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Optimizing Coronary Angioplasty with FFR and Intravascular Imaging

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Abstract
Purpose of Review Percutaneous coronary intervention has changed the approach to coronary artery disease management, but angiography remains the principal method for determining the severity of disease. Because an angiogram only identifies the outline of the lumen, angiography is not the most sensitive or accurate instrument. This leads to significant inter-observer variation in interpretation of intermediate lesions. Additional technologies have been developed to better evaluate the extent of disease and identify potential high risk lesions. This paper reviews the strengths and deficits of these techniques.
Recent Findings Clinical outcomes data validate the use of fractional flow reserve (FFR) for physiologic assessment of coronary artery stenosis. Intravascular imaging technology provides unique anatomic information about atherosclerotic plaque. Optical coherence tomography (OCT) has high resolution for visualizing stents and inner-lumen anatomy such as dissections. Intravascular ultrasound (IVUS) has less spatial resolution but has greater penetrating power and therefore provides a more complete picture of atherosclerotic plaque. VH has not been adequately validated and can be misleading compared with tissue histology. NIRS is an emerging technology and, while promising, has not yet achieved widespread application.
Summary Invasive evaluation is an essential part of coronary artery disease assessment. Some of the techniques in use such as FFR have shown correlation with outcomes and clinical endpoints. Other technologies such as IVUS or OCT provide an anatomic description of the vessel. The use of these imaging tools to describe lesion composition and predict vulnerable plaque has not been as successful or clinically robust.

Keywords Fractional flow reserve · Interventional cardiology · Intravascular imaging

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Introduction

Although it has been 40 years since Andreas Gruentzig performed the first coronary angioplasty, there continue to be significant improvements in devices and techniques for coronary artery interventions. There are also refinements in the methods for visualizing atherosclerotic plaque and assessing the anatomic and functional significance of coronary disease. This review will provide an analysis of the four primary modes of anatomic imaging of coronary disease that go beyond angiography to assist our understanding of atherosclerosis pathology in vivo. As distinguished from anatomic imaging, this review also will discuss the functional assessment of coronary stenoses by fractional flow reserve (FFR) and present how these modalities can be most effectively integrated

into the catheterization laboratory. The imaging modalities to be discussed are the following: intravascular ultrasound (IVUS) grayscale imaging, frequency-domain computerized interpretation of tissue characterization (so called Virtual Histology), optical coherence tomography (OCT), and near-infrared spectroscopy (NIRS).

Current Technology: Intravascular Ultrasound (IVUS)

IVUS produces grayscale images based on the amplitude of an ultrasound signal that is reflected from tissue at a frequency of 20–40 MHz. Real-time images are produced at 30 frames per second as the ultrasound transducer is pulled along the length of an artery lumen. This frequency provides a balance between tissue penetration depth and resolution. A higher frequency would improve resolution but reduce the depth seen. For example, there are ultrasound microscopes that function at a gigahertz frequency which can image individual cells, but can only penetrate 10–20 microns or a couple of cell layers at most making this useful only for monolayer samples such as blood smears [1]. Higher frequency also limits image contrast due to ultrasound reverberation from red blood cells. This makes it more difficult to distinguish intima from vessel lumen [2]. Since its initial clinical use in 1988, IVUS has persisted as a useful tool in interventional cardiology. There are currently two methods of generating IVUS images: an ultrasound transducer at the tip of a catheter that mechanically rotates to sweep out the image cross section and a synthetic aperture device to generate the image from five small transducers at the tip of a fixed catheter. Both systems produce a 2-dimensional grayscale cross section of the artery that resembles a low power histologic view. The main benefit of the synthetic aperture system is that the catheter is coaxial with the guidewire and is easier to manipulate than the mechanically rotating catheters. The synthetic aperture catheter however generates an image at only 20 MHz. Initial studies demonstrated that the resolution of the synthetic aperture system is significantly below that of the mechanically rotating systems, such that clinical information and the extent of plaque are often not as well defined by this system. Lower frequency probes that sacrifice tissue detail for greater depth penetration are used for larger arteries such as peripheral vascular imaging. The image is produced by transmitting the ultrasound wave and measuring the amplitude of the reflected signal to reconstruct a cross-sectional image of the artery. IVUS image interpretation depends on the physical properties of the three layers of an arterial wall to separate their identity: an intermediate echoreflective intima, an echolucent muscular media, and an intensely echoreflective adventitia due to its high collagen content. Plaque composition can be characterized with grayscale IVUS due to differences in acoustic properties [3].

