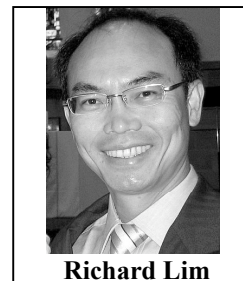


Training Standards and Recommendations for Intervention on Chronic Total Occlusions

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Abstract: Despite major advances in coronary intervention, the recanalization of a chronic total occlusion (CTO) remains a challenge for many interventional cardiologists. Complex anatomy and lesion characteristics demand a special set of skills for procedural success.

Provided patient selection is appropriate, CTO intervention can confer a variety of benefits including relief of angina, improvement in left ventricular function and reduction in ischemic burden. The chances of procedural success are enhanced by having a dedicated CTO program. This involves adequate training of staff, quality control and availability of equipment. A diverse toolkit allows variation in strategy and increases procedural success. Further, skills and equipment are required to manage complications like vessel dissection, perforation and the resultant ischemic or mechanical complications. These procedures can often be lengthy and giving careful consideration to peri-procedural issues like radiation exposure and contrast dose plays a vital role in ensuring optimal patient outcomes and radiation hygiene.

In this article we review the evidence behind indications for CTO intervention and discuss the development of a CTO program.

Keywords: Chronic total occlusion, percutaneous coronary intervention, training standards.

INTRODUCTION

Advances in technology and technical execution in percutaneous coronary intervention (PCI) over the last two decades have revolutionized the management of coronary atherosclerotic disease. The vast selection of guidewires and other hardware plus sophisticated evolution in imaging have rendered almost any lesion amenable to PCI. Further, better anti-thrombotic and anti-platelet therapies have enhanced the durability of these interventions. Despite the progress, chronic total occlusions (CTO) still pose a veritable challenge to many interventional cardiologists who acknowledge that the recanalization of these recalcitrant lesions demands a particular skillset and specialized equipment. This paper outlines a basic framework to build on and adapt to local conditions. It combines our personal largely unbiased perspective with a concise commentary on the requisite training for CTO intervention based on sound understanding of the clinicopathologic fundamentals of a CTO, the indications for attempting CTO recanalization and the tools needed to set up a robust program.

DEFINITION AND EPIDEMIOLOGY

A CTO is encountered in about one-third of patients undergoing coronary angiography [1]. The exact prevalence is

unknown as many are asymptomatic. Studies suggest that up to 89% of patients undergoing PCI for angina are found to have a CTO [2, 3]. While a CTO may cause stable anginal symptoms, only seldom do they precipitate an acute coronary syndrome [2-5].

A vessel is said to be occluded when there is no antegrade flow of contrast past a certain point: this is the “true” occlusion with a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 0. A lesion that allows minimal antegrade contrast passage (TIMI flow grade 1) is considered a functional occlusion. An occlusion is defined as chronic if greater than 3 months’ duration [6], accepting that in many cases, it is not possible to date the exact time of total occlusion.

Attempt rates at CTO revascularization are as low as 13.6%; even high-volume operators attempt only about a fifth of the lesions that they encounter [7]. The lack of enthusiasm (euphemistically termed “therapeutic inertia”) can be attributed to: 1) lack of randomized trial data showing benefit, 2) time constraints, 3) lack of availability of skills and equipment, 4) perception of high upfront costs, and 5) the inescapable notion that the CTO – being a stable lesion that is already occluded – can not get any worse or is unlikely to precipitate an acute coronary event.

CLINICAL RATIONALE FOR ATTEMPTING CTO PCI

In appropriately chosen individuals - acknowledging that by and large the evidence is anecdotal or non-randomized -

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CTO recanalization may have beneficial effects as outlined below:

Relief of Anginal Symptoms

The CTO as an isolated lesion can present with stable exertional angina and re-opening the vessel may result in symptom improvement. This is particularly worthwhile and justifiable when patients would otherwise be referred for bypass surgery even though they are not the best candidate or the anatomy *per se* does not suggest a prognostic benefit from CABG.

