Use of optical coherence tomography in interventional cardiology

Optical coherence tomography (OCT) has offered a greater understanding of coronary atherosclerosis with the ability to visualize plaque and quantify the thin, fibrous cap. Furthermore, OCT is able to traverse many of the limitations of angiography and intravascular ultrasound when imaging coronary stents *in vivo*. These applications are as a result of the use of near-infrared light, permitting an almost 'histological' resolution of the coronary artery. Novel developments with faster OCT pullback speeds (up to 20 mm/s with the next generation Fourier-domain systems) will further simplify the procedural requirements, meaning that the use of a proximal occlusion balloon is eliminated. Hence, OCT is, and will continue to be a unique imaging modality that is able to help improve our understanding of the atherosclerotic process and shed light on the all important interaction between coronary stents and the vessel wall.

KEYWORDS: atherosclerosis ■ coronary artery ■ optical coherence tomography ■ stent

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The use of optical coherence tomography (OCT) within the coronary circulation has been greeted with strong interest amongst cardiologists worldwide. The high resolution afforded by this imaging modality is giving new insights into atherosclerotic plaque and the interactions between the vessel wall and stents following implantation. Such resolution is provided by near-infrared light traveling across sophisticated optics to produce a detailed assessment of the coronary artery. Current technology employing frequency domain (FD)-OCT permits a pullback of 20 mm/s meaning such detail can be acquired in a matter of only a few seconds with no or minimal patient intolerance. This report will review the physical properties of OCT, how this modality differs from conventional intravascular ultrasound (IVUS) and explores the safety and clinical applications of OCT within the coronary circulation.

Optical properties

Optical coherence tomography is an optical analog of ultrasound using light rather than sound to produce an image [1–5]. For OCT imaging, low-coherence, near-infrared light with a wavelength of approximately 1300 nm is used since it minimizes the energy absorption in the light beam caused by protein, water, hemoglobin and lipid. The light waves are reflected by the internal microstructures within biological tissues as a result of their differing optical indices. This technique provides a resolution of 10–20 µm *in vivo* [6]; this level of detail is tenfold greater than the resolution of IVUS (100–150 µm) [5,7].

As the speed of light is much faster than that of sound, an interferometer is required to measure the backscattered light. The interferometer splits the light source into two 'arms' – a reference arm and a sample arm, which is directed into the tissue. The light from both arms is recombined at a detector, which registers the so-called interferogram, the sum of the reference and sample arm fields.

Time domain & frequency domain OCT

The time-domain (TD)-OCT imaging method on which the first-generation systems (e.g., M2 and M3, LightLab Imaging Inc., Westford, MA, USA) are based relies on a moving mirror to scan each depth position in the image. This mechanical scanning process limits the rate at which images can be acquired. The latest generation of OCT systems employ FD-OCT that enables much faster image acquisition rates and pullback speeds. Such systems (e.g., C7, LightLab Imaging Inc.) incorporate a novel wavelength-swept laser as a light source that has a narrow spectral output [4]. FD-OCT systems can acquire images at line rates at least ten-times faster than TD-OCT systems without loss of image quality. This speed advantage results from the elimination of mechanical scanning of the reference mirror and the signal-to-noise advantages of FD-OCT signal processing [4]. Hence, pullback speeds of approximately 20 mm/s or higher are able to be acquired, ensuring *in vivo* detailed vessel characterization in a very

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time-efficient manner. Furthermore, 3D rendering of FD-OCT-acquired pullbacks demonstrates the exciting potential of this technology with imaging of the 3D microstructure of long coronary segments [8]. Table 1 depicts the salient characteristics of TD- versus FD-OCT.

Table 2 lists the differences between OCT and conventional IVUS. The use of light results in a tenfold greater resolution and has seen OCT now be used in clinical studies to assess tissue coverage surrounding coronary stents. In contrast to IVUS imaging however, blood remains an obstacle to OCT imaging and, hence, it must be temporarily cleared during image acquisition. This was initially accomplished by the use of a proximal occlusion balloon catheter and intracoronary flush of lactated Ringer's solution, but can now be accomplished using iso-osmolar viscous contrast flushed via the guiding catheter (see below).

