
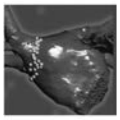
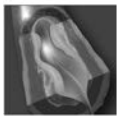

Intracoronary imaging in chronic total occlusions

Chronic total occlusion (CTO) intervention constitutes approximately 10–20% of all angioplasty procedures at selected centers. Benefits of CTO revascularization, in addition to relief of angina, include improvement of left ventricular function, reduced risk of major adverse cardiac events and potentially increased survival. Although several techniques, devices and guidewires have been developed for use in CTO, leading to an increased success rate, limitations of angiography in visualizing occluded arteries makes CTO interventions technically challenging. This article focuses on the principle intracoronary imaging techniques, such as intravascular ultrasound and optical coherence tomography, that may provide guidance during CTO revascularization, improving procedure timing, safety and efficacy.

KEYWORDS: **bifurcation ▪ chronic total occlusion ▪ coronary angiography ▪ efficacy ▪ false lumen ▪ intravascular ultrasound ▪ optical coherence tomography ▪ retrograde technique ▪ revascularization ▪ safety**

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Despite the growing availability of dedicated tools, chronic total occlusion (CTO) interventions still represent a significant technical challenge for interventional cardiologists. The most common cause of procedural failure of percutaneous coronary intervention (PCI) for CTO is the inability to cross the occlusion with a guidewire. The development of intracoronary imaging techniques, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), has improved the success rate for CTO recanalization while also increasing procedure safety and efficacy and reducing the amount of contrast medium, procedural time and irradiation time. IVUS analysis is characterized by an elevated depth-of-tissue penetration and can be used throughout the entire procedure to: identify the optimal wire entry point for the penetration of the proximal fibrous cap; to visualize the guidewire and check its intraluminal position throughout the entire 'blind spot' of angiography; and to assist correct stent deployment (**Box 1**).

To date, OCT is the only recent imaging modality to be anecdotally used in the field of CTO. OCT is characterized by a ten-times higher image resolution than IVUS, it is potentially helpful for the precise identification of the occlusion site. However, as opposed to IVUS, OCT does not allow continuous intracoronary imaging and cannot provide real-time guidance of the wire crossing.

Intravascular ultrasound

■ Intravascular ultrasound: technique & materials in chronic total occlusion

Intravascular ultrasound consists of a miniaturized ultrasound transducer (with a diameter of 0.89–1.0 mm) mounted on a transluminal catheter. The ultrasound probe is generally set at a frequency of approximately 30–50 MHz and a wavelength of 50–30 µm. IVUS is particularly significant for image guidance owing to its resolution (100–200 µm) depth of tissue penetration (2–10 mm) and ability to identify the external elastic lamina [1]. IVUS can provide important information regarding vessel diameter, calcification and plaque distribution; however, its most important advantage is that the process of advancing a guidewire can be accurately monitored. Coronary angiography cannot determine whether a wire has passed through the true lumen or has reached the distal coronary artery via a false lumen or subintimal passage. This difference can be clearly detected with IVUS, allowing a second wire to be guided into the true lumen. Conventional side-viewing IVUS offers real-time interventional guidance for CTO by placing the IVUS catheter in a side branch of the occluded lumen [2] or into a previously created false lumen [3], although complications may occur in the manipulation of IVUS catheters in a false lumen.

The choice of IVUS catheters may differ depending on the CTO anatomy. The 40-MHz IVUS catheter (Atlantis SR Pro, Boston Scientific,

Box 1. Intravascular ultrasound roles for wire cross in chronic total occlusion percutaneous coronary intervention.

- Antegrade technique
  - Identifying entry point of chronic total occlusion segment
  - Support wire re-entry from false to true lumen
- Retrograde technique
  - Support for wire cross
  - Controlled antegrade and retrograde subintimal tracking (CART) technique
  - Reverse CART technique
- Review wire route
- Optimizing stent apposition

CA, USA) with a mechanical scanning system is wrapped up in the protective sheath and provides better image quality, but demands a longer and larger side branch. Conversely, a 20-MHz IVUS catheter (Eagle Eye Gold, Volcano, CA, USA) with a solid-state system is suitable in the case of small and relatively short side branches and in severely angulated side branches.

