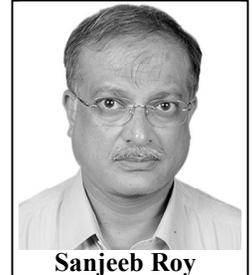


"Role of CT Coronary Angiography in Recanalization of Chronic Total Occlusion"

Sanjeeb Roy* and Jugal Sharma

Department of Cardiology, Fortis Escorts Hospital, Jaipur, India



Sanjeeb Roy

Abstract: Chronic total occlusion (CTO) is considered as the most challenging frontier in interventional cardiology and the last one to be conquered. With availability of state of the art hardware, wires and catheters in particular and increased skills of the operators, the success rate for recanalization of CTO by percutaneous catheter intervention (PCI) has improved. Yet the complications rate and long-term adverse events are high, mostly due to failure in tracking or navigation of hardware through the occluded CTO segment, prolonged exposure to radiation and high doses of contrast used. Therefore, proper selection of patient is of utmost importance. One of the major challenges for successful CTO recanalization is satisfactory visualization of the occluded CTO segment. Conventional invasive catheterization fails to fill the gap and the shortcomings and handicaps of such invasive imaging can be resolved with the use of non-invasive CT coronary angiography (CTCA). CTCA helps to better define the morphological features of the occluded CTO segment, which are established predictors of success, like the actual length of the occluded segment and any calcification or tortuosity in its course. Integration of reconstructed three-dimensional CT coronary images with two-dimensional fluoroscopic images, offers directional guide to select the best angiographic plane for visualization of angiographically "missing segment". With advances in CT technology, CTCA has now become an established technology for pre-procedure evaluation of CTO segment, thereby help in planning and execution of successful PCI.

Keywords: Chronic total occlusion, coronary artery disease, coronary computed tomographic angiography, invasive catheter angiography, percutaneous coronary intervention, revascularization.

INTRODUCTION

Occlusion of native coronary artery, when estimated from the clinical events to be at least more than three months, with no luminal continuity and TIMI (Thrombolysis in myocardial Infarction) 0 or 1 antegrade flow on angiography, has been defined as Chronic Total Occlusion (CTO). Most importantly there should be clinical and / or angiographic evidence of the duration of occlusion to be more than three months old [1].

In nearly one-third of cases referred for diagnostic coronary angiography, CTO have been detected [2]. CTOs are seen in half of those with significant coronary artery disease (defined as >70% stenosis) [3]. On coronary angiography, typically distal vessel after CTO segment, have collateral supply from ipsilateral or contralateral arteries. Such collaterals though may provide adequate supply of blood at rest to retain myocardial viability, but during stress may prove inadequate to meet the demands of distal myocardial bed. This results in ischemia and anginal symptoms. CTOs are most common in right coronary artery (RCA) and least in left Circumflex (LCx) [4]. In nearly one-third of diagnostic coronary angiograms, one or more CTOs were identified [4].

CTOs develop after acute thrombotic occlusion of the artery at the site of fibro-atheromatous plaque. The occlusive thrombus gets organized, undergoing various compositional changes with increasing age. The CTO therefore has an old lumen, intimal plaque and adventitia. The old lumen has an organized thrombus with extensive recanalization and limited at both proximal and distal end by fibrous cap, which is often tough. In CTOs of less than a year of age, the intimal plaque is laden with cholesterol-rich material mixed variably with collagen, calcium and elastin. In older CTOs, fibro-calcific intimal plaque has 25% more calcium, elastin and collagen. The calcium content further increases with aging of CTOs. Neovascularization occurs both in intimal plaque and adventitia. Such channels often communicate with vasa vasorum in adventitia [5]. In autopsy, less than half of CTOs show total occlusion. There was no relation found between severity of stenosis and composition of the plaque or age of the lesion.

