Three-dimensional optical frequency domain imaging in conventional percutaneous coronary intervention: the potential for clinical application

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Introduction

Two-dimensional (2D) frequency domain optical coherence tomography (FD-OCT) has enhanced our understanding of coronary atherosclerotic disease and is increasingly being used in conventional percutaneous coronary intervention (PCI) to elucidate mechanisms of disease and improve our understanding of complex coronary anatomy.

Since the first report of three-dimensional (3D) OCT applied in human coronary vessels,1 the technology has rapidly progressed.2–10 Currently, the main limitation of this technology is the need for off-line creation of 3D reconstructions—prototypes of current generation ‘real time’ (i.e. available peri-procedurally at the ‘push-of-a-button’) remain experimental, work in progress, and are limited by relatively poor image quality/resolution.4 As of now, the potential clinical application of 3D FD-OCT remains undefined.

Recently, the application of this emerging technology to the coronary bifurcation has allowed visualization and assessment of jailed side branches (SideBs) at a level of detail not previously reported.2–7 The assessment of a jailed SideB, after implantation of a bioresorbable scaffold in the main branch (MainB) of a bifurcation, lead to the proposal of a new classification system based on the assessment of the number of compartments the SideB ostium was divided into, with examples of how this may potentially effect the neointimal response and subsequent coverage of the struts.2

More recently, the application of this technology to the coronary bifurcation in patients implanted with conventional metallic stents, utilizing the Terumo optical frequency domain imaging (OFDI) system, was described for the first time.1 Hypotheses related to types of coronary bifurcation (‘parallel’ and ‘perpendicular’ bifurcations) based on the bifurcation angle, and how this leads to certain specific characteristics of the carina, which potentially made the SideB more vulnerable to the effects of carina shift and potential SideB closure, were described. Furthermore, the potential practical application of 3D FD-OCT in guiding the rewiring of the distal compartment of the SideB ostium—jailed with stent struts after MainB stenting—to minimize the risk of floating struts was demonstrated, something not easily achievable with conventional 2D FD-OCT systems or other intravascular imaging modalities.3,4,6 The potential for jailed stent struts at the SideB ostium, to act as a focus for neointimal ‘bridge’ formation and focal restenosis warranting further intervention, has also recently been demonstrated with 3D FD-OCT7—this was not so apparent on the corresponding 2D images; the practical suggestion from these findings was that final kissing balloon post-dilatation should be performed to clear any jailed struts at the SideB ostium. In addition, the use of 3D FD-OCT in potentially guiding the management of acute myocardial infarction has been reported.11 The identification of thrombus and stent malapposition to guide subsequent further aspiration thrombectomy, post-dilatation, and concomitant use of drugs was proposed.

Three-dimensional reconstructions of other intravascular coronary imaging modalities have previously been described; they have however failed to find a useful clinical role.12–18 One of the reasons that potentially makes 3D FD-OCT more clinically applicable is the unrivalled resolution of OCT technology (10–15 μm) compared with other intravascular imaging modalities—coronary angiography: 100–200 μm, computed tomography (CT): 300–500 μm, intravascular ultrasound (IVUS): 100–150 μm, coronary angiography: <200 μm19—and consequent ability to visualize intraluminal structures in unmatched detail. Conversely, with, for

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example, IVUS, this cannot reliably visualize intraluminal structures/detail such as thrombus or stent apposition; furthermore, post-processing of 2D IVUS images is required to allow 3D IVUS reconstructions, thus limiting its application in the catheterization laboratory.\textsuperscript{12,13} Despite the appeal of fusion of other intravascular imaging modalities, such as CT and IVUS,\textsuperscript{20,21} these are still limited by the resolution of the images compared with OCT.

Through a series of off-line 3D reconstructions performed with the Terumo OFDI system, in patients undergoing conventional PCI, followed by technical issues performed in a porcine model, the rapid progression of this emerging technology and the potential for clinical application are proposed. Opinion on the future development of 3D FD-OCT is also discussed.

