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An Update on Clinical Applications of Intravascular Ultrasound

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Abstract

Intravascular Ultrasound (IVUS) has emerged as the first clinical imaging method to visualize atherosclerosis and other pathologic conditions within vessel wall. It is of paramount importance in clarifying situations in which angiography is equivocal or difficult to interpret, choosing the appropriate intervention, and optimizing the results. It is an important tool providing several unique insights into plaque burden, remodeling, and restenosis. In percutaneous coronary intervention (PCI) with drug-eluting stents (DES), IVUS guidance may reduce stent thrombosis. IVUS guidance appears to be most beneficial in complex lesion subsets, such as left main coronary artery (LMCA) and bifurcations. In this review, the author examines the clinical applications of IVUS in current PCI era dominated by use of DES.

Keywords: Intravascular ultrasound; Restenosis; Percutaneous coronary intervention; Stent thrombosis; Left main coronary artery stenosis; Drug-eluting stent

Introduction

IVUS has played a pivotal role in understanding the pathophysiology of coronary atherosclerosis and has facilitated the refinement of diagnostic and therapeutic strategies. The incremental value of IVUS compared to contrast angiography is due to its tomographic perspective and its ability to image vessel wall and atheroma directly. Contrast angiography does not permit visualization of arterial wall even if it allows evaluation of lumen of coronary arteries in planar fashion. IVUS is capable of depicting the arterial wall and lumen of the coronary arteries across the full 360° circumference of the vessel. Although angiography remains the gold standard to assess the extent of coronary atherosclerosis and to guide PCI, IVUS has become an important adjunctive imaging modality.

Normal Arterial Anatomy and Basic Measurements

The normal coronary artery appears as a trilayered structure in IVUS [1,2]. The innermost layer is echogenic intima, the middle layer is the echolucent media, and the outermost layer is the echogenic adventitia (Figure 1). The characteristic trilaminar pattern is not observed in 30-50% of normal coronary arteries; the thin intimal layer reflects ultrasound poorly and often leads to signal drop out and a monolayer appearance [3]. The upper limit of normal intimal thickness is considered to be 0.25 to 0.50 mm [4]. Lumen cross-sectional area (CSA) is determined by tracing the lumen-intima surface. Minimum and maximum lumen diameters are the shortest and longest diameters through the center of the lumen. Because the outer border of adventitia is not distinct on IVUS imaging, total arterial CSA is measured by tracing the trailing edge of media and is referred to as external elastic membrane (EEM) CSA. Atheroma CSA is calculated as EEM CSA minus lumen CSA. As atheroma CSA also includes the area occupied by the media, it is very often referred to as plaque plus media CSA. Atheroma CSA divided by EEM CSA gives rise to percent CSA stenosis or plaque burden.

Insights into Plaque Formation and Distribution

IVUS provides unique insights into biologically mediated processes of vasculature, such as the extent of plaque burden and vascular remodeling. Even angiographically normal or near-normal segment is found to have significant plaque burden in IVUS. This imaging modality very clearly depicts the eccentricity or concentricity of

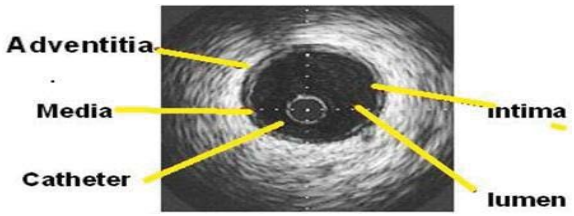

Figure 1: IVUS image showing the trilaminar appearance of normal coronary arterial wall.

atherosclerotic plaque and the relationship of plaque volume to vessel area. Angiographic concentric plaque often appears to be eccentric by IVUS, and *vice versa*.

Arterial remodeling refers to the changes in EEM area occurring during development of atherosclerotic lesions. IVUS makes us understand the relationship between remodeling and clinical presentations in patients with coronary artery disease (CAD). Expansive (positive) remodeling is significantly more prevalent in patients with unstable CAD (Figure 2). Constrictive (negative) remodeling mainly has a prominent role in restenosis after mechanical interventions. Preinterventional positive remodeling predicts no-reflow phenomenon, target lesion revascularization, and in-hospital complications following PCI.