Borgia and colleagues published data from a cohort of 302 patients undergoing CTO recanalization [8]. Only 70% of these patients answered the Seattle Angina Questionnaire (SAQ) that encompasses physical activity limitation, angina frequency and treatment satisfaction. The procedural success rate was 78%. The 3% complication rate was not significantly different between the successful and failed PCI procedures. Patients with a successful CTO PCI had better exercise tolerance, fewer angina episodes and better treatment satisfaction than those with failed PCI ($p < 0.03$). Furthermore, those with failed PCI seemed to have a higher risk of cardiac death (HR 3.39; $p = 0.03$).

The FACTOR trial [9] administered the SAQ to 125 patients at baseline and 30 days after CTO intervention. Successful recanalization was achieved in 55% of cases and associated with fewer angina episodes ($p = 0.019$), improved exercise tolerance ($p = 0.001$) and improved quality of life ($p < 0.001$).

The National Heart, Lung and Blood Institute angioplasty registry showed a 94% reduction in angina class two years after recanalization of single-vessel CTOs [10]. In contrast, Bell *et al.* found no significant difference in angina symptoms 2 years after CTO recanalization [11]. However, a significant number of patients with failed PCI subsequently underwent CABG as compared with those with a successful intervention (58% vs 18%; $p < 0.0001$).

Improvement in LV Function

Multiple studies have shown improvement in left ventricular (LV) ejection fraction (EF) following successful CTO intervention. Patients with non-Q wave MI and absence of full-thickness scar on magnetic resonance imaging (MRI) are likely to benefit the most from opening an occluded artery [12]. It may be difficult to determine the extent of viability as there may be contraindications (*e.g.* older-generation implantable devices) to MRI or accessibility issues with positron emission tomography (PET) scanning. Those that do show an improvement in EF have myocardium that is hibernating – viability sustained by collaterals but not functioning to full potential. These collaterals are often inadequate to prevent ischemia in times of increased metabolic demand.

Chung *et al.* [13] demonstrated this in their series of patients with anginal symptoms and positive stress testing who underwent CTO intervention. Those patients with prior MI and Rentrop grade 3 collaterals had improvement in LV function after PCI unlike those who had poor collaterals. Other studies have shown improvement in both EF [14] and

indices of end-systolic and end-diastolic dimensions [15] following successful recanalization. Interestingly, this was apparent only when the vessel was still patent at follow up, no significant difference being observed if the vessel had re-occluded.

Reduction of Ischemic Burden

The territory subtended by a chronically occluded vessel is often supplied by collaterals. It is important to acknowledge that while collaterals may keep the myocardium viable, they may not match greater metabolic demands and so patients may continue to have symptoms. This was elegantly demonstrated in patients without prior myocardial infarction (MI) by Werner *et al.* [16] when they measured Doppler flow velocities and pressures in collateralized epicardial segments subtended by the occluded vessel before and after recanalization. The collateral pressure index was calculated as the ratio of the distal pressure before and after treatment of the CTO. Adequate collaterals have previously been defined by a pressure of at least 45 mmHg and pressure index of 0.3. They found that 58% of patients had pre-treatment collateral pressures of less than 45mmHg and 78% had a pressure index insufficient to prevent ischemia.

One study showed an improvement in myocardial ischemic burden as defined by single-photon imaging CT (SPECT) or PET after CTO recanalization [17]. Those with moderate to severe ischemia also saw this improvement translate into a mortality benefit. Interestingly, this was only true when the ischemic burden was over 12.5%; when it was less than 6.25%, there was a paradoxical worsening of ischemia after CTO intervention. However, this was a single-center study with a remarkable success rate of 98%; also, only less than a quarter of all the patients that underwent CTO intervention in their analysis were included.

Mortality Benefit

While there is reasonable evidence for intervening on CTOs for relief of anginal symptoms, no randomized trial data exist in support of CTO recanalization for prognostic reasons, whether in patients who are stable or otherwise. Small studies have suggested that patients with CTOs might be worse off in certain situations [18, 19]. This is not the same as stating that treating the CTO *per se* will improve the prognosis. Further, the absence of trials does not equate with absence of benefit so it is entirely possible that a randomized trial, if conducted, could produce a favorable outcome. Equally, such a randomized trial might actually be unequivocally negative.

