Utility of Intravascular Ultrasound in Percutaneous Revascularization of Chronic Total Occlusions
An Overview

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ABSTRACT

Intravascular ultrasound has been used for >20 years to guide percutaneous coronary intervention in different subsets of coronary lesions. During the last decade, the interest in percutaneous coronary intervention for chronic total occlusion (CTO) has increased dramatically, leading to high success rates. Failure of guidewire crossing is the most common reason for failed CTO attempts. Certain angiographic features, such as blunt proximal CTO cap, tortuosity, heavy calcification, and lack of visibility of path in the distal vessel, increase procedural difficulty. A better understanding of the behavior of the guidewire within the CTO segment may represent a key issue to achieve successful outcome. In this respect, intravascular ultrasound imaging might have potential roles in the recanalization of CTOs. In this paper, we focused on the usefulness and the applications of intravascular ultrasound imaging in percutaneous CTO recanalization, underlying its impact on clinical outcome. (J Am Coll Cardiol Intv 2016;9:1979–91) © 2016 by the American College of Cardiology Foundation.

During the last decade, the interest in chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has increased dramatically, leading to important developments in dedicated equipment and techniques (1–3). Although high success rates (80% to 90%) have been reported by experienced operators (4–6), they remained lower than those achieved in conventional angioplasty. Failure of guidewire crossing is the commonest reason for failed CTO attempts. Certain angiographic features such as blunt proximal CTO cap, tortuosity, heavy calcification, and lack of visibility of path in the distal vessel increase procedural difficulty (7). Therefore, a better understanding of the behavior of the guidewire within the CTO segment might represent a key issue to achieve successful outcome.
Intravascular ultrasound (IVUS), a catheter-based imaging technique providing high-resolution cross-sectional images of the lumen and vessel wall, has been used for >20 years to guide PCI in different subsets of coronary lesions (8-10). In CTO PCI, IVUS might have several potential roles: some specific to the key challenge of CTO recanalization (i.e., wire crossing), others in common with complex long calcified lesions such as optimal sizing and expansion of the stents (11).

In this current state-of-the-art paper, we focus on the usefulness and the applications of IVUS in percutaneous CTO recanalization, underlying its impact on clinical outcome.

**SPECIFIC APPLICATIONS OF IVUS IN CTO PCI**

**IVUS APPLICATIONS IN ANTEGRADE APPROACH.**

IVUS has multiple uses in antegrade approach such as resolving proximal cap ambiguity (12-14), facilitating re-entry into the true lumen after subintimal crossing (15,16) and confirming distal true lumen guidewire position.

**Stumpless lesion.** The absence of a well-defined stump is a major limitation for CTO recanalization (17,18). Under the definition of “stumpless,” however, there is often a large variety of conditions going from the easiest scenario of a flush occlusion at the site of a side branch (where the origin of the side branch is clear and the direction of engagement of the occlusion indicated by retrograde filling with a short occlusion segment), to impossible cases when the side branch seamlessly continues into the main vessel and, because the occluded segment is long enough, there is absolutely no clue where the artery originates.

Multislice computed tomography can offer an indication on direction and presence of tortuosity and calcification at the entry point and along the occluded segment (19). However, even the most sophisticated co-registration system is unable to truly offer direct guidance during the procedure, a unique advantage offered by IVUS.

The general principle is that the IVUS probe is advanced into the side branch and during pull-back the precise location of the occlusion and the presence of calcium are identified. Any side branch originating at the site of occlusion can be used provided it is large enough to accept an IVUS probe and there are no extreme angulations or ostial stenosis (or calcification) preventing the insertion of the IVUS probe.

There are 2 ways to support the guidewire engagement into the occlusion stump by IVUS (Figures 1 and 2). The first is direct on-line guidance with the probe left at the site with the best view of the stump so that the wire position can be monitored on-line and a successful entry of the wire, ideally centrally, in the stump can be documented. Unfortunately, this method requires large guiding catheters to fit together the IVUS catheter and the CTO microcatheter (8-F for Corsair [Asahi Intec, Aichi, Japan]/Turnpike [Vascular Solutions, Minneapolis, Minnesota], 7-F for Finecross [Terumo, Tokyo, Japan]) or similar probes. A second disadvantage is that the bulky IVUS probe may deflect away guidewires and microcatheters from the stump and preclude simultaneous contrast injections. This is particularly true for a side branch having a shallow angle with the occluded vessel.

