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INTRAVASCULAR IMAGING (E REGAR AND U LANDMESSER, SECTION EDITORS)

Development of Tissue Characterization Using Optical Coherence Tomography for Defining Coronary Plaque Morphology and the Vascular Responses After Coronary Stent Implantation

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Abstract Cardiovascular disease is associated with a high burden of mortality secondary to acute coronary events. Assessment for vulnerable plaque and an understanding of the etiology of stent failure by intravascular imaging may facilitate a greater understanding of the underlying processes responsible for adverse clinical outcomes and guide future therapy. This review focuses on the role of optical coherence tomography in tissue characterization and highlights future advances within the field providing potential enhancement of image interpretation.

Keywords Atherosclerosis · Optical coherence tomography · Vulnerable plaque

Introduction

Significant advances in atherosclerosis and particularly acute coronary syndrome (ACS) therapy have been made through enhanced noninvasive and invasive techniques for the investigation and treatment of coronary heart disease [1]. These advances have resulted in a reducing incidence of ACS [2], however, ACS remains the most common indication for percutaneous coronary intervention (PCI). Consequently, significant attention has been given to the identification of atherosclerotic plaques prone to future events.

The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial prospectively investigated 697 patients presenting with acute coronary syndrome and requiring PCI [3••]. The culprit lesions were treated by conventional PCI and then 3 vessel gray-scale and radiofrequency intravascular ultrasonographic imaging was performed. Patients were followed for a median 3.4 years and all major adverse cardiovascular events (MACE) were adjudicated to be related to the culprit or nonculprit lesions. A MACE rate of 20.4 % was observed at 3 years, with the majority of events relating to rehospitalization with unstable or progressive angina. Adverse events relating to the culprit or nonculprit lesions detected during the index intervention were observed in 12.9 % and 11.6 % of patients, respectively. As observed previously [4], the angiographic severity of nonculprit disease at baseline (32.3 %± 20.6 %) did not predict future events. However, event-related plaques were characterized by a plaque burden ≥70 %, a minimal lumen area ≤4 mm^2 and thin-cap fibroatheroma (TCFA) classified by radiofrequency intravascular ultrasonography (VH-IVUS).

Although the PROSPECT study has defined lesion specific characteristics of future vulnerability it is important to understand the limitations of the trial. Despite more than 50 % of all nonculprit events relating to TCFA, VH-IVUS identified more than 500 TCFAs within the entire cohort and only 26 were the site of recurrent events. This mismatch between the detection of high-risk plaque and event rate is most likely a reflection of the limited resolution of VH-IVUS (150–200 μm). TCFA were first identified as 'vulnerable' plaques in a cohort of sudden cardiac death patients [5]. The fibrous cap, overlying a lipid-rich core, measured less than 65 μm in 95 % of all patients with plaque rupture and therefore, 65 μm was selected as a marker of vulnerability. This definition far exceeds the resolution of IVUS and, consequently, the virtual-histology definition of TCFA, requiring necrotic core in contact with the lumen, can only detect plaque with a fibrous cap thickness < 150–200 μm. Optical coherence tomography (OCT) provides

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a significantly higher resolution (10 μm) therefore, has a clear advantage over VH-IVUS in the detection of TCFA and may facilitate improved characterization of plaque tissue components.

This review will outline the current and future status of OCT-derived tissue characterization in defining de novo plaque morphology and stent-related vascular responses.

Tissue Characterization Utilizing OCT

Yabushita and colleagues were the first to report objective OCT imaging criteria to differentiate tissue components of atherosclerotic plaque [6]. More than 300 arterial specimens (aorta, carotid bulb, and coronary tissue) were harvested from 90 cadavers, of which 48 had symptomatic cardiovascular disease. OCT imaging was undertaken within 72 hours of harvesting, at 37 °C, prior to formalin fixation and histologic processing. Examination of the OCT and histologic images facilitated the generation of distinct features for OCT characterization of fibrous, fibrocalcific, and lipid-rich areas. Fibrous tissue exhibited homogenous, highly backscattering (ie, signal-rich) plaque devoid of signal-poor areas. Fibrocalcific plaques revealed signal-poor regions with sharply delineated upper and/or lower borders, whilst lipid-rich plaques showed diffusely bordered, signal-poor regions. Overall agreement between OCT image criteria and the consensus histopathologic diagnosis was high (κ=0.83–0.84) and high levels of sensitivity and specificity were established with good intra- and inter-observer reliability.

Despite clearly defined qualitative OCT characteristics for most components of atherosclerotic tissue, limitations of OCT characterization have been encountered. Two major limitations have been reported; first, OCT's limited depth of penetration (1–2 mm in diseased segments) may mask deep tissue structures. Consequently, there is a risk of false positive generation of fibrous plaque and false negative classification of fibrocalcific and fibrolipidic plaques [7, 8]. Second, distinguishing well-delineated and diffuse/scattered transition zones within fibrous tissue can be challenging, thereby leading to misclassification of calcium or lipid [8]. The ambiguity of OCT imaging most likely reflects the heterogeneity of plaque composition and the frequently observed mixed composition of advanced plaque, containing calcium, necrotic core, and extracellular lipid pool. Consequently, simple classification of fibrous, calcific and lipidic tissue is not sufficient to provide accurate tissue characterization. Instead coronary plaque should be considered in terms of its morphology, rather than the individual components.