Patients suffering ST elevation myocardial infarction (STEMI) who also have CTOs in non-infarct related arteries (IRA) appeared to have a higher 30-day mortality than those with non-occlusive multi-vessel disease (MVD), although the CTO itself was not an independent predictor of cardiac death [18]. An observational study of 1417 consecutive patients undergoing primary PCI found a 1-year mortality rate of 35% in those with a CTO in the non-IRA as compared to 16% in those with non-occlusive MVD and 8% in those with no significant disease in the non-IRA [19]. Other studies indicate that a CTO is associated with lower EF [20] and is an independent predictor of mortality

in patients with acute MI and cardiogenic shock who survive the index event [21].

Several randomized trials have been registered on <http://clinicaltrials.gov>. The Evaluating XIENCE V and LVF in PCI on Occlusions after STEMI (EXPLORE) trial will determine whether recanalizing a CTO in a non-IRA one week after primary PCI will improve outcomes. The Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion (DECISION-CTO) trial will examine patients with at least one CTO and angina or silent ischemia. The EuroCTO study aims to randomize 1200 patients to revascularization or medical therapy, evaluating a primary endpoint of quality of life at 12 months and major adverse cardiovascular events at 36 months.

Who Should Undergo CTO Intervention

Currently therefore, the dearth of randomized trial and robust mortality data means there is insufficient evidence to recommend CTO recanalization for prognostic or pre-emptive reasons. Only those on maximal medical therapy including at least two different anti-anginal agents with persisting angina might be considered appropriate candidates for palliative CTO PCI [22]. Patients who are found to have a CTO in a non-IRA during primary PCI and continue to have LV dysfunction despite “optimal” medical therapy may benefit from CTO revascularization provided there is sufficient myocardial viability. This notion might conceivably relate to elevating patients above the LVEF threshold for a “prophylactic” implantable defibrillator.

Developing a CTO Program

Embracing CTO revascularization is no small undertaking and a unit seriously intending to include CTO PCI in their repertoire may be better served by starting a dedicated program with specific objectives and review processes in place rather than attempting CTO PCI on a proactive *ad hoc* basis. The following are some aspects to consider when embarking on such a program:

Personnel – The Team

Like any other interventional or surgical procedure, the success of complex PCI is largely influenced by the quality of the team performing it. Even a highly trained operator may find it challenging to consistently perform successful complex PCI if not supported by skilled nurses and technicians. The approach to CTO intervention should parallel that taken toward transcatheter aortic valve replacement where a ‘heart team’ is not just performing the procedure itself but is also actively involved in the pre- and post-procedural evaluation and care to achieve the best outcomes.

The ideal dedicated team of cardiac nurses, technicians, radiographers and at least two interventionalists at each center should be highly experienced and have been involved in a large number of elective and emergency PCI procedures. The operator should have personally performed a large number of PCI cases and be current with their skills and knowledge. Ongoing procedural involvement helps in maintaining

operator skills. General guidelines have previously recommended a minimum of 75 PCI procedures a year to maintain operator competence [23]. There is evidence to suggest that continued exposure and higher volumes improve the success of CTO PCI; in the case of retrograde techniques, outcomes seem to significantly improve once an operator has performed 125 cases [24].

In recognition of the special expertise and dedication required for sustaining a successful program, many serious operators will have devoted themselves to a sub-specialty period of CTO PCI training in the highest-volume CTO PCI centers. Traditionally, Japan has led the way and many Japanese “CTO masters” continue to advance the field across the globe by way of publication, participation in major meetings, hosting overseas fellows or visitors and demonstrating live cases outside of Japan.

Having an experienced CTO operator proctor the team during the initial few cases is invaluable indeed mandatory and can transform potential nightmare cases into straightforward procedures. Individual operators differ in approach and confidence so the learning curve may be challenging for some and it is presumptuous to stipulate a fixed number of procedures that should be performed under supervision before an operator becomes independent. Ideally, that dynamic point on the learning curve is reached by mutual agreement between proctor and pupil. Proctors (most of whom are industry-sponsored) are also charged with the responsibility to over-ride any potential conflict of interest and provide firm advice should training standards appear not to be attainable in any particular center. Nowadays, it should be unheard of for programs to fail if properly choreographed, given that the operators involved are very much a self-selected passionate and highly skilled group.