Procedural requirements for image acquisition

As light is unable to penetrate through red cells, blood needs to be cleared from within the coronary artery during image acquisition. This can be accomplished by a number of methods, dependent on the system used.

■ TD-OCT: balloon occlusion technique

Traditionally, the first-generation TD-OCT systems use a proximal balloon occlusion method whereby a balloon is positioned proximally in the vessel and inflated simultaneously during intracoronary flush. In such systems, the proximal occlusion balloon catheter (Helios, Goodman Co., Japan), an over-the-wire 4.4 Fr catheter (inner diameter: 0.025 inches) is advanced distal to the region of interest using a conventional angioplasty guide wire (0.014 inches) [9]. The guide wire is then replaced by the OCT image wire (0.019 inches maximum diameter), and the occlusion balloon catheter is withdrawn proximal to the segment to be assessed leaving the imaging wire in position. During imaging acquisition, coronary blood flow is removed by continuous flush of Ringer's lactate solution via the end-hole of the occlusion balloon catheter at a flow rate of 0.5–0.7 ml/s during simultaneous balloon inflation (0.5–0.7 atm) [9].

Table 1. Salient characteristics of time-domain versus frequency-domain optical coherence tomography.

Parameter	TD-OCT*	FD-OCT‡
Axial resolution (μm)	15–20	15–20
Lateral resolution (μm)	25–30	25–30
Scan diameter (in saline; mm)	6.8	8.3
Frame rate (f/s)	Up to 20	100
Lines per frame	Up to 240	450
Maximum pullback speed (mm/s)	3.0	20

**Based on the LightLab Imaging Inc. (Westford, MA, USA) M2 and M3 system.*
‡Based on the LightLab Imaging Inc. C7 FD-OCT system.
FD: Frequency domain; OCT: Optical coherence tomography; TD: Time domain.

■ TD-OCT: nonocclusive technique

Faster OCT pullback speeds have meant that this rather cumbersome technique of blood clearance has been replaced by contrast flush through the guiding catheter during simultaneous image acquisition. Iodixanol (Visipaque™, GE Health Care, Cork, Ireland) is the contrast agent that is preferentially used for flushing during the nonocclusive method [10]. The advantage lies in its higher viscosity relative to other agents, which permits optimal blood clearance for OCT imaging at the given flush volumes through the guiding catheter. This agent has also been shown to have a lower propensity to cause ventricular fibrillation (VF) given its lower osmolality, higher viscosity and higher concentration of sodium and calcium chloride molecules compared with other nonionic media [10–14]. Finally, all such OCT procedures must be performed during therapeutic systemic anticoagulation with liberal use of nitroglycerin to minimize spasm during vessel instrumentation.

■ FD-OCT: nonocclusive technique

With the current commercial FD-OCT system (C7), the dedicated imaging wire (DragonFly, LightLab Imaging Inc., Westford, MA, USA) is advanced over a standard guidewire via a rapid exchange system. When it is positioned distal to the region of interest, pullback is commenced at 20 mm/s during a short flush of contrast through the guiding catheter [4]. This can be performed either manually or via an automated injector system with flush speed varying depending on the target vessel and its size to achieve adequate blood clearance.

Procedural safety

Optical coherence tomography is an invasive imaging modality and hence has a number of inherent risks. Yamaguchi *et al.* examined the feasibility of OCT and IVUS imaging in 76 patients [15]. Although transient chest pain and electrocardiographic changes caused by imaging were not considered as part of their study, there were no adverse events reported following both IVUS and OCT, with the latter being performed exclusively using the occlusive method.

More recently, Barlis *et al.* reported a large multicenter registry of 468 patients having OCT across six European sites [10]. The technique was performed using an occlusion balloon in 256 (54.7%) patients while the nonocclusive approach was used in the remaining 212 (45.3%) cases. The most frequent observation was transient chest pain during OCT image acquisition (47.6% of cases). In all patients this settled following cessation of imaging and was significantly more frequent in patients imaged using the occlusive compared with the nonocclusive technique (69.9 vs 20.8%; $p < 0.001$). VF occurred in five (1.1%) patients and was linked to deep guide catheter intubation during flushing or the use of the proximal balloon. Several studies have shown that the incidence of VF during coronary angioplasty is approximately 1.5% [16,17], with the rate dropping down to approximately 0.6% for diagnostic procedures [18,19]. In addition to ischemia, other mechanisms have also been identified including reperfusion, electrolyte imbalances, coronary instrumentation, osmolarity and electrolyte composition of contrast agents and intracoronary thrombus [10,20–26].