In defining plaque morphology it is important to understand the pathophysiology of atherosclerosis. Plaque development originates with adaptive intimal thickening, macrophage and foam cell deposition, lipid accumulation, inflammatory cell infiltration, and migration of smooth muscle cells into the intima [9]. More advanced atheroma exhibit a dense accumulation of extracellular lipid, inflammatory cells, cell death, an increase in fibrous connective tissue, calcification, and new vessels [10]. The American Heart Association (AHA) generated a schema to histologically classify atherosclerotic plaque according to its maturity/complexity (Table 1). Virmani and colleagues have subsequently reported their findings from postmortem studies of patients suffering sudden cardiac death and have suggested a modified classification providing clarity to the AHA definition of complex type VI lesions, and relevance to the clinical sequelae of disease progression/acute coronary events [11]. The modified classification focuses upon the progression of atherosclerotic plaque disease and presence of thrombus, indicating an acute event. Important emphasis is placed on the 3 most common events precipitating myocardial infarction: plaque rupture, plaque erosion and calcified nodule (Fig. 1). Consequently, it is clear that Yabushita et al's original tissue classification and the inherent limitations of characterization lack sufficient detail to accurately classify plaque. More recently, the international working group for intravascular OCT standardization and validation have generated definitions for qualitative image interpretation of intimal thickening, fibrous plaque, fibrocalcific plaque, necrotic core, fibroatheroma, TCFA, macrophage accumulations, intimal vasculature, cholesterol crystals, and thrombus [12••].

Intimal thickening and fibrous plaque demonstrate homogenous high backscatter. Extensive fibrotic plaque may obscure the normal trilaminar structure of the arterial wall and consequently interpretation of deep structures must be undertaken with a degree of caution. The extracellular matrix components of fibrotic plaque can exhibit variable signal intensity and it has been proposed that proteoglycans and type 3 collagen exhibit lower signal intensity. Fibrocalcific plaque is distinguished by clearly delineated areas of signal poor tissue with sharp borders, generated by the abrupt interface between fibrotic and calcific tissue. Extracellular lipid attenuates the light with minimal backscatter but deeper tissues may still be visualized. Necrotic core is characterized by a signal poor heterogeneous structure with a poorly delineated/diffuse margin and significant attenuation obscuring deep structures. The definition of an OCT TCFA is keenly debated, as the histopathologic definition of a fibrous cap thickness<65 μm includes a degree of tissue shrinkage incurred during tissue processing. Consequently, the fibrous cap thickness threshold in-vivo is likely to be higher, with one study suggesting a vulnerable plaque thickness<188 um [13]. The fibrous cap overlies necrotic core and some studies have included a criteria that the necrotic core should subtend an arc that is greater than 90°. Macrophage exhibit highly attenuating and scattering properties, consequently, they are characterized by

Table 1 AHA classification of vascular lesions—adapted from Lessons from Sudden Cardiac Death Virmani et al. [11]

AHA classification		Plaque type	Morphology	Maturity
Type 1 lesion		Initial lesion	Fatty dot or Fatty streak	Early
Type II lesion	IIa	Progression-prone		
	IIb	Progression-resistant		
Type III lesion		Intermediate lesion (pre-atheroma)		
Type IV lesion			Atheromatous plaque, fibrolipidic plaque, fibrous plaque	Advanced
Type V lesion	Va	Fibroatheroma		
	Vb	Calcific lesion	Calcified plaque	
	Vc	Fibrotic lesion	Fibrous plaque	
Type VI lesion		Lesion with surface defect ± hematoma ± thrombotic deposit	Complicated lesion/plaque	

small signal rich punctate lesions in the vessel wall and with deep attenuation that can inhibit deeper tissue characterization. Colocalization with necrotic core and calcification can make interpretation challenging. Intimal vessels are characterized by small sharply delineated signal-poor voids within intimal plaque and can be seen to extend through multiple

