Interpretation of Coronary Artery Disease with Intravascular Ultrasound

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Abstract

The fact that coronary angiography has limitations in terms of precise estimation of atherosclerosis has been partially overcome during the last years by the use of new imaging techniques. Intravascular ultrasound (IVUS) is currently the gold-standard technique for the assessment of the morphology of coronary arteries and atherosclerotic plaques in vivo and an irreplaceable guiding tool for interventional procedures. This chapter summarizes the basic principles along with some newer perspectives of this methodology and evidently highlights not only the use in clinical practice but also the contribution in clinical outcomes.

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Keyword

Atherosclerosis • Coronary angiography • Intravascular ultrasound (IVUS) • Drug eluting stents (DES) • Technical characteristics and detection capability • Basic measurements

Abbreviations

CAD	Coronary artery disease
FFR	Fractional flow reserve
IVUS	Intravascular ultrasound
MI	Myocardial infarction
MLA	Minimum lumen area
NIRS	Near infrared streptoscopy
OCT	Optical computed tomography
RF	Radiofrequency
VH-IVUS	Virtual histology intravascular ultrasound

Key Facts

- Cardiovascular diseases account for approximately more than one third of all deaths worldwide. Atherosclerosis, a disease of the vessel wall, is the major cause of cardiovascular diseases such as heart attack or stroke.
- Most sudden deaths and myocardial infarctions occur from coronary thrombosis caused either by rupture of a thin fibrous cap or surface erosion in the absence of cap disruption.
- The thin-cap fibroatheroma (TCFA) is now regarded as the main type of rupture-prone and thrombosis-prone vulnerable plaque.
- A typical IVUS pullback contains more than 3000 consecutive cross-sectional frames of the examined coronary artery.
- The beneficial impact of intravascular ultrasound (IVUS)-guided versus angiography-guided percutaneous coronary interventions with stent implantation is well established.
- 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.

Dictionary of Terms

IVUS An interventional imaging modality using ultrasound to obtain real time images of the coronary and other vessels of human body.

IVUS pullback The acquisition of an IVUS sequence consists of inserting an ultrasound emitter, carried by a catheter, into the arterial vessel and pulling the probe from the distal to the proximal position (pullback).

Image resolution Transducers with ultrasound frequencies ranging between 20–50 MHz are used (usually 40 MHz). High frequencies provide excellent theoretical resolution, as the ultrasound wavelength that determines the maximum resolution is inversely proportional to frequency.

VH-IVUS A special software that analyzes the unfiltered backscattered IVUS signal mapping with designated colors different tissue components.

Palpography An alternative method of processing the radiofrequency signal for the determination of the elastic properties of plaques that are susceptible to rupture. This method evaluates the local mechanical properties of the tissue using the distortion caused by intraluminal pressure.

CE-IVUS The use of conventional gray scale IVUS with the injection of contrast agents (microbubbles) to record qualitatively and quantitatively the flow of microbubbles in human atherosclerotic plaques, mainly within the microvessels and neovasculature.

VH-TCFA A fibroatheroma without evidence of a fibrous cap: >10 % confluent NC with >30° NC abutting the lumen in at least 3 consecutive frames.

Introduction

In general, pathogenesis of coronary artery disease relates to the slow or rapid and substantial progression of atherosclerosis. Then again, ischemic 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 (Naghavi et al. 2003a, b; Ambrose et al. 1988; Ambrose and Dangas 2000; Fuster et al. 1992a, b; Virmani et al. 2000, 2006; Dangas et al. 1997).

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 which use ultrasound or

optics we are beginning to see beyond angiography (Ambrose and Dangas 2000; Ambrose et al. 1988; Fuster et al. 1992a, b; Virmani et al. 2000).

However, in patients with coronary artery disease, the most important factor with respect to outcome is the presence and extent of inducible ischemia. Treating ischemic lesions improves outcome, but treating nonischemic lesions affects the outcome in a negative way. In patients with stable coronary artery disease, physiologically guided percutaneous coronary intervention (PCI) improves patient outcome as compared with medical therapy alone. In patients with functionally nonsignificant stenoses medical therapy alone resulted in an excellent outcome, regardless of the angiographic appearance of the stenosis (Tonino et al. 2009; De Bruyne et al. 2012).