Clinical applications

The most exciting applications of OCT lie in its ability to clearly define coronary stents and atherosclerotic plaque. With the increased scrutiny placed on stents and, in particular, drug-eluting stents (DES), OCT can provide unique information regarding strut apposition and tissue endothelialization, both key factors linked with stent thrombosis [27].

■ Stent strut apposition

Apposition of stent struts as assessed by OCT has created considerable interest. A number of groups have proposed classification systems of how to define apposed and malapposed struts. Tanigawa *et al.* divide struts into three categories: first, embedded into the vessel wall; second, protruding into the lumen but still apposed to the vessel wall; and third, malapposed strut with complete separation of the strut from the wall by a distance greater than the strut thickness [9]. Guagliumi *et al.* propose a four-tier classification with [28]: Totally embedded struts (Type I);

- Embedded subintimally without disruption of lumen contour (Type II);
- Completely embedded with disruption of lumen contour (Type IIIa);
- Partially embedded with extension of strut into lumen (Type IIIb);
- Complete strut malapposition (blood able to exist between strut and lumen wall; Type IV).

Table 2. Comparison between intravascular ultrasound and optical coherence tomography.

Parameter	Optical coherence tomography	Intravascular ultrasound
Dynamic range (dB)	90–110	40–60
Axial resolution (μm)	10–15	100–150
Lateral resolution (μm)	25–40	150–300
Tissue penetration (mm)	1–2	4–8
Pullback speed (mm/s)	20	0.5–1.0

Studies using OCT in the acute setting following stent implantation have demonstrated a high proportion of malapposed struts, even after optimal high pressure postdilatation, with this phenomenon being particularly evident in regions of stent overlap [29]. In an evaluation of OCT findings following stent implantation to complex coronary lesions, Tanigawa *et al.* examined a total of 6402 struts from 23 patients (25 lesions) and found 9.1 ± 7.4% of all struts in each lesion treated were malapposed [30]. Univariate predictors of malapposition on multilevel logistic regression analysis were: implantation of a sirolimus-eluting stent (SES), presence of overlapping stents, longer stent length and type C lesions. Likely mechanical explanations for malapposition of stent struts include increased strut thickness, closed cell design or acute stent recoil. The latter has been demonstrated in SES to be in the range of 15%, despite the use of high-pressure balloon dilatation [31]. Furthermore, OCT has also been applied to the assessment of strut morphology and apposition in bifurcation lesions treated with dedicated stents (e.g., Tryton bifurcation stent) giving insights into the precise relationship between struts at both the main and side branch, particularly at the carina [32]. While these findings are impressive and helpful for the improvement of future stent designs, the clinical relevance and potential long-term sequalae of malapposed struts as detected by OCT are currently unknown. Figure 1 demonstrates the clarity of detail provided by OCT to visualize malapposed stent struts.

■ Stent strut tissue coverage

Unlike conventional stents, which develop circumferential coverage with an average thickness of 500 μm or more, well visualized with IVUS and angiography, DES delay and prevent the