Logistics

CTO cases should be pre-booked and ‘cold’. CTO recanalization can be an unpredictably lengthy procedure so it is best to have dedicated lab time set aside. This could be any time in the week when a lab does not deal with other elective or emergency cases. Clearly a small or busy center with only one lab or no spare lab time will struggle to win over other interventional colleagues, lab users, referring clinicians or hospital management. Advanced imaging support is crucial. On-site cardiothoracic surgery is desirable but not mandatory; the operator, in deciding what CTO cases might be appropriate to tackle, takes into account individual case complexity, institutional policies and of course operator experience. Some cases will even have been referred by cardiac surgeons.

Notwithstanding the vast variation in lab organization, funding, resources, care setting, referral pathways, reimbursement and politics internal and external, it is preferable that the hospital management is supportive of a CTO program. Equipment can be expensive, hard to source or require special regulatory pre-approval. An information session with hospital management and other stakeholders explaining the intricacies, benefits and fiscal implications of CTO intervention is desirable to help ensure an auspicious launch of a CTO program and ongoing 360-degree support.

Quality control

A local CTO conference or club at regular intervals depending on case volume should be an integral element of a successful program. This should be attended by referring cardiologists, operators, trainees, support imaging colleagues and all relevant staff thereby facilitating the identification and correction of system issues, discussion of case appropriateness and procedural strategies, learning points, complications and continuing education opportunities. PCI databases should be configured to capture essential elements to promote ongoing quality assurance. There is merit in devolving PCI data management to a higher or neutral authority for the purpose of using defined and agreed performance indicators to improve individual and institutional outcomes. Whether data are de-identified or not, the devil as always is in the detail and the difficulties in achieving universal acceptance for such initiatives are not peculiar to CTO PCI quality control.

PERI-PROCEDURAL CONSIDERATIONS

Pre-procedural Imaging

Prior assessment of anatomical characteristics such as length of occlusion, side-branches and collaterals and nature of proximal and distal cap allows for adequate planning of the procedure, cuts down procedural time and improves success rate.

When contemplating recanalization, it is desirable to perform diagnostic angiography with dual catheter injections at 25cm field size and no panning. The right anterior oblique view is best suited for visualization of septal collaterals. Other views can be used for epicardial collaterals. Features that predict lower procedural success include a) long segment occlusion > 20 mm, b) absence of nipple, c) presence of a side-branch and d) significant disease or poor visualization of distal vessel [3, 25-30]. Care should be taken to avoid large radiation and contrast doses during diagnostic studies.

Intravascular ultrasound (IVUS) is currently used to define vessel architecture where a side-branch arises close to the proximal cap. Commercially available IVUS systems are side-looking so the IVUS catheter is inserted into the side-branch and the proximal cap punctured under ultrasound guidance. Forward-looking IVUS arrays will significantly alter the way we approach the proximal cap [31]. The same applies to optical coherence tomography (OCT); forward-looking catheters can potentially delineate micro-channels and external elastic membrane with enhanced accuracy.

Other modalities like CT coronary angiography can be used to delineate the length of occlusion, presence of side-branches and state of the distal vessel, but the presence of calcium degrades image quality and makes it less attractive as a planning tool. MRI should be used to determine the viability of myocardium subtended by the occluded vessel if echocardiography is insufficiently definitive.

In summary, prior to intervention, it is essential to obtain good quality angiographic images of the target and donor vessels including the collateral supply. The viability of the underlying myocardium should be defined by means of echocardiography coupled preferably with MRI. IVUS can

be used to delineate the proximal cap if a sizeable side-branch is present.

Toolkit

Table 1 provides an example of the equipment that should be readily available when attempting CTO PCI. This is by no means exhaustive, the choice being somewhat bewildering and personal preferences dynamic and ever evolving. A standard range of 6, 7 and 8 Fr guide catheters should be stocked in addition to workhorse CTO guidewires including a 0.009” tip polymer jacketed wire as well as stiff wires. The commonest cause of a failed PCI is inability to cross the lesion with a guidewire [25].

Table 1. CTO PCI Toolkit.