Progression–Regression Analysis

IVUS measured changes in intimal or the plaque volume has been increasingly used as a surrogate endpoint in clinical trials of

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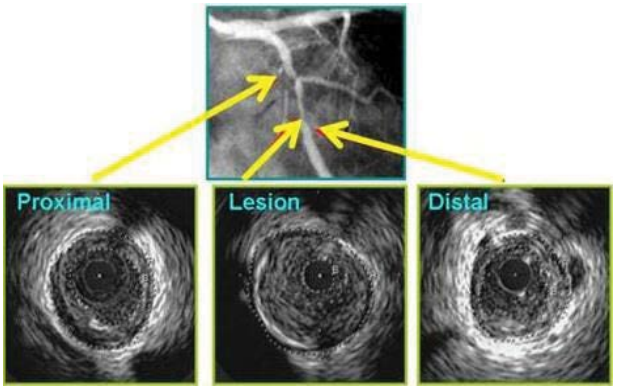

Figure 2: Expansive remodeling in left circumflex artery (LCx).

natural history of atherosclerosis and in monitoring the results of pharmacologic interventions. It needs to be answered whether IVUS measured disease progression or regression would reflect an increased or decreased risk of future cardiovascular events. A discrepancy between the imaging endpoint and clinical outcome has been shown in some studies, even if many trials suggest significant association [5-8]. Trials employing Integrated Backscatter (IB)-IVUS or Virtual Histology (VH) have demonstrated plaque stabilization by anti-atherosclerotic agents, despite no change in total plaque volume observed by conventional IVUS [9,10]. There is renewed interest in the concept of "plaque regression with development of Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. PCSK9 expressed in atherosclerotic plaque, is likely to be responsible for vascular inflammation and apoptosis [11]. Insights regarding the assessment of the impact of PCSK9 inhibitors on the composition and behavior of stable and vulnerable plaque may come from the GLAGOV (GLobal Assessment of Plaque reGression With a PCSK9 antibOdy as measured by intraVascular Ultrasound) study, which is currently in active enrollment (NCT01813422). It needs to be seen whether this promising therapy survives through the arduous clinical testing pipeline.

Pre-interventional Assessment

Angiographic lesion ambiguity

IVUS plays important role in clarifying situations in which angiography is ambiguous or difficult to interpret. The minimum lumen area (MLA) is the most important IVUS criteria to defer intervention in intermediate lesions. In the assessment of LMCA disease, angulations, calcification, or ostial location may lead to poor catheter engagement and erroneous angiographic interpretation. Often LMCA trunk is short and lacks a "normal" segment for comparison. Aortic cusp opacification or 'streaming' of contrast may obscure the ostium, requiring the angiographer to engage the LMCA with the catheter and depend on the reflux of the contrast to visualize the ostium. Bifurcation and trifurcation into daughter branches may preclude accurate assessment. In these situation IVUS can provide additional information. Less than half of the angiographically equivocal LMCA lesions have significant stenosis [12]. IVUS can also differentiate true ostial and "pseudo-ostial" lesions (Figure 3).

Strategic plaque assessment

Angiographic hazy lesions represent various morphologies, including calcification, dissection, thrombus and excessive plaque burden with remodeling (Figure 4). IVUS entails the presence, location and extent of calcification that can impact results of intervention. Lesions with circumferential superficial calcium may need plaque modification with rotablation before intervention, which facilitates procedural success and prevents stent under expansion. IVUS measures accurately the amount and distribution of plaque, lesion length and vessel size which can guide optimal sizing of device to be employed. With regards to bifurcation lesions, it can provide valuable anatomical evaluation of plaque burden, plaque location, lumen size not only in the main branch (MB) but also in the side branch (SB).