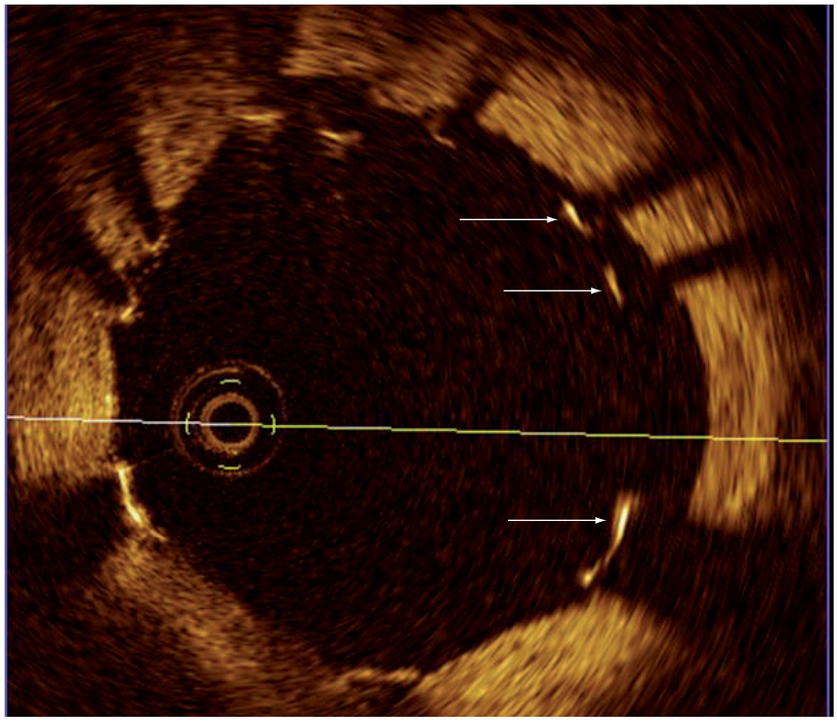

Figure 1. Optical coherence tomography cross-section at 3 weeks following stent implantation. Scattered malapposed stent struts are seen in the 12 to 3 o'clock position.

hyperplastic response so that the average late lumen loss for DES can be lower than 100 µm [33,34], which means this amount of corresponding intimal thickening is difficult to detect by IVUS. Furthermore, although coronary angioscopy is able to visualize strut tissue coverage, this highly specialized technique lacks the ability for quantification. Hence, OCT is an attractive alternative, able to circumvent many of these limitations, and, with its high resolution, can precisely assess the *in vivo* tissue responses following stent implantation (Figure 2) [35].

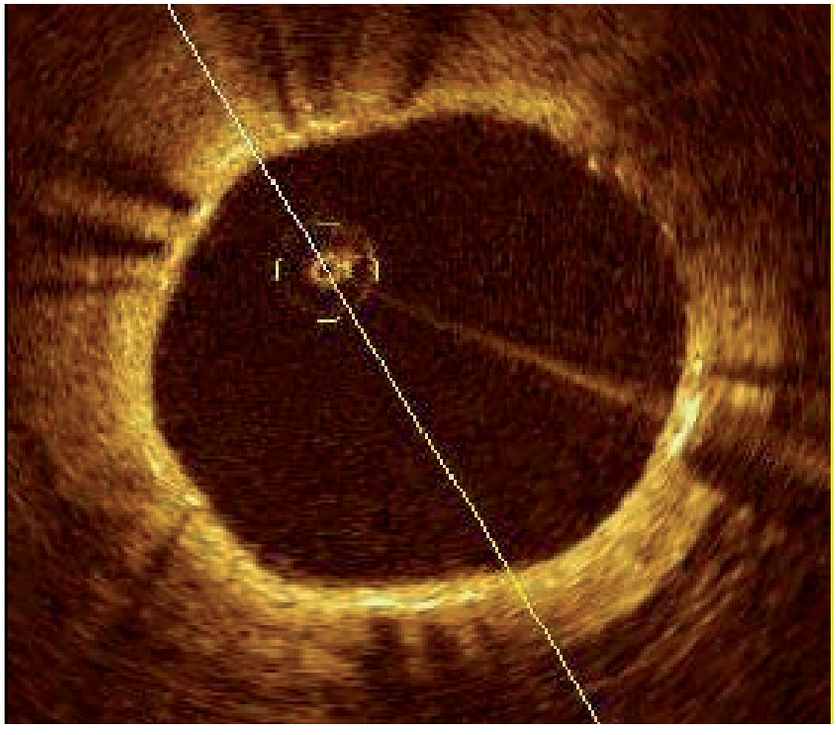

Figure 2. Optical coherence tomography demonstrating the thin tissue coverage of a drug-eluting stent 6 months following implantation.

