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REVIEW

Evolution of intravascular assessment of coronary anatomy and physiology: from ultrasound imaging to optical and flow assessment

Elias Sanidas[*] and George Dangas[*,†]

[*]Cardiovascular Research Foundation, New York, NY, USA, [†]Mount Sinai Medical Center, New York, NY, USA

ABSTRACT

The fact that coronary angiography has limitations in terms of precise estimation and progression of atherosclerosis has been partially overcome during the last years by the use of new techniques. Catheter-based invasive modalities are of a profound clinical importance in regard to accurate assessment of coronary anatomy and physiology and the choice of the appropriate treatment strategy for each patient. Also their potential in clinical investigation projects is of great interest. This current review summarizes the basic principles of these methodologies and evidently highlights not only their use in clinical practice but also their contribution in clinical outcomes.

Keywords Clinical outcomes, intravascular imaging.

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Introduction

In general, pathogenesis of coronary artery disease relates to the slow or rapid and substantial progression of atherosclerosis. Then again, ischaemic mechanisms reflect an imbalance between myocardial blood supply and oxygen demand in regard to plaque rupture or superficial erosion with subsequent thrombosis of angiographically mild lesions (vulnerable plaques). The thin-cap fibroatheroma (TCFA), a metabolically active lesion with a large lipid-rich necrotic core and thin fibrous cap, is considered to be the most common type of rupture-prone and thrombosis-prone plaque [1–9].

During the past, our knowledge about the genesis, progression and characterization of atherosclerosis was based mainly on cross-sectional histopathological studies. Coronary angiography has several limitations in assessing plaque burden, calcification, eccentricity, stenosis severity and also how to implant a stent properly and recognize acute and chronic complications. It is only over the last few years that with the advent of catheter-based devices and techniques that use ultrasound or optics, we are beginning to see beyond angiography [3–6,8].

However, in patients with coronary artery disease, the most important factor with respect to outcome is the presence and extent of inducible ischaemia. Treating ischaemic lesions improves outcome, but treating nonischaemic lesions affects the outcome in a negative way. In patients with stable coronary artery disease, physiologically guided percutaneous coronary interventions (PCI) improve patient outcome as compared with medical therapy alone. In patients with functionally non-significant stenoses, medical therapy alone resulted in an excellent outcome, regardless of the angiographic appearance of the stenosis [10,11].

These are all important clinical aspects that can be addressed in catheterization laboratory setting using invasive assessment of coronary anatomy and physiology.

Intravascular ultrasound

Historically, the first true intravascular ultrasound system (IVUS) was designed by Klass Bom and his colleagues in Rotterdam in 1971. It was conceived as an improved technique for the visualization of cardiac chambers and valves. However, the first transluminal images of human arteries were recorded by Paul Yock and his associates in 1988. Ever since IVUS is useful during stent implantation to assess lesion severity, length and morphology before stent implantation; to optimize stent expansion, extension and apposition; and to identify and treat possible complications after stent implantation [12].

Intravascular ultrasound function is based on the general principles summarized in Table 1 [13]. There are two types of IVUSs for clinical use: the solid-state electronic phased array

Table 1 General principles of intravascular ultrasound (IVUS) image acquisition

1	Conversion of electrical energy into sound waves via piezoelectric crystals
2	Transmission and detection of sound waves reflected by tissues using a transducer
4	Conversion of sound waves into electrical energy
4	Amplification and processing of the electrical energy and conversion to an image
5	Projection of that image on the device's computer screen, from where it can be analysed or stored

transducer and the mechanical single-element rotating transducer. The solid-state electronic phased array transducer has 64 stationary transducer elements around the tip that image at 20 MHz, and it is commercially available as the 5F compatible Eagle Eye Catheter (Volcano Corp. Rancho Cordova, CA, USA). Benefits of the solid-state catheter include enhanced trackability due to the coaxial design and lack of nonuniform rotational distortion artefacts seen with rotational systems. Conversely, the 6F compatible mechanical systems offer a more uniform pullback and greater resolution due to the higher ultrasound frequency. Mechanical systems are available commercially as the 40-MHz iCross or Atlantis SR Pro catheters (Boston Scientific, Santa Clara, CA, USA) and the Revolution 45-MHz catheter (Volcano Corp.) [14].

Based on studies comparing preprocedural IVUS to flow wire, pressure wire or nuclear perfusion imaging in terms of clinical outcome, most feel that a lumen area < 4.0 mm^2 in a proximal epicardial artery excluding left main is a flow-limiting stenosis [15–17].

The advantage of IVUS guidance contributed primarily to decreased rates of in-stent restenosis and repeated revascularization in the bare metal stent (BMS) era, mainly by achieving larger acute lumen dimensions while avoiding increased complications [18,19]. The MUSIC trial was the first study, followed by a sequence of many others later who established IVUS criteria for optimal stent implantation. According to proposed MUSIC criteria, excellent expansion is evident when the minimum lumen area in the stent is > 90% of the average reference lumen area (Table 2). All the proposed criteria for IVUS optimization used in different studies have relied on distal reference or on mean reference vessel for stent or postdilatation balloon sizing. However, this fact reduces the potential to optimally increase the lumen size particularly in long lesions with overlapping stents and in vessels with distal tapering [18–21].