Assessment of plaque composition by pre-interventional IVUS may predict the occurrence of distal emboli during stenting that may result in the "slow-flow" or "no-reflow" phenomenon leading to peri-procedural myocardial infarction (MI). The most consistent risk factors for this phenomenon, determined by IVUS, are the presence of attenuated plaque (Figure 5), thrombus, large plaque burden, lipid pool-like imaging, and positive vessel remodeling [13,14]. Pre-intervention lipid or necrotic core in IB-IVUS or VH relates to findings suggestive of distal emboli [15-18]. The thrombus aspiration or distal protection device deployment might be useful during PCI if such lesions are found.

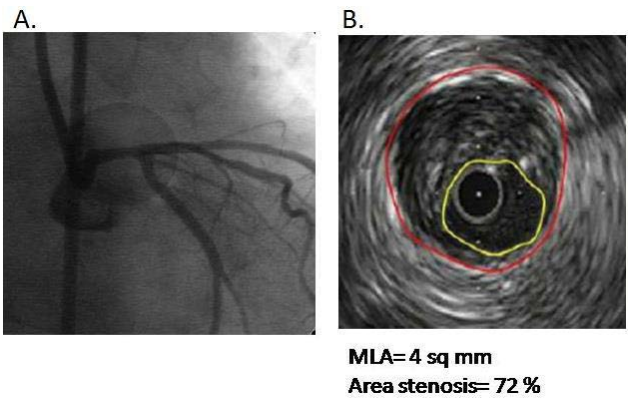

Figure 3: A. Equivocal left main coronary artery (LMCA) ostial lesion; **B.** The same lesion appears significant in IVUS.

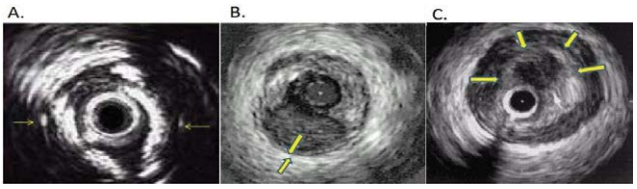

Figure 4: A. Superficial calcification; **B.** Dissection; **C.** Thrombus.

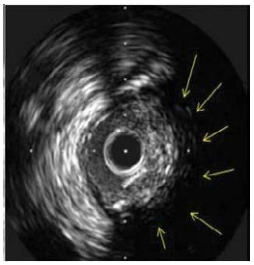

Figure 5: Signal attenuation on IVUS.

Assessment of Intermediate Coronary Lesions

Non-LMCA lesion

Angiographic assessment of hemodynamic significance accurately of intermediate or moderate lesions between 40% and 70% stenosis remains a challenge for interventional cardiologist [19,20]. Also there exists significant inter- and intraobserver variations in angiographic interpretation [19]. Few studies have suggested fairly good correlation between anatomic data by IVUS and ischemia by physiological assessments. Prior studies suggested that MLA ≥ 4 mm^2 by IVUS had a diagnostic accuracy of 89% in identifying a coronary reserve flow ≥ 2, whereas MLA < 4 mm^2 correlated well with fractional flow reserve (FFR) [20-22]. While trying to predict if anatomical criteria are functionally significant, it is important to understand that MLA is only one variable. Other factors are lesion length, vessel size, entrance and exit angles and forces and the amount of myocardium subtended by the lesion. Not surprisingly, other studies suggested different MLA values to predict FFR. Kang et al. found much lower cutoff of MLA < 2.0 mm^2 to predict FFR < 0.80 [23]. Another study reported that IVUS MLA < 2 mm^2 predicts ischemic FFR < 0.75 [24]. Taken together, these studies demonstrate that MLA ≥ 4.0 mm^2 may identify nonischemic lesions for which PCI can be deferred. However, the significance of an MLA < 4.0 mm^2 should be considered in terms of vessel size, lesion length, area stenosis, plaque burden, and the amount of myocardium subtended by the lesion [23,24]. Whereas FFR is preferred tool for intermediate lesion assessment, an algorithm for IVUS-guided PCI of non-LMCA lesion is suggested (Figure 6) [25].