In most cases, serial examinations with IVUS are performed so that the puncture is done at the site where the angiographic roadmap shows the IVUS transducer when the probe was detected, but without the benefit of a continuous IVUS acquisition. Once the puncture is made where the stump was visualized on IVUS, subsequent IVUS passes are needed to confirm the intraluminal position of the guidewire. Especially if the side branch is relatively parallel to the CTO vessel, the wire progression can be monitored successfully for at least the first critical few millimeters. Reinserting the IVUS probe will show the highly reflective guidewire within the CTO stump and follow it in its first path or, vice versa, suggest immediate withdrawal and trying a different entry point.

The use or at least the availability of IVUS for stumpless lesions is highly recommended and may prevent subintimal entry at proximal cap due to the wrong identification of the CTO stump. Specific expertise for this indication is highly recommended and proctoring by an experienced CTO operator liberally using IVUS is mandatory to extract the full potential information from the IVUS imaging.

**Antegrade re-entry.** This second modality of IVUS guidance for antegrade CTO recanalization differs from stump identification because the IVUS probe must be inserted on the wire already within a subintimal position following a failed attempt at re-entry. A short-tip Volcano Eagle-Eye (Volcano, Rancho Cordova, California) is the preferred device because of the short distance between tip and IVUS sensor but occasionally smaller IVUS catheters (regular Eagle Eye [Volcano] or Opticross [Boston Scientific, Marlborough, Massachusetts]) can be directly inserted avoiding pre-dilation. In most cases, however, especially if the calcium burden is not excessive, the IVUS probe will follow the path successfully crossed by a microcatheter.
A nontapered, highly radiopaque, stiff wire such as a Miracle 6 or 12 (Asahi Intec) is preferred to insert the IVUS probe, with particular attention not to inadvertently advance these wires too far subintimal. Occasionally, the first stiff subintimal wire breaks into a side branch beyond the occlusion (e.g., a septal/diagonal in the left anterior descending artery or a right ventricular branch/acute marginal branch in the right coronary artery), still with no access to the distal vessel but offering the opportunity of a safe insertion, certainly within the vessel architecture, of the IVUS probe. Dilation with a small balloon up to the ostium of this side branch can be used more liberally if the IVUS probe does not advance and may occasionally by itself allow re-entry with a second wire.

The technique of IVUS-guided re-entry is often misleadingly called “distal” re-entry. In reality in most cases, the help offered by IVUS is the identification of a better and more central position where to engage a second guidewire within the occlusion, so that the start point of examination is at the proximal cap (identified by IVUS), and the second guidewire is advanced in parallel in a central position, finally breaking into the true lumen filled by retrograde blood (Figure 3).

This technique is one of the most difficult to learn in CTO recanalization and its use is more successful in the capable hands of Japanese operators who use complex algorithms to identify the direction where the new guidewire should puncture/be steered to remain in the true lumen. In the West, the application of the much easier purely angiographic technique of distal re-entry using a dedicated flat balloon with 2 side-ports (StingRay, Boston Scientific) has almost completely replaced IVUS guided re-entry. Occasionally, however, confirmation that the true distal lumen...
is within reach before attempting a re-entry with the StingRay can make the operator more confident in using a relatively bulky device and extra-stiff wires.

A parallel wire technique, leaving the first guidewire in the subintimal space and advancing a dual lumen catheter such as a Crusade (Kaneka, Osaka, Japan), may also benefit from a confirmation of the position of the true lumen and relationship with the first guidewire using IVUS.

**IVUS APPLICATIONS IN RETROGRADE APPROACH.**
During retrograde CTO procedures, the IVUS probe (always advanced on an anterograde guidewire) can be useful in the following situations: retrograde guidewire crossing and reverse controlled antegrade retrograde tracking (CART) technique.

**Retrograde guidewire crossing.** In a first-line retrograde approach, IVUS could be useful for guidewire crossing in particular situations such as ostial occlusions or bifurcations with blunt stump.

