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Optical coherence tomography for guidance in bifurcation lesion treatment

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Abstract

Optical coherence tomography (OCT) has higher resolution than IVUS (approximately 10 times), with the potential to precisely measure lumen diameters in the variable geometry of a bifurcational lesion and to identify superficial lipid laden plaques and calcium, relevant to confirm the severity of the lumen obstruction before treatment and guide location and diameter of the stent. In addition, OCT produces fewer strut-induced artifacts and offers precise evaluation of strut apposition in a real-life clinical setting. The increase in the speed of image acquisition consequent to the introduction of frequency domain OCT allows rapid pull-back at a speed of 2 cm/sec, minimising the amount of contrast required to clear blood during image acquisition, with an average injection of 10-18 ml required for the maximal length currently available of 5.6 cm. This allows serial OCT acquisitions, typically before treatment if the lesion is not very severe and flow is expected to be present around the OCT catheter, after predilatation and to assess and guide stent expansion. Repeated OCT examinations at follow-up may help to detect presence and characteristics of strut coverage, a potential predictor of late stent thrombosis. These applications are of particular interest in the context of bifurcational lesion treatment because this condition is still associated with a higher number of malapposed stent struts and frequent impairment of stent expansion, explaining the higher incidence of stent thrombosis and restenosis.

In this article, all potential applications of OCT for bifurcational lesion treatment are explored. The use of OCT to characterise plaque components, and to optimise stent expansion and strut apposition are first discussed in detail. The conclusion of the article highlights some future research and technological developments that promise to expand the role of OCT further still.

Abbreviations

BMS	bare metal stent
CSA	cross-sectional area
DES	drug eluting stent
FFR	fractional flow reserve
ISA	incomplete stent apposition
IVUS	intra-vascular ultrasound
MB	main branch
MLA	minimum luminal area
OCT	optical coherence tomography
SB	side branch

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Introduction

Implanting a stent in a bifurcation is a leap into the unknown. Is the lesion truly significant? How is the plaque distributed in the main vessel and side branch and which are its characteristics? What is the relative diameter of the three segments involved? Is the lesion prepared well enough to allow the stent to expand easily? Have I opened the stent at the origin of the side branch well enough? Do I need a second stent for the side branch and, if yes, which is the best technique? Are the struts well apposed or are they hanging in the middle of the lumen? Is it feasible to appose them to the wall and how to do it?

All these questions are very difficult to answer with conventional angiography because the superimposition of the two branches at the bifurcation and its complex three-dimensional structure prevent a detailed assessment of the severity of the stenosis before treatment as well as of the residual stenoses after stent expansion. Frequently fibrocalcific stenoses are present at the ostium of the daughter branches and respond poorly to treatment. Virtual histology with IVUS has shown a greater prevalence of vulnerable plaques in the proximal main vessel, often eccentric and located in the segments of low shear stress opposite to the carina. How does the stent interact with these active plaques? Does the haziness and filling defects present after treatment correspond to prolapse or thrombus? Will all those grossly unapposed struts often completely missed with angiography and poorly visible with intravascular ultrasound eventually endothelialise and when?

These are some of the most important questions a technique with a 10 µm resolution such as OCT can easily answer in the treatment of bifurcational lesions with stents, however we still do not know if and which of these answers is relevant to the patient outcome and how to interpret them. OCT is a too new a technique to have sufficiently large and prolonged follow-up results to correlate the findings with the relatively rare adverse events now observed with second generation drug eluting stents and the current adjunctive pharmacologic treatment. Still it is logical to believe that very poor expansion, gross malapposition and stent distortion, protruding plaques and thrombus, very delayed strut coverage are ominous signs which should be avoided and corrected if feasible and safe. OCT can tell us which are the best stents and techniques of implantation to avoid or minimise all these phenomena.

The aim of this manuscript is to describe the method of investigation to safely achieve optimal intracoronary imaging of the main vessel and side branch across a bifurcation before and after treatment, discuss specific elements which may complicate the assessment of lesion severity before and after treatment, with special attention for the ostium of the side branch, report results observed with various stents and techniques of implantation,and review specific results of strut coverage across bifurcations. In the spirit of cooperation of the European Bifurcation Club[1] the various topics are addressed by different groups with specific expertise in the field.

