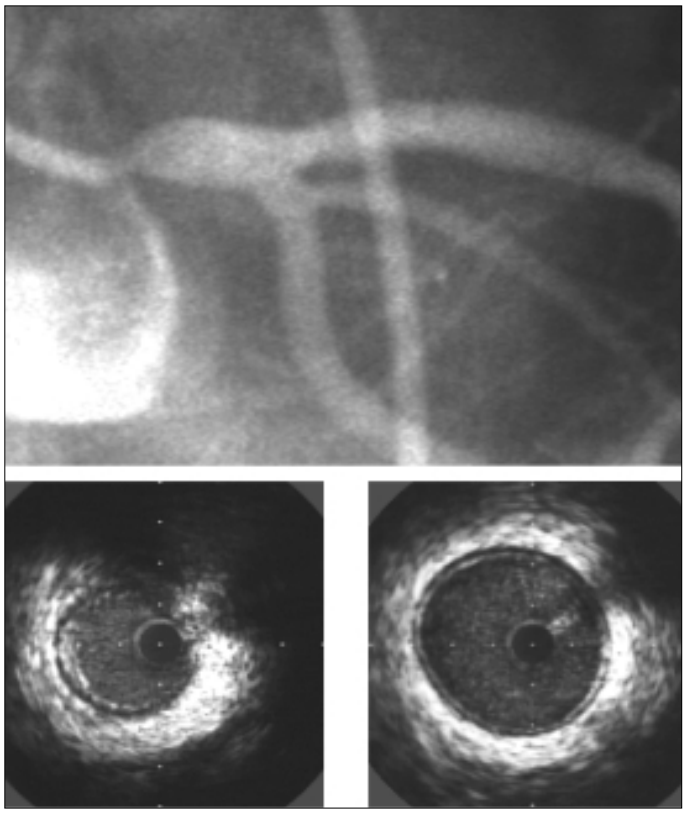

Figure 6. Coronary angiography shows ostial stenosis of the left main coronary artery. But the left main ostium has only mild disease by IVUS (left lower panel). In addition, ostial lumen is smaller than lumen of the distal left main (right lower panel)(From Sipahi I, Ziada KM, Kapadia S, Nissen SE. An approach to coronary imaging with IVUS. In: Holmes DR Jr, Ellis SG, editors. Strategic Approaches In Coronary Intervention, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 61, with permission)

IVUS- intravascular ultrasound

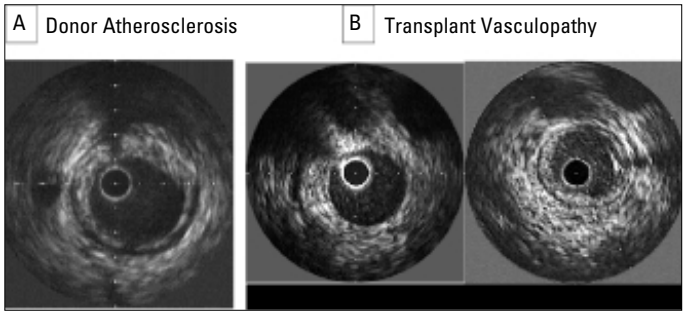

Figure 7. The eccentric lesion in panel A is from the IVUS image of proximal LAD coronary artery performed 1 month after cardiac transplantation and is an example of donor-transmitted atherosclerosis. Since the lesion has developed at a previously normal site in panel B, this is an example of transplant vasculopathy (From Sipahi I, Ziada KM, Kapadia S, Nissen SE. An approach to coronary imaging with IVUS. In: Holmes DR Jr, Ellis SG, editors. Strategic Approaches In Coronary Intervention. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 62, with permission)

IVUS- intravascular ultrasound, LAD- left anterior descending artery

Assessment of complications after intervention: Coronary dissections and intramural hematomas are not uncommon after the interventions. Intravascular ultrasound is a sensitive method for their identification and localization (Fig. 9). In case of dissections, the presence of side branches, presence of all three layers of the vessel wall and less echogenic blood reflection indicate that IVUS catheter is in the true lumen rather than the false lumen (76). The reason of angiographic haziness after stenting at the edges of stented segment can be evaluated by IVUS. Dissection, thrombus, calcification or significant step-down of luminal area is the reason in most cases (35). Stent implantation or balloon dilatation may lead to axial redistribution of atherosclerotic