A large meta-analysis of randomized trials comparing IVUS- versus angiographic-guided BMS implantation ($n = 2193$ patients) showed that IVUS guidance was associated with significantly lower rate of angiographic restenosis, repeat revascularization and overall major adverse cardiac events (MACE), but had no significant effect on myocardial infarction (MI) [22].

Stent implantation in drug-eluting stent (DES) era is associated with very few clinical events. However, the issue of adequate stent implantation becomes even more important with DES, especially in regard to complex, multivessel and/or left main coronary artery stenting. IVUS predictors associated with PCI failures and increased adverse outcomes with DES include stent underexpansion, edge-related problems such as

Table 2 Optimal stent expansion criteria adopted in the MUSIC study

IVUS criteria defining optimal stent deployment	
1	Complete apposition of the stent The stent is apposed against the vessel wall over its entire length
2	Adequate stent expansion
2A	MSA $\geq$ 90% of the average reference lumen area or MSA $\geq$ 100% of lumen area of the reference segment with the lowest area when the MSA is < 9.0 mm^2
2B	MSA $\geq$ 80% of the average reference lumen area or MSA $\geq$ 90% of lumen area of the reference segment with the lowest lumen area when the MSA is > 9.0 mm^2
3	Symmetric stent expansion Defined as minimum lumen diameter divided by maximum lumen diameter ≥ 0.7

MSA, minimum stent area; IVUS, intravascular ultrasound.

residual reference disease (geographic miss) and dissections, as well as acute and especially late incomplete stent apposition (malapposition) [23–26].

In patients with complex lesions (i.e. bifurcations, long lesions, chronic total occlusions or small vessels) treated exclusively with DES, the use of IVUS demonstrated a benefit in minimum lumen area after stenting when compared to angiography alone. However, no statistically significant difference was found in MACE up to 24 months. In the above randomized AVIO trial, the newly proposed criteria for optimal stent expansion were based on the optimal balloon size that should be used for postdilatation. An important attribute of the AVIO criteria is that they can be useful in long lesions, as the stent is evaluated at different segments throughout its length. In addition, these criteria take advantage of the larger vessel size due to positive remodelling [27].

Whether IVUS guidance reduces stent thrombosis (ST) and improves clinical outcomes associated with DES treatment is considered to be controversial. Latest data suggest that IVUS-guided PCI reduce ST and improve long-term mortality when compared with angiography-guided PCI after DES implantation. In a very recently published meta-analysis of 11 clinical studies (n = 19,619), IVUS-guided DES implantation as compared with angiography-guidance alone was associated with a reduced incidence of death, MACE and ST [28].

Likewise, ADAPT-DES was a prospective, multicentre, real-world study of 8583 consecutive patients at 11 international centres undergoing DES implantation to determine the frequency, timing and its correlation between early and late ST. During the index procedure, IVUS was used in 3349 patients. IVUS use resulted in longer stent length and larger stent size without increasing periprocedural MI. These data drawn from the largest prospective registry of IVUS use to date suggest that IVUS guidance during DES PCI may result in less ST beginning at the time of implantation, as well as fewer myocardial infarctions [29].

Left main coronary arterial lesions are proven to be notoriously difficult to be accurately evaluated by angiography alone. Angiographic appraisal of left main disease correlates very poorly with IVUS and fractional flow reserve (FFR) determinations of lesion severity. This is related to high intra- and interobserver variability as well as the angiographic underestimation of left main dimensions. Moreover, the extent of left main bifurcation plaque burden by IVUS influences PCI outcome, and in general, PCI of distal left main bifurcation lesions are related to poorer prognosis. IVUS is very useful in distinguishing significant from insignificant left main disease, the distribution of plaque and planning the appropriate treatment strategy [30].

By applying predefined IVUS criteria for the assessment of intermediate left main lesions, De La Torre *et al*., showed that an IVUS-derived cut-off of 6 mm^2 can safely determine which intermediate left main lesions require revascularization [31].

In the MAIN-COMPARE registry, 975 patients underwent unprotected left main stenting; of those, 756 had IVUS guidance and 219 did not. In particular, the comparison between 145 equivalent matched groups of patients who received DES showed that IVUS guidance in left main PCI was associated with reduced long-term MI and mortality. According to the same data, the optimal minimum stent area (MSA) in left main lesions to prevent target lesion revascularization (TLR) was 8.7 mm^2 [32].

Lately, IVUS has been shown to be an adjunctive imaging technique for the crossing of coronary chronic total occlusions (CTO), the performance of complex aortic, carotid and peripheral artery endovascular procedures without excluding even vein intervention [33].

Different anatomic criteria should be used according to myocardial mass and/or anatomic variation of coronary artery. As minimum lumen area (MLA) by IVUS has a high negative predictive value, it can be used to exclude the presence of ischaemia. Recently, an IVUS-derived MLA $\geq$ 2.4 mm^2 was proposed to exclude functionally significant disease, but below that cut-off, poor specificity limits its value for physiologic assessment of lesions [34]. This is due to the fact that MLA is vessel size dependent and better correlated in large diameter vessels. The optimal MLA cut-off varies with regard to vessel location, vessel size and lesion severity. Patients post-MI and with reduced LV have higher cut-off MLA. Still, there is no single IVUS or optical coherence tomography (OCT) widely accepted criterion which can be used instead of physiologic lesion assessment. An example of multimodality assessment of an intermediate lesion in a current cath laboratory setting is given in Fig. 1.