Technique of examination

Frequency domain imaging has greatly increased the speed of acquisition of OCT images and has attenuated the negative impact of the need to examine the vessel clear from blood by replacing it with a crystalloid solution. This is most commonly achieved with the use of pressure injection of contrast because the viscosity of contrast is ideal to avoid mixing with blood and its consequent artifacts. Other crystalloid solution have been proposed to avoid the nephrotoxicity of contrast but they are either not as efficient as contrast (e.g., saline) or the hurdle to obtain registration for intracoronary make them impractical. A high rate (approx. 3-5 mL/sec) infusion is generally used to ensure optimal image quality. However, the increased acquisition speed of FD-OCT means that it is generally capable of providing information on several centimetres of vessel in one pullback without using excessive amounts of contrast.

The Dragonfly OCT catheter requires to be filled with undiluted contrast using a special high pressure syringe to overcome the resistance offered by the small lumen and the high viscosity of Visipaque. After connection with the laser generator and activation, a red light indicates the position of the source. The system performs a self-calibration and the rotation is interrupted to reduce the risk of damage during insertion. The short Monorail tip is limited to the distal 2-3 cm, up to the point reached by the optical fibres. Following passage of a standard 0.014" steerable guidewire past the area of interest, the OCT imaging catheter is advanced until the distal tip marker of the OCT catheter is positioned distal to the lesion or stent to be examined. The catheter's fibre-optic core is then activated on the peripheral imaging console, contrast injected and an automated pullback starts whilst contrast clears the blood from the vessel. A longitudinal cross section of the entire vessel length is displayed immediately on the peripheral console (Figure 1). The most recent software also allows an automatic detection of the lumen area in all consecutive cross-sections with the reconstruction of an area function diagram showing the individual areas and the percentage area stenosis compared with the reference area identified by the user. On line three-dimensional reconstruction is also available, directly showing malapposition, plaque prolapse, thrombus. The rapid speed of acquisition allows minimisation of the artifacts due to the systo-diastolic motion of the artery. Programs for the automatic assessment of the distance of all malapposed struts to the vessel wall and for the measurement of the thin layer of intimal thickening observed months after implantation of drug eluting stents are not yet integrated in the current systems but are applied with success if images of high diagnostic quality without blood induced artifacts have been acquired. An expected further increase in the acquisition speed (currently 100 images/sec with the LightLab Dragonfly system [LightLab Imaging Inc., Westford, MA, USA], due to increase to 180/sec, while the Terumo OCT [Terumo Corp., Tokyo, Japan] already generates 160 images/sec) is due to facilitate the acquisition of the entire diseased segment and the reduce the contrast use.

Assessment of lesion severity with OCT: specificity of measurements across bifurcations

Selection of the appropriate bifurcational stenting strategy is crucial in achieving optimal results. However, currently available classification schemes are based on angiography and are therefore