Usefulness of IVUS in specific chronic total occlusion morphologies: crossing of 'stumpless' chronic total occlusion

Angiographically, it can often be difficult for the operator to identify the ideal entry point to the CTO, particularly in occlusions at bifurcation points that are generally 'stumpless' or 'flush', including, for example, those lacking a tapered stump useful for guidewire orientation. In stumpless CTO, IVUS-guided optimal penetration of the proximal cap requires a side branch that is large enough to accommodate the IVUS catheter, as well as the use of a large-bored guiding catheter, currently at least 7 Fr (Figure 1). The optimal point to penetrate the proximal cap will be close to the carina of the bifurcation, since older and harder atheroma at the bifurcation sites is usually located opposite to the side branch, while plaque components located close to the side branch are more likely to be newer and softer, and the carina is generally spared from atherosclerosis until the last stages of CTO development [4]. On the other hand, stumpless CTO lesions with a side branch arising from the occlusion are known to pose a significant challenge and are characterized by a significantly lower success rate as they frequently contain calcium, which makes CTO penetration particularly difficult, and there is no angiographic route for the guidewire that tends to easily slip into the side branch, owing to the preferential localization of calcium on the opposite side. Moreover, formation of intramural hematomas is easier in this type of lesion [5,6]. Three possible solutions have been proposed for the recanalization of stumpless CTO lesions; a retrograde approach via a collateral channel (Figure 2) [7]; the use of computed tomography (CT) angiography to identify lesion characteristics [8]; and IVUS-guided antegrade wiring. However, the retrograde approach requires specific guidewires and a sufficient supply of large diameter collaterals to conduct both wires and balloons, while CT cannot provide real-time information. IVUS-guided techniques, when feasible, can identify the entry point, guide wire passage in real time and provide accurate information of the target lesion such as lumen area, plaque size, distribution and composition (Figure 3). IVUS can be a useful tool for the detection of procedure-related vessel damage and subintimal wire tracking. Tsujita *et al.* used IVUS to compare guidewire manipulation-related vessel injury between the conventional antegrade approach and the retrograde approach [9]. They performed IVUS in 48 *de novo* CTO lesions, of which 23 lesions were treated via the antegrade approach and 25 lesions were treated via the retrograde approach. Although the CTO length was much longer in the retrograde approach group, at the end of the procedure, thrombolysis in myocardial infarction flow grade 3 was obtained in all patients. However, the incidence of the composite end point – subintimal wiring, angiographic extravasation, coronary hematoma or IVUS-detected coronary perforation – was higher in the retrograde approach group [9].

IVUS to guide optimal stenting in chronic total occlusion

Intravascular ultrasound is also a useful tool for analyzing stent apposition. One recent IVUS report indicated that subintimal drug-eluting stent (DES) implantation during a CTO PCI caused multiple late-acquired malappositions owing to coronary aneurysm formation [9]. A strong correlation exists between postprocedural IVUS minimum stent area and the incidence of restenosis [10]. Furthermore, Erlich *et al.* have reported a case of acute stent thrombosis after multiple subintimal stenting [11]. IVUS studies demonstrated that stent thrombosis after DES implantation is related to a smaller minimum stent area, especially in patients who developed stent thrombosis while using clopidogrel, and to higher proximal residual plaque burden [12]. Gaster *et al.* evaluated the clinical implication of IVUS-guided PCI, demonstrating that in the IVUS-guided group, 78% of patients remained completely event-free (Q-wave acute myocardial infarction, repeat PCI, coronary artery bypass graft or death) versus 59% in the non-IVUS-guided PCI group, with an odds ratio of 2.5 in favor of IVUS guidance [13]. Although these studies have been performed in nonocclusive lesions, optimal stent expansion may also improve long-term outcomes in CTO lesions.

Limitations of IVUS-guided wiring

The intravenous ultrasound-guided wiring technique has two potential limitations. First, it cannot provide information on the course of the vessel distal to the occlusion and a bilateral coronary angiography is generally required to visualize the distal part of CTO lesion. Second, IVUS cannot be used in cases of side branches with diameters smaller than those of the IVUS catheters.