Radiofrequency virtual histology – VH-IVUS

Virtual histology intravascular ultrasound (VH-IVUS) is an imaging modality that allows tissue characterization of vascular lesions. It is based upon the spectral analysis of the primary raw backscattered ultrasound wave (radiofrequency (RF)-based signal). Depending on the frequency of the used IVUS catheter, the technique has an estimated axial resolution (based on the resolution of the 20-MHz IVUS catheter) of approximately 200 μm (Table 3). Once the spectral signatures of four tissue types (fibrous tissue, fibrofatty tissue, necrotic core and dense calcium) are determined, these signatures are programmed into software, either on the IVUS console or on stand-alone software packages, for the analysis of patient data. Radiofrequency IVUS plaque components are colour-coded as dense calcium (white), necrotic core (red), fibrofatty (light green) and fibrous tissue (dark green) [35]. A case of grey-scale and VH-IVUS imaging correlation is shown is Fig. 2.

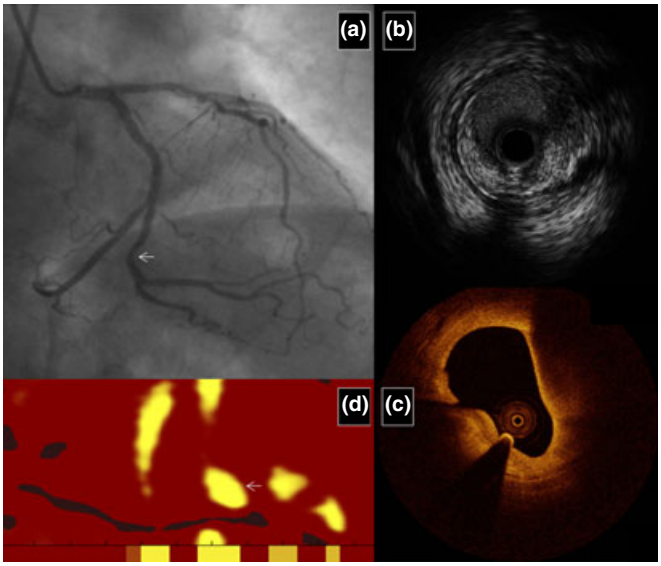

Figure 1 Multimodality assessment in the cath laboratory. An intermediate angiographic lesion located at the distal LCX (a). The minimum lumen area (MLA) measured by intravascular ultrasound (IVUS) was 4.0 mm^2 and the plaque burden 63% (b). The MLA by OCT was 3.9 mm^2 (c). The related chemogram showed yellow areas indicating lipid core plaque (d). Physiologic lesion assessment after intravenous administration of adenosine demonstrated a fractional flow reserve (FFR) of 0.80. The lesion was finally treated with a drug-eluting stent (DES).

Ex vivo validation of VH images directly with the histopathology sections provided accuracies of up to 97% [35,36]. Independent studies have demonstrated *in vivo* a relatively high level of accuracy and reproducibility of VH-IVUS in human arteries utilizing directional coronary atherectomy specimens, yielding predictive accuracies of up to 95% in non-ACS patients [37,38].

The PROSPECT trial tried to assess the natural history of atherosclerosis by studying 697 patients with ACS after successful PCI of a culprit lesion under optimal medical therapy using angiography plus three-vessel imaging including grey scale and radiofrequency VH-IVUS. In patients with ACS, both culprit and nonculprit lesions were equally likely to spur subsequent adverse events such as cardiac death, cardiac arrest, MI or rehospitalization due to unstable or progressive angina over 3 years. Independent predictors of a future cardiovascular event were plaques classified as VH-TCFAs (fibroatheroma without evidence of a fibrous cap: > 10% confluent NC with > 30° NC abutting the lumen in at least three consecutive frames) with a plaque burden > 70% and a minimum lumen area < 4 mm^2 (Fig. 3) [39].

Table 3 Technical characteristics and detection capability of the described imaging techniques

	IVUS	OCT	VH-IVUS	NIRS
Technical characteristics				
Frequency (MHz)	20–45	NA	20–45	NA
Frame rate	10–30	100–160	10–30	NA
Pullback speed (mm/s)	0.5–1	20–40	0.5–1	0.5
Axial resolution (μm)	70–200	10–25	70–200	NA
Tissue penetration (mm)	> 5	1–2	> 5	1–2
Ease of use	+++	++	++	++
Need for contrast	No	Yes	No	No
Detection capability				
Lipid/necrotic core	+	++	++	+++
Fibrous cap	+	+++	+++	No
Thrombus	+	++	No	No
Calcium	+++	++	+++	No
Plaque rupture	++	+++	No	No
Attenuated plaque	+++	No	No	No
TCFA (thin-cap fibroatheroma)	No	+++	++	+
Dissection	++	+++	No	No
Stent expansion/ apposition	++	+++	No	No
Stent strut coverage	+	+++	+	No

NA, not applicable; IVUS, intravascular ultrasound; OCT, optical coherence tomography; VH-IVUS, virtual histology intravascular ultrasound; NIRS, near-infrared spectroscopy.
Low capability (+), moderate capability (++), high capability (+++).