CLINICAL PRESENTATION

CTOs are frequently present with symptomatic angina. However, 10-15% of patients undergoing PCI for CTOs are asymptomatic [6, 7] and few (9-18%) have unstable angina [6-9]. Most of the cases of CTO undergoing PCI have stable or progressive angina, while asymptomatic patients are on medical management. In several studies, history of prior myocardial infarction was found in 42-68% of angiographically proven CTO [6-10]. In those without prior history of

*Address correspondence to this author at the Director, Interventional Cardiology, Fortis Escorts Hospital, Jaipur, Rajasthan, 302017, India; Tel: (Mob.) +919829644459; Fax: +91-141-2547002; E-mail: roysanjeeb@gmail.com

myocardial infarction, stress-induced reversible perfusion defects are observed on single-photon positron emission CT (SPECT) imaging, as shown in a series by He *et al.* [11] and Enein *et al.* [12] with single vessel CTO. To detect reversible perfusion defects in CTO, adenosine SPECT imaging has been found to be more sensitive than exercise-induced stress imaging [13].

RATIONALE FOR REVASCULARIZATION

In CTOs, restoration of normal blood flow has been shown to relieve symptoms (angina), improve ventricular function and prolong survival, particularly in those with reversible ischemia in relevant myocardial territory [6, 14-22]. This has been demonstrated after successful PCI of CTO in the Prospective Total Occlusion Angioplasty Study – Societa Italiana di Cardiologia Invasiva (TOAST-GISE), where there were reduced cardiac death or MI (1.1% vs. 7.2%; $p=0.005$), need for coronary artery bypass surgery (2.5% vs. 15.7%; $p < 0.0001$) and greater freedom from angina (88.7% vs. 75%; $p=0.008$) in 12 month follow-up for 390 lesions attempted in 369 patients. Successful PCI was also associated with better 1-year event-free survival (OR 0.24; $p=0.018$) in over all study population. Contradictorily, in another study successful recanalization was not associated with survival free of death and cardiovascular re-hospitalization [23].

Choice of treatment modality depends on symptoms, documented ischemia, presence of multi-vessel disease and general condition of the patient. PCI is to be considered, when CTO is responsible for ischemic symptoms, with procedure success being at least moderately high and anticipated procedure related risk being low. Major determinant for successful PCI is the ability to cross CTO lesion with guide wire. The challenge to cross is due to three-dimensional imaging of the occluded segment visualized based on inputs from two-dimensional conventional invasive coronary angiography, which does not delineate the anatomical and morphological complexities of the CTO lesion. Such technical and procedural complexities of PCI in CTO and uncertainty of clinical benefit, widens the gap between frequency of CTO and application of PCI to reopen the occluded segments. Presence of CTO was the most common reason for referral to bypass surgery in ear-

lier trials (EAST, BARI) [24, 25]. PCI in CTO, when compared to non-CTO lesions is associated with higher risks due to prolonged procedure time, increased radiation dose, increased contrast dose, higher complication rate and lower success rate [26]. Once successful, the prognosis is comparable to PCI in non-CTO, while in those with unsuccessful events, major adverse cardiac events (MACE) were more frequent (30 day MACE – 5.5% vs. 14.8%) [27]. This underscores the importance of careful selection of case with high possibility of success and clinical benefit to the patient.

INVASIVE CORONARY ANGIOGRAPHY IN CTO

Prior to the availability and widespread use of CT coronary angiography, invasive coronary angiography (CAG) had been the only tool to assess morphology of coronary lesion. However, conventional invasive coronary angiography has essentially been a ‘lumenogram’, and therefore CTO lesion appears to halt the antegrade flow of contrast at the point of occlusion. The distal vessel is visualized by contrast filling through the collaterals (bridging or contralateral source) when present and the CTO segment appears to be a missing segments between the two ends. Conventional invasive angiogram fails to define the condition of vessel wall, the exact path or length or angulation through the occlusion, the presence of side branches, the composition of CTO and the ‘proximal’ and ‘distal’ caps at either end.

The clinical and anatomical predictors of unsuccessful PCI of CTO includes – more than 3 months duration of occlusion, presence of moderate and severe calcification, more than 15 mm length of occluded segment, blunt CTO stump, presence of bridging collateral, tortuosity in vessel proximal to and involving CTO, and presence of side branch at the level of occlusion (Table 1). PCI of CTO solely based on conventional invasive angiogram, which cannot define these morphological features, is the major reason for failure in this subset [17-19, 27, 28]. J-CTO score (Multicenter CTO registry in Japan) (Table 1) developed using presence or absence of these angiographic variables predicts success rates of crossing CTO segment in 30 minutes and helps in better case selection [29].