Latest developments

Particularly challenging CTO lesions have led to the necessity of developing newer techiniques to improve the success rate of CTO crossing and outcome after revascularization. Forward-viewing IVUS catheters would obviate the need for the side branch and, combined with 3D reconstruction techniques, would allow the visualization of the lesion distal to the occlusion and provide a real-time map of the occluded vessels [14]. Nevertheless, to date no study has systematically assessed the efficacy and safety of using forward-looking IVUS in the PCI of CTO. IVUS-based techniques such as elastography [15], radio-frequency tissue characterization [16] or virtual histology [17] may help identify the mechanical properties and composition of CTOs, but would have to be revised and revalidated in a forward-looking configuration.

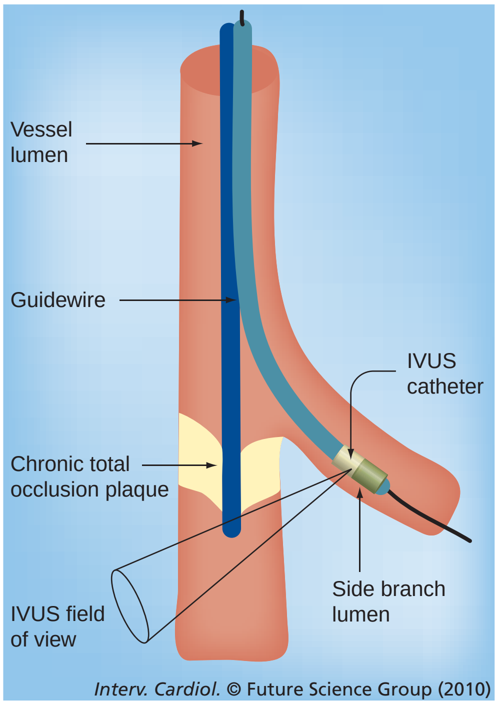

Figure 1. Intravascular ultrasound guidance to detect chronic total occlusion entry point.
IVUS: Intravascular ultrasound.

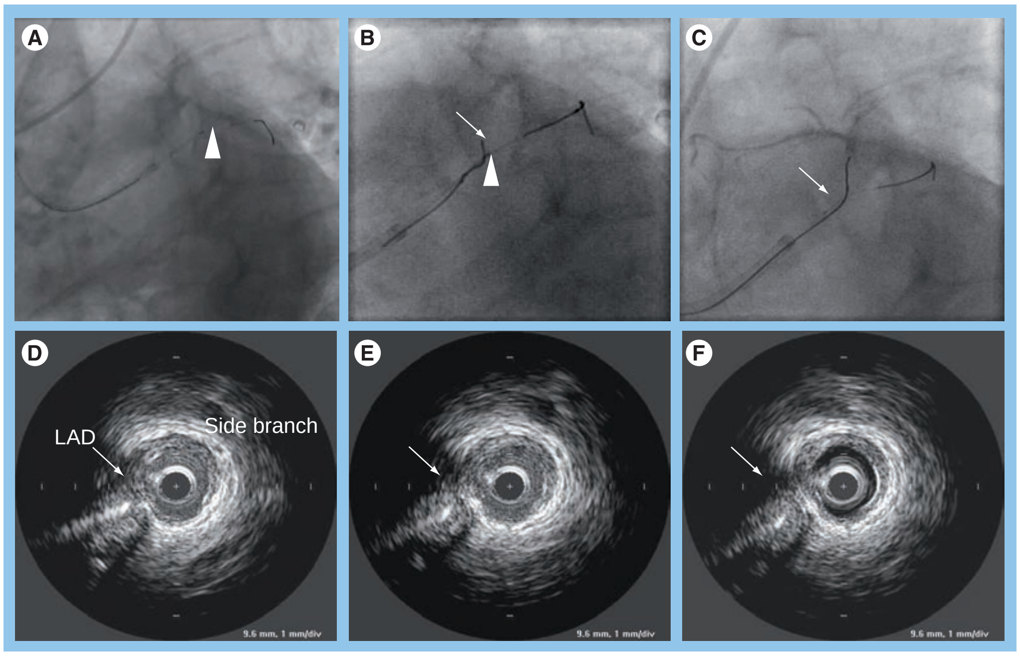

Figure 2. Intravenous ultrasound-guided recanalization of a stumpless chronic total occlusion lesion of the left anterior descending artery (Sacred Heart University-Gemelli Hospital case). **(A–C)** Guidewire advanced into LAD (arrows); intravascular ultrasound probe is positioned in a side branch (arrowheads). **(D–F)** Intravascular ultrasound analysis from a side branch shows wire passage (arrows) through LAD occlusion.
LAD: Left anterior descending.