In case of ostial CTO lesions, an IVUS probe should be placed immediately in the very ostial segment. In this position, it is possible to visualize the exact location of the retrograde guidewire and its re-entry in the true lumen. Without intravascular images, the retrograde guidewire, pushed in the intimal plaque, could cause aortic dissection in case of ostial CTO of the right coronary artery (Figure 4). Similarly, in ostial left anterior descending CTO, the retrograde guidewire could be subintimal in the distal pre-divisional left main and in true lumen in the mid left main. With no IVUS assessment, externalization of retrograde guidewire and subsequent PCI may lead to left circumflex occlusion. With an IVUS probe positioned in the ostial left circumflex, the operator can recognize this dangerous situation and modify the position of retrograde guidewire at the level of the distal LM (Figure 5).

In case of bifurcations with blunt stump (e.g., left anterior descending diagonal branch), a complex situation consists of an intrastent CTO, where the stent
is implanted from the main vessel to the side branch, with the CTO entry point located in the middle. In this case, antegrade recanalization may be very challenging, while retrograde approach, supported by IVUS, is often more feasible. An IVUS probe, located in the side branch can clarify the retrograde guidewire position in CTO entry point and facilitate the re-entry in the true lumen within the stent struts (Figure 6).

Otherwise, a retrograde approach can be used as a bail-out strategy when an anterograde guidewire goes subintimal. In this case, an IVUS probe over the antegrade wire can clarify and confirm the exact position of the retrograde guidewire in the true lumen proximal to the CTO body. In this way, even the retrograde guidewire can be handled under direct visualization of IVUS into the proximal true lumen. Reverse CART. When retrograde guidewire crossing is unsuccessful, a dissection and re-entry retrograde technique is mandatory to achieve success. The most frequent is the reverse CART technique, characterized by antegrade subintimal dilation to create a connection channel in the same space between antegrade and retrograde guidewires.

It is important to keep in mind 4 possible anatomic situations in which the antegrade and retrograde guidewires could be engaged into the CTO body. These situations can be recognized only by IVUS evaluation (Central Illustration).

In comparison with the traditional technique, the IVUS-guided reverse CART technique offers the following advantages:

- Evaluation of antegrade and retrograde guidewires positions compared with CTO body and optimal balloon sizing for medial disruption. IVUS provides information on true CTO vessel size and plaque components distribution, thereby potentially reducing perforation risk.
- Selection of the appropriate position within CTO vessel where to create connection between antegrade and retrograde guidewires (more proximally or more distally) when initial reverse CART strategy is unsuccessful due to severe calcifications (Figure 7).

In addition, after successful reverse CART, it could be sometimes impossible to externalize the retrograde guidewire into the antegrade guiding catheter. In this situation, IVUS can show a connection only in some mid-distal portion of the vessel and not in the proximal segments; so the only possibility is to use the child-in-mother facilitated technique, making re-entry possible in a segment different from the ostium (Figure 8).
Finally, after externalization of retrograde guidewire, IVUS-guided stenting helps to avoid contrast injections that could create or worsen antegrade or retrograde subintimal dissection.

**LIMITATIONS OF IVUS IN CTO PCI.** The big enemy for IVUS applications in CTO PCI is calcium, obscuring the position of the occlusion stump behind a calcium plate or impairing the detection of the collapsed true lumen. Attempts to overcome these limitations using optical coherence tomography, which can see through calcium are limited by the need to remove blood with contrast, forcing an extension and enlargement of the dissection plane. Optical coherence tomography-guided systems for re-entry have been used successfully (20) in peripheral occlusions, but remain too bulky to find routine intracoronary application. Another main limitation of IVUS is that the probe is side-looking, so that the catheter must be inserted into the occlusion to image it. Forward-looking probes have been tested in peripheral vessels, but not as yet within the coronary circulation.

The use of IVUS along with other equipment can be difficult or even impossible when small (6-F) guide catheters are used. Nonetheless, the use of double guiding catheter technique (one for IVUS probe and one for crossing guidewire) in some cases might overcome such a limitation. Finally, image interpretation can be challenging, especially by less experienced operators.

**IVUS AND STENTING OPTIMIZATION IN CTO PCI**

Despite the use of drug-eluting stents (DES), PCI in CTO remains challenging because of the increased risk of restenosis and re-occlusion (21). After opening a CTO, IVUS represents a useful tool able to provide information about lesion length, morphology, and identification of a landing zone for stents implantation. After stenting, expansion, apposition, and extension can be optimized with IVUS assessment.