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

Intravascular Ultrasound (IVUS)

The first IVUS system was designed 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 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 (Mintz et al. 2001).

IVUS function is based on the general principles summarized in Table 1 (Sanidas et al. 2008). There are two types of IVUS systems for clinical use: the solid-state electronic phased array transducer and the mechanical single-element rotating transducer. The solid-state phased array transducer has 64 stationary transducer elements around the catheter tip that image at 20 MHz, and it is commercially available as the 5 F compatible Eagle Eye Catheter (Volcano Corp. Rancho Cordova, California). Benefits of the solid-state catheter include enhanced trackability due to the coaxial design and lack of nonuniform rotational distortion artifacts seen with rotational systems. Conversely, the 6 F 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, California) and the Revolution 45 MHz catheter (Volcano Corp., Rancho Cordova, California) (McDaniel et al. 2011).

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 less than 4.0 mm^2 in a proximal epicardial artery excluding left main is a flow-limiting stenosis (Abizaid et al. 1998; Nishioka et al. 1999; Takagi et al. 1999).

The advantage of IVUS guidance has 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 (Fitzgerald et al. 2000; Oemrawsingh et al. 2003). The MUSIC trial was

Table 1 General principles of 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 analyzed or stored

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 $\geq$0.7

MSA minimum stent area

the first study, followed by a sequence of many others later that established IVUS criteria for optimal stent implantation. According to the 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 (de Jaegere et al. 1998; Fitzgerald et al. 2000; Oemrawsingh et al. 2003; Russo et al. 2009).

A large meta-analysis of randomized trials compared IVUS versus angiographic guided BMS implantation and 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) (Parise et al. 2011).

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 like residual reference disease (geographic miss) and dissections, as well

as acute and especially late incomplete stent apposition (malapposition) (Choi et al. 2011, 2012; Fujii et al. 2005; Claessen et al. 2011).

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 comparing 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 was 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 remodeling (Chieffo et al. 2013).

Whether IVUS guidance reduces stent thrombosis (ST) and improves clinical outcomes associated with DES treatment considered to be controversial. Latest data suggest that IVUS-guided PCI reduce stent thrombosis 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, IVUS-guided DES implantation as compared with angiography guidance alone was associated with a reduced incidence of death, MACE, and stent thrombosis (Zhang et al. 2012).

Likewise, ADAPT-DES was a prospective, multicenter, real-world study of 8583 consecutive patients at 11 international centers undergoing DES implantation to determine the frequency, timing, and its correlation of early and late stent thrombosis. 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. This data drawn from the largest prospective registry of IVUS use to date suggests that IVUS guidance during DES PCI may result in less stent thrombosis beginning at the time of implantation as well as fewer myocardial infarctions (Witzenbichler et al. 2014).

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 is related in general with poorer prognosis. IVUS is very useful in distinguishing significant from insignificant left main disease, the distribution of plaque, and planning the appropriate treatment strategy (Oviedo et al. 2010).

By applying predefined IVUS criteria for the assessment of intermediate left main lesions De La Torre et al. showed that an IVUS-derived cutoff of 6 mm^2 can safely determine which intermediate left main lesions require revascularization (de la Torre Hernandez et al. 2011).

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

Table 3 Basic IVUS measurements

Parameter	Definition – calculation
Vessel diameter	The maximum diameter of the vessel
Lumen diameter	The maximum diameter of the lumen
Vessel area	The circle around the external elastic membrane
Lumen area	The circle around the lumen interface
Stent area	The circle around the stent struts
Plaque area	Vessel area – lumen area
Plaque burden	Vessel area – lumen area / vessel area × 100
Stenosis site	The site with the minimum lumen area
Proximal reference	All the above measurements within 5 mm proximal to a stenosis
Distal reference	All the above measurements within 5 mm distal to a stenosis
Positive remodeling	The enlargement of vessel area compared to proximal reference
Eccentricity	Maximum plaque diameter – minimum plaque diameter at the same frame

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 (Park et al. 2009).

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 (Rathore et al. 2010).