Similarly, the VIVA study was a prospective analysis of 170 patients with stable angina or ACS who underwent three-vessel VH-IVUS before and after PCI. At a median of 1.7 years, 19 lesions (13 nonculprit and 6 culprit) resulted in MACE (death, MI, unplanned revascularization). Nonculprit lesion factors associated with nonrestenotic MACE were VH-IVUS thin-capped fibroatheroma (TCFA) and plaque burden > 70% TCFA, plaque burden > 70% and minimum lumen area < 4 mm^2 were linked with total MACE, suggesting that VH-IVUS can identify plaques at an increased risk of subsequent events [40].

Other VH-IVUS data suggested that coronary atherosclerotic plaques with thrombus have very similar compositional characteristics as assessed with grey scale and especially VH-IVUS regardless of whether the angioscopic images showed plaque

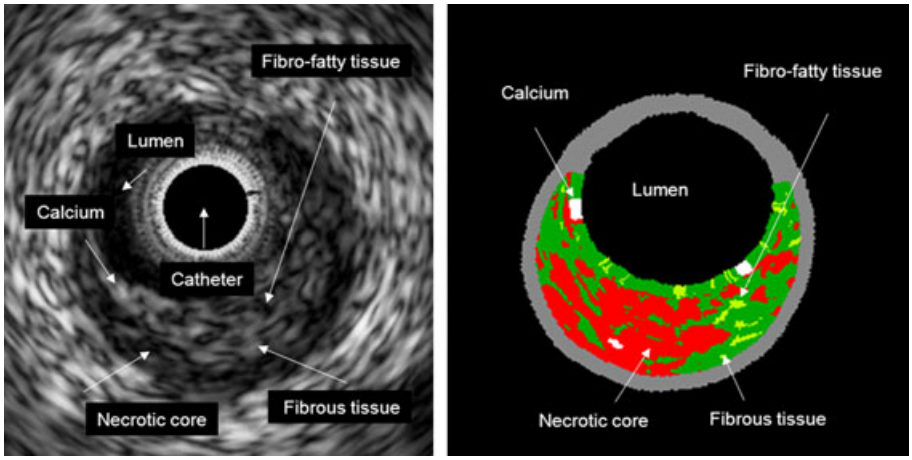

Figure 2 Grey-scale and virtual histology intravascular ultrasound (VH-IVUS) imaging correlation. These two cross-sectional frames depict the same arterial location and allow visualization of a significant eccentric atherosclerotic plaque. Grey scale and intravascular ultrasound (IVUS, left) can easily identify lumen and plaque borders, but virtual histology VH-IVUS (right) provides additional information regarding the compositional plaque characteristics.

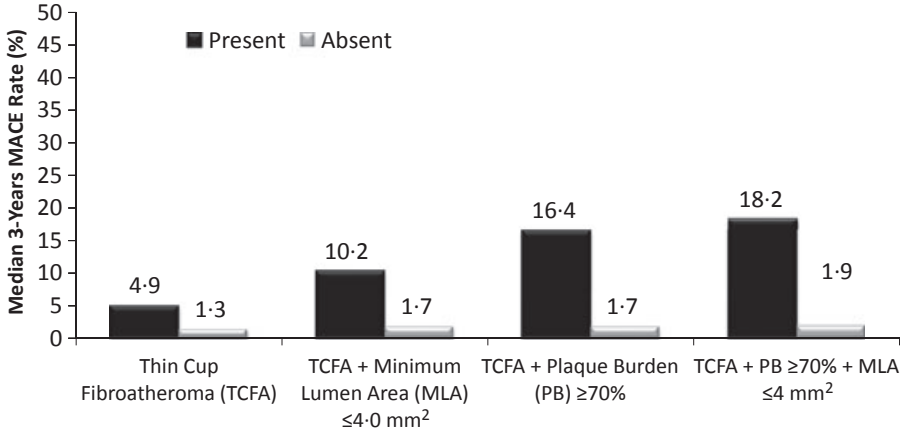

Figure 3 Data from the PROSPECT trial. VH-TCFAs and nonculprit lesion–related events. The combination of large plaque burden (IVUS), small lumen area and a large necrotic core without a visible cap (VH-TCFA) can identify lesions that are at especially high risk for future adverse cardiovascular events.

rupture or absence of plaque rupture. Similarity of VH-IVUS plaque composition (percentage NC and percentage VH-TCFA) in lesions with or without plaque rupture implies a spectrum of underlying morphologies to explain thrombosis in the absence of a ruptured plaque including classic erosions, small (and undetectable) plaque ruptures and potentially unruptured TCFAs with superimposed thrombosis [41].

Controversies exist regarding the association between plaque composition and distal embolization phenomenon after PCI. A large meta-analysis including sixteen studies of 1697 patients using IVUS and VH-IVUS data showed that the plaque volume and the necrotic core are closely related to this phenomenon [42].