Optical coherence tomography can reliably detect early and very thin layers of tissue coverage on stent struts. Several small studies have recently been published highlighting the application of OCT in the detection of stent tissue coverage at follow-up. Importantly, OCT permits the quantification of tissue coverage with high reliability [36]. Matsumoto *et al.* studied 34 patients 6 months following SES implantation [37]. The mean neointima thickness was 52.5 microns, and the prevalence of struts covered by thin neointima undetectable by IVUS was 64%. The average rate of neointima-covered struts in an individual SES was 89%. Nine SES (16%) showed full coverage by neointima, whereas the remaining stents had partially uncovered struts. Similarly, Takano *et al.* studied 21 patients (4516 struts) 3 months following SES implantation [38]. Rates of exposed struts and exposed struts with malapposition were 15 and 6%, respectively. These were more frequent in patients with acute coronary syndrome (ACS) than in those with non-ACS (18 vs 13%; $p < 0.001$ and 8 vs 5%; $p < 0.005$, respectively). The same group have recently reported 2-year follow-up OCT findings with the thickness of neointimal tissue at 2 years being greater than that at 3 months (71 ± 93 µm vs 29 ± 41 µm, respectively; $p < 0.001$) [39]. Frequency of uncovered struts was found to be lower in the 2-year group compared with the 3-month group (5 vs 15%, respectively; $p < 0.001$) and, by contrast, prevalence of patients with uncovered struts did not differ between the 3-month and the 2-year group (95 vs 81%, respectively), highlighting that exposed struts continued to persist at long-term follow-up.

Chen *et al.* used OCT to image SES and bare-metal stents (BMS) at different time points following implantation [40]. Of the ten SES and 13 BMS imaged, the authors identified a significantly higher number of incompletely apposed and uncovered stent struts in patients receiving SES compared with BMS. The results of these small observational studies are compatible with evidence from animal and human post-mortem series showing that DES cause impairment in arterial healing with

incomplete re-endothelialization and persistence of fibrin possibly triggering late stent thrombosis [27,41,42].

In a small, randomized trial of a polymer versus polymer-free DES, OCT was performed at 3-month follow-up and found a significantly large percentage of malapposed, uncovered and protruding struts in the SES (Cypher®, Cordis, Johnson & Johnson) compared with a nonpolymer SES (Yukon®, Translumina, Hechingen, Germany) [43]. In this study, Moore *et al.* hypothesized that the profile and thickness of the polymer-based SES and its permanent polymer may have a bearing on these findings and may potentially influence the long-term risk of stent thrombosis with the polymer being a contributing factor to stent failure [43]. Longer term follow-up with serial OCT stent interrogations may help address such issues definitively.

Plaque assessment

Several imaging modalities have been used to assess and identify vulnerable plaque (VP), including coronary angioscopy, IVUS and magnetic resonance imaging. Recently, there has been significant interest in the field of VP detection using OCT [44–52]. Several morphologic features described in autopsy series are of particular interest in these VPs. These include the presence of a thin fibrous cap, a necrotic lipid core [11,12] and the accumulation of macrophages [13]. However, at this point in time, no longitudinal studies have been performed to assess the prognostic value of OCT-derived plaque characterization.

Optical coherence tomography is highly sensitive and specific for the characterization of plaques when compared with histological examination [53–55]. Yabushita *et al.* performed an *in vitro* study of more than 300 human atherosclerotic artery segments [56]. When compared with histological examination, OCT had a sensitivity and specificity, respectively, of 71–79% and 97–98% for fibrous plaques, 95–96% and 97% for fibrocalcific plaques, and 90–94.5% and 90–92% for lipid-rich plaques. Furthermore, the inter- and intra-observer variability of OCT measurements were high (κ values of 0.88 and 0.91, respectively) [55]. *In vitro* comparisons of OCT with IVUS have demonstrated superior delineation by OCT of structural details such as thin caps, lipid pools or tissue proliferation [57]. An *in vitro* comparison of OCT, integrated backscatter IVUS (similar methodology to virtual histology [VH]-IVUS) and conventional IVUS found that OCT had the best potential for tissue characterization of coronary plaques, with higher sensitivity and specificity compared with the other imaging modalities [58].