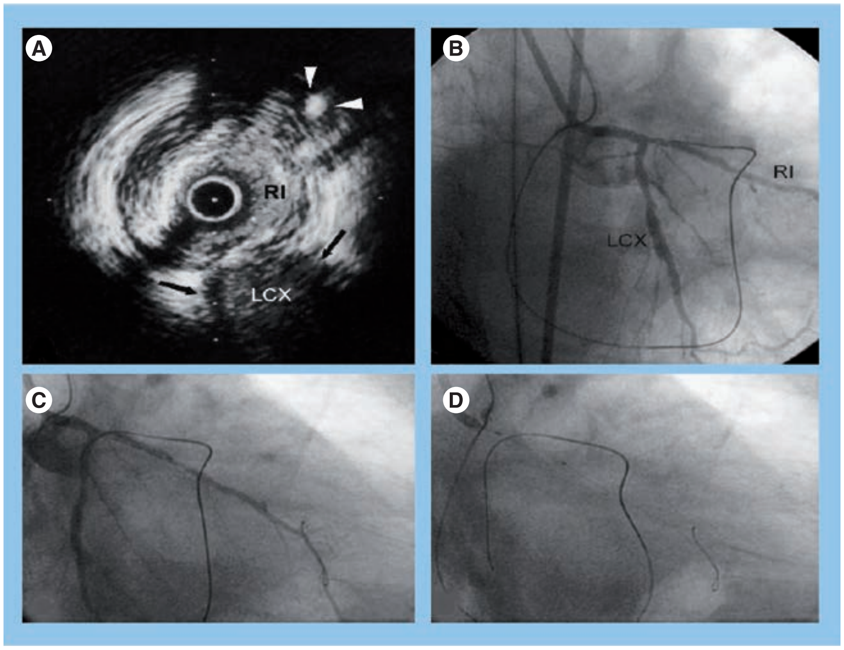

Figure 3. Recanalization of a stumpless chronic total occlusion lesion of the left anterior descending artery using retrograde approach. (A) Intravascular ultrasound analysis from the RI with left circumflex artery evidence (black arrows) and the guidewire in the left anterior descending artery (white arrowheads). **(B–D)** Guidewire advanced into LCx.
LCx: Left circumflex; RI: Ramus intermedius
Reproduced with permission from [36].

In ostial or paraostial CTO, the traditional antegrade approach presents many difficulties, such as wire slippage into another epicardial coronary artery and the numerous branches. These difficulties can be overcome with IVUS-guided ostial CTO puncture and the parallel-wire technique or using a retrograde approach intervention through an intercoronary channel (collateral), which can be an epicardial channel, interatrial channel, intraseptal channel (septal collateral) or a bypass graft [18].

A recently developed technique useful in cases of very complex CTO is the controlled antegrade and retrograde subintimal tracking (CART) technique [19], which consists of creating a small subintimal space in the distal part of the CTO using a small balloon over the retrograde wire. After deflation of the retrograde balloon, the antegrade wire is passed into the subintimal space. In the newest reverse CART technique [20], after creating a subintimal space with a small balloon over the antegrade wire, the retrograde wire is passed into the subintimal space. However, there is a danger of retrograde coronary dissection and subsequent ischemia in the territory of another epicardial coronary artery. This danger is particularly high with the reverse CART technique, as the antegrade balloon inflation and the retrograde wire passing can both cause left main dissection. However, the recently published first CART registry has confirmed that the bilateral approach for CTO lesions using the CART technique is feasible, safe and has a higher success rate than other approaches (Figure 4) [21].