Human coronary atherosclerosis is a dynamic process with potential for the replacement of fibrous tissue by necrotic core. VH-IVUS proved to be beneficial in assessing these intraplaque compositional changes and the outcome of pharmacological treatment. The results of the multicentre IBIS-2 trial showed that prolonged pharmacological inhibition halted this process by stabilizing the increase in necrotic core compared to the placebo group, indicating a direct effect on human atheroma. Regarding the course of coronary plaque regression by statin therapy, another VH-IVUS analysis showed that plaques began to reduce the volume of fibrofatty and fibrous components in the early phase, associated with a transiently increased necrotic core component. Furthermore, even in the case of plaque progression, statins caused a reduction in the necrotic core. However, statin therapy did not halt the incidence in plaque vulnerability [43–45].

Virtual histology intravascular ultrasound may be also useful in the assessment of complex lesions. A comparison of the distribution of necrotic core in coronary bifurcations showed that bifurcation lesions appear to have a larger plaque burden with a more vulnerable plaque composition compared to nonbifurcation lesions [46].

However, other recent data in small cohorts demonstrate that physiologic lesion assessment with FFR does not correlate beyond plaque burden with plaque composition or lesion phenotype as assessed by VH-IVUS [47].

In conclusion, although VH-IVUS is an excellent research tool, there are currently no robust data supporting its routine use in PCI.

Optical coherence tomography

Optical coherence tomography is an optical analogue of IVUS using instead of ultrasound the back-reflection of near-infrared light from optical interfaces in tissue in order to create cross-sectional images. It has a microscopic resolution of 10 μm with a high frame rate up to 160 frames/s and allows real-time intracoronary imaging during high-speed pullback in a range between 5 and 40 mm/s (usually at 20 mm/s), based on the available OCT system. Because light cannot penetrate through a blood field, the acquisition of an OCT image sequence requires a bolus of crystalloid solution (mainly contrast) injected through the guiding catheter in order to clear or flush the blood from the lumen [48]. Despite this disadvantage, OCT has a pronounced ability to assess coronary microstructure; address luminal areas; measure neointimal volume; determine the patterns of proliferation; quantify endothelialization to monitor antiplatelet therapy; and guide everyday PCI procedures [48,49]. A typical example of OCT imaging is shown in Fig. 4.

Due to its accuracy in the detection of superficial plaque components, the high resolution of OCT can identify thin fibrous cap and directly measure the fibrous cap thickness clearly even if it is < 100 μm. Thus, it has the ability to identify thin-cap fibroatheromas (TCFAs), which are considered to be the precursor lesion of plaque rupture defined as plaques with fibrous cap < 65 μm thick. OCT allows us to recognize plaque ruptures, fibrous cap erosions, intracoronary thrombus and TCFA *in vivo* more frequently compared to other invasive imaging techniques [50]. Moreover, OCT estimates the area of calcification more accurate than those by IVUS and it might be a better clinical tool to quantify calcified plaque and calcium thickness [51].

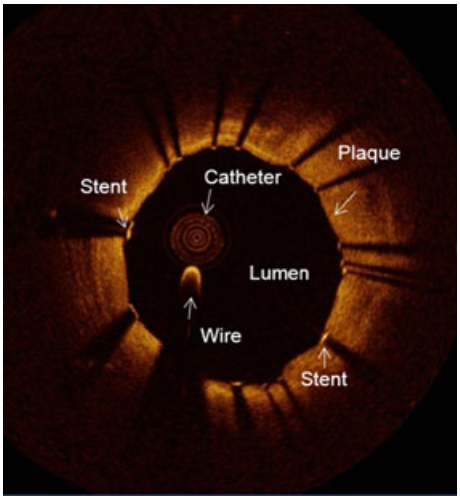

Figure 4 OCT imaging. Intracoronary imaging with OCT following poststent implantation. Arrows indicate the different structures identified. The high resolution allows an excellent view of the lumen and the stent struts. Conversely, the poor penetration compromises the ability to see the extent of the plaque towards the vessel wall.

Recently, it was shown by OCT that in acute coronary syndromes, culprit ruptured plaques are not uniformly distributed throughout the coronary tree, but seem to be predominately located in the proximal segments of the coronary arteries. Also, the morphology of culprit plaques seems to differ throughout the coronary arteries [52]. OCT is useful to predict procedural-related PCI complications including slow flow, microvascular obstruction and side branch occlusion after main branch stenting. In patients with STEMI, TIMI-3 flow after thrombolysis is associated with the morphological characteristics of the culprit lesion as determined by OCT [53]. Independent predictors of periprocedural MI as those identified by OCT are TCFAs, ruptured and attenuated plaques, intrastent thrombus and intrastent dissection [54–56]. By imaging, TCFAs and microthrombi OCT can also predict microvascular obstruction after PCI. In a study from Japan, 83 patients with ACS were examined by OCT to investigate whether OCT could predict no reflow after PCI. OCT-TCFAs were more common in the no-reflow group than in the normal reflow group. The frequency of no reflow and deterioration of final TIMI blush increased according to the arc of lipid [57].

Optical coherence tomography can also predict plaque progression. Researchers used OCT to evaluate morphological characteristics of nonsignificant coronary plaques that develop rapid progression in 53 patients with coronary artery disease. Plaque progression was defined as an increase in MLD of > 0.4 mm on QCA during 7-month follow-up. OCT-based complex characteristics of TCFA, microchannels and fibrous cap disruption revealed by OCT were the potential predictors of subsequent plaque progression. Based on these findings, these lesion characteristics discoverable by OCT such as TCFAs, fibrous cap disruption and macrophage infiltration might be inappropriate for stent-edge landing zone [58].