Data from randomized trials comparing the usefulness of IVUS-guided versus angiography-guided...
angioplasty in complex, long lesions and CTOs have emphasized the importance of a larger minimal lumen diameter after DES. However, what criteria should be used for IVUS optimization? And what parameters should be included in registries to predict future restenosis and re-occlusion? There are currently no well-established defined criteria.

In the AVIO (A prospective, randomized trial of intravascular-ultrasound guided compared to angiography guided stent implantation in complex coronary lesions) trial (including only 16% of CTOs) (22), the investigators measured the “optimal balloon size” that should be used for post-dilation, averaging the media-to-media diameters of the distal and proximal stent segments, as well as at the sites of maximal narrowing within the stent. The value was rounded to the lower 0.00 or 0.50 mm. For values of ≥3.5 mm, the operator could downsize the balloon diameter as per clinical judgment. Any segment inside the stent with a cross-sectional area less than the target criteria for the optimal balloon size was considered underexpanded and post-dilation was performed with a noncompliant balloon, selected according to the optimal balloon size. To avoid persistent dissections, the AVIO criteria were reduced by 10% at the proximal and distal stent edges. In lesions treated with overlapping or long stents, operators were encouraged to employ multiple balloons of different sizes if tapering of the vessel was evident.

Kim et al. (23) used looser criteria. Indeed, in the IVUS-guided group, stent size and length were selected by on-line IVUS measurements, and adjunct high-pressure dilation was performed at the operators’ discretion.

In the IVUS-XPL (Effect of Intravascular Ultrasound-Guided vs Angiography-Guided Everolimus-Eluting Stent Implantation) randomized trial, IVUS use was allowed at any step of PCI in the IVUS-guided stent implantation group (24). IVUS evaluation before and during PCI was left to the operator’s discretion, whereas IVUS examination was mandatory after PCI. The criterion for stent optimization was defined as a minimal lumen cross-sectional area greater than the lumen cross-sectional area at the distal reference.
segments. At follow-up, the rate of major adverse cardiac events (MACE) was lower in the IVUS group. However, this latter trial only included long lesions and excluded CTOs.

In the AIR-CTO (Angiographic and clinical comparisons of intravascular ultrasound- versus angiography-guided drug-eluting stent implantation for patients with chronic total occlusion lesions) trial (25), IVUS guidance criteria before DES implantation were as follows: 1) the stent was required to cover the entire diseased segment (including distal, CTO, and proximal segment) with the landing zone at the site with minimal plaque burden; 2) the ratio of stent/vessel diameter was 0.8 to 1.0; and 3) post-dilation with a pressure of ≥18 atm using a noncompliant balloon should be performed for all lesions. Post-procedural IVUS assessment was performed in the IVUS-guided group and efforts were made to achieve the following IVUS-defined success criteria: good apposition, stent minimal stent area of >80% of reference vessel area, symmetry index of >70%, and no dissections greater than a type B. At angiographic follow-up, in comparison with the angiography-guided group, the IVUS-guided group had lower in-stent late lumen loss (0.28 ± 0.48 mm vs. 0.46 ± 0.68 mm; p = 0.025), and lower restenosis of the “in-true-lumen” stent (3.9% vs. 13.7%; p = 0.021).

So what criteria can we recommend using IVUS to optimize results after DES implantation in CTO PCI? This question is still not fully answered. The use of distal reference vessel size may not be accurate based on the observed concentric remodeling in CTOs (26). Nonetheless, if a relatively healthy segment can be identified, a step up to a more accurate stent diameter can be possible.

**IMPACT OF IVUS USE IN CTO PCI ON OUTCOME**

Different meta-analyses have reported the advantage of IVUS-guided over angiography-guided PCI for the entire cohort of patients with diseased patent coronary arteries treated by DES implantation (8-10).

In a retrospective study, Hong et al. (27) compared the outcome between the IVUS-guidance group and the angiography-guidance group in 201 propensity
score-matched pairs from the Multicenter Korean Chronic Total Occlusion Registry. At the 2-year follow-up, although IVUS-guided CTO PCI was not associated with a reduction in overall MACE, IVUS-guidance seemed to be associated with a reduction of stent thrombosis and myocardial infarction compared with angiography-guided CTO PCI. Furthermore, target lesion revascularization occurred...
less frequently in the IVUS guidance group, especially for long CTO lesions (27).