Optical coherence tomography

Optical coherence tomography is an imaging modality that uses the interference of light reflected back from the tissue with light from a reference arm to form an image based on the depth-resolved reflectivity of the sample, with a penetration depth of 2–3 mm. Cross-sectional images are generated by measuring the echo

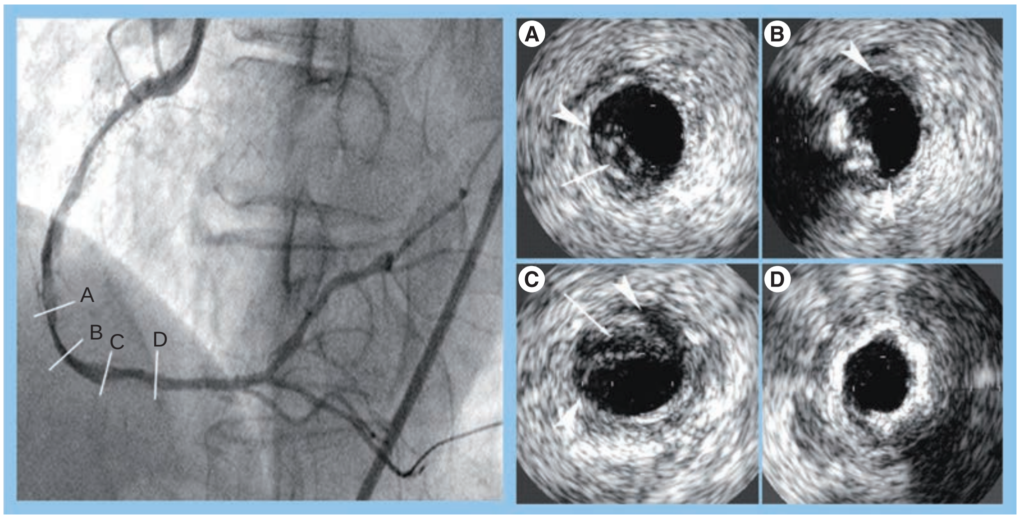

Figure 4. Intravascular ultrasound visualization of retrograde microcatheter and of the antegrade wire in the subintimal space in a chronic total occlusion intervention by the controlled antegrade and retrograde subintimal tracking technique.
Reproduced with permission from [19].

time-delay and intensity of light that is reflected or back-scattered from internal structures in the tissue. Current OCT images are obtained with a near-infrared electromagnetic radiation, with a peak wavelength in the 1280–1350 nm band, a 10–15 µm tissue axial resolution, a 94 µm lateral resolution at 3 mm and a maximal scan diameter of 6.8 mm. The principle advantages of OCT are the increased resolution (tenfold higher image resolution than IVUS) at the cost of poorer penetration through tissue and blood (Figure 5) [22].

The high resolution and contrast of OCT can provide significantly more detailed morphological information than IVUS, improving assessment of stent deployment and PCI acute complications. In particular, OCT is more sensitive in detecting coronary dissection during PCI [23].

The main obstacle to the adoption of OCT imaging in clinical practice is that OCT cannot produce images through a blood field, as it requires clearing or flushing blood from the lumen. In the occlusive technique, during imaging acquisition, coronary blood flow is stopped by inflating a proximal occlusion balloon and flushing a crystalloid solution, usually Ringer's lactate, through the end-hole of the balloon catheter at a flow rate of 0.5–1.0 ml/s. The vessel occlusion time should be adjusted according to patient symptoms and severity of ECG changes [24]. More recently, a nonocclusive mode of acquisition has become available, which does not require proximal balloon occlusion. A standard intracoronary guidewire is generally used to cross the target lesion and to enable insertion of an over-the-wire intracoronary probe. The guidewire is then switched for a specific LightLab OCT (M2 LightLab Imagewire™, Westford, MA, USA) and pull-back is performed at the highest available speed during simultaneous infusion of a viscous iso-osmolar solution through the guiding catheter [25]. Experiences with both occlusive and nonocclusive OCT image acquisition show the technique to be safe. A multicenter registry of OCT compared occlusive and nonocclusive technique safety in 468 patients [26]. Transient chest pain and ECG ischemic changes were observed in 48 and 45% of patients, respectively, and were significantly more frequent in patients imaged using the occlusive compared with the nonocclusive technique. Major complications included ventricular fibrillation (1.1%), air embolism (0.6%) and vessel dissection (0.2%). There were no cases of coronary spasm or major adverse cardiac events during or after OCT examination [26].