Different anatomical criteria should be used according to myocardial mass and/or anatomical 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 ischemia. Recently, an IVUS-derived MLA $\geq$ 2.4 mm^2 was proposed to exclude functionally significant disease, but below that cutoff, poor specificity limits its value for physiological assessment of lesions (Kang et al. 2011). This is due to the fact that MLA is vessel size dependent and better correlated in large-diameter vessels. The optimal MLA cutoff varies with regard to vessel location, vessel size, and lesion severity. Patients post MI and with reduced LV have higher cutoff MLA. Still, there is no single IVUS or optical coherence tomography (OCT) widely accepted criterion which can be used instead of physiological lesion assessment. All basic IVUS measurements are shown in Table 3 (Mintz et al. 2001). An example of IVUS assessment of an intermediate lesion in a current cath lab setting is given in Fig. 1.

Radiofrequency IVUS Data Analysis (VH-IVUS)

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-based – RF-based – signal). Depending on the

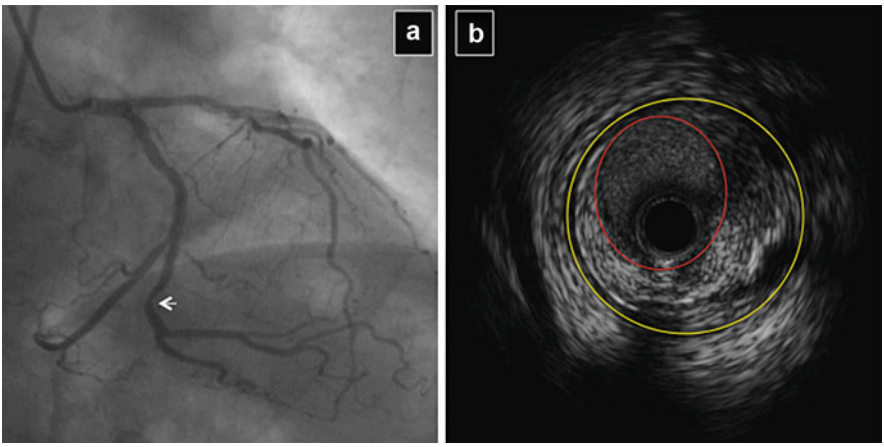

Fig. 1 Intravascular ultrasound assessment in the cath lab. An intermediate angiographic lesion located at the distal LCX (**a**). The minimum lumen area (MLA – *red circle*) measured by IVUS was 4.0 mm^2 and the plaque burden (*yellow circle*) 63 % (**b**)

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. 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 stand-alone software packages, for the analysis of patient data. Radiofrequency IVUS plaque components are color coded as dense calcium (white), necrotic core (red), fibrofatty (light green), and fibrous tissue (dark green) (Nair et al. 2007). Technical characteristics and detection capability of IVUS and VH-IVUS are mentioned in Table 4. A case of grayscale and VH-IVUS imaging correlation is shown in Fig. 2.

Ex vivo validation of VH images directly with the histopathology sections provided accuracies of up to 97 % (Garcia-Garcia et al. 2009; Nair et al. 2007). 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 (Nasu et al. 2006, 2008).

The PROSPECT trial tried to assess the natural history of atherosclerosis by studying 697 ACS patients after successful PCI of a culprit lesion under optimal medical therapy using angiography plus three-vessel imaging including grayscale and radiofrequency VH-IVUS. In ACS patients, 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 3 consecutive frames) with a plaque burden >70 % and a minimum lumen area <4 mm^2 (Stone et al. 2011).

Table 4 Technical characteristics and detection capability of IVUS and VH-IVUS

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

NA Not applicable
Low capability (+), moderate capability (++), high capability (+++)