Intracoronary OCT is an excellent tool to assess the delicate stent strut, vessel wall interaction, healing process, neointimal coverage and structural changes in the bioabsorbable vascular stent scaffolds over time, because light can usually penetrate nonmetallic materials [59]. While the lumen area decreased from baseline to 6 months' follow-up by 25%, total loss in lumen area over 24 months was 11%. More than a third of stent struts were completely absorbed and were morphologically not discernible from the vessel wall. The remaining visible stent

struts were virtually all apposed against the vessel wall. All struts showed complete tissue coverage [60]. A more recent study using again bioabsorbable scaffolds showed excellent stent strut coverage through time and minimal late stent malapposition [61]. Of note, the introduction of these platforms for the treatment of coronary artery disease has prompted the re-evaluation of the edge vascular response, one of the predisposing factors for in-segment restenosis (stent and 5-mm proximal and distal margins) and ST. The OCT-based assessment of the edge vascular response showed proximal edge lumen loss; however, larger cohorts are needed to validate these preliminary results [62].

Neoatherosclerosis is a recently described complication, which may happen after DES or BMS implantation. It is defined as atherosclerosis developing within the neointima of a stent. Although relatively rare, its presence is related to the occurrence of stent restenosis and thrombosis; actually, it might be a common pathway but its predictors are not well established yet. It occurs earlier in DES (18–24 months) than it occurs in BMS (4–5 years). Moreover, it appears with greater frequency in all types of DES than in BMS although most of the current data come from first-generation DES. Neoatherosclerosis can present as either late ISR (late catch-up, especially as ACS) or VLST and may be responsible for the majority of very late DES thrombosis and is best detected using OCT [63].

Bottom line, OCT can be safely performed for the evaluation of vulnerable plaques such as plaque rupture, erosion and superimposed thrombus. In general, it discloses more additional procedural information such as dissections, stent apposition and edge-related problems not recognized by angiography. Moreover, observational data have supported that on top of angiography during PCI, OCT is potentially associated with increased clinical benefit [64]. Chronic DES evaluation including strut coverage, subclinical thrombus and neoatherosclerosis is promising but needs prospective evaluation for clinical implication. Some of the OCT limitations are as follows: it cannot able to penetrate red thrombus, the flow must be re-established before imaging, thrombectomy prior to the examination affects the findings regarding neoatherosclerosis, and finally, stent measurements are not the same as with IVUS. Quantitative appraisal seems to be consistent with IVUS but needs more practical experience to establish OCT-guided stenting. Further blinded trials should be encouraged in order to better clarify the correlation of uncovered stent struts with ST. In the meantime, ongoing interventional OCT studies are already evaluating the potential benefits of novel stent technology.

Near-infrared spectroscopy

Near-infrared spectroscopy is an imaging modality created to identify in vivo the chemical composition of an atherosclerotic plaque. Infrared region is the most reliable for the documentation of complex molecules because each bond vibration contributes to a fingerprint of the molecule. Identification of a lipid core plaque is based on the distinction of cholesterol spectral features differentiating cholesterol from the other chemicals present and especially collagen. This method has an estimated sensitivity and specificity validated in human coronary autopsy specimens more than 85% *ex vivo* [65,66].

The near-infrared spectroscopy (NIRS) system provides real-time chemical measurements in the coronaries. It includes a console, a pullback motor unit, a rotation device and a catheter that automatically scans the artery like IVUS. Spectra were processed by algorithm and displayed as a chemical image of lipid-rich plaque probability (called the 'chemogram'), which is depicted as yellow. The system acquires 1000 measurements/12.5 mm, and each measurement interrogates 1–2 mm^2 of lumen [65]. The newly available LipiScan IVUS (InfraReDx, Inc., Burlington, MA, USA) combines a 40-MHz rotational IVUS imaging system along with the NIRS advanced technology. This allows a complete visualization of coronary structure and plaque morphology together with a detailed chemical map of the vessel for the simultaneous detection and localization of lipid core plaques (LCP) [67].

Near-infrared spectroscopy is highly accurate to detect LCP in human coronary arteries. It shows the existence and distribution of necrotic core, but not the amount nor the fibrous cap thickness. Increasing evidence is accumulating linking a lipid core plaque to vulnerable plaque, lesions at risk for embolization and ST [68]. Of interest, the first results of the single-centre, prospective and randomized YELLOW trial in patients with multivessel disease showed that aggressive statin therapy reduces the lipid composition of significant atherosclerotic plaques, as those were determined by NIRS potentially contributing to stabilization [69].

As part of a continuing goal to improve the understanding of coronary artery disease and the effect of LCP, the COLOR has been established and is currently enrolling patients. The COLOR (Chemometric Observation of LCP of Interest in Native Coronary Arteries Registry) is a prospective, multicentre observational study of patients undergoing near-infrared spectroscopy. A primary objective of the registry is to help better understand the linkage between NIR signals indicating the presence of a lipid-rich plaque and subsequent coronary events. Initial findings indicate that the absence of LCP is associated with a good prognosis, while a yellow plaque is associated with subsequent events. The COLOR is also expected to provide additional information about the relationship between LCP and the complications of stenting [70].