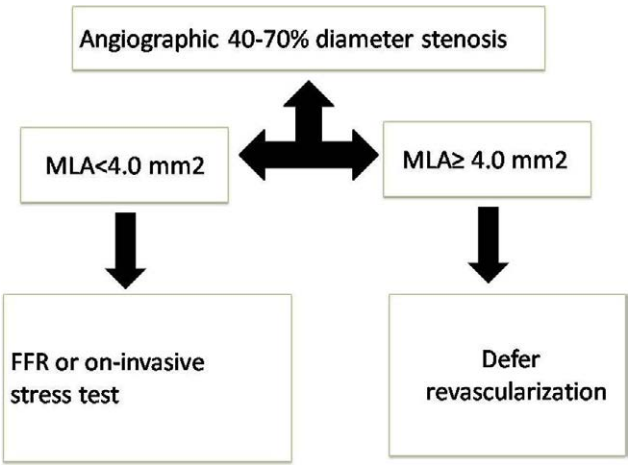

Figure 6: Proposed IVUS criteria for assessing intermediate non- left-main coronary lesions.

LMCA lesion

As LMCA lesions are short, often calcified and diffuse involving the ostium or bifurcation, IVUS plays a pivotal role in assessing the significance of these lesions, which are notoriously difficult to accurately assess with angiography alone. An IVUS derived MLA of 5.9 mm^2 and minimum lumen diameter (MLD) of 2.8 mm is found to correlate accurately with FFR of < 0.75 across LMCA lesions [26]. Additionally, with intermediate LMCA stenoses, an MLA value > 6.0 mm^2 identifies patients at low risk for adverse events with deferred revascularization [27]. Another LMCA study with clinical end-points has suggested that an MLA of 7.5 mm^2 should be used as the cut-off value for performing revascularization [28]. FFR should be preferred over IVUS for intermediate LMCA lesion assessment given the limitations of a single MLA to predict hemodynamic significance. However, if IVUS is utilized, revascularization may be deferred in patients with MLA ≥ 6.0 mm^2 as these values are not indicative of ischemia and have favorable outcomes. For an MLA < 6 mm^2, FFR or noninvasive stress test should performed given the discrepancy with the IVUS MLA cutoff (4.5 to 6.0 mm^2) that correlates with FFR (Figure 7) [25].

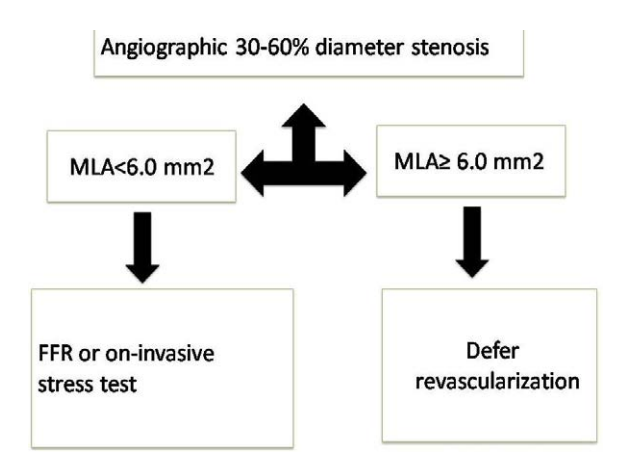

Figure 7: Proposed IVUS criteria for assessing intermediate left main coronary lesions.

IVUS-Guided PCI with DES

Restenosis

In DES era restenosis could be due to persistent vessel wall injury, sub-optimal stent expansion, asymmetric strut distribution, stent fracture, polymer peeling or drug in homogeneity and drug failure. Studies evaluating IVUS guidance in PCI with DES are mostly retrospective in nature. DES demonstrated no significant difference in restenosis with or without optimal stent expansion as defined by MUSUIC (Multicenter Ultrasound Stenting in Coronaries) criteria [29]. The HOME DES (Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment using Drug Eluting Stents with or without the IVUS Guidance) randomized trial demonstrated that IVUS-guidance led to more frequent post dilatations, higher balloon inflation pressures, and larger balloon sizes, but it did not result in lower rates of target vessel revascularization (TVR) or major cardiac events [30]. Optimal stent deployment was defined as complete apposition of the stent struts, no edge dissections, and adequate stent expansion (defined as either minimum-stent area [MSA] >5.0 mm^2 or >90% of the distal reference lumen area. In one study with DES, the only independent predictors of angiographic restenosis were post procedural final MSA less than 5.5 mm^2 and IVUS-measured stent length greater than 40 mm [31].