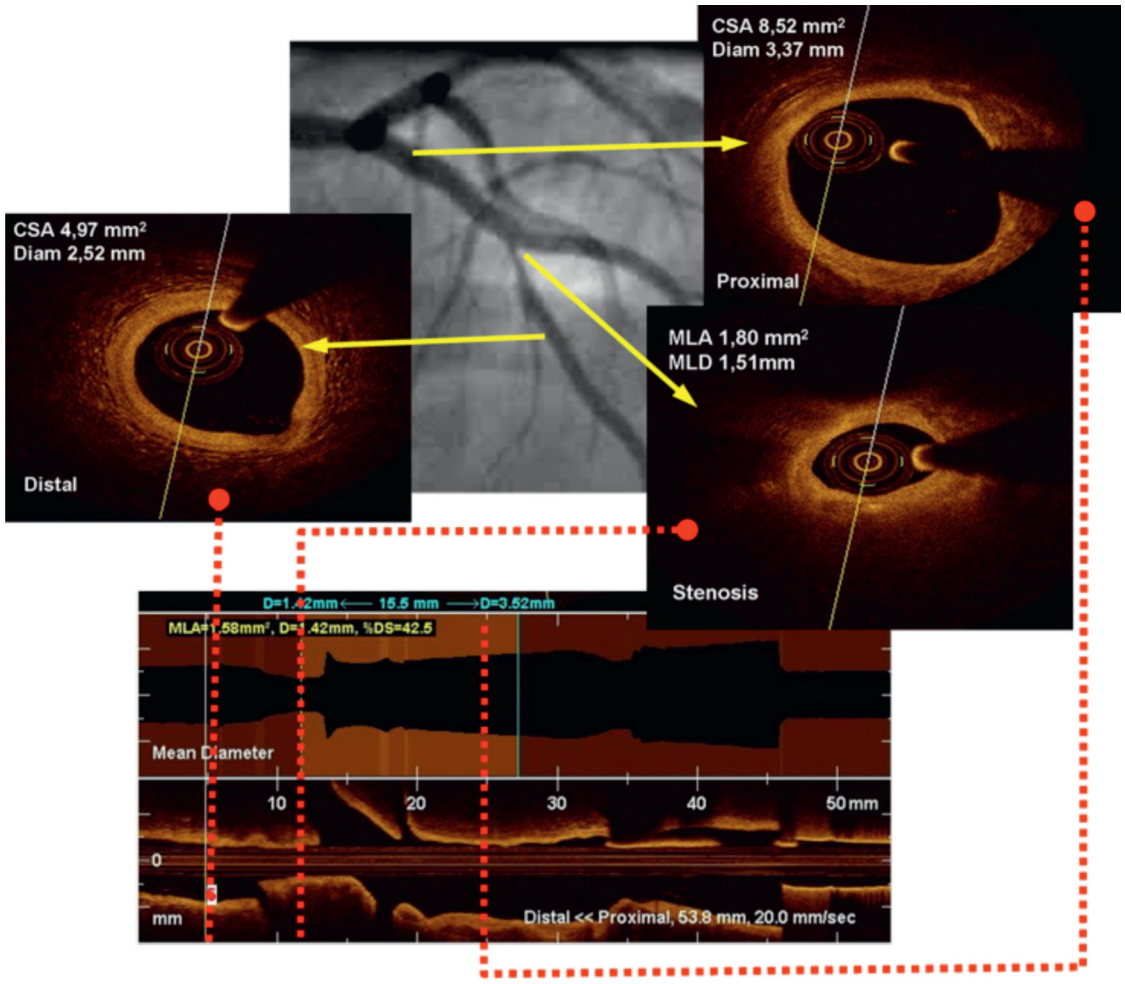

Figure 1. Automated online detection of the lumen contour provides an immediate quantification of the vessel average diameter. Accurately sizing the reference vessel diameter in a reference proximal and distal to the side branch is essential for correct sizing of the stent and postdilatation balloon. In the longitudinal reconstruction (lower panel) the origin of the first diagonal branch is evident at 13 mm the from the pull-back origin.

limited by the inherent inability of this imaging modality to exactly determine atheroma distribution and volume at the bifurcation level, nor can angiography identify the characteristics which may potentially complicate the procedure and adversely affect outcome. Accurate determination of the stenosis severity, diameter of the vessels involved, lesion length and location in both the main branch (MB) and side branch (SB) – as well as the morphological and compositional characteristics of the plaque such as calcification, lipid content, and thickness of the fibrous cap– are important parameters that can guide treatment decisions.

Optical coherence tomography (OCT) provides high quality images of the lumen-intima interface thereby allowing au<tomatic lumen area measurements that can be used to characterise stenosis severity with a very good reproducibility. Regarding plaque characterisation, OCT can identify lipid-laden, fibrotic, calcific and thrombus-containing plaques and macrophages[2] while it also allows measurement of the fibrous cap contributing to the identification of plaques at high risk of rupture[3]. Yet, because of a limited tissue penetration the adventitia cannot consistently be depicted and plaque burden assessed. Lumen area stenosis describes the relative decrease in luminal cross-sectional area (CSA) at the site of disease, in percentage, compared to lumen CSA in a "normal appearing" reference segment in the same coronary artery. Given the inability of the currently available OCT systems to consistently visualise the outer border of the vessel, accurate measurements of the degree of luminal area stenosis are somewhat more difficult than with IVUS. While IVUS uses percent area stenosis (< 60%) as an essential parameter to identify the reference, OCT is unable to offer this information and relies on absolute lumen measurement, requires good integration of the OCT and angiographic images as well as good operator experience. Also of note is the fact that lumen measurements derived from OCT are systematically smaller than those derived from IVUS, a difference attenuated but not cancelled by the use of a non-occlusive technique. Yamaguchi et al performed OCT and IVUS studies in 76 single non-bifurcation/non-left main stem native coronary artery lesions with a luminal diameter stenosis <99% and length <20 mm as estimated visually on angiography and found that the values obtained for minimal lumen diameter and area from OCT were significantly correlated with those obtained from IVUS. However both values by OCT which was performed with a balloon-occlusion technique were significantly smaller than those measured by IVUS (MLA mean difference,

0.4 mm^2)[4]. The reduced pressure in the distal artery due to the balloon dilatation was expected to be the cause of the phenomenon. In a sample of four vessels (one left anterior descending artery and four left circumflex arteries), Gonzalo et al compared the lumen dimensions obtained by IVUS with those obtained with OCT with and without balloon occlusion as well the OCT measurements with both techniques. OCT measurements were shown to be consistently smaller compared to IVUS; the mean relative difference for MLA between IVUS and OCT with and without occlusion was 55.5% and 29% respectively[5]. OCT measurements obtained with the occlusive technique were also shown to be consistently smaller compared to non-occlusive technique; mean relative difference 28%. The smaller dimensions measured with OCT as compared to IVUS may be due to the better delineation of the lumen border and the lack of ring-down artifact observed with IVUS.