IVUS is useful in situations where angiography may not be diagnostic or provide complete information, particularly in ostial lesions, where vessels overlap, or tortuous segments. While ultrasound is very good at identifying high-density matter such as calcification, it is less exact at differentiating between fibrous, necrotic plaque, and fatty tissue. This limits the utility of IVUS in tissue characterization of necrotic or vulnerable regions. As the ultrasound wavefront interacts with calcified tissue, intense echoreflections are produced which creates a shadowing effect distal to calcified tissue. This limits the use of IVUS to see the complete depth of tissue behind large calcified plaques.

Assessment of Lesion Severity

There is significant inter-observer variation in angiographic interpretation of intermediate lesions (defined as 40–70% diameter stenosis), and visual assessment alone does not accurately predict the severity of these lesions in comparison to FFR and IVUS [4, 5, 6•]. Accurate assessment is of particular importance for left main coronary artery (LMCA) lesions as revascularization reduces mortality compared to medical therapy for significant LMCA disease [7]. One IVUS study of angiographically ambiguous LMCA lesions showed that, while IVUS found 44.3% of these lesions to be significant, quantitative coronary angiography (QCA) only identified 13% [8]. Although FFR has become the gold standard in determining whether a lesion is physiologically significant, assessing the significance of LMCA lesions may not be accurate with FFR if there are additional downstream sequential lesions. As LMCA disease is commonly associated with bifurcation lesions and multivessel coronary artery disease, IVUS can be useful as an adjunct to determine how to best approach LMCA lesions. A meta-analysis of 11 studies showed that IVUS-derived LMCA minimal lumen area (MLA) of 5.4 mm^2 had 90% sensitivity and specificity in predicting a significant FFR. However, the authors commented that the current guidelines for MLA may lead to misclassification in up to 20% of lesions and suggest lower MLA cutoffs [9]. LITRO, a prospective multicenter validation study, evaluated the use of a predefined MLA cutoff to determine the course in intermediate LMCA lesions [10]. Revascularization was performed on MLA below 6 mm^2 or deferred for MLA above 6 mm^2. After a two-year follow-up period, death and event-free survival were not significantly different between the two groups. The study did note a large scatter between both groups in angiographic parameters. Based on the above data and other smaller studies, an IVUS-derived MLA threshold of <6.0 mm^2 has generally been used to indicate lesion significance. It should be noted, however, that two studies in Asian populations found a lower optimal MLA threshold of 4.8 and 4.5 mm^2 for ischemia [11, 12]. This finding may reflect lower body mass and relative coronary size in this population. Ideally, the MLA should be indexed for body size in future trials for accurate comparisons.

For non-LMCA lesions, there is no optimal MLA cutoff due to significant heterogeneity in vessel size and area of myocardium supplied. Lumen cross-sectional area values between 3 and 4 mm^2 have been proposed, and older studies showed overall low event rates for patients in whom percutaneous coronary intervention (PCI) was deferred based on IVUS MLA >4 mm^2 [13]. More recent studies have shown MLA to have only limited diagnostic accuracy in predicting ischemia [9, 14–17]. This should not be surprising as MLA is only one of many factors that may cause clinically significant ischemia. FFR is the preferred tool to determine ischemia as it integrates the physiologic characteristics of MLA, lesion length, entrance and exit forces, and amount of myocardium supplied [18]. The 2014 expert consensus statement from the Society of Cardiovascular Angiography and Intervention (SCAI) discourages IVUS measurement alone to recommend revascularization of non-LMCA lesions [19]. If IVUS is performed, a MLA of >4 mm^2 can likely be used as a threshold to defer revascularization based on available evidence for non-LMCA lesions. With MLA of <4 mm^2, additional functional testing is recommended to determine flow limitations.

In patients with new stenosis in previously stented segments, IVUS can help identify the mechanism of disease and potentially change treatment strategy. Significant neointimal proliferation or neoatherosclerosis may require additional drug-eluting stents within the original stent. However, if the cause of restenosis is stent underexpansion, mechanical optimization with appropriately sized balloon angioplasty may be sufficient. With both bare-metal stent (BMS) and drug-eluting stent (DES), stent underexpansion seen on IVUS but not appreciated on angiography has been shown to be a significant contributor to in-stent restenosis [20•, 21]. Another concern is late incomplete stent apposition (malapposition) thought to be due to regional expansive remodeling from the toxicity of the first generation sirolimus-eluting stents. Studies are inconclusive, however, on whether this finding predisposes to thrombotic events [22, 23]. It appears that malapposition alone is not thrombogenic, except when a deep ulcer is caused by a toxic substance such as sirolimus [24, 25].