Recently, 2 prospective, randomized controlled clinical trials have examined the role of IVUS in stent optimization during CTO PCI. Kim et al. (28) randomized 402 patients with CTOs to IVUS-guided versus angiography-guided stenting. At 12 months, the incidence of MACE (composite of cardiac death, myocardial infarction, or target vessel revascularization) was lower in the IVUS-guided group (2.6% vs. 7.1%; \( p = 0.035 \)), as was the composite endpoint of death or myocardial infarction (0% vs. 2.0%; \( p = 0.045 \)) (28). However, this latter study was underpowered because of the low events rate observed in both groups.

In the AIR-CTO trial, Tian et al. (25) randomized 230 patients to IVUS versus angiography guidance for CTO recanalization. Although the rate of definite and/or probable stent thrombosis at 2 years was significantly lower in the IVUS-guided group (0.9% vs. 6.1%; \( p = 0.043 \)) (25), this study lacked statistical power because of the limited sample size and the low rate of events. Furthermore, there were no differences in the composite MACE and in the individual component of clinical adverse events between the 2 study groups at 1- and 2-year follow-ups (25). Otherwise, IVUS could be useful in treating CTO patients with impaired renal function as it might reduce (in theory) the need for contrast. However, in these 2 randomized trials, IVUS use was not associated with a reduction of contrast load (25,28). Hence, the clinical benefit of IVUS guided CTO PCI has not been proven yet; further studies are required to better determine it.

**EDUCATIONAL CHALLENGES OF IVUS USE IN CTO PCI**

Despite its usefulness, IVUS remains underrepresented within CTO PCI, and limited to 10% to 20% of procedures (29,30). The question therefore arises, why is the use of IVUS within CTO PCI not more widespread?

Although the answer is multifaceted, representing an amalgam of financial (cost of equipment, reimbursement issues) and educational factors in absence
of well-established proof of clinical benefit, there is little doubt that improving the knowledge of where and how IVUS is used among interventionalists’ community will increase its use and therefore potentially improve patient outcomes. So, are there educational challenges specific to the use of IVUS within CTO PCI and if so, how could these be addressed?

INDICATIONS FOR USE. The indications for use of IVUS within CTO PCI should be as fully defined as possible. This is especially the case where there are specific technical requirements, such as the use of IVUS to define the proximal CTO cap. In such situations, it may not be sufficient to merely describe how IVUS is used, but may be necessary to supplement by illustrations and filmed material. Indeed, this represents an example of where contrasting educational forums may be complementary. An explanation of how to use IVUS to define a proximal CTO cap may be described theoretically by a position paper, be explained further by a “live” case example, but increase in uptake only after “hands-on” proctoring, where the physician is able to perform the technique under direct guidance from an experienced colleague. This multifaceted approach to education works best for situations where there is a technical challenge associated with the use of IVUS.

IMAGE INTERPRETATION. Interpretation of IVUS images should be as simplified as possible with recurrent links with vessel anatomy and CTO pathology reinforced to aid learning and illustrate the analogous situation. This is especially the case within CTO PCI, where vessel anatomy may be distorted and unfamiliar. Furthermore, image interpretation benefits greatly from clinical context, which is particularly pertinent within a nonclinical learning environment. Here reference to case progression and angiographic markers will help to contextualize the images.

CASE LIBRARIES AND SPECIFIC COURSES. As with any learning experience, exposure to a range of possibilities will help with understanding. This may be difficult and inefficient to achieve by isolated physician experience. Pooling experiences with the use of edited case libraries offers the opportunity to
benefit from a much broader range of cases and clinical scenarios. The format of such a library is key: the less specific the material, the less effective it will be. To work most effectively, material should be searchable, tightly edited, and have the learning points apparent. The psychology of learning is such that reinforcement is often required to emphasize key points, but this may be achieved with a number of separate cases.

In addition, attending specific CTO courses with a dedicated section on IVUS interpretation, allows a focus on problem solving and image interpretation not generally possible within a normal clinical environment. When properly delivered (often within a relatively small group) this will allow the sharing of experience and problem solving delivered by expert users.

**REFERENCES**


**CONCLUSIONS**

The usefulness of IVUS within CTO PCI is apparent, both on an anecdotal basis, where the individual use of IVUS can facilitate case efficiency, but more fundamentally, where the use of IVUS to guide stent implantation might improve patient outcomes. Efforts should be made to widespread its use among CTO operators, and further studies with larger patient populations are required to better determine the clinical impact of IVUS guidance for CTO lesions.

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