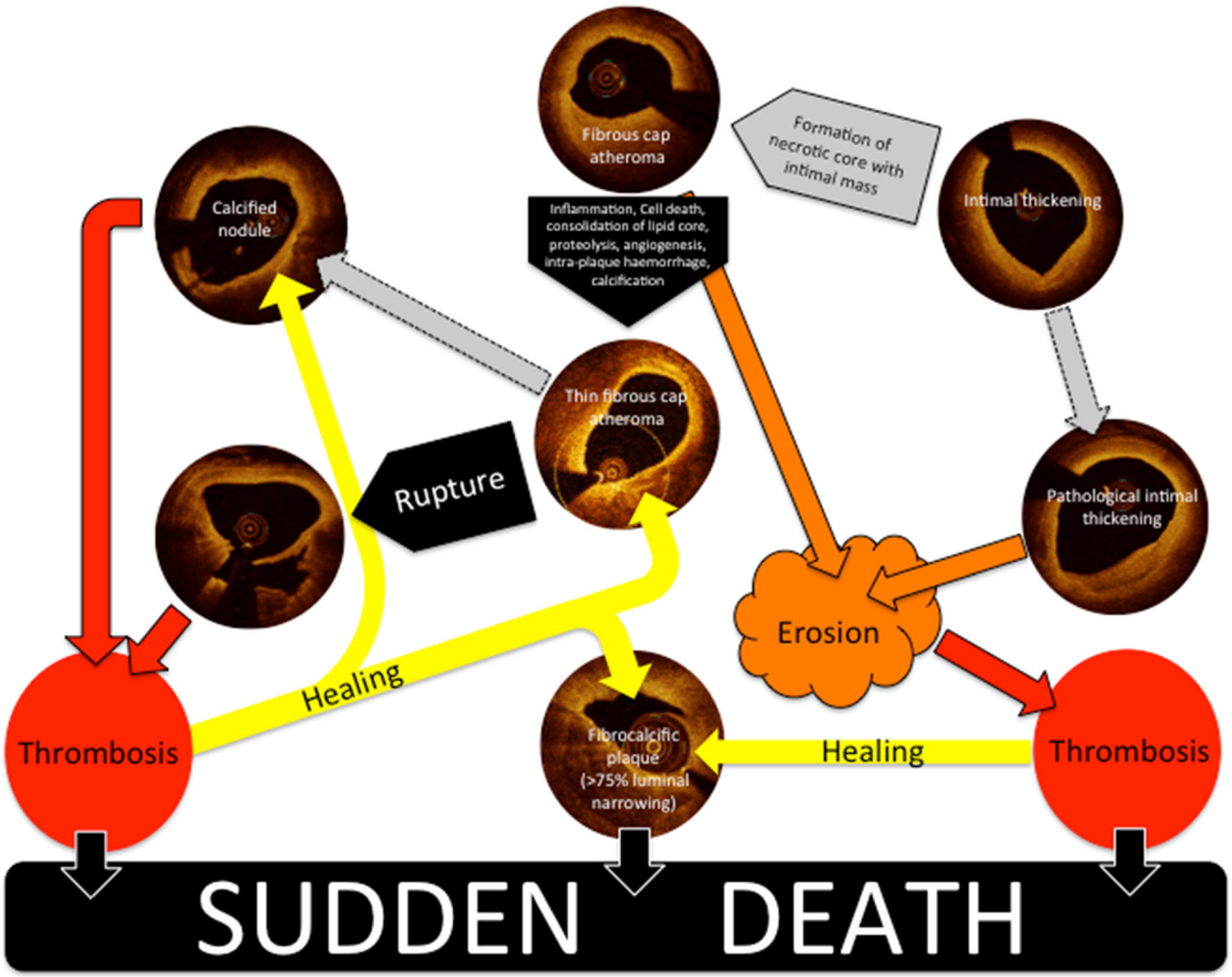

Fig. 1 A simplified scheme illustrating the development and progression of atherosclerotic lesions, with modification of the original AHA plaque definitions (adapted from Virmani et al. 11). Lesion types are depicted by OCT examples, with processes involved in plaque progression highlighted in the links between plaque types