These findings highlight that the cut-off values for a severe stenosis validated for IVUS cannot be automatically applied in cases of stenoses evaluated with OCT, with a risk of overestimating stenosis severity. Indeed, all patients studied by Gonzalo et al had a MLA>4 mm^2 when measured by IVUS while four of these had MLA<4 mm^2 when measured by OCT with an occlusion balloon technique[5]. Evaluation of the severity of the SB ostial stenosis is known to be crucial in guiding bifurcational stenting; in case a SB of adequate size and distribution contains ostial stenoses ≥50% extending >5 mm form the carina a two-stent technique is usually selected[6]. The presence and longitudinal extent of a SB ostial cannot be accurately evaluated with angiography, as shown by the discrepancy of angiographic and functional measurements of ostial lesion severity measured with a pressure wire and FFRmyo. The combination of OCT and IVUS-virtual histology in the assessment of bifurcations lesions has been shown to improve the detection of plaques with a larger amount of necrotic core and a thin fibrous cap. The proximal wall opposite to the flow divider represents the area with lowest shear stress and higher risk of developing vulnerable plaques and vessel rupture. (Figure 2). This area represents the landing zone of multiple struts layers in cases of two-stent techniques (crush, T-stenting with minimal protrusion) where incomplete stent apposition and non-uniform strut deployment and hence drug distribution may occur. These findings may at least explain the worse outcomes in bifurcational lesion stenting irrespective of the technique used provided that plaques with larger lipid core are more likely to produce distal embolisation and no-reflow and hence periprocedural myocardial infarction.

Clinical application of OCT to guide interventions: influence of technique and stent selection on expansion and apposition

Incomplete stent apposition (ISA) is commonly defined as separation of a stent strut from the vessel wall in an area not related to a side branch. This definition, typical of the IVUS analysis in large trials of short "on-label" lesions where only small branches could be involved, is meaningless when applied to large bifurcations where the technique is expected to reduce or eliminate malapposition. If a strut is separated from the wall by more than the sum of the metal and polymer thickness then it is considered to be not apposed (malapposed). The number of malapposed struts, minimal distance from the vessel wall, and incomplete stent apposition area can also be measured. An example of malapposition at the side branch bifurcation is offered in Figure 3. Recent OCT studies have demonstrated higher numbers of malapposed struts following stenting than previously suggested by

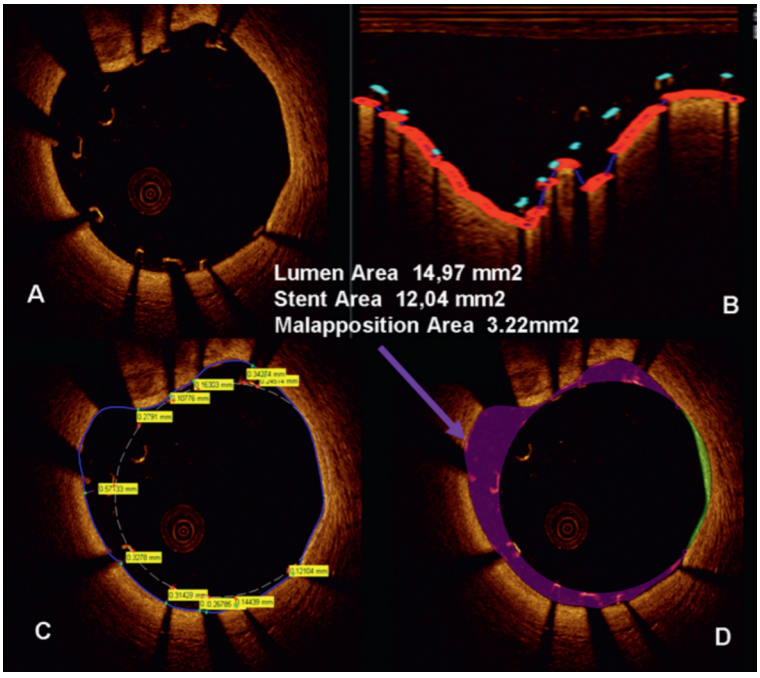

Figure 2. Application of a prototype system for automatic detection of malapposed struts. The stent struts and the underlying vessel wall (A) are automatically detected and displayed in a linear format (B), and with the individual distances of each malapposed strut. The lumen area, malapposed area, and stent area are automatically calculated and displayed. (Courtesy of Giovanni Ughi, PhD, and Tom Adrianssens MD, PhD)