As a result of its high axial resolution, there is no doubt that OCT is the *in vivo* gold standard for identifying and measuring the thickness of the fibrous cap (Figure 3); an *in vivo* study found a significant difference in minimal cap thickness between acute myocardial infarction (AMI) and stable angina patients, with median (interquartile range) values of 47.0 µm (25.3–184.3 µm) and 102.6 µm (22.0–291.1 µm) respectively ($p = 0.02$) [59]. On top of its reliability as a tool to measure the thickness of the cap *in vivo*, recent post-mortem and *in vivo* studies have shown that OCT is capable of evaluating the macrophage content of infiltrated fibrous caps [60,61].

Recently, Sawada *et al.* studied 56 patients with angina (126 plaques) using both VH-IVUS and OCT [62]. A total of 61 plaques were diagnosed as IVUS-derived thin cap fibroatheroma (TCFA) and 36 plaques as OCT-derived TCFA. A total of 28 plaques were diagnosed as definite TCFA indicating that neither modality was able to definitively localize TCFA; however, using both imaging modalities resulted in a greater pick-up rate. This study was limited, however, by the lack of definitive histological confirmation (namely as it was an *in vivo* analysis) and only used IVUS to localize TCFA.

Kubo *et al.* used OCT, together with IVUS and angioscopy, to assess plaque characteristics in 30 patients presenting with AMI [44]. The imaging devices were consecutively used following initial mechanical thrombectomy and found the incidence of plaque rupture by OCT to be 73%, which is significantly higher than that detected by both angioscopy (47%; $p = 0.035$) and IVUS (40%; $p = 0.009$). The incidence of TCFA was 83% in this patient population and only OCT was able to estimate the fibrous cap thickness (mean: 49 ± 21µm). Furthermore, intracoronary thrombus was observed in all cases by OCT and angioscopy, but was identified in only 33% of patients by IVUS ($p < 0.001$).

Recently, Gonzalo *et al.* studied 30 patients with 103 bifurcations using VH-IVUS and OCT [63]. Of the 103 lesions, 17.4% were found to contain TCFA with the overall percentage of necrotic core decreasing from the proximal to distal segments of the bifurcation (16.8 vs 13.5%, respectively; $p = 0.01$). Cap thickness conversely increased (130 ± 105 µm vs 151 ± 68 µm for proximal and distal rim, respectively; $p = 0.05$) highlighting the predilection