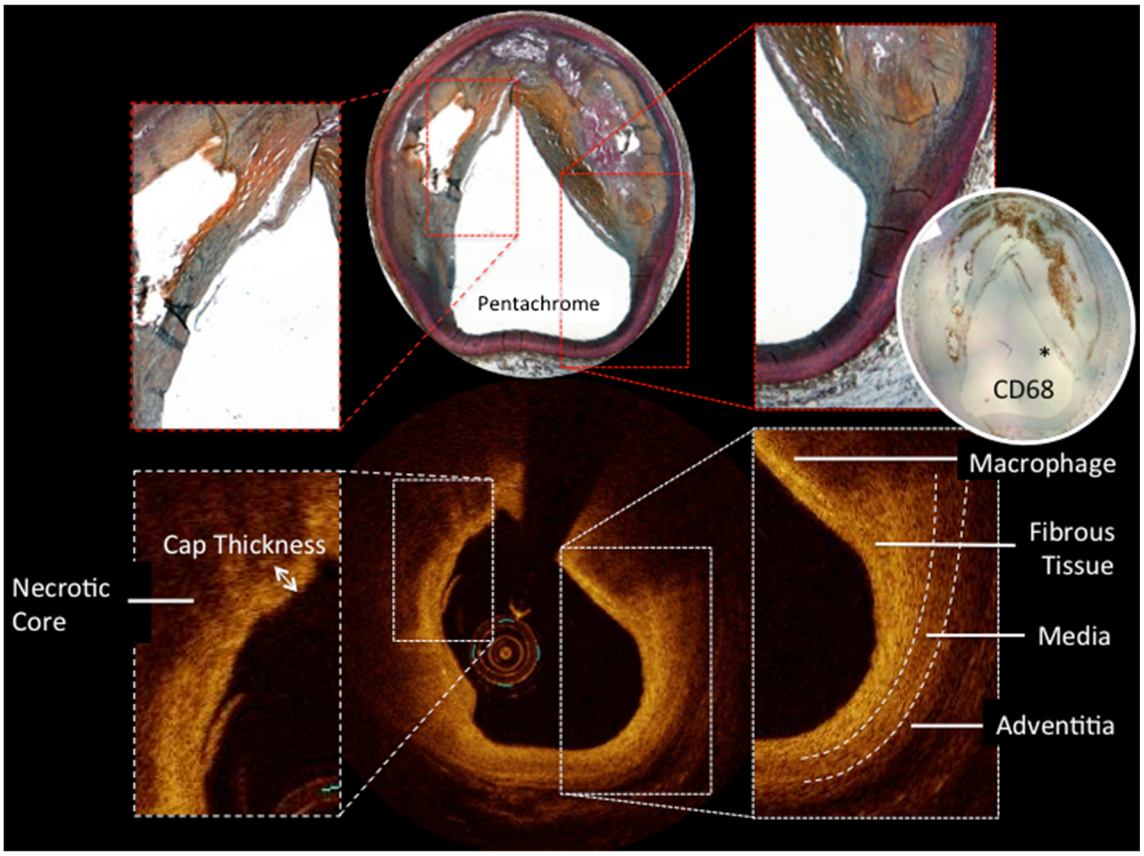

Fig. 2 Ex vivo OCT evaluation of an advanced atherosclerotic plaque matched with histology (pentachrome and CD68 macrophage staining) with evidence of thick-cap fibroatheroma, macrophage infiltration (brown stain on CD68 insert—asterisk denotes luminal macrophage infiltration highlighted on OCT image) and necrotic core

contiguous frames, often exiting into the lumen or adventitia. Cholesterol crystals are usually associated with fibrous cap or necrotic core and appear as thin high signal areas. Thrombus characterization by OCT is well-described, particularly the ability to differentiate between red and white thrombus. Red thrombus, containing an abundance of erythrocytes, is associated with high signal and high attenuation whereas the white thrombus, a platelet-rich tissue, has poor signal and low attenuation. Thrombi are usually visualized as a mass attached to the vessel wall or floating in the lumen. Figure 2 represents matched 'ex vivo' OCT and a histologic evaluation of an advanced atherosclerotic lesion, acquired from the Bristol Coronary Biobank, demonstrating many of the tissue components defined by the international working group (for a comprehensive review of matched OCT and histology imaging of atherosclerotic plaque development we would suggest referring to Otsuka and colleagues review article [14•].

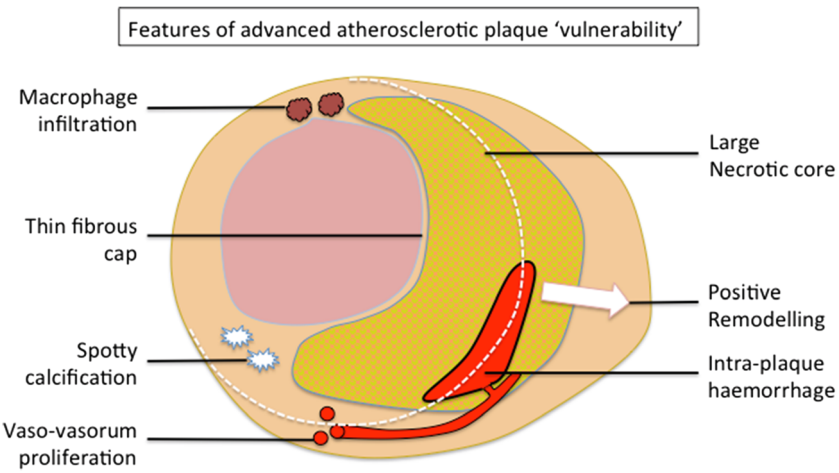

Fig. 3 A graphical representation of features of advanced atherosclerotic plaque 'vulnerability'