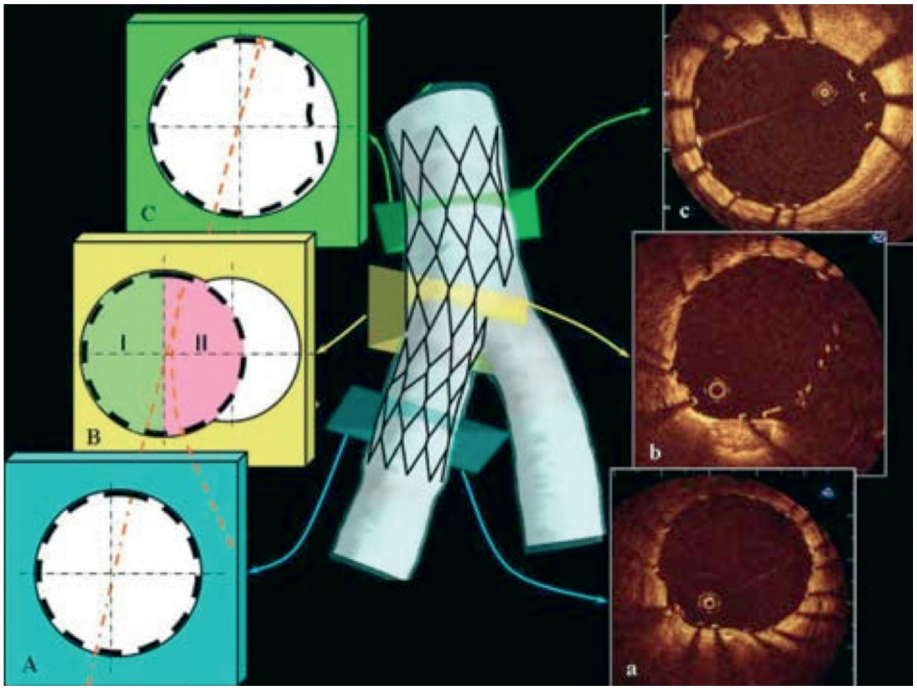

Figure 3. Use of OCT to assess stent apposition at the bifurcation. The lesion is divided into distal (A), bifurcation (B), and proximal (C) segments. The bifurcation (B) is further divided into two halves, that nearer the main vessel wall (I) and that facing the side branch ostium (II). The strut apposition is measured by taking the distance from the luminal surface of the strut to the nearest vessel wall. Malapposed struts are shown a 3 o'clock (panel C), and across the entire origin of the SB (2 to 5 o'clock) in the panel B. (Reproduced with permission, Revista Espanola de Cardiologia)

IVUS studies, even after high pressure post-dilatation and particularly in segments of stent overlap. For example, Tanigawa et al used OCT to examine a total of 6,042 stent struts from 25 lesions and found that 9.1% of all struts were malopposed[9]. Logistic regression analysis identified overlapping stent struts, longer stents, Cypher Select stents, and type C lesions as univariate predictors of malapposition. The higher number of malapposed stent struts more frequently seen with Cypher Select stents, perhaps reflects their closed cell design and thicker stent struts. Stent overlap has been associated with incomplete strut apposition in a separate study, which noted that despite aggressive stent optimisation using high-pressure balloons, overlapping stent segments showed higher rates of ISA (42%) than in proximal (20%) and distal (10%) stent segments[10]. These findings may in part account for the previously reported delay in endothelialisation of such segments.

Specific to the bifurcation, Tyczynski et al used OCT to examine the success of stent strut apposition in 31 patients who underwent stenting for bifurcation lesions. Of these, 17 patients underwent simple cross-over stent implantation (main vessel stenting followed by kissing balloon dilatation), while 14 underwent more complex reconstruction of the bifurcation using the Culotte or T-stenting techniques[8]. The authors found that strut malapposition occurred most frequently at the side branch ostium. The use of a technique of bifurcational stenting did not significantly increase the prevalence of strut malapposition compared with a simple technique, perhaps due to the use of the kissing balloon technique to ensure improved strut apposition in this group.