**Methodology for undertaking off-line three-dimensional frequency domain optical coherence tomography reconstructions**

Three-dimensional frequency domain optical coherence tomography reconstructions of patients who underwent conventional PCI from the original First-In-Man study intracoronary Terumo OFDI system (Terumo Corporation, Tokyo, Japan),\textsuperscript{22} and of a single patient from a further ongoing study,\textsuperscript{22} are presented. All 3D reconstructions were performed at baseline as per the study protocol. The high-speed Terumo OFDI system is capable of acquiring 160 frames/s during the catheter pull-back, to a maximum speed of 40 mm/s; all images were acquired with a motorized pull-back of 20 mm/s. Comparatively, the current generation LightLab DragonFly C7 system (LightLab Imaging Inc., Westford, MA, USA) is capable of 100 frames/s. The higher frame rate of the Terumo OFDI system appears to be the primary reason why it is capable of producing superior 3D FD-OCT reconstructions compared with the current generation LightLab C7 system.\textsuperscript{3,22}

The methodology for off-line 3D reconstructions has previously been described.\textsuperscript{2} In brief, manual detection of every strut in each cross-section, using bitmap sequences (704 × 704 pixels) generated from prior 2D OFDI frames, was performed and 3D reconstructions were generated utilizing volume-rendering software (INTAGE Realia, KGT, Tokyo, Japan).

Technical issues relating to image quality are also demonstrated in a porcine model.

**Nomenclature for three-dimensional frequency domain optical coherence tomography reconstructions**

‘Fly-through’ views indicate a selected still image of an internal view of a vessel looking either downstream (proximal to distal vessel) or upstream (distal to proximal vessel). The fly-through (internal) view of the vessel is akin to the view obtained during endoscopy or angioscopy showing the internal lumen of the vessel.

Longitudinal views are a cut-away view of the vessel down the longitudinal axis with the internal lumen viewed externally—
wherever possible a view without the guide-wire shadow is shown. External views are taken from outside the vessel with views to show the internal vessel at the region of interest.

**Three-dimensional reconstructions**

**Assessment of simple lesions**

**Proximal right coronary artery lesion**

A severe proximal right coronary artery (RCA) lesion treated with a $3.0 \times 18$ mm Xience V drug-eluting stent (Figure 1) is demonstrated on coronary angiography (left images). Three-dimensional longitudinal reconstructions pre- and post-intervention are illustrated. The longitudinal 3D reconstructions represent the horizontal segment of the RCA before the first curvature—the use of the white arrows, identifying the jailed SideBs, will help the reader to co-register the 3D reconstruction with the coronary angiogram. Note the almost identical characteristics of the minimum lumen area on coronary angiography and 3D reconstruction (yellow arrows), indicative of the high resolution of OCT. Also present are one non-jailed SideB (striped white arrow) proximal to the implanted stent, and two jailed SideBs (white arrows) within the implanted stent, in both the coronary angiogram and 3D reconstruction.

**Aorto-ostial right coronary artery lesion**

A significant RCA aorto-ostial lesion (not illustrated) was directly stented with a $3 \times 15$ mm Xience V stent (Figure 2, upper left image). Post-procedural longitudinal (right image) and downstream fly-through (lower left image) 3D reconstructions are demonstrated. Note the jailed SideB in the downstream fly-through view (lower left image), and the guide catheter tip (white arrow), with some of the same render as the vessel, applied by the volume-rendering software. Yellow asterisks highlight the ostium of the right ventricular (RV) branch seen on coronary angiography and longitudinal and fly-through 3D reconstructions. From a technical perspective—one of the difficulties with imaging the aorto-ostial lesions is ensuring that the catheter tip is sufficiently disengaged from the coronary ostium to allow visualization with the OCT imaging wire during the pull-back, but close enough to allow injection of contrast for blood clearance—with inevitable over-spilling of contrast in the aortic cusps—and thus allow appropriate imaging.²⁴