Table 1. Angiographic predictors of failure for percutaneous interventions on chronic total occlusions.

Angiographic variables	J-CTO score
<ul style="list-style-type: none"> • Moderate to severe calcification • Length of occluded segment of >15 mm • Blunt stump as opposed to tapered stump • Duration of ≥ 180 days • Tortuosity of proximal segment • Presence of antegrade bridging collaterals • Side branch at occlusion site • Absence of antegrade flow 	Entry Shape (tapered-0/ blunt-1) Calcification (absence-0/ presence-1) Bending > 45° (absence-0/ presence-1) Occlusion length (< 20 mm-0/ ≥ 20 mm-1) Re-entry lesion (no-0/yes-1) Category of difficulty (Total points) <ul style="list-style-type: none"> • Easy (0) • Intermediate (1) • Difficult (2) • Very difficult (≥ 3)

CT CORONARY ANGIOGRAPHY IN CTO

In initial days, electron beam CT (EBCT) scan had been used to detect and quantify coronary artery calcium [30], but it has now become a surrogate predictor of coronary artery disease. More than 130 Hounsfield units (HU) attenuation value is closely related to presence of calcified plaque in coronary artery. EBCT however tend to underestimate total plaque burden in the coronary tree.

Detection of calcification in CTO segment is pivotal in predicting procedural difficulty and success. Calcification in CTO segment is an independent predictor of procedural failure for recanalization of CTO [18]. Location and magnitude of calcification within CTO segment are important. Extremely heavy calcium introduces artifacts in CTO images (beam hardening and partial volume artifact), and is also associated with increased likelihood of adverse events during PCI. Finding true lumen also becomes a challenge in eccentrically and variably distributed calcium.

Over the years, rapid advancement has occurred in CT imaging. Introduction of multi-slice CT (MSCT) scanners with 64 or more slices in one gantry rotation has improved spatial and temporal resolution and has been increasingly used for non-invasive CT coronary angiography (CTCA). Faster rotation times and decrease in slice thickness have reduced partial volume effects and motion artifacts, thereby improving the visualization of coronaries and morphological details of the occlusive lesions. In the recent studies, the quantitative and qualitative diagnostic values of CTCA have been found to be comparable to invasive CAG with limitations [31]. CTCA exhibited good accuracy in delineating morphological features of coronary plaque, fairly classifying and quantifying plaque volumes and calcification, in proximal coronary tree in particular [32]. CTCA has therefore been increasing applied to study CTO segment prior to PCI [33, 34].

In CTCA axial images, multi-planar reformation (MPR) and maximum intensity projection (MIP), CTO segment completely show a lack of contrast opacification of arterial lumen (Fig. 1). Contrast opacification of distal vessel, which is mostly diminutive as compared to proximal vessel, suggests well-developed collaterals in chronically occluded ves-

sel. Distal vessel opacification beyond totally occluded segment therefore depends on collateral filling. Lack of contrast in distal vessel is usually indicative of acute or subacute occlusion and associated with higher success during PCI. Post processing reconstructions (MPR, MIP and 3D volume rendering), help to characterize the occluded segment (both in longitudinal extent and cross-sectional images), which has a different attenuation than surrounding non-vascular tissues. It provides accurate roadmap with fairly good spatial resolution. In CTCA, different segments of coronary arteries can be rotated around any axis in the 3-D volume rendering (3D-VR) images. This helps to visualize and get orientation of “missed segment” so that proper guide-wire can be selected and navigated through the block. However, this exercise requires substantial manual input, and has potential for erroneous tracking like into the side branch. CCTA not only helps in better understanding the course of occluded segment, but also delineates the morphological details like its length, tortuosity, angulations within, location of side-branches, stump morphology (blunt or tapered), caliber of proximal and distal vessel, plaque mass and composition and distribution of calcium in the CTO segment [35-41] (Fig. 2a-c). However, given its limitation in spatial resolution, total and subtotal occlusions cannot be reliably differentiated in CTCA.