Transplant Vasculopathy

IVUS has been applied to our understanding of heart transplantation, where IVUS has been used to study progressive coronary intimal thickening and early cardiac allograft vasculopathy (CAV) [26]. Outcome studies established an IVUS-derived intimal thickness increase of more than 0.5 mm at 1 year to be predictive of future major adverse cardiac events (MACE), mortality, graft loss, and angiographic CAV by 5 years [27]. More recent data in the current era of immunosuppression and routine statin use post-transplant suggests that paradoxical negative remodeling is also a powerful predictor of poor long-term outcome as well as intimal thickening [28, 29]. Rejection and chronic pericardial inflammation have been implicated in this finding of negative remodeling. IVUS remains an important clinical tool to establish prognosis and as a research tool to assess the effectiveness of various post-transplant therapies.

Bridging and Coronary Anomalies

IVUS is also uniquely suited for the interrogation of dynamic processes. Myocardial bridging is an anomaly in which the coronary artery takes an intramyocardial course resulting in vessel compression during systole. While usually benign, significant bridging may lead to myocardial ischemia. It has been observed that atheroma does not form within the intramyocardial segment; however, there is increased atherosclerosis proximal to the bridging. IVUS is considerably more sensitive than angiography in detecting systolic compression, and the characteristic "half-moon" echolucent band seen with IVUS is a specific finding for myocardial bridging [30, 31]. Anomalous origin of a coronary artery from the opposite sinus of Valsalva (ACAOS) with an intramural course within the aorta is associated with myocardial ischemia and sudden cardiac death [32]. Although noninvasive coronary computed tomographic angiography (CTA) or coronary magnetic resonance angiography (MRA) can delineate the anomalous course, IVUS is more accurate in characterizing systolic compression, a slit-like ostium, and intramural proximal folding within the aortic root wall [33, 34]. Similarly, LMCA compression in primary pulmonary hypertension with pulmonary arterial dilation can be seen with coronary CTA, but IVUS can be used to define the diameter and length of the artery during stenting [34]. The use of FFR in these conditions has been described, but specific protocols and ischemic thresholds have not been well validated [35–37].

Optical Coherent Tomography (OCT)

OCT uses near-infrared light via fiber optics to obtain high-resolution images which can distinguish structures about 10 microns apart. The resolution is significantly higher than with IVUS, which can usually resolve two points 100 microns apart in the circumferential direction. OCT has faster image acquisition and uses a smaller imaging catheter than required for IVUS. The higher resolution comes at the cost of tissue penetration; OCT is only able to see 2 mm into the vessel from the inner edge of the endothelium. Saphenous vein grafts (SVGs) and LMCA are often too large to be adequately imaged by OCT. OCT is also not suitable for use with dynamic processes, such as myocardial bridging and ACAOS, as the rapid automated pullback cannot image a segment over the entire cardiac cycle or at the ostium of the coronary arteries. Large and complex plaques are often 2–3 mm thick and so information about the base of the plaques is lost. An advantage

of OCT is the ability to present high detailed endothelial anatomy, dissections, stent struts, and their relative location to the vessel wall (Fig. 1). In comparison to angiography alone, OCT observations may improve outcomes [38]. The increased resolution also defines areas of dissection and intimal disruption in greater detail; however, these small protrusions and minor disruptions have not been shown to have clinical significance [39]. The OCT platform is stable and makes acquiring images easier. It does not appear that the higher resolving power of OCT produces improved outcomes over the information provided by IVUS. Both imaging methods demonstrate that underexpanded stents predispose to both restenosis and stent thrombosis. Two significant limitations of OCT include the inability to image a vessel with no-reflow as the blood needs to be cleared with contrast for the imaging to occur. Also, OCT often does not penetrate to the coronary external elastic membrane (EEM) and so cannot adequately assess vessel plaque burden. Recent work with an extensive comparison of OCT and histology after stenting demonstrates that OCT, although accurate in describing geometric shapes, is unable to accurately distinguish tissue composition of atherosclerotic plaque such as calcium or lipid [40].