**Stent malapposition**

**Embedded, protruding, and malapposed struts**

As the OCT light cannot penetrate metallic struts, OCT can only image the endoluminal strut border. Consequently, a ‘shadow’ is cast behind the metallic strut, and the adjustment for the thickness of the strut and polymer is therefore required to determine the apposition of the stent strut. Based on this phenomenon, stent
strut apposition by post-implantation OCT has been defined as embedded, protruding, or malapposed.\textsuperscript{25} With an embedded strut, the strut is buried in the intima for more than half its thickness; consequently, the shadow the strut casts is projected through the vessel wall, with no shadowing visible on the endoluminal vessel surface on post-implantation 2D and 3D FD-OCT imaging (Figure 3A). With a protruding strut, the stent strut is apposed to the intima but not embedded;
consequently, a shadow appears to be ‘cast’ on the vessel surface and wall (due to the thickness of the metallic strut and polymer which the OCT light cannot penetrate)—this represents a potential limitation of 3D FD-OCT, as the protruding struts erroneously gives the impression of strut malapposition, when it is in actual intimal contact (Figure 3B). With a malapposed strut, there is no intimal contact with the stent strut and vessel wall and appropriately leads to a shadow on the vessel surface and wall (Figure 3C).

Overlapping drug-eluting stents
Overlapping Xience V stents, used to treat a long segment of disease consisting of severe tandem lesions arising from the proximal first diagonal, are demonstrated (Figure 4). Downstream fly-through 3D reconstructions demonstrate embedded, protruding (yellow circles), and occasional malapposed struts (yellow arrow). Note the malapposed ‘interductile hinge’ and the shadow it casts on the vessel wall visible in the 3D reconstruction (Figure 4)—for comparison, an interductile hinge in an actual Xience V stent is illustrated in Figure 3A (yellow arrows). Corresponding 2D OFDI frames of the overlap are shown (top left image).

Thrombus and stent malapposition
Primary percutaneous coronary intervention: thrombus and consequent stent malapposition
Three-dimensional reconstructions are illustrated, post-implantation of a 3.0 × 24 Xience V drug-eluting stent with prior aspiration thrombectomy, following an inferior wall ST elevation myocardial infarction with occlusion of the mid-RCA. Downstream fly-through views (Figure 5A), post-stent implantation, demonstrate a large volume of thrombus (white arrows) and consequent stent malapposition at the proximal stent edges (yellow arrows)—note the shadow the malapposed struts cause on the proximal vessel wall (white arrows) and thrombus adhering to the stent strut at the coronary bifurcation. A longitudinal view of the same vessel (Figure 5B) demonstrates the extent of the thrombus (white arrows) and consequent stent malapposition at both stent edges (yellow arrows); also evident are over-hanging struts, with thrombus attached, at the bifurcation (upper white arrow). If the interventional cardiologist saw the 3D reconstruction after stent implantation, this is likely to have been crucial in the subsequent decision-making process in the use of further aspiration thrombectomy, post-dilatation, and concomitant use of drugs such as glycoprotein IIb/IIIa inhibitors. Further aspiration thrombectomy and post-dilatation of the stent were performed with angiographic resolution of the thrombus (not illustrated).

Coronary bifurcation
The promising potential clinical application of coronary bifurcations with 3D FD-OCT has recently been described by our group2,3 and is beyond the scope of this paper. Examples of 3D FD-OCT in the coronary bifurcation to demonstrate its potential clinical application are illustrated below.

Right ventricular branch of the right coronary artery
Close-up views of the RV branch of the RCA (Figure 6) from the previous study (Figure 5A and B) demonstrate the thrombus adhering to the over-hanging struts of the SideB. The principle of a ‘parallel bifurcation’ is demonstrated—note the corresponding 2D OFDI frames on the left—with the parallel origins of the MainB and SideB at their respective point of take-off. The carina (labelled) appears interposed between the parallel origins of the MainB and SideB at their respective point of take-off; if further MainB post-dilatation was undertaken alone with larger angioplasty balloons, it may be speculated that this would lead to carina shift and potential SideB closure.