Forward-looking OCT has a high enough resolution to clearly visualize microvessels and the different layers of the vessel wall [27]. Several variants of conventional side-viewing OCT exist and could be adapted to forward-looking OCT, such as polarization sensitivity imaging (which can assess the concentration of collagen within the coronary artery [28]), elastography (useful for assessment of mechanical properties of the plaque [29]), OCT-based Doppler techniques (for evaluation of the presence of flow in the microvessels of a CTO [30]) and optical coherence reflectometry (OCR) [31]. The Safe-Cross® wire (Kensey Nash Corp., PA, USA) is a forward-looking system that utilizes the principle of OCR for guidance, coupled with the ability of radiofrequency ablation. Hoye *et al.*, using this OCR system in a series of 29 CTOs that could not be crossed with conventional wires, reported a success rate of 51.7% with no complications [32]. Using the same device, Wong *et al.* obtained a success rate of 90% in a small case series of patients with CTO lesions with unsuccessful recanalization by the conventional guidewire technique [33]. This technology can help operators to follow the guidewire precisely

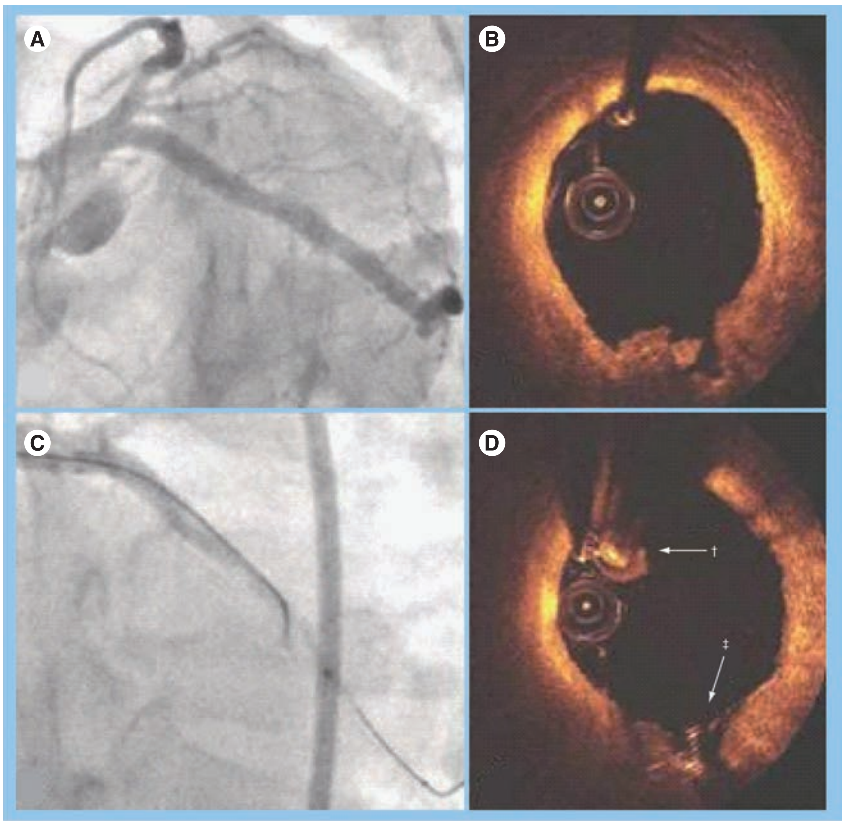

Figure 5. Optical frequency domain imaging guided crossing of a stumpless chronic total occlusion. (A) Chronic total occlusion (CTO) of the posterolateral branch originating from a dominant left circumflex artery. **(B)** Preinterventional optical frequency-domain imaging (OFDI) showed the localization and morphology of the CTO entry point. **(C)** Venture catheter with a deflectable tip and OFDI imaging probe in the left circumflex artery. **(D)** There is a visible shadow from the Venture catheter and leading guidewire for the OFDI probe (†). OFDI confirmed good position of the guidewire (‡) puncturing the entry point of the CTO. Reproduced from [34].

through the CTO lesion, thereby minimizing the risk of perforation, and the radiofrequency ablation system increases the crossing potential of the wire.