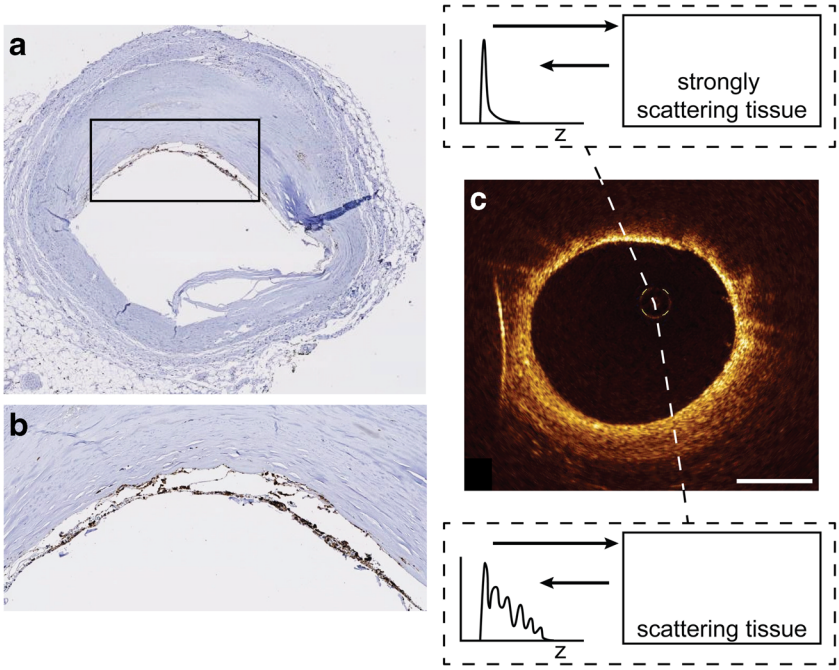

Fig. 4 An example of pseudo-thin capped fibroatheroma (TCFA). Panel A represents pathologic intimal thickening (human autopsy specimen), consisting of a thin layer of dense macrophage proliferation, magnified in Panel B (CD68 Immunohistochemistry with brown staining indicating macrophage). The matched OCT image (Panel C) shows a deep shadow cast by the macrophage layer, which obscures the fibrous material of the plaque and could lead to misinterpretation as a TCFA. The panels above and under the image show the decay of OCT signal as a function of depth z for fibrous tissue (mild scattering; bottom) and macrophages (strong scattering; top). The intensity in the OCT beam is depleted by strong attenuation and no information can be obtained on the tissue deeper in the wall

The modified AHA plaque classification and international working group for intravascular OCT definitions for qualitative OCT classification of plaque tissue components provide cardiologists an exciting opportunity to further our understanding of atherosclerosis pathophysiology. Defining plaque vulnerability remains a major goal and the high resolution of OCT and potential for accurate tissue/plaque characterization is providing new insights, even facilitating real-time assessment of a plaque event [15]. Numerous markers of vulnerability have been highlighted, including thin fibrous cap, large necrotic core, spotty calcification, macrophage infiltration, intra-plaque hemorrhage, vasa vasorum proliferation, and outward remodeling (Fig. 3) [16]. Despite the clear advantage of OCT over IVUS in defining fibrous cap thickness and cellular components of the plaque, the limitation of penetration depth significantly impacts on the ability to define plaque burden, an important parameter in defining future plaque events confirmed by the PROSPECT trial [3••].

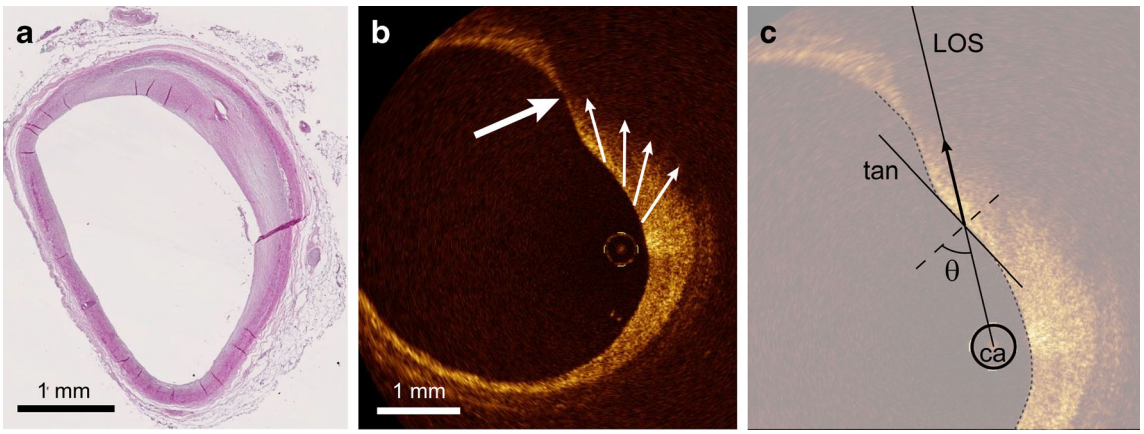

Fig. 5 A mild fibrous plaque (human autopsy specimen) imaged by hematoxylin and eosin stain in conventional histology (Panel A). When visualized by OCT (Panel B), a signal-poor region with diffuse borders appears (*large arrow*), which would be identified as a lipid-rich plaque according to tissue classification [6], and could be identified as a TCFA. The eccentricity of the catheter (CA) leads to a slanted line-of-sight (LOS; *small arrows* in B) and with low to moderate signal attenuation produces a signal-poor area for large angles of incidence θ (Panel C)