IVUS-Virtual Histology (VH)

Up to 5.8% of patients who undergo PCI will have an intervention for a nonculprit lesion within a year [41]. It would be useful to be able to identify, during the index procedure, the areas most likely to progress. Angiography is inadequate at identifying these areas as they are often not anatomically flow-limiting. The frequency domain of ultrasound backscatter signals has been used to identify the components of atherosclerotic plaque. The algorithm, developed by the Department of Biomedical Engineering at the Cleveland Clinic, was given the name Virtual Histology™ (VH) or spectral analysis plaque classification methodology [42]. On the grayscale IVUS image, intense white echoes with distal shadowing correspond to calcium, gray areas represent fibrous tissue, and echolucent zones indicate lipid filled or necrotic plaque. The difference between the two techniques is that with the grayscale image, the observer is making the determination of ultrasound intensity while with frequency backscatter, it is determined by a computer that has been programmed with an algorithm to interpret the tissue composition automatically for the operator. The question is how accurate is this computer algorithm?

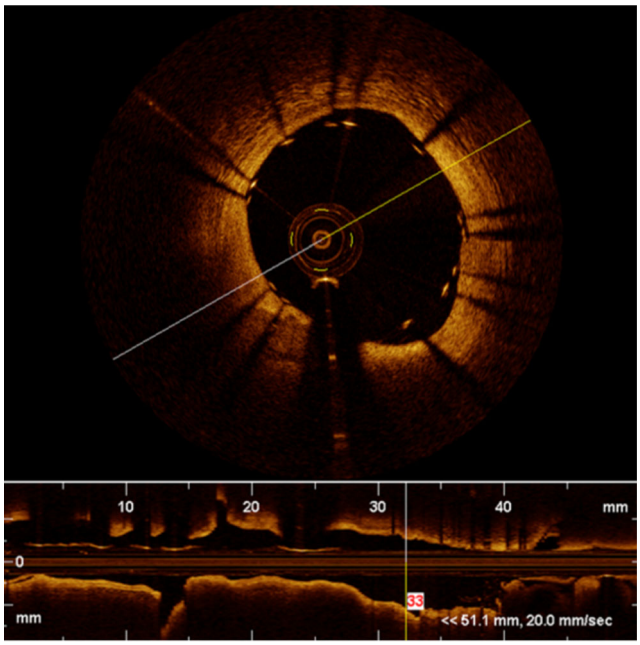

Fig. 1 OCT image after stent deployment showing the stent struts and lumen of the vessel in coaxial and longitudinal views

Initial ex vivo evaluation of fibrous, fibrofatty, necrotic core, and dense calcium regions was reported to show a good correlation with histology [42]. There was a concern that the tight selection parameters of the lesions studied may limit the generalization to clinical application. There was also a variation in the pathologists' interpretation of the histology. A panel of four pathologists agreed among themselves only 23% of the time and three agreed only 75% of the time. The VH algorithm was consistent with about half of the consensus pathology interpretation, and images were not compared with the grayscale interpretation from a mechanically rotating IVUS catheter. The authors suggested that the generated tissue map resolution is about 246 μm radially so a thin fibrous cap less than 65 μm may not be seen adequately and may be lumped in with other areas of disease, such as dense calcification, and that the entire lesion would be mistakenly described as vulnerable plaque. Thrombus identification was also limited due to its poorly defined spectral signature. Significant intraobserver variability exists in assessment of VH imaging due to the variability in the processing of the algorithm and in the definition of thin-capped fibroatheroma (TCFA). Further, it is not clear what significance to attribute to TCFA surrounding areas of dense calcification, which is commonly portrayed on VH images [43]. Another area of concern is that when ultrasound waves at 20–40 MHz interact with calcified segments in atherosclerotic plaque, there is intense reflection from the surface of the calcified nodule and there is no penetration of the waves into the plaque or past it and thus there is no information behind the dense reflective region. This is why there is "shadowing" behind calcified plaque on IVUS grayscale images. In VH images, there is usually a red border interpreted as "necrotic core" around white calcium. In addition, deep in the plaque behind the calcium, VH shows green fibrous or lime-colored areas representing lipid-filled tissue. There is insufficient ultrasound information behind dense calcium either on grayscale or frequency backscatter. The VH algorithm does not permit a region of indeterminate values so information is generated based on assumptions. Areas of

high density can cause reflection and reverberation artifact in the reflected waves so that regions around calcifications are coded as necrotic (red). Translating the data into clinical practice is not possible without the corresponding histology, which is not available until after death. Another concern is that the current VH system uses the synthetic aperture catheter. The resolution of this catheter is not equal to the mechanically rotating IVUS catheters and so VH is also impaired by lower spatial resolution, which further degrades the reliability of VH.