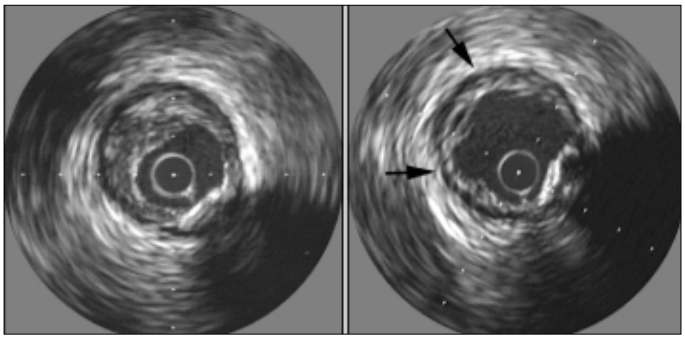

Figure 8. Successful removal of part of the atheroma from an eccentric lesion (left panel) with directional atherectomy is shown by arrows in the right panel (From Sipahi I, Ziada KM, Kapadia S, Nissen SE. An approach to coronary imaging with IVUS. In: Holmes DR Jr, Ellis SG, editors. Strategic Approaches In Coronary Intervention. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 64, with permission)

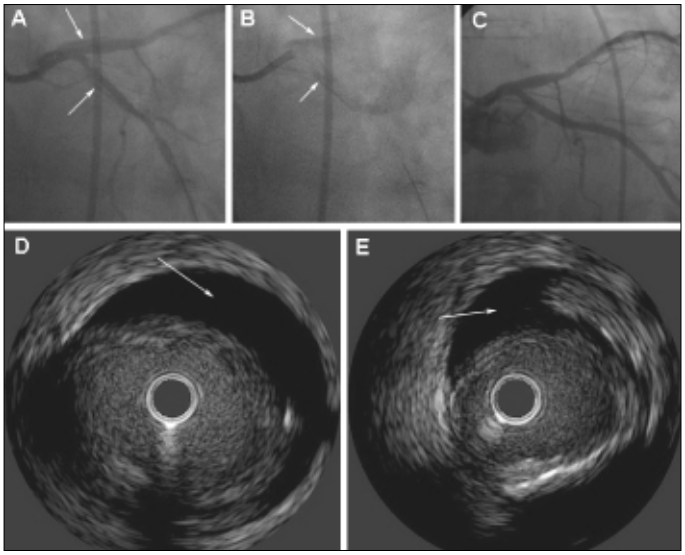

Figure 9. After cutting balloon angioplasty of left circumflex coronary artery, staining of left circumflex, LAD and left main coronary arteries was determined (arrows in panels A and B). IVUS revealed a long intramural hematoma involving left main (arrow in panel D) and LAD coronary arteries (arrow in panel E) as well as left circumflex. No further intervention was performed and there was no luminal compromise 3 months after the initial procedure (panel C) (From Sipahi I, Ziada KM, Kapadia S, Nissen SE. An approach to coronary imaging with IVUS. In: Holmes DR Jr, Ellis SG, editors. Strategic Approaches In Coronary Intervention. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 65, with permission)

IVUS- intravascular ultrasound, LAD- left anterior descending artery

plaque from the lesion to the reference segments (77). This may compromise the ostium of the side branch and can be assessed by IVUS.

Progression-regression analysis: Changes in luminal dimensions detected by coronary angiography are not reliable in the assessment of the progression-regression because of the confounding role of the ongoing remodeling in the coronary arteries (78, 79). Since volumetric measurements by IVUS can detect even small changes in the plaque volumes or intimal thicknesses after the treatment, IVUS analysis is commonly used in the progression-regression trials (Fig. 5).

Everolimus was compared with azathioprine to determine its effect on cardiac allograft vasculopathy in recipients of a heart transplant (51). A total of 634 patients were randomly assigned (1:1:1 randomization) to receive 2 different doses of everolimus or azathioprine, in combination with cyclosporine, corticosteroids, and statins. Intravascular ultrasound showed that the average increase in maximal intimal thickness 12 months after transplantation was significantly smaller in the two everolimus groups than in the azathioprine group. The incidence of vasculopathy was also significantly lower.

In the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) trial, 502 patients with serum low-density lipoprotein (LDL) cholesterol concentrations of 125 to 210 mg/dl were randomised to receive either 80 mg atorvastatin or 40 mg pravastatin for 18 months (80). Intravascular ultrasound images were taken at the baseline and at the completion of the study. The pravastatin group showed an increase in percent change of the atheroma volume (+2.7%; p=0.001, compared with baseline). However, the atorvastatin group showed no change in the same parameter (-0.4%; p=0.98, compared with baseline). When 2 groups were compared, progression rate was significantly lower in the atorvastatin group (p=0.024). This study showed that aggressive statin treatment is preferred to moderate therapy in patients with CAD.