Pre-procedure CTCA evaluation in PCI of CTO has yielded favorable results in many studies. Mollet *et al.*, were the first to point out its utility. They suggested that CTO lengths of more than 15 mm and calcification involving more than 50% of cross sectional image to be the most important predictors of failure for CTO PCI [39]. Pre-procedure CTCA guidance using 16-slice CT, improved procedural success in other studies by Yokoyama *et al.* [34] and Soon *et al.* [40]. They found that CTCA more accurately visualized angulations (not delineated in CAG), route of CTO segment, and distribution, length and amount (or degree) of luminal calcium within the CTO segment. This showed greater impact and improved the CTO-PCI success even in complex and / or calcified lesions, than by conventional CAG. In more recent studies by Kaneda *et al.* [33] and Choi *et al.* [42], improved success were demonstrated using 64-slice CT. In these studies, significant predictor of failure included duration of the occlusion, length of the lesion and the high segmental radiologic density [42]. Involvement of



Fig. (1). Lack of contrast opacification (missing segment) and opacification of distal segment with less intense opacification (suggesting collateral filling), signifies chronic total occlusion. It profiles the geometry and composition of totally occluded lesion.

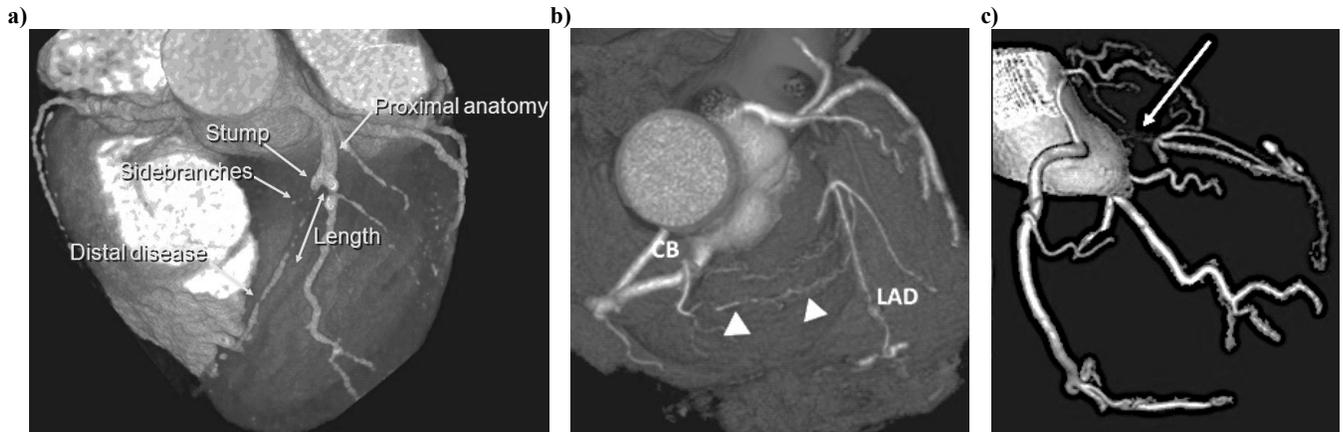


Fig. (2). a, b and c: Post-processing reconstructions and three dimensional volume-rendering images profiles the missing segment in LAD (length, tortuosity, side branches, calcification of CTO segment, proximal stump, and status of distal vessel bed filling from collaterals from the RCA).

the right coronary artery, being affected by motion artifact, was found to have lower success rate for revascularization than left anterior descending and circumflex [33].

Disadvantages do cloud CTCA. CTCA needs more control of heart rate and radiation exposure becomes substantial as pre-procedure CT adds to radiation during CTO-PCI [43]. Due to lack of soft tissue contrast enhancement, luminal borders are difficult to localize in CTCA. Newer advancements have ameliorated some of the disadvantages. ECG-pulsed modulations of tube current [44] and use of dual source CT scanners (DSCT) [45-47] have reduced exposure to higher radiation dose. As DSCT acquires data at twice the speed, it eliminates need for heart rate control and improves image quality and interpretation. Lesion characterization, calcium distribution and interpretation of distal vessel fared better with the use of DSCT. Rolf *et al.* [48] and Singh *et al.* [49], in their studies reported improved success for CTO-PCI with the use of pre-procedure DSCT.