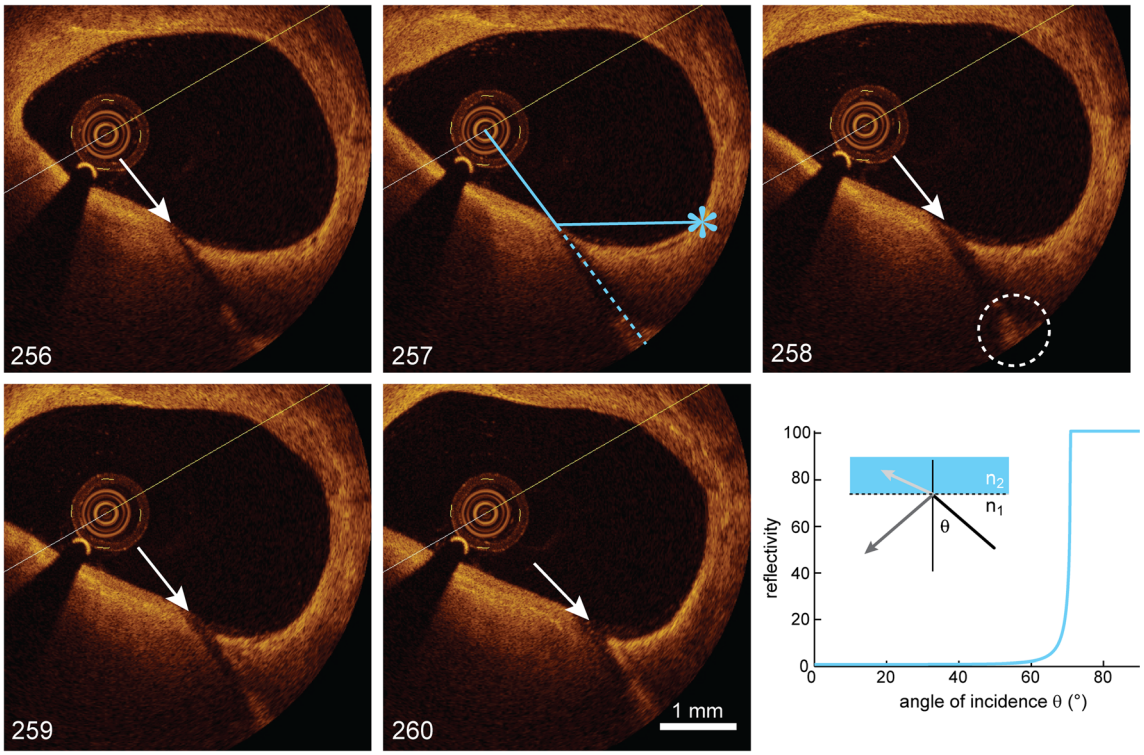

Fig. 6 An example of internal reflection of the OCT beam—a dark linear artifact appears in a series of frames, which may be interpreted as a rupture or a side branch. The artifact relates to total internal reflection of the OCT beam at a tissue interface for large angles of incidence 0, as illustrated in frame 257. The beam reflects at the interface between the flush-media filled lumen and the artery wall, is scattered by the tissue at * and retraces its path back to the catheter. The longer path through the lumen shows as a dark line; the signal from the tissue appears as a brighter feature circled in frame 258. This condition occurs at the interface from a high-refractive index n_1 (=1.44 for Visipaque) to a lower index n_2 (≈1.35 for tissue) as sketched in the bottom right panel. This graph shows the interface reflectivity as a function of θ for the refractive index contrast applicable in IVOCT

Additional pitfalls in the qualitative assessment for markers of vulnerability with OCT have been highlighted [17]. The strongly scattering properties of macrophage can mislead operators to classify plaque with luminal-surface macrophage infiltration as TCFA, because of the attenuating properties of the inflammatory infiltrate and consequent low-signal area deep to the thin rim of luminal tissue (Fig. 4). Irregularity of the luminal contour and nonuniform positioning of the OCT catheter within the vessel can also generate artefacts suggestive of TCFA and plaque rupture. Frequently the OCT catheter lies adjacent to the luminal border because of vessel geometry; consequently the radial penetration of the light beam is non-uniform. Light penetrating the vessel wall at a low angle of incidence has a longer path of travel, compared with light penetrating the vessel perpendicularly. The longer path of travel through tissue results in signal dropout and risks misinterpretation as lipid or TCFA (Fig. 5). Similarly, a very shallow angle of incidence can result in the appearance of luminal discontinuity and a 'ghosting' artifact in the deeper tissue, misinterpreted as a plaque rupture or small sidebranch (Fig. 6).

Clinical application of OCT as a tissue-characterizing tool is likely to be challenged by the limitations of qualitative assessment and the subsequent potential for misinterpretation. Consequently, parametric imaging techniques have been proposed to improve the accuracy and ease of interpretation. Attention has focused on measurement of the OCT signal intensity and attenuation characteristics of tissue.

Quantitative image analysis requires an understanding of the fundamental principles of OCT. As near-infrared light penetrates vascular tissue the light beam loses power in an exponential fashion, determined by the nature of the tissue the light is passing through [18]. The loss of light intensity is attributed to the attenuation coefficient (μ_t), which is made from the sum of scattering (μ_s) and absorption (μ_a).