The PROSPECT trial studied the predictability of VH imaging for future cardiac events. The hypothesis was that VH could identify thin cap fibroatheromas (TCFAs) that are vulnerable to rupture [44]. This was a large trial of 697 patients lasting 3.4 years. Baseline plaque burden of at least 70% CSA, a minimal luminal area of 4.0 mm^2 or less, and the presence of thin-cap fibroatheromas were independent predictors of subsequent nonculprit lesion-related major adverse cardiovascular events (MACE). MACE was predicted by VH-TCFAs in 4.4 vs 1.2% (OR 3.35; $p = 0.0002$). However, the other significant identifiers of MACE were plaque burden greater than 70% (OR 5.03; $p = <0.001$), minimal lumen area <4.0 mm^2 (OR 3.21; $p < 0.001$), or the combination of the two. These latter two measurements were obtained from the grayscale images and were the greatest predictor of events, suggesting that VH may be providing incrementally little new information beyond what is available from a grayscale image. Most of the adverse events predicted by VH-TCFA were episodes of unstable angina as distinguished from harder end points such as cardiac death, myocardial infarction, or cardiac arrest. About 51% of the nonculprit-related events occurred at a VH-TCFA region, so VH was neither sensitive nor specific for MACE events.

In another study, in vivo coronary plaque assessment was used to correlate VH data with histology and evaluated the differences in plaque composition between subjects with stable angina pectoris and acute coronary syndrome (ACS) [3]. The histologic assessment was made from tissue obtained by directional atherectomy from the area imaged. The study did identify regions of necrotic core as significantly more frequent at the suspected sites of ACS but so were areas of calcification ($p < 0.05$). This was a small single-center study that had 307 VH and IVUS images from 30 participants in the analysis. The histology obtained from directional atherectomy was limited to the surface of the plaques and so does not address deeper tissue of the plaque in the vessel wall. The authors found that areas behind calcification were difficult to interpret by VH and that VH was unable to characterize thrombus well. This is important during ACS when plaque erosion is likely to generate thrombus and leads to errors in tissue characterization by the software.

Necrotic core lesions are complex by histology. The VH interpretation that there was a higher preponderance of calcification in necrotic lesions led to the suggestion that calcification may be a marker of an unstable lesion [45]. This was not corroborated by other studies, suggesting that the VH interpretation that vulnerable plaque is associated with calcification may be an artifact generated by the computer algorithm of VH [46]. A study by Thim et al. compared VH-generated images to histology in adult atherosclerosis-prone minipigs. They found no correlation between the necrotic core size assessed by VH and the histology findings. Further, they found that VH IVUS may miss necrotic core when calcification in the necrotic core is not present or not detected. Additionally, their data suggest that VH IVUS may interpret fibrosis as necrotic core, which is probably less likely with grayscale IVUS [47••]. It is important to note, however, that the pig atherosclerosis model is not the same as a mature human plaque. The induction of disease in these animals was achieved by a high-cholesterol diet for 18 weeks and coronary artery injury using an oversized angioplasty balloon [48]. Another example of the limitation of VH is the interpretation of echolucency as a sign of tissue homogeneity and therefore is an indication of vulnerable plaque [50, 51]. In grayscale IVUS, echolucency represents areas of high lipid content, but there is no convincing evidence that VH can differentiate the content of those areas and identify it as a necrotic core [49]. Due to the issues described, Virtual Histology can be misleading. The VH program may fill in a lumen and show it as fibrous tissue leading to physicians performing an intervention on nonsignificant lesions (Fig. 2). There is no data to show that VH improves PCI outcomes or provides a clinical outcome advantage over grayscale IVUS.