With advancement in CT technology, newer lesion characteristics have also been evaluated as predictors of success for CTO-PCI. Presence of linear intra-thrombus enhancement within the occluded CTO segment has been postulated to represent micro-vascularization and hence recanalization of lumen. These are 100-500 micron channels, not unusual in the setting of CTO and are better visualized in CTCA using 128 slices. Li *et al.* in their small study found its presence to be a predictor for better outcome in CTO-PCI [50].

Another leap in technological advancement occurred with fusion of a 3-D CTCA images with real-time angiographic images. This would further facilitate success of crossing of CTO with guidewire during CTO-PCI with improved accuracy and interpretation of morphological and anatomical assessment and barriers in the pathway. This was made possible using additional tools like AgioCT software (Shina systems, Caesarea, Israel), which in split-screen display the diastolic frame angiographic (CAG) CTO image and 3D reconstructed CTCA images in same angulations. The 3D CTCA images are then overlaid by 2D angiographic images. Such a co-registration helps in better visualization of anatomic and morphological characteristics of CTO and the angulation, geometry and complex luminal path for guide

wire direction and advancement, especially in tortuous and heavily calcified lesions, thereby improving safety and success of CTO-PCI. Prior understanding of CTO lesion in such circumstances helps to formulate and execute a strategy or modify the current conceptualized strategy that would prove to be more appropriate and targeted to the current intervention. It would additionally reduce the procedure time, contrast dose and radiation exposure. This software also helps in selecting best C- arm angulations that minimize foreshortening and overlap of vessels and that too in less than 30 seconds. Co-registration has two technical limitations – it allows visualization in real time of static, not dynamic, during intervention and its utility is limited to those with high quality CTCA available prior to PCI. Using this system, based on co-registered images, Roguin *et al.* [51], achieved success in 16 of 25 cases in their study. Failure in 3 cases was due to heavy calcium and long lengths of CTO. In remaining 6, PCI was not attempted due to inputs from the co-registered images.

Magnetic navigation system (MNS), another technological advancement in CTO-PCI uses Niobe MNS (Stereotaxis, St Louis, MO, USA) with 0.08 Tesla magnetic field from two generators placed on either side of fluoroscopy table [52]. This helps in precise stereotactic control of tip of magnetically enabled wire to cross a lesion. Modest success has been reported with use of MNS in CTO [53]. In this regard, Patrick Serruys suggested three stages for the treatment of CTO [54]. In the first stage, the use of MNS to steer the guide wire across the CTO lesion. In the second stage, the use optical coherence tomography (OCT) or intra-vascular ultrasound (IVUS) or CTCA cross-section images to ‘look forward’ within vessel to ensure ideal wire position in true lumen. In the final stage, use ablative power at the tip of wire to recanalize CTO lesion. In MNS, CTCA provides 3-D static roadmap with details of occluded segment, but in future the availability of dynamic roadmap for real time assessment will ease the guidewire advancement. Endoluminal view and MPR slices will simultaneously be accessible, along with automated update of magnetic vector with guidewire advancement. This will provide operator prior knowledge of lesion in front of wire. For recanalization of CTO, magnetically enabled wire with radiofrequency abla-

tion capacity is being evaluated for use with the 3-D CTCA roadmap.

CONCLUSION

PCI of CTO has been the last frontier conquered. Success rate depends on selection of case and complexities of the CTO. CTCA prior to PCI, helps in understanding of the geometry, angulation, complex luminal path and composition of the CTO and hence the likelihood of procedural success, albeit at an extra dose of radiation and contrast. This helps in planning and execution of interventional strategy particularly for guidewire advancement, improving safety and procedural success, especially in tortuous and heavily calcified lesions. It may also reduce the procedure time, contrast dose and amount of radiation exposure to the patient and operator during PCI. Integration of conventional coronary angiogram with CTCA and MNS is technological advancement, which possibly would aid and increase the success rate of PCI on CTO.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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