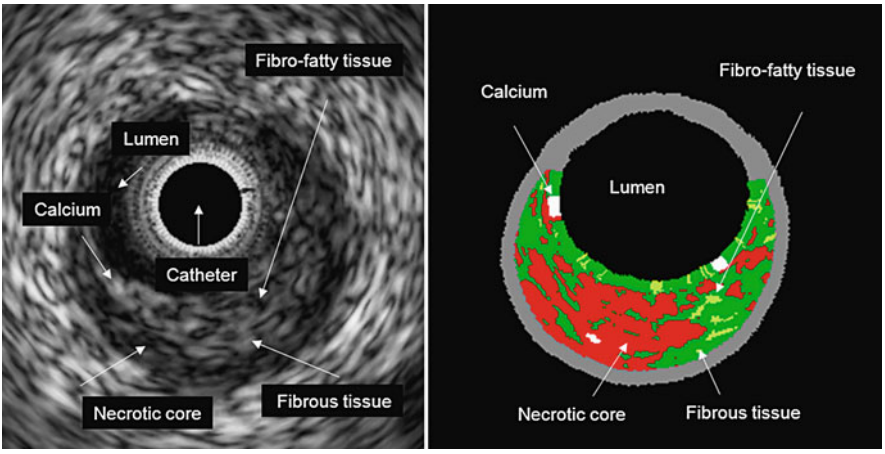

Fig. 2 Gray scale and VH-IVUS imaging correlation. These two cross sectional frames depict the same arterial location and allow visualization of a significant eccentric atherosclerotic plaque. Gray scale intravascular ultrasound (IVUS, *left*) can easily identify lumen and plaque borders but virtual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

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 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 increased risk of subsequent events (Calvert et al. 2011).

Other VH-IVUS data suggested that coronary atherosclerotic plaques with thrombus have very similar compositional characteristics as assessed with grayscale and especially VH-IVUS regardless of whether the angioscopic images showed plaque rupture or absence of plaque rupture. Similarity of VH-IVUS plaque composition (percent NC and percent 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 (Sanidas et al. 2011).

Controversies exist regarding the association between plaque composition and distal embolization phenomenon after PCI. A large meta-analysis including 16 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 (Jang et al. 2013).

Human coronary atherosclerosis is a dynamic process with potential for 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 multicenter IBIS-2 trial showed that prolonged pharmacological inhibition halted this process by stabilizing the increase of necrotic core comparing 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 (Serruys et al. 2008; Taguchi et al. 2013; Nozue et al. 2013).

VH-IVUS 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 (Garcia-Garcia et al. 2010).

However, other recent data in small cohorts demonstrate that physiological lesion assessment with fractional flow reserve (FFR) do not correlate beyond plaque burden to plaque composition or lesion phenotype as assessed by VH-IVUS (Brugaletta et al. 2012).

Despite the obvious advantages of IVUS-VH regarding the structure of the atheromatous plaque and its potential correlation to clinical end points, there are certain limitations. First, although IVUS-VH can discriminate between some of the

less echogenic components of the plaque (e.g., necrotic core and fibrofatty tissue), separating other soft plaque components, including thrombus, is not currently possible. Moreover, shadowing caused by dense calcific areas can adversely affect correct identification of plaque components. Second, with regard to TCFA identification, it is of note that IVUS-VH axial resolution does not exceed 150 μm and its spatial resolution is even lower (240 μm), while the histological definition of TCFA includes a fibrous cap of 65 μm or less, which means that IVUS-VH cannot accurately assess the thickness of the vulnerable fibroatheroma fibrous cap. Third, IVUS-VH cannot identify cellular components of the vulnerable plaque, such as T-cells and macrophages (Hartmann et al. 2009; Sawada et al. 2008).

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

Future Directions

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 (Gogas et al. 2013; Bourantas et al. 2008; Teeuwen et al. 2011).

Recently, another RF-based processing method has been presented for in vivo coronary plaque tissue characterization: the i-MAP-IVUS (Boston Scientific, Santa Clara, California). From a methodological point of view this software is comparable to the VH-IVUS system; however, there are differences, such as the applied color scheme: (1) Fibrous tissue (light green), (2) Lipid tissue (yellow), (3) Necrotic core (pink), and (4) 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 (Sathyanarayana et al. 2009; Garcia-Garcia et al. 2011).

Beyond the classic VH analysis that provides qualitative and quantitative information of the different plaque components in terms of their percentage and area (mm^2) within the plaque region, a novel approach has been also proposed. By post hoc analysis of VH-IVUS images, the computational quantification of new structural features of coronary plaques has been shown to provide new compositional and structural indices which indicate spatial distribution, heterogeneity, and dispersity of each VH-IVUS-derived component within the plaque area and also with respect to the plaque-lumen border (Papaioannou et al. 2014).

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 (Schaar et al. 2003).