OCT is also currently being used to assess the procedural success of new bifurcation stenting technologies. Ferrante et al used OCT to assess the efficacy of the Tryton dedicated side branch stent (Tryton Medical, Inc., Durham, NC, USA) in nine patients, and found that malapposed stent struts were more frequently seen at the level of the bifurcation than in the proximal and distal stent in the main vessel[11]. In particular, the highest proportion of malapposed struts was seen towards the ostium of the side branch. Also, in the ongoing OPEN I study, OCT was initially used to assess adequate deployment of a new self-expanding nitinol stent (Stentys, Princeton, NJ, USA) that can be disconnected by balloon angioplasty to provide access to the side branch and full ostium coverage[12]. These studies demonstrate that in addition to its previously described roles in plaque, lesion and stent assessment, the use of OCT will be of vital importance in the development of new stenting technologies designed to tackle complex bifurcation lesions.

Late strut coverage: specific considerations for bifurcational lesions

It should be noted that the high resolution provided by OCT imaging allows for assessment, not just of strut apposition, but also of strut coverage and endothelialisation at follow-up, an issue that has been noted to be of particular relevance at the bifurcation.

In an early study by Chen et al comparing the coverage of bare-metal and sirolimus eluting stents, it was noted that stent struts in the bifurcation were highly prone to complications[13]. Specifically, the authors noted that struts in bifurcations were more often abnormal at follow-up, including several struts that were covered with thrombus, surrounded by a thick tissue layer, or completely uncovered. Subsequently, a sub-study of the ODESSA trial (Optical coherence tomography for Drug Eluting Stent SAfety), designed to evaluate

healing of overlapping stents, looked in particular at bifurcation segments with side branch diameters larger than 1.5 mm by angiography[14]. The authors examined the incidence of uncovered struts at three bifurcation locations - specifically opposite the side branch ostium, adjacent to the ostium, and in the side-branch ostium – and found variable patterns of strut coverage amongst different stent technologies. For example, paclitaxel-eluting stents were found to have the highest proportion of uncovered struts in the side-branch ostium, while sirolimus-eluting stents had the most uncovered struts in the main vessel opposite the ostium of the bifurcation.When considered together these two studies point to some of the inadequacies of our existing stent technologies for the treatment of complex bifurcation lesions. A need currently exists for further imaging research to clarify the most favourable stenting strategy for any individual case, and the efficacy of new bifurcation stenting technologies towards this end.

Future developments

Future generations of OCT equipment will include several technological advances that promise to enhance the capabilities of this imaging method even further. For example, immediate automated online detection of the lumen area after pullback will assist in the rapid assessment of the vessel morphology and minimum lumen area. (Lightlab C7, St Jude Medical, St. Paul, MN, USA) This may be particularly useful for guidance of interventions in bifurcations, where knowing the reference diameter of the vessel distal and proximal to the side branch is critical in correctly sizing the diameter and length both of the stent and post-dilatation balloon. In addition, the recent development of OCT with online 3D reconstruction allows the operator to obtain a 3D visualisation of the lesion and to plan a strategy accordingly. Initial experience of using 3D OCT reconstruction has revealed how 3D images may provide a unique tool for guidance during complex intervention in bifurcation and potentially improve stenting results (Figures 4 and 5).

Side branch ostium restenosis still remains the Achilles heel of bifurcation stenting. Opening the stent strut at the side branch ostium is considered critical to avoid coverage with neointimal tissue and risk of stent thrombosis. Several parameters affect side branch opening during bifurcation stenting, for example the platform design and the size of the balloon[9]. In addition, bench silicone models and previous computer simulations of bifurcation stenting have shown that cell crossing is a factor that has a large impact on the results of ostial dilatation[15]. To efficiently open a stent at the SB ostium, current recommendations suggest attempting to recross the wire through the most distal cell of the main vessel stent; crossing to the side branch through a proximal cell provides no scaffolding of the side branch ostium and leaves many struts unapposed near the carina, reducing the strut-free SB ostial area[1]. It can, however, be difficult in practice to