Stent thrombosis

When compared to angiography-guided strategy, IVUS guidance reduced rates of stent thrombosis at both 30 days and 12 months in one study [32]. IVUS guidance is found to be an independent predictor of freedom from stent thrombosis. IVUS studies have suggested that stent under expansion, edge dissections, incomplete stent apposition (ISA), incomplete lesion coverage, geographic miss, tissue prolapse, and residual thrombus as risk factors of stent thrombosis [33-40]. Of these, edge dissection, stent under expansion, and ISA has been the most extensively studied.

Edge dissection

IVUS is more sensitive than angiography for detecting edge detection. The incidence of persistent edge dissections by IVUS after DES implantation is approximately 10%, of which almost 40% are not detected by angiography [41]. High grade dissections (defined by IVUS as lumen area narrowing < 4 mm^2 or dissection angle ≥ 60°) should be stented to avoid early stent thrombosis [40]. However, low grade and angiographically silent edge dissections may not be associated with higher rates of adverse events, and there is no consensus on their optimal management.

Strut fracture

By IVUS, strut fracture is defined as longitudinal strut discontinuity and is categorized as strut separation, strut subluxation, or strut intussusceptions [42]. The incidence of DES fracture is 0.8% to 7.7% which might lead to stent thrombosis or restenosis [42]. Strut fracture may reduce the local drug delivery to the arterial wall affecting the mechanical scaffolding of the lesion segment. Irregular edge of the fractured struts may give chronic stimuli to the vessel wall under cardiac movement. Fractures occur around areas of increased rigidity (overlapping stents), higher radial forces (longer stents), hypermobile vessel, tortuosity, calcified lesions [43].

ISA

ISA is defined as separation of one or more strut from the vessel wall, with evidence of blood speckle behind the strut in a segment not associated with any side branches. It can occur acutely after stent deployment (acute ISA) or is observed over a time (late-acquired ISA). Acute ISA can be observed in 8-30% DES recipients. It results from stent underexpansion, or insufficient stent comformability in calcified or complex-shaped lesions (Figure 8). It appears to be associated with variable rates of persistent ISA at follow-up [44,45]. However, it may not lead to increased cardiac events at 1 year [34,46].

Late ISA (ISA at follow-up) could be either persistent baseline ISA (late-persistent) or newly developed ISA in regions that were previously opposed (late-acquired ISA) (Figure 9). Incidence of late-acquired ISA is four times higher in patients with DES versus Bare metal stent (BMS) [39]. The most commonly reported mechanisms for late ISA are positive remodeling of the vessel, dissolution of thrombus present as baseline, or delayed-type hypersensitivity reaction [33,47]. There are mixed data regarding the risk of stent thrombosis associated with late ISA. A recent meta-analysis reported a significantly higher risk of late or very late thrombosis in patients with late ISA [39]. Regardless of many inconclusive studies, most interventional cardiologists would strive to achieve complete apposition of all stent struts after deployment of stent.

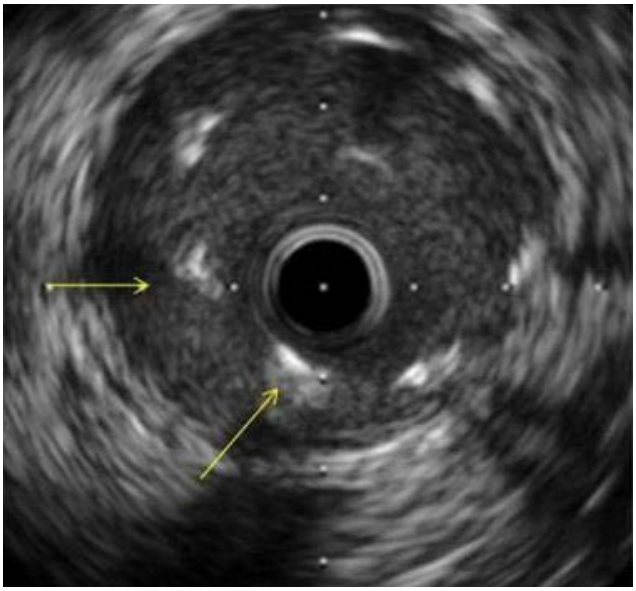

Figure 8: Gross acute incomplete stent apposition.