Bifurcation stent
A V-shaped bifurcation lesion involving two obtuse marginal (OM) branches of the atroventricular (AV) circumflex, with severe ostial disease in the first OM branch, was treated with a 2.5 × 18 mm Nile Croco™ bifurcation stent implanted in the diseased branch, with the SideB of the stent deployed into the other branch of the bifurcation; TIMI-3 flow of the AV circumflex, with no angiographic pinching of the ostium, remained throughout. Longitudinal 3D FD-OCT reconstructions of the pre- and post-intervention bifurcation are demonstrated with corresponding 2D coronary angiograms (Figure 7A)—the ostium of the AV circumflex is not
visualized in the longitudinal 3D reconstructions illustrated, as it exists in a different plane to the ostia of the OM branches. For comparison, a Nile Croco™ bifurcation stent deployed in a phantom model of a bifurcation is illustrated (inset figure of far right image). Note the area of malapposition with the corresponding shadowing on the vessel wall in the proximal stent edge (yellow arrow)—the corresponding 2D OFDI frames are illustrated (Figure 7B). The remainder of the stent appeared to be relatively well apposed; there was however evidence of under-deployment (Figure 7A, white arrow) when compared with the phantom model.

Fly-through downstream views of the treated vessel, pre- and post-intervention, are illustrated (Figure 7C)—within this view, no malapposition or floating struts are evident at the bifurcation. For comparison, corresponding 2D cross-sectional OFDI frames post-implantation are illustrated below.

**Miscellaneous**

**Stent under-deployment and strut malapposition at the ostium**
Severe proximal OM coronary disease was directly stented with a 2.5 × 15 mm Xience V stent up to the ostium of the vessel; no post-dilatation was performed (Figure 8A and B).

Figure 8A demonstrates pre- and post-longitudinal 3D reconstructions with corresponding angiograms. White double arrow in the post-implantation longitudinal 3D reconstruction is suggestive of stent under deployment (lower right image), as also seen in the corresponding coronary angiogram lower left image. Note the cardiac motion artefact in the post-implantation longitudinal 3D reconstruction (marked with an electrocardiographic signal), leading to the ‘elongation’ of the struts (the mechanism is explained in Figure 10) and the malapposed strut at the ostium, with the shadow it casts on the vessel wall (yellow arrow, lower right image). Changing the endoluminal point of view, for instance with different views in the longitudinal plane (not illustrated) or with fly-through views looking downstream (Figure 8B, upper left image: yellow arrow) or upstream (Figure 8B, upper right image: yellow arrow), can help visualize stent malposition, which subsequently can be confirmed on corresponding cross-sectional 2D OFDI frames if necessary (lower images). The corresponding 2D OFDI frames suggest the presence of several ‘floating’ malapposed struts at the ostium—yellow arrows indicate the same malapposed strut seen in the 3D reconstructions.

**Assessment of the extent of plaque rupture**
Diagnostic coronary angiography was performed in a patient with a background of multiple cardiac risk factors and stable angina. Close review of the distal left main stem on coronary angiography suggested possible plaque rupture as evidenced by minor irregularity (Figure 9, inset upper right image: yellow arrow), with no flow-limiting lesion evident. The area of concern was not easily recognizable on 2D FD-OCT imaging—with only a high index of suspicion that an abnormality was present—close review of the individual 2D cross-sectional OFDI individual frames and 2D longitudinal views (in multiple different planes) was undertaken. If ‘real-time’ 3D FD-OCT was available, this would have potentially immediately highlighted the area of concern and allowed immediate focused assessment with the corresponding 2D imaging. Two-dimensional OFDI frames were subsequently highly suggestive of plaque rupture on 2D axial and longitudinal views (lower images: yellow arrows). Three-dimensional reconstructions demonstrated
the visible plaque rupture in the distal left main stem—yellow arrows in downstream fly-through (upper left image) and longitudinal (upper right image) views. The patient was medically treated.

**The principle of three-dimensional reconstructions performed in a non-diseased porcine model**

Two-dimensional OFDI were undertaken in a non-diseased porcine model implanted with a Xience V drug-eluting stent, to allow for the assessment of the technical issues relating to undertaking 3D PD-OCT reconstructions. The porcine study has previously been described and was approved by the Institutional Animal Care and Use Committee. The study was conducted in accordance to the American Heart Association guidelines for pre-clinical research and the Guide for the Care and Use of Laboratory Animals (NIH, 1996).

**Cardiac motion artefacts**

During the early ejection phase, the speed of the cardiac contraction is at the most rapid and faster relative to the pull-back speed of the OFDI probe during image acquisition. This consequently can potentially cause a cardiac motion artefact as illustrated (Figure 10A).