Optical Attenuation

The optical attenuation coefficient can be extracted from the raw OCT data and allows differentiation of the major components of the atherosclerotic plaque. Measurement of optical attenuation and tissue characterization has been validated ex-vivo and translated into in-vivo catheter-based image acquisition [19, 20]. Interestingly, 2 important markers of atherosclerotic plaque vulnerability were found to associate with

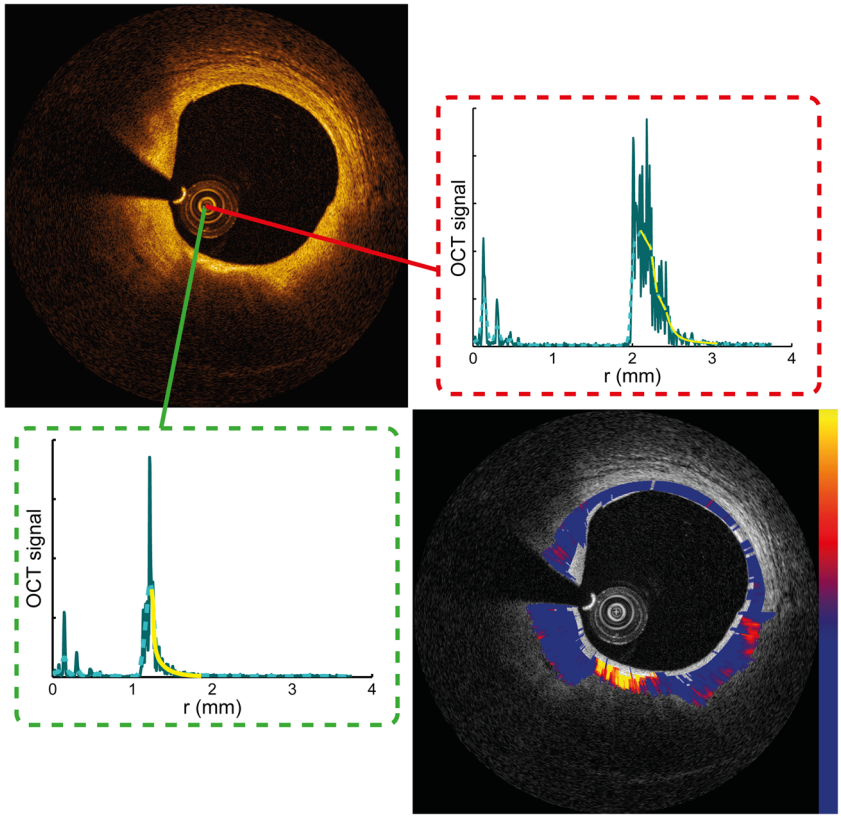

Fig. 7 *Top left* an OCT image of a mixed plaque. The local tissue attenuation can be imaged by performing a quantitative analysis of the OCT signal, illustrated in the graphs for the green and red lines respectively. *Bottom right* the resulting attenuation coefficient is color coded and overlaid on the original OCT image

high optical attenuation: necrotic core and macrophage infiltration both demonstrated optical attenuation values ≥10 mm^{-1}. Whereas, fibrous and calcific tissue were found to have low attenuation coefficients (μ_t = 2–4 mm^{-1}, see Fig. 7).

The ability to differentiate necrotic core is potentially advantageous in overcoming some of the ambiguity of qualitative tissue characterization. Earlier in this review we highlighted that the AHA classification for atherosclerosis demonstrates presence of lipid/macrophage from the earliest form of plaque, and therefore, tissue characterization limited to detecting presence or absence of lipid may not be able to distinguish between early plaque and advanced fibroatheroma [21]. Therefore, attenuation analysis may facilitate characterization of necrotic core and advanced plaque types.

Back-Scatter and Grey-Scale Intensity (GSI) Analysis

The scattering properties of plaque tissue components have been proposed as another parameter for analysis. Fibrous tissue and macrophage provide significant backscatter and high signal intensity. Quantification of macrophage infiltration was first described in 2002 by Tearney et al. [22]. The nature of macrophage, i.e., large with mixed content, results in strong and heterogeneous optical scattering, and the variance of the scatter intensity can be quantified as a normalized standard deviation (NSD). The NSD within plaque tissue has subsequently been validated against histologic quantification of macrophage infiltration using immunohistochemical techniques. High NSD on OCT image analysis positively correlated with histologic macrophage density (r=0.84, $P<0.0001$) [22].

More recently, grey-scale intensity (GSI) analysis of OCT images has been used to assess the maturity of the neointimal healing response following stenting [23]. OCT frames were converted to grey-scale signal and pixel-intensity was extracted from raw data in the absence of any data processing of the images. Normalization of the brightness was achieved by defining grey-scale values in each frame for the lumen (lowest intensity) and a stent strut/guide wire (highest intensity). Validation in an animal model of stent healing and human cadaveric specimens confirmed the ability of GSI to distinguish mature and immature neointima. Immature neointima was characterized by a relative paucity of SMCs, with inflammatory cell infiltrate and fibrin and correlated with a low GSI. The sensitivity and specificity of mature neointimal tissue detection in animal (96 % and 79 %, respectively) and human (89 % and 71 %, respectively) tissue was high.

Polarization-Sensitive OCT

Polarization-sensitive OCT (PS-OCT) measures tissue birefringence in addition to the morphologic OCT image.

Polarization refers to the direction of oscillation of a light wave, where a standard light source oscillates in a single plane, a polarized light beam is composed of 2 light sources oscillating at 90° to each other, these sources can be in-phase or out of phase. Passage of polarized light through highly organized tissue, such as collagen, results in a phase shift that can be detected. The birefringent optical property of collagen initially led to development of PS-OCT assessment of collagen integrity in osteoarthritic cartilage [24].