Near-Infrared Spectroscopy (NIRS)

Near-infrared spectroscopy (NIRS) is a newer imaging technology that uses a laser wavelength that is absorbed by components of cholesterol plaque. The machine provides a grayscale IVUS image with a superimposed "chemogram™" that corresponds to the intensity of lipid within the plaque (Fig. 3). This technology has been validated by a careful histologic comparison study which demonstrated that large lipid-rich plaques can be identified by the NIRS catheter [52]. This is different than a VH-computerized interpretation of ultrasound frequency as NIRS uses a different physical means of identifying the biochemistry of atherosclerotic plaque. A significant question about this technology is how it can be used in terms of treatment once a lipid-rich plaque is identified, beyond aggressive medical therapy. There is anecdotal evidence suggesting that recognition of a large lipid-laden plaque could help prevent distal embolization during coronary angioplasty by placing a protection device. A separate study using both NIRS and VH demonstrated that the association between the two modalities is weak for either lipid or calcification [53]. The lipid-rich plaque (LRP) study seeks to repeat the

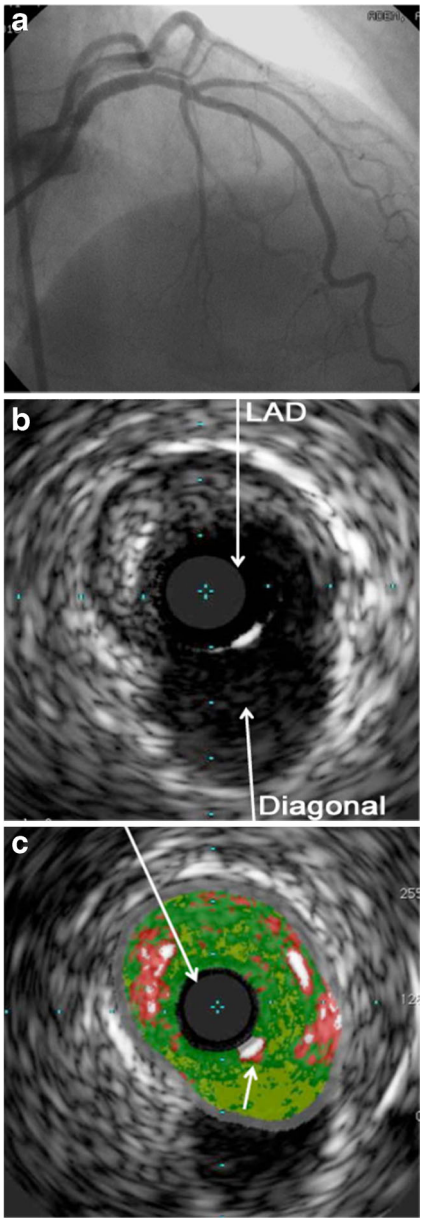

Fig. 2 **a** Left coronary angiogram in cranial PA projection. There is mild narrowing of the mid LAD just after the bifurcation with the diagonal and first septal perforator vessel. **b** Grayscale intravascular ultrasound image reveals mild plaque formation between 9 o'clock and 3 o'clock in the *LAD* just at the bifurcation with the *diagonal* artery. **c** Corresponding Virtual Histology™ (VH) provides an image of extensive atheroma plaque at the bifurcation that encroaches upon the catheter. The estimation of the residual lumen by VH was 3.6 mm^2 which severely overestimates the degree of stenosis. Based on this VH image, the physician inappropriately placed a coronary artery stent in the LAD

PROSPECT trial with NIRS to identify vulnerable plaques and predict clinical events. There is also an interest in using NIRS to observe how aggressive lipid-lowering medical therapy such as with statins or PCSK9 agents may quantitatively reduce the coronary lipid plaque burden. Further, Madder et al. have looked at the utility of NIRS in the setting of acute myocardial infarction to identify large lipid core plaques at the site of rupture and thrombus formation [54].

Imaging Interventional Applications

Prior to PCI, IVUS may be useful in determining the extent of disease and calcification in planning an interventional strategy. The presence of extensive concentric superficial calcification may signal the need for plaque modification with a rotational atherectomy device to achieve adequate stent expansion. Conversely, lesions with deep or eccentric calcification may achieve adequate lumen expansion with balloon dilatation and stent placement alone. IVUS imaging can be used to select adequate stent length to avoid "geographic miss," an important contributor to long-term adverse events [55].

Immediately after stent deployment, IVUS can identify areas of stent underexpansion usually at fibrotic or calcified plaque, stent malapposition where struts are not in contact with vessel wall, or edge dissections. Stent underexpansion has consistently been associated with stent restenosis and thrombosis with both BMS and DES [56–60]. A number of studies suggest that the optimal minimal stent area (MSA) to prevent restenosis is >5 mm^2 for DES and 6.5 mm^2 for BMS, although there is significant heterogeneity among the studies [61–65]. Small, nonflow-limiting edge dissections usually heal with time and do not appear to influence long-term outcomes [66, 67].