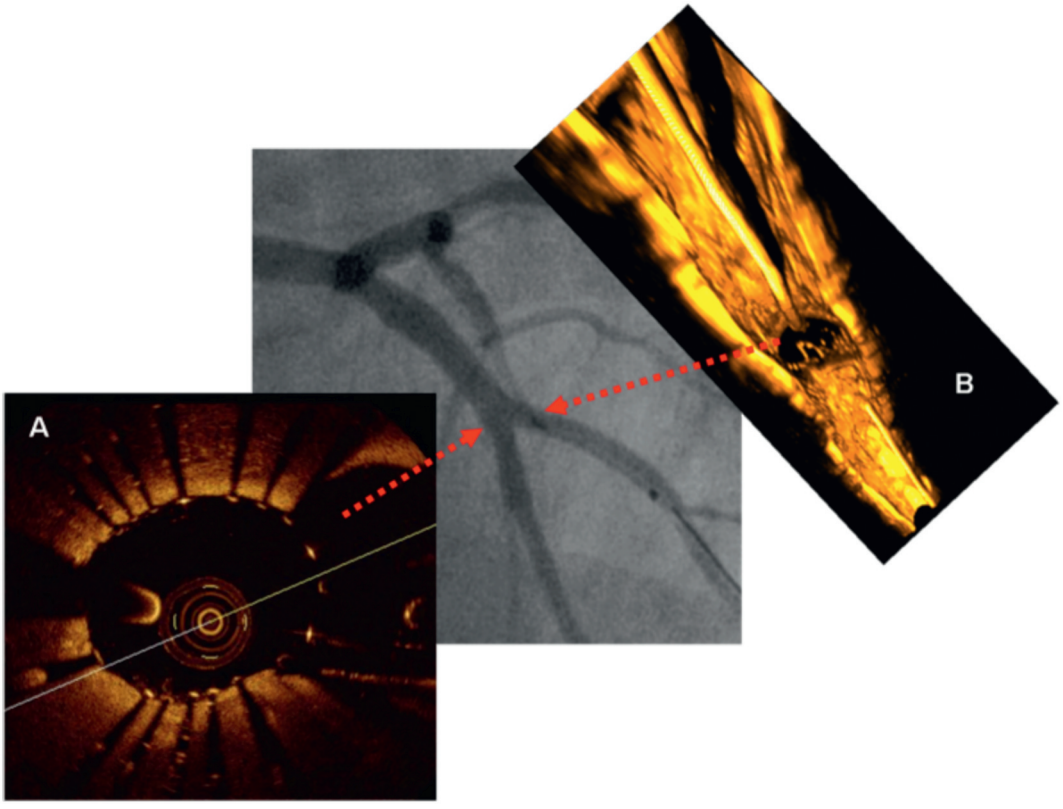

Figure 4. After stenting with a 3.0x28 mm zotarolimus eluting stent and final kissing balloon inflation (3.0+2.5 balloon), OCT shows the presence of malapposed struts present at the SB ostium near the carina. (A) Visualisation of the stent struts at the ostium using 3D OCT reconstruction reveals the path of the wire to the SB. (B) Crossing to the SB through the right cell is essential to achieve a good SB ostial dilatation. When the SB is dilated through a proximal cell as in this case, stent struts are left malapposed toward the carina. Online 3D OCT may provide a new tool for guiding bifurcation stenting and wiring of the SB to avoid undesirable proximal cell crossing.