Optical coherence reflectometry images can be obtained by two main technologies – time domain and frequency domain. Optical frequency domain imaging (OFDI) is a new generation of optical intracoronary imaging. Basic OCT characteristics do not change when moving from time domain to frequency domain OCT. OFDI has the advantage of an improved signal-to-noise ratio, allowing an increased imaging acquisition speed with comparable or improved image quality compared with the earlier time domain systems. OFDI may help to identify the entry point and facilitate entry into the true lumen with a stiff wire in CTO lesions with angiographically invisible stump [34]. Recently, Takarada *et al.* published a study of comparison between frequency domain and time domain OCT, demonstrating a reduced time of image acquisition and a higher rate of clear image segments with frequency domain OCT compared with time domain OCT [35]. However, while there has been a significant improvement, OFDI still does not provide continuous intracoronary imaging unless blood is cleared from the artery. This makes the technique difficult for real-time positioning of the wire toward the CTO entry point.

The advantage of OCT is due to its high resolution and it will undoubtedly be useful for evaluating plaque composition and neointimal coverage after DES implantation.

Conclusion

The capability of IVUS for real-time imaging without the need for blood clearance renders it the most commonly used system for CTO intraprocedural imaging. However, OFDI is able to offer new capabilities in plaque characterization, which may aid complex CTO interventions.

Future perspective

Intravascular ultrasound has become a cornerstone of CTO PCI, guiding operators while negotiating very difficult procedures, helping the optimization of implanted stent and finally providing precious clues that have helped our understanding of CTO biology and pathophysiology. We believe that IVUS will remain extremely useful in the majority of CTO procedures, especially when improved technology will lead to further miniaturization and greater trackability of the IVUS catheters.

Conversely, in our opinion, OCT usefulness during CTO procedures will remain very limited, especially owing to the need for total blood clearing and the limited depth of penetration. Morever, the clinical relevance of the very detailed pictures that can be obtained with OCT remains to be established.

Executive summary

Intravascular ultrasound analysis principles

- Intravascular ultrasound (IVUS) consists of a miniaturized ultrasound transducer set at a frequency of approximately 30–50 MHz and a wavelength of 50–30 µm, mounted on a transluminal catheter.
- IVUS can provide information about vessel wall and diameter, calcification and plaque distribution.

Intravascular ultrasound-guided chonric total occlusion revascularization

- Intravascular ultrasound offers real-time interventional guidance for chronic total occlusion (CTO) by placing the IVUS catheter in a side branch of the occluded lumen or into a previously created false lumen.
- IVUS can guide the operator to identify the ideal entry point to the CTO, particularly in occlusions at the bifurcation, stumpless occlusions and ostial occlusions.
- IVUS may have an important role in optimizing stent implantation and for the detection of procedure-related vessel damage in both antegrade and retrograde techniques.
- In recent years, the controlled antegrade and retrograde subintimal tracking (CART) technique and the newest reverse CART technique have been developed for cases of very complex CTO.

Optical coherence reflectometry analysis principles

- Current optical coherence reflectometry (OCT) images are obtained with near-infrared electromagnetic radiation that is reflected or back-scattered from internal structures in tissue and is based on the depth-resolved reflectivity of the sample.
- OCT images can be obtained by two main technologies – time domain and frequency domain. The latest technology has the advantage of an improved signal-to-noise ratio, allowing an increased imaging acquisition speed with comparable or improved image quality when compared with the earlier time domain systems.
- The advantage of OCT is due to its high resolution and it will be useful to evaluate the plaque characterization and neointimal coverage after drug-eluting stent apposition.

Conclusion

- IVUS-guided percutaneous coronary intervention during CTO revascularization has accumulated excellent clinical experiences and is the most commonly used intracoronary imaging modality in this setting.

Financial & competing interests disclosure

Christian Hamilton-Craig is supported by the National Heart Foundation of Australia and Queensland International Fellowship. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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