There are a number of studies of PCI with IVUS guidance compared to angiographic guidance alone. These trials have shown mixed results, and many were nonrandomized, underpowered, or had widely differing primary end points or treatment strategy in response to IVUS findings. Two meta-analyses of randomized studies in the BMS era concluded that IVUS guidance increased final MLD, decreased angiographic restenosis by about 5%, and decreased repeat revascularization but had no significant effect on death and MI rates [68, 69]. The AVIO trial is a contemporary randomized multicenter trial comparing IVUS-optimized DES implantation to angiographic guidance alone in complex lesions [70]. Final minimal lumen diameter (MLD) as determined by QCA was significantly larger in the IVUS group; however, there was no significant difference in MACE after 24 months. Three large meta-analyses of randomized and observational studies in the DES era suggest IVUS guidance in DES implantation resulted in lower death, MI, and stent thrombosis [71–73]. These clinical outcomes were thought to be driven by longer stents covering diseased vessel segments and larger final MLD in the IVUS-guided groups. Most recently, a large randomized multicenter trial (IVUS-XPL) compared IVUS guidance to angiography guidance for implantation of everolimus-eluting stents in 1400 patients with lesions longer than 28 mm [74]. At 1 year, MACE was lower in IVUS-guided patients (2.9% vs. 5.8%, $p = 0.007$) predominantly due to ischemia-

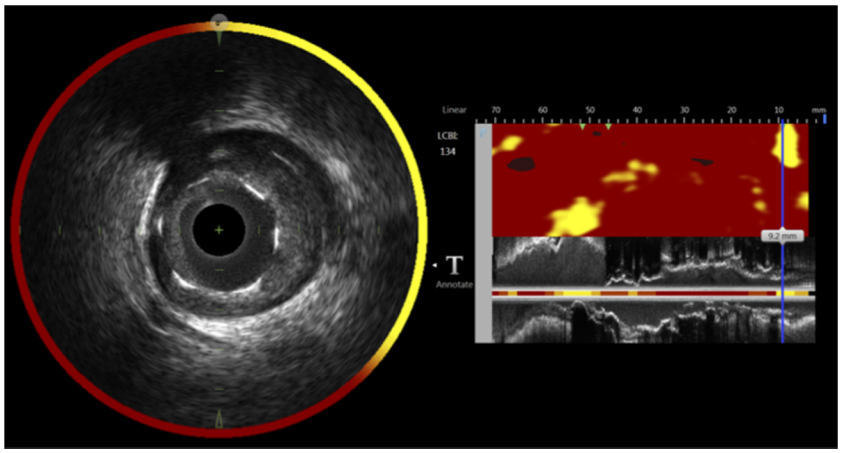

Fig. 3 Near-infrared spectroscopy (NIRS). Combining IVUS imaging with the chemogram™ overlay to provide information about cholesterol content within the plaque in relation to the coronary artery

driven target lesion revascularization (TLR). The bulk of the existing evidence suggests that IVUS guidance with PCI should be considered when dealing with long or complex lesions such as bifurcations.

A special area of interest is IVUS guidance during PCI of LMCA. Despite a lack of adequate randomized trials, the use of IVUS to optimize LMCA PCI has been recommended [75, 76]. Data supporting this practice comes largely from nonrandomized registry data with comparison against matched cohorts. Most of these studies show improved long-term outcomes with IVUS guidance [77–79]. It is doubtful that there will ever be an adequately powered randomized trial to test the efficacy of IVUS-guided PCI of LMCA. Given the challenges of assessing LMCA with angiography alone and potential negative clinical sequelae of suboptimal PCI results in this setting, consensus of opinion favors routine use of IVUS in LMCA PCI. With the advent of bioresorbable coronary scaffolds, intravascular imaging is even more important to ensure adequate lesion preparation prior to stent placement. The limited expandability, immediate recoil, and low radial strength of these devices create particular challenges if they are undersized or underexpanded [80]. Aggressive post-dilation after deployment may risk stent strut fracture. The incidence of early device thrombosis may be improved with more meticulous lesion preparation and more frequent intravascular imaging guidance [81].