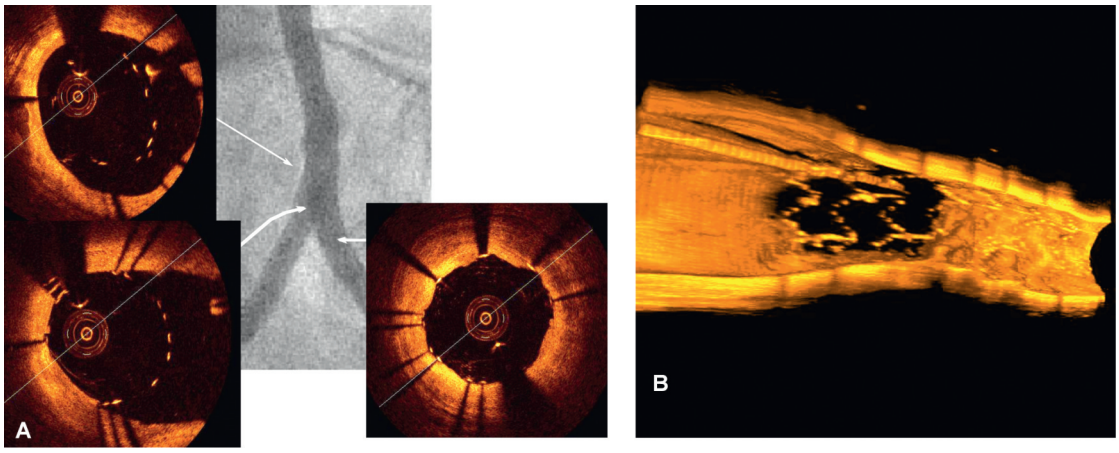

Figure 5. Panel A, intravascular optical coherence tomography pullback in a left circumflex (LCx) artery stented with a 2.5 mm everolimus eluting stent before recrossing the wire to SB for ostial dilatation. The operator intended to implant the stent just distal to the origin of the obtuse marginal, but OCT shows that, despite the optimal angiographic result, grossly malapposed struts are present. In panel B, the 3D reconstruction of the OCT image clearly indicates that the wire is within the stent and crossed a distal cell.

ensure that the SB has not been accessed through a proximal cell. This is particularly critical for SB with a relatively low take-off angle where the ostium area is the largest. Using 3D OCT reconstruction, the side branch guidewire can be easily tracked. Thus it becomes possible for the interventionalist to check that crossing to the side branch is satisfactory and one can further anticipate the result after balloon dilatation or implantation of a second stent and final kissing-balloon Inflation.

In addition to its use in clinical practice and research, OCT can provide valuable new insights into plaque biology in basic research, for example examining the role of shear stress on atherosclerotic plaque development. Maintenance of a physiologic, laminar shear stress is important for vascular homoeostasis, and shear stress directly affects endothelial function; it has anti-inflammatory and antiproliferative actions, and thereby protects against atherosclerosis. In contrast, low, negative, or disturbed shear stress, together with other risk factors for atherosclerosis, contributes to local endothelial dysfunction. This typically occurs near arterial bifurcations, branch ostia and inner curvatures.

To validate this concept of early atherosclerotic plaque build-up, OCT was performed in streptozotocin-induced diabetic swine fed an atherogenic diet. Every three months, invasive imaging with OCT was performed. After nine months on the diet, small intimal proliferations could be demonstrated by OCT typically occurring at low shear sites (Figure 6). These OCT images support earlier observations that early atherosclerotic lesions typically occur, but are of course not limited to, branching points in the vasculature.

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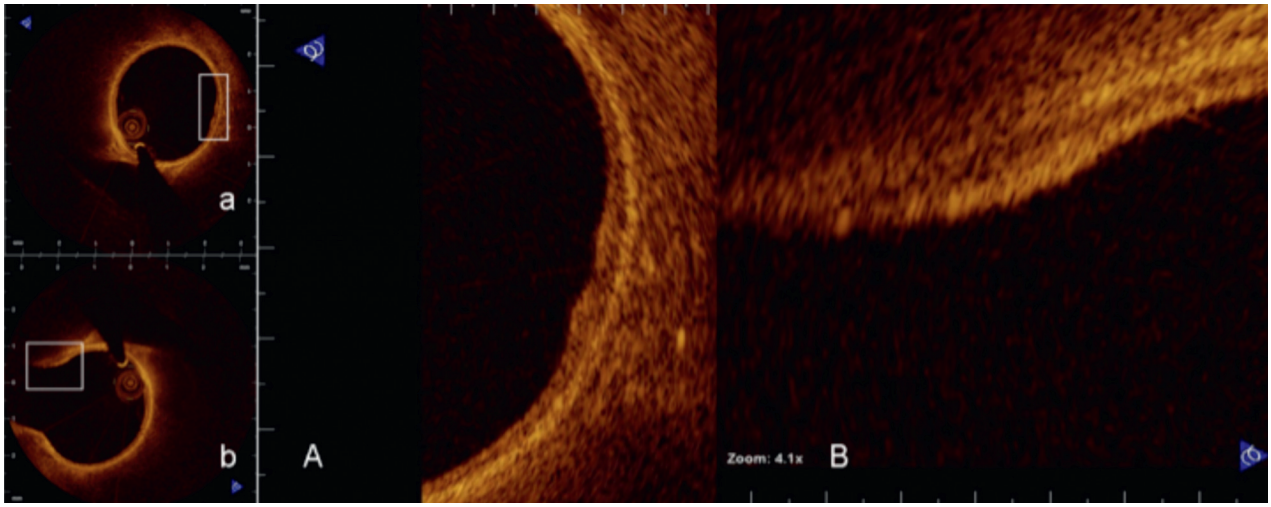

Figure 6. Earliest atherosclerotic changes opposite to the side branch ostium (panel a and insert 4-times magnified in panel A), and at the upstream edge of the side branch (panel b and insert 4-times magnified in panel B).

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