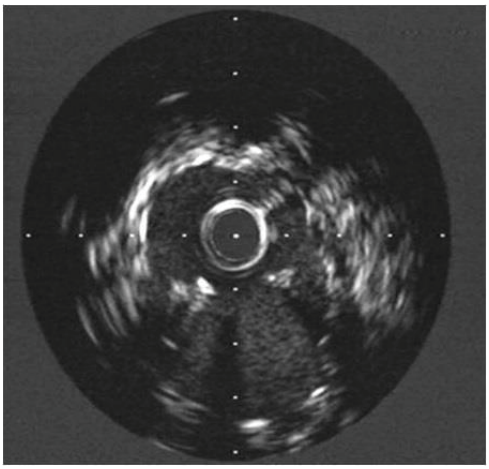

Figure 9: Late incomplete sent apposition due to double barrel created by simultaneous kissing stents.

Guidance for Unprotected LMCA Intervention

IVUS is helpful in determining treatment strategy and in optimizing the stent procedure (Figure 10). The most comprehensive level of level of evidence in favor of IVUS-guided approach for PCI of LMCA stems from a post-hoc analysis of the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) trial [48] in which there was a trend toward lower 3-year mortality with IVUS-guided strategy versus angiography alone. The mechanism of benefit is postulated to be related to reduced rates of sudden cardiac death related to late stent thrombosis. IVUS plays a crucial role in assessment of plaque shift, especially after PCI of LMCA bifurcation, and is also critical for the optimization of post-intervention MLA. With a single crossover stenting, a post-intervention ostial left circumflex (LCX) MLA of ≥ 4 mm^2 is associated with a restenosis rate of 6% compared with 50% in those with ostial LCX MLA of ≤ 4 mm^2 With two stenting strategy, a post-intervention ostial LCX MLA of ≥ 5.5 mm^2 is associated with restenosis rate of 15% compared with 67% in those with ostial LCX MLA of ≤ 5.5 mm^2 [49]. The best IVUS-MSA criteria that predicted angiographic ISR were 5.0 mm^2 for the LCX ostium, 6.3 mm^2 for the left anterior descending (LAD), 7.2 mm^2 for the polygon of confluence (POC), and 8.2 mm^2 for the proximal LMCA [50].

Guidance for Bifurcation Lesion Intervention

Suboptimal stent deployment in bifurcation lesions, particularly with 2- stent strategy, increase the risk of stent thrombosis and restenosis (particularly at SB ostium). Pre-intervention IVUS interrogation can

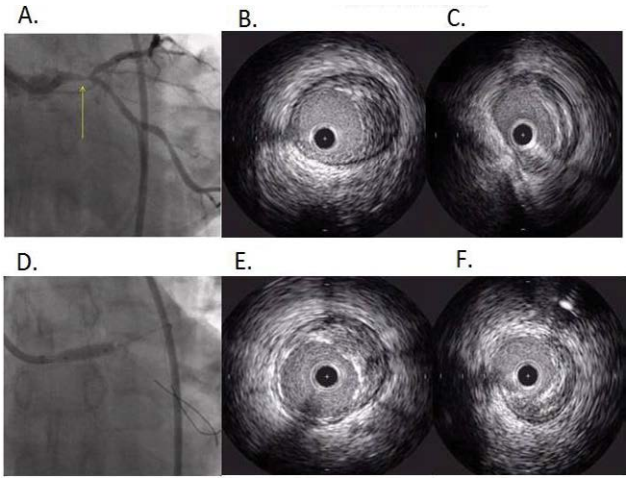

Figure 10: A. Angiography showing LMCA bifurcation with Mild LCx disease; **B.** IVUS revealing significant left anterior descending (LAD) artery ostial disease; **C.** IVUS showing mild LCx disease with minimum lumen area (MLA) of 5.5 mm^2; **D.** LMCA-LAD stent crossover followed by in-stent dilatation; **E.** Post PCI stent cross sectional area(CSA) of 6.5 mm^2 at LAD ostium; **F.** Ostial LCx MLA 4.6 cm^2.