Since the heart contracts with longitudinal (along the longitudinal axis of the vessel) and rotational movements, this can lead to differing types of motion artefacts such as elongation, repetition, or rotational motion artefacts as illustrated in Figure 10B. Solid white arrow indicates an elongated strut; broken white line indicates repetition of same struts due to the forward and backward motion of the vessel over the imaging wire during imaging acquisition in the early ejection phase; white arrowheads indicates rotation due to the twisting motion of the coronary artery over the imaging wire. An example from a human study is shown in the fly-through view (looking upstream in the LAD) of an elongation artefact (Figure 10C).

**The trade-off between pull-back speed, cardiac motion artefacts, and image resolution of the three-dimensional reconstructions**

Differing pull-back speeds were used to assess image quality and frequency of cardiac motion artefacts in the non-diseased porcine model. Three-dimensional FD-OCT reconstructions were performed from 2D OFDI acquisitions with pull-back speeds of 20, 30, and 40 mm/s (Figure 11). With faster pull-back speeds (40 mm/s), the frequency of the cardiac motion artefacts consequently reduces due to a shorter period of time during imaging acquisition for cardiac motion to occur. This however comes at the expense of a lower longitudinal resolution (due to a thicker slice thickness: 0.25 mm) giving a more ‘grainy’ appearance. Conversely, with slower pull-back speeds (20 mm/s), the image resolution increases because of a greater longitudinal resolution (due to a ‘thinner’ slice thickness: 0.125 mm); this is however at the expense of an increased frequency of cardiac motion artefacts due to a longer imaging acquisition time period. A trade-off between image resolution (as determined by the pull-back speeds) and the frequency of cardiac motion artefacts is therefore necessary to ensure the ideal 3D reconstruction.

The recommendation for the Terumo OFDI system, in our experience, is a pull-back speed of 20 mm/s; this will allow optimal imaging while limiting cardiac motion artefacts; cardiac motion artefacts however will still occur as previously illustrated (Figure 9C). For the LightLab C7 system, because of the poorer resolution of the 3D reconstructions, we recommend a pull-back speed of 10 mm/s to improve the resolution; this however comes at the expense of substantially increased frequency of cardiac motion artefacts, with the risk of one of these artefacts occurring at the region of interest. Future generations of 3D FD-OCT systems, in our opinion, need to have much higher frame rates (200–300 frames/s +) to allow for even rapid pull-back speeds.
backs (40 mm/s +)—this will potentially lead to higher resolution 3D reconstructions with limited cardiac motion artefacts.

**Potential clinical application and opinion for the future development of three-dimensional frequency domain optical coherence tomography technology**

Due to the unrivalled resolution of OCT compared with other intravascular imaging modalities, it is the author’s opinion that the potential clinical application of this technology, as a complimentary tool to 2D FD-OCT is real, and if available at the ‘push-of-a-button’ when 2D intravascular imaging is performed, will provide a global perspective with subsequent targeted assessment with 2D FD-OCT imaging as required. Furthermore, the 3D reconstructions are intuitively easier to understand compared with the 2D images, which further adds to the appeal of this emerging technology.

The current prototypes of online 3D FD-OCT systems have the capacity to automatically detect struts based on their specific optical characteristics, such as the reflective properties of the metallic struts. The further requirements from industry to potentially make 3D FD-OCT a clinical reality include the improvement in automatic strut detection, higher frame-rate systems with rapid pull-back speeds to improve the resolution of the 3D reconstruction and reduce the likelihood of cardiac motion artefacts, automatic volume rendering of a sufficient calibre to allow for high-resolution imaging, dedicated quantitative software for analyses, and a user-friendly interface to allow for full virtual navigation of the vessel. With the latter, as previously illustrated, sometimes several views—such as longitudinal and fly-through views—are required to best visualize the area of interest; with the volume-rendering software utilized in the cases in this paper, practically any view of the vessel was achievable with relative ease. It should also be emphasized that the concept of virtual navigation (fly-through) of the coronary vessel is not new, having previously been implemented for many years in the magnetic navigation catheterization laboratory.