As discussed already, coronary plaque vulnerability has been demonstrated to associate with thinning of a fibrous cap and consequently PS-OCT has the potential to provide a more sensitive measure of the collagen/extra-cellular matrix structure of coronary plaques and offer useful information regarding the mechanical integrity of plaques. PS-OCT birefringence of coronary tissue has been shown to correlate with collagen content [25]. Subsequently, development of the PS-OCT technique has provided the ability to distinguish thick and thin-fiber collagen, and determine the organization of fibers, with greater disarray leading to less birefringence [26]. A high density of SMC and thick fiber collagen increases the birefringence of PS-OCT images and may, therefore, correlate with increased plaque stability. The simultaneous acquisition of PS-OCT with the morphologic characteristics obtained with conventional OCT could provide a powerful assessment of plaque vulnerability, through detection of thin-fibrous cap, large necrotic core and poor birefringence indicative of low collagen content.

Qualitative and quantitative parametric analysis of OCT imaging offers great potential for the characterization of atherosclerosis and additionally is providing new insights into the vessel response to stenting, particularly in-stent restenosis. The first report of OCT evaluation of restenotic coronary segments detailed variations in lumen contour, intraluminal material, presence of microvessels, and the optical properties of the neointimal tissue (tissue structure and backscatter property), initially simply reported as homogenous, heterogeneous and layered [27]. Similar to the qualitative characterization of de novo atherosclerosis, it was postulated that the homogeneous pattern represented smooth muscle cells, and the heterogeneous or layered patterns represented extracellular matrix, such as proteoglycans, and laminar thrombus. Patients presenting with ACS were found to more frequently have an irregular lumen contour suggestive of fresh thrombus. Subsequently, it was observed using OCT that neointima within bare metal stents often transforms into advanced atherosclerotic tissue, with lipid-laden areas, neovascularization and the potential for luminal disruption and thrombus formation [28], a process now coined as 'neoatherosclerosis'.

Recently, OCT imaging of neointima has been correlated with histology in a swine model of restenosis [29•] and clearly reproduced the findings of Gonzalo's original report, demonstrating homogenous, heterogeneous, and layered patterns of neointima formation. The homogenous tissue was demonstrated to contain a higher content of fibrous connective tissue, whereas fibrin deposits were more frequently associated with the heterogeneous pattern. Peri-stent inflammation and neovascularization was evident more commonly in areas of layered and heterogeneous neointimal formation, compared with homogenous tissue, and appeared to associate with greater trauma (external elastic lamina rupture). Unfortunately the swine model is limited by the nature of the restenotic response within normal juvenile arterial tissue and the absence of a complex atherosclerotic milieu. A similar study has been undertaken in an atherosclerotic rabbit model, utilizing qualitative OCT characterization and GSI analysis [23] (discussed above).

Conclusions

OCT has provided new insights into the progression of atherosclerosis, markers of vulnerability, and acute and long-term stent results. However, at present OCT does not feature within the international guidelines because of a lack of randomized evidence demonstrating its benefit. Interestingly, a recent consensus statement from the Society of Cardiovascular Angiography and Interventions (SCAI) has suggested that OCT is 'probably beneficial' in the determination of optimal stent deployment and 'possibly beneficial' in the assessment of plaque morphology [30].

There is no doubt that the resolution of OCT provides the clearest information currently available for in vivo assessment of coronary plaque morphology, assessment of immediate stent results and stent failure. We would advocate that the use of intravascular imaging is mandated in the setting of stent failure to maximize the chance of defining the etiology and minimizing the chance of future events. Despite our conviction regarding OCT's utility in stent failure, we must acknowledge that the technology has limitations and that image interpretation requires experience. We hope that this review has highlighted potential pitfalls and will limit misinterpretation. A key message for Interventional Cardiologists and their allied health professional team is to take time to analyze the images acquired, with dynamic review of multiple frames. Misinterpretation is more likely in the event of characterization from a single frame (composed of a spiral reconstruction of a 200 μm thickness of coronary artery).

Detection of vulnerability may continue to appear aspirational with the current limitations encountered in health care systems and inherently risk prediction would be best achieved with non-invasive investigations and subsequent medical management strategies [31••]. However, the majority of coronary intervention continues to stem from ACS presentations and consequently, invasive evaluation of risk, in the setting of culprit lesion intervention, is currently justified. All imaging modalities have potential limitations and it may be that a

combined imaging approach could offer improved detection of markers of vulnerability [32].

However, we have demonstrated how tissue characterization by OCT offers the potential for enhancing our understanding of the pathophysiology of atherosclerotic plaque development and stent failure, and, importantly, facilitates detection of vulnerable plaque and could ultimately guide patient-tailored interventional treatment strategies to optimize outcomes.

Compliance with Ethics Guidelines

Conflict of Interest Stephen White, Gijs van Soest, and Thomas W. Johnson declare that they have no conflict of interest.

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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- • Of importance
- •• Of major importance

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