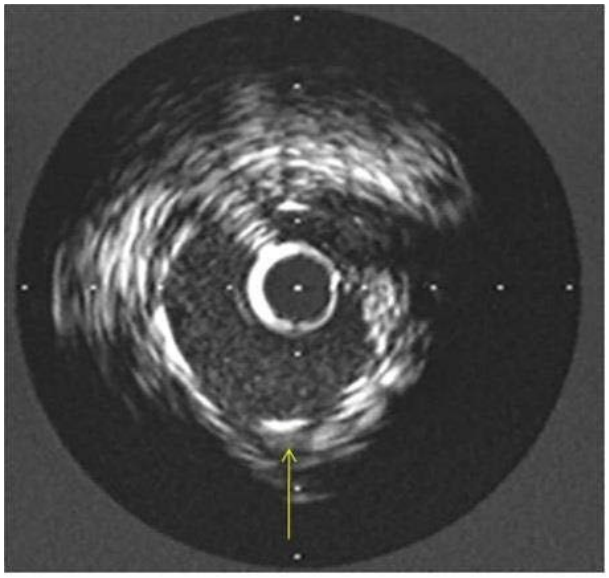

Figure 11: IVUS picture depicting underexpansion of stent.

provide valuable information in the optimal selection of bifurcation PCI strategy, by assessing plaque morphology, burden and distribution at the SB ostium. In one study, with regard to non-LMCA bifurcations, IVUS guided PCI with DES was associated with significantly lower rates of death or myocardial infarction than angiography guidance [51]. Pre-intervention IVUS of the SB is useful in predicting the likelihood of SB compromise due to plaque and/or carina shift after single-stent deployment in the MB. Post procedural stent expansion and apposition, particularly at carina level, is also important to guide optimal dilatation of the SB ostium and kissing-balloon dilatation that might enhance long term outcome of these, technically challenging subset of lesions.

Guidance for In-Stent Restenosis

IVUS is useful in differentiation of restenosis related predominantly to intimal hyperplasia versus mechanical complications, such as stent fracture or stent under expansion (Figure 11). If the cause is stent under expansion, an IVUS-guided high-pressure angioplasty with a noncompliant balloon should be mode of treatment to avoid deployment of a second stent, especially with DES restenosis. Balloon-alone angioplasty may also be appropriate in the presence of very focal lesions due to neointimal hyperplsasia in both BMS and DES. If in-stent resteosis is diffuse, then restenting with DES is often warranted. Restenting should also be thought if stent fracture is found as a cause of restenosis [43].

Guidance for Chronic Total Occlusion (CTO)

CTO is often considered the final frontier for PCI because of low early success rate and high restenosis rate. The success of PCI for CTO depends mainly on crossing the lesion with a wire. IVUS can be extremely useful in ensuring that the guidewire is parked within the lumen (true or false), and helps in identifying the optimal entry point within CTO cap [52]. IVUS is useful for identifying the site where the wire has entered from true to false lumen; assessing the length, depth, and a circumferential extent of false lumen caused by the wire; identifying where and if the wire has re-entered the true lumen . IVUS guided wiring technique is effective to capture a true lumen when wire handling has failed with angiographic guidance [53,54]. It also has been utilized successfully during more complex techniques such as reverse controlled antegrade and retrograde tracking (CART) that revolutionized CTO recanalization [55].

Guidance for Saphenous Veinous Graft (SVG) Intervention

As SVG grafts are often larger sized than native vessels making angiographic size assessment more difficult, IVUS guidance during PCI may be particularly important. In fact oversized stents (stent to reference vessel ratio >1.0) result in greater rates of periprocedural myocardial necrosis and distal embolization without reducing 9-month revascularization rates [56,57]. Stent oversizing also may lead to graft perforation. IVUS, therefore, should be used to select appropriately sized stents for SVG PCI.