The development of dedicated software, which ultimately is what this technology is reliant upon, is of paramount importance. Dedicated volume-rendering software to achieve consistent and reproducible application of volume rendering—as has been achieved with spiral computed tomography—and dedicated quantitative software for the analyses of the 3D constructions are both crucial to allow for comparable, reproducible 3D reconstructions and quantitative data, which can have potential widespread clinical and research applications.

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**Figure 8** (A) Stent under-deployment and malapposition at the coronary ostium: longitudinal three-dimensional reconstructions, pre- and post-intervention, are illustrated with the respective coronary angiograms. (B) Malapposition at the coronary vessel ostium: three-dimensional reconstructions with downstream (upper left) and upstream (upper right) fly-through views and corresponding two-dimensional optical frequency domain imaging frames (lower images), demonstrating a single malapposed strut at the ostium (yellow arrows).

**Figure 9** Plaque rupture: demonstrated on three-dimensional longitudinal and downstream fly-through views with corresponding two-dimensional optical frequency domain imaging frames and coronary angiogram.
Potential clinical applications of the 3D technology include to allow for the global assessment of areas of possible stent malapposition—by the presence of shadow on the vessel wall as seen with protruding and malapposed struts—which may warrant subsequent closer review with 2D imaging to help ascertain areas requiring further post-dilatation; conversely, if malapposition is obvious on the 3D reconstruction, the operator may simply elect to undertake further post-dilatation. To aid with this process, automatic colour coding of apposed, protruding, or malapposed struts may be achievable.

The application of this technology within the coronary bifurcation has previously been described and is a further promising area of the potential for this emerging technology.2,3 Trying to visualize the complex anatomy of the bifurcation and the effects of intervention is difficult and not always reliable with 2D imaging.2,3 The addition of quantitative measurements, as previously discussed, may have a potential clinical application in the measurement of the SideB ostial area after MainB stenting, to allow assessment as to whether the SideB is haemodynamically obstructed.3 Angiographic assessment of pinched SideB after MainB stenting has previously been shown to be unreliable, with only one-quarter (27%) of SideB with angiographic residual narrowing $\geq$ 75% being found to be functionally significant on subsequent pressure wire studies.3,32

Other potential clinical applications previously demonstrated include the identification and localization of the extent of thrombus and need for subsequent further aspiration thrombectomy, post-dilatation, and concomitant use of peri-procedural anticoagulants—conversely, thrombus cannot be visualized by the IVUS and if this imaging modality was used, the operator would effectively have to make an educated guess as to whether malapposition is
present or not; a greater understanding of stent conformability, in particular at the coronary ostium; the identification of other intravascular abnormalities such as ruptured plaque (Figure 9) and even stent under-expansion.

Although OCT is not the intravascular imaging modality of choice for the assessment of stent under-expansion due to the limited penetration of OCT in intravascular tissue—whereas IVUS would be more ideal in identifying the media-to-media width for appropriate vessel sizing—the 3D reconstructions still identified an area where stent under-expansion was clearly evident (Figure 8) and may have guided the operator to undertake further post-dilation, with or without IVUS guidance. Furthermore, the introduction of quantitative measurements with 3D-OCT may allow defining of these lengths of interest on longitudinal 3D views that may also guide subsequent intervention.

The addition of tissue characterization within 3D FD-OCT reconstructions are further promising areas of research in this technology; these have previously been performed offline and would have the potential to aid in the identification of clinically useful areas of interest, such as lipid pools and vulnerable plaque. Fusion imaging of 2D FD-OCT and IVUS virtual histology has recently been described; this may subsequently be achievable with 3D FD-OCT. Furthermore, the development of 2D and 3D ‘microscopic’ OCT—with a resolution of 1–2 μm—has also very recently been shown to provide remarkably clear pictures of cellular and subcellular features, associated with atherogenesis and thrombosis in human cadaveric coronary arteries.

The realization of the full potential of this emerging technology within interventional cardiology clinical practice—as appears to be currently the case in the field of ophthalmology with, for example, 3D visualization of the retina—is required from clinicians and industry in order to allow the future development and validation of this innovative technology.

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comparison with intravascular ultrasound and quantitative coronary angiography.