Chronic total occlusion (CTO) represents another major technical challenge in interventional cardiology. By resolving vessel anatomy, IVUS has emerged as the dominant procedural imaging modality to identify entry point, vessel path, direct wire re-entry into the true lumen, and procedural complications such as hematoma or perforation [82]. The use of a solid-state imaging catheter is preferred because of the shorter distance of the transducer from the catheter tip as well as better trackability. A retrospective propensity-matched analysis showed that IVUS-guided CTO PCI had reduced stent thrombosis and TLR compared to an angiography-guided strategy, especially in long lesions [83]. AIR-CTO is a randomized trial that also showed less late lumen loss (LLL) in IVUS-guided CTO PCI compared to an angiography-guided strategy [84]. The rate of MACE however was not significantly different between the two strategies. A larger trial powered for hard specific outcomes will be necessary to answer this question.

Fractional Flow Reserve (FFR)

Initially described by Pijls and De Bruyne, FFR assesses the functional significance of a coronary artery narrowing by comparing the pressure found distal to a lesion to the reference pressure typically measured at the tip of the guide catheter under conditions of chemically induced hyperemia. FFR has become a powerful tool in the cath lab because of several studies that correlated FFR values with clinical outcomes. The DEFER, FAME, and FAME 2 trials were pivotal in bringing FFR into the forefront of clinical practice.

Early validation of FFR compared it to thallium scintigraphy, dobutamine stress echocardiography, and coronary angiography [85, 86]. A ratio below 0.75 corresponded with reversible ischemia in single vessels as identified on the noninvasive tests. Nuclear stress testing was used as the indicator for physiologic ischemia to arrive at the best FFR cutoff value as well as the appropriate hyperemia protocol [87]. The DEFER trial randomized 181 patients with FFR ≥0.75 to PCI or medical management alone. Five-year follow-up demonstrated excellent clinical outcomes in all patients with FFR ≥0.75 and no additional benefits with PCI compared to medical therapy alone [88]. The FAME study was a multicenter prospective trial, which included patients with multivessel coronary artery disease. It compared PCI guided by angiographic visual assessment to PCI guided by FFR assessment (PCI was deferred if the FFR was >0.80). Patients treated based on the FFR ratio required fewer stents than the

angiographically guided PCI cohort. At 1 year, there was a significant reduction in composite end point of death, nonfatal myocardial infarction, and repeat revascularization in the FFR-guided group. The FAME 2 trial then looked at comparing medical management and stent placement in patients with an FFR below 0.8 to optimal medical care alone. The study had to be terminated early due to divergence of the primary end points. The FFR-guided stent group had a 4.3% event rate compared to 12.7% in the medical arm (driven primarily by urgent revascularization) [89, 90]. Currently, the FAME 3 trial is evaluating if FFR-guided implantation of a second-generation Resolute Integrity stent is noninferior to coronary artery bypass surgery in multivessel disease.

In areas of diffuse disease, a pullback of the FFR wire during continuous adenosine infusion shows the FFR ratio throughout the vessel length. If a step-up is encountered, it can identify where the principal stenotic segment may be. However, after stenting of the primary lesion, it is important to repeat the FFR measurement because treatment of the primary lesion increases flow through the vessel and permits more accurate FFR measurement of residual lesions [91]. Post-PCI FFR also has been shown to reclassify angiographically satisfactory lesions as ischemic, prompting additional intervention to optimize final results [92, 93]. In the setting of acute myocardial infarction (AMI), the validity of FFR is questionable. The flow is typically not normal under these conditions, and there may be ongoing microvascular injury preventing maximal hyperemia; thus, the FFR result may be misleading during AMI. After the acute phase of injury, there may be benefit to FFR assessment in culprit lesions or after stenting [94]. FFR seems to be reliable for nonculprit lesions assessed during AMI as the myocardium perfused by those arteries is separate from the myocardium undergoing acute injury [95].

Conclusions

Invasive assessment of coronary stenoses in addition to angiography is useful for a variety of reasons. Physiologic analysis with FFR has strong clinical outcome data to demonstrate that it can be used reliably to determine if a stenosis should have an intervention. IVUS imaging is still useful if the question raised concerns anatomy such as the extent or presence of disease, the size of the vessel, or the adequacy of stent deployment. OCT can also be used to answer these anatomic measurement questions, but OCT has limited power and is not appropriate for making diagnoses about plaque composition. NIRS is a new tool that provides insight into the chemical composition of plaque and promises to be an important research tool. So called Virtual Histology (VH) is a computerized model that has poor correlation with histology, can be misleading, and in our opinion should be abandoned in favor of the other imaging technologies.

Compliance with Ethical Standards

Conflict of Interest Drs. Abudayyeh, Tran, and Tobis have no conflicts of interests to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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