Radiofrequency (RF) Ivus

To overcome the limitations of qualitative visual interpretation of the IVUS images and for improved characterization of plaque composition, several post-processing methods for computer-assisted quantification have been developed during the recent years. These are VH-IVUS (Volcano Therapeutics, Rancho Cordova, CA, USA), iMAP-IVUS (Boston Scientific, Santa Clara, CA, USA), IB-IVUS. VH-IVUS has been compared with actual histology from directional coronary atherectomy specimen's coronary arteries from ex-planted heart with overall moderate predictive accuracies (80-94%) [58,59]. Similar validation studies have also been performed for iMAP and IB-IVUS [60]. These imaging technologies have limitations like the inability to accurately detect thrombus and characterize plaque behind calcium due to acoustic shadowing [61]. In addition, these 3 IVUS platforms are not able to detect thin-cap (<65 μm) fibroatheromas (TCFAs) [60-62]. IB -IVUS provide higher diagnostic accuracy for tissue characterization than VH-IVUS in autopsy study [63]. In large multicenter PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial, 697 patients of ACS were enrolled and underwent

PCI of all culprit lesions followed by 3-vessel VH-IVUS imaging [64]. The investigators reported that only 11% of patients had high event rate (i.e. 17%) in association with TCFAs with MLA ≤ 4 mm^2 and plaque burden ≥ 70%. Although high-risk focal regions can be detected with VH-IVUS, the predictive power of vulnerable plaque to cause a clinical event remains low.

Current Recommendation of IVUS

As there is no clear cut existence of guidelines on the routine use of IVUS guided angioplasty, the interventionist should weigh the risks and benefits of this procedure before its application. IVUS is definitely beneficial in optimal stent deployment (complete stent expansion and apposition and lack of edge dissection or other complications after implantation), and the sizing of the vessel undergoing stent deployment [65]. It is probably beneficial in appraising the significance of LMCA lesion and, employing a cutoff MLA 6 mm^2, assessing whether revascularization is warranted [65]. IVUS could possibly be useful for the assessment of plaque morphology. Contraindication for IVUS guidance, are small vessels, tortuous vessels and degenerated vein grafts.

Does IVUS Have a Future in Era of Optical Coherence Tomography (OCT)?

Even if OCT results in superior lumen border detection compared to IVUS, it has a limited penetration depth, which is an obvious shortcoming for total vessel size assessment and vascular remodeling, and implies the inferiority of OCT in progression-regression trials compared to IVUS. However, OCT is able to depict and measure clearly TCFA prone to rupture rather than IVUS [65]. On the other hand, RF-IVUS provides quantification of different plaque components which are displayed in simply color-coded images. The interpretation of OCT images is more difficult. Differentiation of lipidic and calcified plaques may be quite challenging with OCT as both can have low image intensities [66]. Considering the advantages and limitations of both IVUS and OCT for the assessment of vulnerable plaque, the combined use of RF IVUS and OCT may be suggested to improve its detection [66]. Even if OCT is likely to take over some of the current indications of IVUS, is a much younger technique which still has to prove its value. In nut shell, IVUS would still have a future in OCT era.

Conclusion

IVUS has played an integral role in evolution of interventional cardiology. In an era of more complex PCI, it remains an important armamentarium for the modern-day interventional cardiologist. Pre and post intervention IVUS evaluation can improve the clinical outcome and resolve doubts about ambiguous lesions. It has a pivotal role in guiding stent deployment, particularly for complex lesions like bifurcations, LMCA, CTO, in-stent restenosis, and SVG lesions. Tissue characterization is an emerging technology that is based on signal analysis, which provides further insight into lesion survey and complication prevention. The development of forward- looking IVUS systems, combined near-infrared spectroscopy and IVUS platforms, combined IVUS (including RF- analysis) and OCT would be promising tool for the ambitious interventionalists in near future.

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