In the apolipoprotein A-I Milano trial, 47 acute coronary syndrome patients were randomised to five weekly intravenous infusions of placebo or recombinant apolipoprotein A-I Milano/phospholipid complexes (ETC-216) at 15 mg/kg or 45 mg/kg (81). Baseline IVUS was performed within 2 weeks after an acute coronary syndrome event. Intravascular ultrasound analysis was repeated after the five infusions. The mean atheroma volume decreased in the combined ETC-216 groups (1.06 ± 3.17%; p=0.02, compared with baseline) whereas it remained the same in the placebo group (0.14 ± 3.09%; p=0.97, compared with baseline). The absolute reduction in the atheroma volume was 4.2% from baseline in the combined treatment group (p<0.001). These results provided encouragement to the investigators that worked on high density lipoprotein cholesterol raising strategies.

In the CAMELOT (Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis) study, effects of different antihypertensive drugs on cardiovascular events in patients with CAD and well-controlled blood pressure were evaluated (82). Patients (n=1991) were randomised to the amlodipine up to 10 mg/day, enalapril up to 20 mg/day or placebo for 24 months. Atherosclerosis progression was analysed by IVUS in a subgroup of 274 patients. There was a progression in the placebo group (p<0.001, compared with baseline) and a trend toward progression in the enalapril group (p=0.08, compared with baseline) and no change in the amlodipine group (p=0.31, compared with baseline). There was a slower progression in a subgroup of the amlodipine-treated patients with baseline systolic blood pressures greater than the mean (129/78 mmHg) (p=0.02, compared with placebo). This study demonstrated that optimizing blood pressure control in patients with CAD is important in battling atherosclerosis in hypertensive patients.

In recently published ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial, the effect of very high statin therapy (rosuvastatin 40 mg/day) on the regression of coronary atherosclerosis was evaluated by IVUS imaging (83). Coronary atheroma burden was assessed at baseline and after 24 months of treatment. After 24 months, serial IVUS examinations were available in 349 patients. In this study, on treatment mean LDL cholesterol level of the patients was 61 mg/dL. The mean change in percent atheroma volume for the entire vessel was -0.98% (P<0.001 versus baseline). The mean change in atheroma volume in the most diseased 10-mm subsegment was -6.1 mm^3 (p<0.001 versus baseline). Change in total atheroma volume showed a mean reduction of -14.7 mm3 (p<0.001 versus baseline). This study indicated that very low levels of LDL cholesterol are needed to achieve the regression of atherosclerosis.

In another recently published trial, the effect of ACAT (acyl-coenzyme A:cholesterol acyltransferase) inhibition on the progression of coronary atherosclerosis was evaluated in 408 patients with angiographically documented CAD (84). Patients were randomised to receive either ACAT inhibitor pactimibe (100 mg/day) or placebo. Intravascular ultrasound was repeated after 18 months. The change in percent atheroma volume was similar in both groups. As compared with baseline values, the normalized total atheroma volume showed significant regression in the placebo group, but not in the pactimibe group (p=0.03). The atheroma volume in the most diseased 10-mm subsegment regressed by 3.2 mm3 in the placebo group, as compared with a decrease of 1.3 mm3 in the pactimibe group (p=0.01). After publication of this study, pactimibe development program was discontinued.

Currently, there are several ongoing IVUS progression-regression trials testing the anti-atherosclerotic efficiency of various classes of drugs, including cannabinoid-1 receptor blockers, thiazolidinediones and cholesteryl ester transfer protein inhibitors.

What are the limitations of IVUS?

Calcium forms a barrier to the penetration of ultrasound signal. It is a big problem if there is heavy superficial calcium. Other artifacts (e.g., guide-wire artifact, ring-down, digital subtraction, slow flow, motion artifact, non-uniform rotational distortion, catheter obliquity) also affect IVUS image quality negatively. In addition, it has certain complication risks due to its invasive character. The size of IVUS catheters causes a

limitation during imaging of coronary arteries with a diameter stenosis of more than 50%, a diameter of less than 2 millimeter and an extreme tortuosity.

What are the complication risks?

Complication rate is low if it is performed by an experienced interventional cardiologist (85). It is a safe procedure (86). Coronary spasm may be seen in 1-3% of the cases. It is usually resolved by intracoronary nitroglycerin. Coronary dissection and total occlusion may occur in less than 0.5% of the patients. During passage of the IVUS catheter through a small vessel or a heavy stenosis, transient ischemia may be seen. It was shown that repeated IVUS examinations after heart transplantation did not cause angiographically evident acceleration of transplant CAD and it was concluded that serial IVUS imaging was a safe method (43).

Conclusion

Intravascular ultrasound has provided a new perspective for imaging the coronary arteries. Information obtained from IVUS analysis affects the assessment and management of the patients with coronary artery disease. It is now an important complementary imaging modality of the catheterization laboratories.

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