The CANARY (Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow) study is a pivotal trial to evaluate criteria for defining a LCP that is at high risk of

rupturing during standard-of-care therapy and causing intra-procedural complications such as distal embolization. This study is designed to evaluate the relationship between coronary plaque composition and small embolic particles during coronary stent implantation. Hypothetically, if plaques that require treatment are at higher-than-normal risk of causing these kinds of events, even life-threatening, precautionary measures should be applied to mitigate the risk or result of a complication [71].

Prospective and therapeutic studies are required in order to validate these observations and then maybe establish a cut-off value regarding the amount of the significant lipid core that can lead to future events.

Fractional flow reserve

Physiologic measurement of coronary flow and perfusion plays a major role in the management of patients with coronary artery disease. Fractional flow reserve is defined as the maximum achievable blood flow in the presence of a stenosis divided by maximum flow in that same distribution as it would be if the supplying artery was normal. FFR can be calculated by pressure measurements in the coronary circulation under maximum hyperaemia using a pressure wire. Theoretically, normal FFR equals 1.0 for any vessel. FFR has been extensively validated against noninvasive ischaemia testing and discriminates ischaemic and nonischaemic lesions with an accuracy of 95% [72].

Performing PCI on all angiographically identified stenoses, regardless of their potential to induce ischaemia, reduces the benefit of relieving ischaemia by exposing the patient to an increased stent-related risk, whereas systematic measurement of FFR can maximize the benefit of PCI by accurately discriminating the lesions for which revascularization will provide the most benefit from those for which PCI may only increase the risk [73]. Only ischaemia-driven revascularization has been shown to improve the rate of survival and decrease the risk of myocardial infarction among high-risk patients with an ACS. Routine measurement of FFR in patients with multivessel coronary artery disease defers safely nonischaemic lesions and reduces significantly the rate of the composite end point of death, nonfatal myocardial infarction and repeat revascularization at 1 year after PCI with DES. In addition, in patients with stable coronary artery disease and functionally significant stenoses, FFR-guided PCI plus the best available medical therapy as compared with the best available medical therapy alone resulted in significantly improved clinical outcomes. This improvement was driven by a dramatic decrease in the need for urgent revascularization. In patients with functionally nonsignificant stenoses, medical therapy alone resulted in an excellent outcome regardless of the angiographic appearance of the stenosis [10,11].

Hence, functional assessment is of paramount importance before revascularization. The ongoing randomized prospective FAME 3 trial is currently enrolling patients with three-vessel disease amenable to FFR-guided PCI and revascularization with DES or coronary artery bypass grafting (CABG). An FFR value < 0.80 defers patients from any kind of interventional treatment [74].

Assessment of stenosis severity with FFR requires that coronary resistance is stable and minimized. This is usually achieved by the administration of pharmacological agents such as adenosine. The instantaneous wave-free ratio (iFR) has been recently introduced as the instantaneous pressure ratio across a stenosis during the wave-free period when resistance is naturally constant and minimized in the cardiac cycle. It follows similar methodology as FFR performed by the standard pressure wire, but without the need of adenosine-induced hyperaemia and with the same high reproducibility and diagnostic efficiency with FFR [75,76]. The iFR concept challenges the dogma that 'maximal hyperaemia' is always needed for stenosis assessment. The first results from the RESOLVE multicentre international study showed that 57% of 1539 patients spared from adenosine, maintaining a 94% of overall classification agreement with FFR. Also, the iFR threshold for an FFR value < 0.80 is 0.9 [77]. Likewise, the DEFINE is a prospective, randomized study that intends to clarify whether disagreement in the adenosine zone is clinically meaningful. Additionally, the upcoming ADVISE 2 study will further explore the relationship between iFR and other haemodynamic indices [78].

Fractional flow reserve constitutes the method of choice for functional assessment of coronary stenoses. PCI guidance with FFR defers patients, nonischaemic lesions and disease treatment contributing to improved clinical outcome. The relationship between morphological lesion characteristics and functional significance (FFR < 0.80) is an evolving field or research requiring prospective clinical validation. Of interest, innovations in the physiology space when used with modern wires can help not only to assess but to monitor distal physiology throughout the procedure and easily document before and after intervention.

Future prospective

To date, several different modalities have been proposed regarding the three-dimensional (3D) reconstruction of the coronary arteries integrating angiographic and IVUS data. These methods are mainly based on the fusion of data obtained by biplane angiography and IVUS using a segmentation algorithm for the detection of the regions of interest in IVUS images and a new methodology for the extraction of the catheter path from angiographic images. All of them can provide

rapid coronary reconstruction allowing accurate estimation of lesion dimensions and determination of plaque distribution and volume. Similarly, 3D OCT is a novel technique enabling 3D imaging of the intracoronary lumen [79–81].