Sheaths	7F, 8F 25cm and 45cm sheaths
Guide Catheters	LCA: EBU ¹ 3.0, 3.5, 4.0, 4.5; AL 0.75, 1.0, 2.0; RCA: JR4, 5(radial access); XBRC ² ; AL 0.75; AR MOD; MPA 1, 2
Guidewires	Workhorse guidewires Fielder XT ³ , Fielder FC ³ - for crossing micro-channels Pilot 200 ³ - For dissection re-entry Confianza Pro 12 ² - for cap penetration
Microcatheters	OTW balloons 1.25, 1.5mm Terumo Finecross MG ⁴ Asahi Tornus ⁵ 2.1Fr Asahi Corsair ⁵
Special Equipment	Bridge Point System ⁶ (CrossBoss, Stingray Balloon, Stingray Wire) Guideliner ⁷ 6Fr, 8Fr
For managing complications	Embolisation coils 0.014” and 0.018” Snares Covered Stents 2.5mm, 3.0mm, 3.5mm Pericardiocentesis kits

¹Medtronic, Minneapolis, MN, USA.; ²Cordis Corporation, Warren/Bridgewater, NJ, USA.; ³ Abbott Laboratories, Abbott Park, IL, USA.; ⁴Terumo Medical Corporation, Somerset, NJ, USA.; ⁵ASAHI Intecc USA, Inc., Santa Ana, CA, USA.; ⁶Bridge Point Medical, Plymouth, MN, USA.; ⁷Vascular Solution Inc., Minneapolis, MN, USA.

With refinement in imaging resolution, upfront selection of a tapered tip hydrophilic wire for probing a micro-channel or a stiff tip wire for puncturing the cap may be preferable to gradual escalation through wires of increasing tip stiffness.

CTO intervention has been revolutionized by novel approaches e.g. the Controlled Antegrade and Retrograde sub-intimal Tracking (CART) technique involves creating a limited dissection plane at the site of the CTO while having a

wire in the proximal and distal true lumens and then bridging the two true lumens with the help of a low-profile balloon and support microcatheters [32]. Technical nuances are constantly refined and evolving and keeping up with the requisite hardware as they become available and being conversant with their capabilities and limitations improve the chances of success.

Managing Complications

The common problems that can arise from complex PCI involve vessel dissection, perforation and rupture. Having an action plan for such eventualities can significantly improve outcomes. The CTO PCI operator should formalize a pathway to manage such potentially catastrophic complications in addition to having readily available the basic rescue tools like pericardiocentesis kits, covered stents and embolization coils.

Patient Consent

Patient consent according to the usual institutional policy is appropriate. It is wise to ensure the patient specifically understands that CTO PCI is a high-risk procedure with limited evidence of prognostic benefit. Peri-procedural risks like radiation exposure and contrast nephropathy become significant during prolonged procedures and should be communicated clearly to the patient. If relevant, patients should be offered alternative therapies *e.g.* surgery or medical therapy. Any such discussions are best documented in the hospital records.

Radiation and Contrast Exposure

Due to longer fluoroscopy times and a greater number of cine acquisitions, the patient can be subjected to a large radiation dose. Notwithstanding that different labs report different measures of radiation dose, long-term effects like dermal atrophy and telangiectasia are noted when single-site skin doses exceed certain thresholds *e.g.* 10 Gy [33]. It is wise to abort the procedure if the lesion has still not been crossed by 8 Gy of skin dose. Appropriate measures like collimation and altering working angles should be employed to avoid large skin doses. The patient should be reviewed in 3 to 4 weeks if the skin dose exceeds 12 Gy.

Iodinated contrast doses of greater than 5ml/kg should prompt measurement of serum creatinine 3 to 5 days after the procedure. In general, contrast volumes should be limited to no greater than 4X the creatinine clearance or estimated glomerular filtration rate. All patients should have appropriate hydration and discontinuation of potentially nephrotoxic agents before and after the procedure. Patients with pre-existing renal impairment should ideally be reviewed by their nephrologist prior to the procedure.

CONCLUSION

CTO intervention has been described as the final frontier in interventional cardiology – until of course the next big challenge presents itself, interventional cardiology being such a rapidly evolving field. While randomized trials investigating long-term survival benefits from this procedure are awaited, there is ample and accepted evidence to suggest that

it is useful in palliating intractable angina. Centers embarking on this journey of CTO intervention should be adequately resourced and prepared in terms of skilled personnel and equipment. Continuing education, review of cases and complications and quality control form a cornerstone of an ongoing successful CTO interventional program.

CONFLICT OF INTEREST

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

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