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 (Malek et al. 1999). It has been also found that coronary artery wall shear stress is associated with the progression and transformation of atherosclerotic plaque and arterial remodeling in a prospective study of 20 patients with coronary artery disease (Samady et al. 2011). Also the combination of plaque burden, wall shear stress, and plaque phenotype – as assessed by VH-IVUS and 3-D artery geometry and blood flow profile – has incremental value for prediction of coronary atherosclerotic plaque progression and vulnerability (Corban et al. 2014).

Contrast-enhanced IVUS imaging (CE-IVUS) is a novel, yet clinically available, technique that has the potential to enhance IVUS-based in vivo characterization of atherosclerotic plaques by detecting the density of vasa vasorum and the neovasculature that nourish the plaque and the vessel wall. Recent evidence has suggested that the presence and proliferation of vasa vasorum neoangiogenesis in the plaque can be correlated to an increased inflammation process leading to plaque vulnerability. Based on this evidence, IVUS is used in combination with contrast agents (microbubbles) for the qualification and quantification of extraluminal blood perfusion which might be an indication of vasa vasorum. The method is supported by a custom-made software (Vavuranakis et al. 2007, 2008).

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 periadventitial tissue (Wang et al. 2012; Bourantas et al. 2013).

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. Finally, molecular imaging agents may enhance identification of specific molecular processes within the plaques (Stefanadis et al. 1999; Wilensky et al. 2006; Jaffer and Weissleder 2005).

Limitations

Despite the profound advantages of IVUS in the assessment of atherosclerosis in vivo their major limitation is mainly related to the fact that it is invasive. In order to provide their unique information it is mandatory to be held in a cath lab setting under experienced operators and staff. 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 under consideration. From a technical point of view the need to catheterize each vessel individually is also a matter of time and concern and relies always on 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 artifacts 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 inaccurate and misleading interpretation and in a not-favorable 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 remains a restriction to their worldwide spread.

Potential Applications to Prognosis, Other Diseases or Conditions

Among other applications, IVUS has evolved a niche role in assessing the proper deployment of stents at the conclusion of an endovascular intervention. The role of imaging modalities in the management of peripheral arterial disease (PAD) is crucial, with conventional digital subtraction angiography (DSA) considered the gold standard tool for the diagnostic assessment and endovascular treatment of PAD. IVUS has the ability to overcome several pitfalls of DSA. IVUS can image vessels in a cross-sectional plane and provide information regarding the morphology of the lesion and the vessel wall, precise cross-sectional measurements, and the location of important branch vessels. It also provides spatial relationships between a deployed stent and the vessel wall, including the adequacy of stent apposition.

Another recent advancement contributing to the accuracy of diagnosis of renovascular disease, namely renal stenosis and fibromuscular dysplasia (FMD), is the use of IVUS. IVUS gives a detailed understanding of the severity of the stenosis and assists in accurate sizing of balloons. Also, utilizing IVUS to evaluate restenosis after endovascular therapy for FMD can be extremely valuable.

The use of IVUS has also been expanded in endovascular venous procedures in order to identify the mechanisms of acute vein closure as well as incomplete stent apposition after intervention. It has been used on femoral, internal carotid,

subclavian, brachiocephalic, polpiteal veins and/or even vein grafts after bypass surgery. A potential limitation is that the absence of adjacent artery or anatomical landmarks is often not available or can be misleading. Nonetheless, IVUS and venography provide complementary data for diagnosis, sizing, results, and complications.

Finally, recent specialized modifications, such as novel hybrid and integrated built-up systems, enhanced image resolution software, 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 its clinical use.

Summary Points

- This chapter focuses on the interpretation of coronary artery disease with intravascular ultrasound (IVUS).
- Coronary angiography often underestimates the degree of intraluminal stenosis and does not gauge the size of the plaque itself.
- IVUS provides real-time, high-resolution images of the coronary arteries and unique insights of atherosclerotic plaque morphology such as size, eccentricity, and calcification.
- IVUS can be also used for a detailed evaluation of stent implantation by assessing lesion morphology, vessel size, lumen dimensions, apposition, and plaque distribution before and after stenting.
- Processing the IVUS radiofrequency signal using the VH-IVUS software offers a more precise tissue characterization of the composition of atherosclerotic plaques.

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