Recently, another RF-based processing method has been presented for in vivo coronary plaque tissue characterization, the i-MAP-IVUS (Boston Scientific). From methodological point of view, this software is comparable to the VH-IVUS system; however, there are differences, such as the applied colour scheme: (i) fibrous tissue (light green), (ii) lipid tissue (yellow), (iii) necrotic core (pink) and (iv) calcium (blue). Furthermore, the applied IVUS catheter is the 40-MHz rotating single-element catheter instead of the 20-MHz mechanical one used with VH-IVUS. *Ex vivo* validation demonstrated accuracies at the highest level of confidence as 97%, 98%, 95% and 98% for necrotic, lipid, fibrotic and calcified regions, respectively [82,83].

Elastography is another IVUS-based method that has been used to assess the deformation of plaques through the changes in intracoronary pressure that occur during the cardiac cycle, reflecting the mechanical properties of the vessel wall. This technique can characterize the softness of plaques, which might be a sign of vulnerability prior to rupture [84]. Of interest, IVUS has also been used to study shear stress produced by coronary artery blood flow, which may explain the localization of early plaque, TCFAs and culprit lesions. The technique uses 3D images of the vessel and computational fluid dynamics to calculate the force directed along the endothelial surface of the vessel wall resulting from the friction associated with blood flow. Plaque formation is more likely to originate at sites that have lower shear stress which predisposes to inflammation and endothelial dysfunction [85]. Furthermore, contrast-enhanced IVUS (CE-IVUS) after the injection of microbubbles has the potential to detect the vasa vasorum present in advanced -plaques that might be an additional feature of vulnerable plaques [86].

Chemically specific optical absorption spectra can be used for tissue identification in ultrasonic imaging of atherosclerosis. Recent experimental developments using a combined IVUS/photoacoustics imaging system indicate that sound and light is the way to go for the diagnosis of vulnerable plaque. This hybrid imaging technique combines the advantages of high spatial resolution of ultrasound with contrast of optical absorption. Photoacoustic imaging can distinguish the major lipid components of atherosclerotic plaques and also differentiate between lipids present in atherosclerotic plaques from lipids present in peri-adventitial tissue [87,88].

The utility of a combined approach based on the use of OCT and VH-IVUS has been recently proposed to better characterize deep lesion components. Possibly, in the near future, a real-time application of OCT algorithms able to characterize plaque components and identify local signs of inflammation will facilitate OCT detection of plaque vulnerability [89,90].

Additional efforts may include the development of a magnetic resonance catheter–based system that can identify lipid-rich tissue or even imaging catheters able to measure thermal gradients associated with inflammation in the coronary arteries. An ideal futuristic concept involves the potential use of a single catheter and pullback with the fusion of NIRS-IVUS in 3D. Finally, molecular imaging agents may enhance the identification of specific molecular processes within the plaques [91–93].

Limitations

Despite the profound advantages of all the above methods in the assessment of atherosclerosis *in vivo*, their major limitation is mainly related to the fact that they are invasive. In order to provide their unique information, it is mandatory to be held in a cath laboratory setting under experienced operators and stuff. Although the rate of procedural complications remains low (1%), it still exists. It includes a wide variety of related pitfalls including mainly vasospasm and less often dissections, perforations and induced arrhythmias. Prolonged radiation exposure and increased contrast usage should be also taken into consideration. From technical point of view, the need to catheterize each vessel individually is also a matter of time and concern and relies always to the experience and skills of the interventional cardiologist. Anatomically speaking, another restriction is related to their limited capability of imaging small-diameter vessels and aorto-ostial lesions. In addition, as with any visualization modality, certain artefacts may occur such as the ring down, geometric distortion effect, blood speckle, nonuniform rotational distortion or even broken catheters and devices. Another major concern is that image analysis should be always performed by experts with obtained training in the field; otherwise, it might lead to an inaccurate and misleading interpretation and in a not favourable outcome. Last but not least, the high cost of these machines and catheters and the occasionally limited availability of each product due to approval or distribution issues remain a restriction to their worldwide spread.

The aforementioned limitations underlie some of the reasons that these modalities are not yet routinely used in clinical practice and have currently a partial but vital adjunctive role to angiography. However, the future is likely to reveal an increase in its use among cardiologists, particularly in the interventional arena. Recent specialized modifications, such as novel hybrid and integrated built-up systems, enhanced image resolution softwares, the use of 3-D reconstructed images, the analysis of radiofrequency backscatter data, the use of automated detection techniques and the development of this knowledge, may all help expanding their clinical use.

Conclusions

The current literature review indicates that there is no single modality able to identify all the relevant characteristics of coronary plaques leading to cardiovascular events. Evidently, the use of FFR is the best way to determine whether PCI are indicated, while the use of IVUS or OCT can further optimize results and clinical outcomes. The contemporary interventional anatomy and physiology coronary applications need to offer incremental clinical benefit balancing along with reasonable cost to be considered successful. Apparently, the most appropriate way to answer each clinical question raised is to choose the right modality for each patient just as in the rest of medicine.

Disclosures

None related to the manuscript.

Address

Cardiovascular Research Foundation, 111 East 59th street 12 floor, 10022 New York, NY, USA
(E. Sanidas); Mount Sinai Medical Center, 111 East 59th street 11 floor, 10022 New York, NY, USA (G. Dangas).
Correspondence to: George Dangas, MD, PhD, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1030, New York, NY 10029-6574, USA. Tel.: 212-241-7014; fax: 212-241-0273; e-mail: george.dangas@mountsinai.org

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