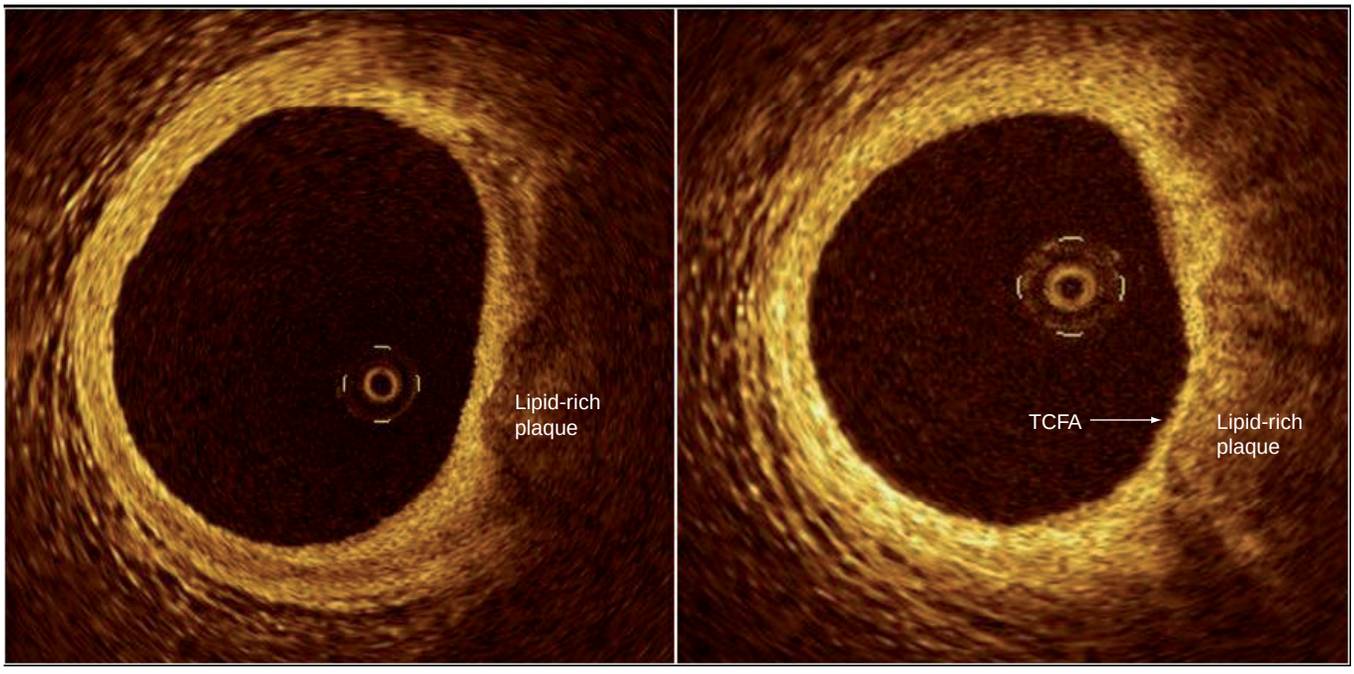

Figure 3. Cross-section from the left anterior descending artery. Demonstrating a poorly reflective signal within the coronary vessel consistent with lipid-rich plaque. Overlying this plaque is a bright, homogeneous and reflective thin structure consistent with TCFA. TCFA: Thin cap fibroatheroma.

of the proximal segment of the bifurcation to contain thin fibrous cap and a greater proportion of necrotic core. Such data may help provide clearer insights as to why such lesions have a greater complication rate compared with nonbifurcation disease.

Limitations of OCT

Faster pullback speeds now used with FD-OCT systems have significantly simplified the procedural requirements during imaging. Nevertheless, the need for a blood-free environment requires transient clearance of blood from the vessel and this still adds an element of complexity when compared with IVUS. The presence or absence of tissue strut coverage is clearly as defined by the resolution of OCT, and struts with no visible tissue could have had a thin covering of tissue (<10 µm), although at this level the biological protection of the neointima has been debated [64].

Tissue penetration using OCT is limited to approximately 1.5–2 mm, meaning that regions around the external elastic lamina are more often not visible, thus arterial remodeling is difficult to determine. Nevertheless, much of the interest in interventional cardiology lies in the interaction between the lumen and vessel wall and, therefore, OCT remains particularly effective at characterizing this.

Finally, OCT results in an abundance of data that require off-line image interpretation. At present, this process remains quite cumbersome although there is emerging evidence that automation of this process may significantly reduce the analysis time while maintaining excellent inter- and intra-observer reproducibility [36,65].

Future perspective

The ability of OCT to provide high-resolution imaging *in vivo* is the most significant concept circumventing the limitations of other imaging modalities such as angiography and IVUS. The identification of vulnerable plaque and the examination of tissue coverage following stent implantation have meant OCT has a clear role to play in future research looking at atherosclerosis and in providing a possible explanation to long-term stent thrombosis. With even faster pullback speeds and simplification of the procedural requirements, as with the current FD-OCT system, OCT will become more accessible to a greater number of centers and operators worldwide. Such advances will also see OCT consistently applied as a multivessel diagnostic modality, able to provide a truly representative assessment of the entire coronary tree while giving never before seen *in vivo* detail of within the coronary artery.

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Executive summary

Optical properties

- Optical coherence tomography (OCT) uses near-infrared light with a wavelength of 1310 nm.

Time- versus Fourier-domain OCT

- The optical properties of OCT determine the scan length and pullback speed during image acquisition with Fourier-domain systems allowing a very fast 20 mm/s pullback speed.

Procedural requirements

- Image acquisition needs to be performed in a blood-free environment. This is now accomplished by flushing of contrast within the coronary artery.

Clinical applications

- OCT is well placed to characterize atherosclerotic plaque and also to assess stent strut apposition and tissue coverage in great detail.

Limitations

- OCT is an invasive technique. Tissue penetration is limited to up to 2 mm meaning that the external elastic lamina is generally not visualized.

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