4

CHRONIC TOTAL OCCLUSIONS

Christopher L.F. Gade, MD

S. Chiu Wong, MD

EXECUTIVE SUMMARY

Although recent consensus has clearly defined chronic total occlusions (CTO), prevalence remains unclear and attempted percutaneous coronary intervention (PCI) remains low. Histopathologically, CTOs are characterized by fibrous caps, varying degrees of “soft” and “hard” plaque, and neovascularization, with the latter two increasing with the age of the CTO. Multiple registries show that successful PCI of CTOs can improve symptoms, left ventricular function, and mortality. Drug eluting stents significantly improve long term outcomes in CTOs compared with bare metal stents. Novel techniques have greatly enhanced procedural success, and include “parallel” and “seesaw” wire techniques, balloon anchoring, subintimal tracking and reentry (STAR), retrograde approach, contralateral injection, and intravascular ultrasound guidance. Improvements in wire technology have largely been responsible for improved procedural success in PCI of CTO, while application of new technologies hold promise to significantly better outcomes. Magnetic resonance and computed tomography simaging are already employed in formulating treatment strategies and their role in the treatment of CTOs is likely to increase.

Introduction

Recent consensus has defined a chronic total occlusion (CTO) as a lesion of at least 3 months duration with thrombolysis in myocardial infarction (TIMI) grade 0 or 1 flow (1). Data regarding the occurrence of CTOs remains somewhat limited; Kahn et al. found the prevalence to be almost one-third of all patients referred for angiography (2). Attempts at CTO revascularization represent a small portion (8-15%) of all PCIs (3-6). While procedural success rates between 55% and 90% have been reported (7,8), the presence of a CTO is often cited as a reason for medical or surgical management of coronary artery disease (CAD). For example, in the Bypass Angioplasty Revascularization Investigation (BARI) trial, 68% of patients ineligible for percutaneous revascularization had one or more CTOs (3).

Most CTOs are not completely occluded when examined under the microscope (9). They are characterized by a mix of luminal plaque, thrombin, fibrin, inflammatory cells (in the intima, media, and adventitia), and neovascular channels. The plaque is composed of a collagen rich extracellular matrix, intra and extracellular lipids, smooth muscle cells, and calcium. The proximal and distal caps have higher concentrations of collagen and calcium (fibrocalcific) while the composition of the core correlates with CTO age. Older CTOs have higher concentrations of fibrocalcific material ("hard plaque"), while CTOs present for less than 1 year have more cholesterol clefts and foam cells among less fibrous material ("soft plaque"). This may, in part, explain the greater success in crossing these younger CTOs. Neovascularization starts early and increases with time. Studies suggest that there is inwardly directed neovascular channel growth from the vaso vasorum of the adventitia (9,10). Large (> 250 μm) neovascular channels in the plaque and adventitia of CTOs older than 1 year may represent bridging collaterals, which have been associated with lower procedural success rates (9, 11,12). However, with better equipment and increased operator experience, this association may have to be re-evaluated.

Percutaneous Coronary Intervention of CTOs

While no prospective, randomized, controlled trials of PCI vs. medical or surgical treatment of CTOs have been conducted, multiple retrospective studies have shown the potential benefit of PCI. Successful treatment improves anginal symptoms, exercise tolerance, and left ventricular function (13). In addition, it lessens the incidence of major adverse cardiovascular events (MACE), including mortality, when compared to patients in whom the procedure failed (14-16). In their 20 year retrospective study, Suero et al.(14) found that compared with an unsuccessful recanalization attempt, successful PCI of a CTO reduces MACE by 2.2% (3.2% vs. 5.4%; $p = 0.023$) and offers a 10-year absolute survival benefit of 8.5% (73.5% vs. 65.1%; $p = 0.001$). The prospective Total Occlusion Angioplasty Study (TOAST-GISE) showed that revascularization of a CTO is associated with a 6.1% absolute risk reduction of cardiac death or myocardial infarction (MI) (1.1% vs. 7.2%; $p = 0.005$), as well as with significant reductions in angina and the need for bypass surgery at 1-year follow-up (16).

Use of Drug-Eluting Stents for CTOs

While most PCI failures are due to an inability to cross the lesion, failure of patency after successful angioplasty has also been a common and discouraging complication. Restenosis and reocclusion rates (at 6-9 month angiographic follow-up) have traditionally been very high in CTOs treated with angioplasty alone (33-74% and 7-34%, respectively), and the use of bare metal stenting (BMS) brought only moderate improvement (22%-55% and 2%-16%, respectively) (7).

Since the advent of drug-eluting stents (DES), multiple registries and case series have demonstrated significantly lower restenosis, reocclusion, and revascularization rates with both sirolimus- and paclitaxel-eluting stents (17,18). Recently, the first prospective, randomized data demonstrating the superiority of DES to BMS in the treatment of CTOs was reported. The Primary Stenting of Occluded Native Coronary Arteries (PRISON II) study randomized 200 patients with a CTO to receive a bare metal Bx Velocity™ stent or a sirolimus-eluting Cypher® stent (Cordis, Miami Lakes, FL) (19). Significant reductions in all angiographic and most clinical outcomes were reported at 6-month follow-up, including MACE (20% vs. 4%; $p < 0.001$), in-stent late loss (1.09 mm vs. 0.05 mm; $p < 0.0001$) and reocclusion (13% vs. 4%; $p < 0.04$).

Novel PCI Techniques in CTO

In an attempt to improve success rates, multiple novel PCI techniques have been developed (Table 1 and Figure 1). The *parallel wire technique* leaves the initial wire in place if it passes into a dissection plane, using it as a reference point to assist in passing a second wire through the true lumen. The *seesaw technique* uses two wires supported by microcatheters to probe the lesion for the true lumen. *Balloon anchoring* makes use of a balloon placed in a side-branch vessel to provide increased support for wire passage (20). The *subintimal tracking and reentry (STAR) technique* involves passage of the CTO via subintimal dissection with subsequent distal lumen reentry. This technique, which has been associated with a reintervention rate of 52.4%, is used when attempts to recanalize the true lumen have failed (21). The *retrograde approach* makes use of collaterals by which the lesion is approached in a distal to proximal manner. A robust collateral system is generally required. This technique is supported by *contralateral injection*, which is also frequently used to assist in guiding antegrade approaches (Figure 1). Finally, *intravascular ultrasound* (IVUS) can be employed to distinguish the true from false lumen by looking for side branches and by evaluating the position of the guide wire within the vessel.

Novel PCI technologies in CTO

Up to 90% of aborted attempts to open a CTO are due to inability to pass the wire. As a consequence, the majority of innovation has been directed at improving CTO crossing.

Guidewires. Newer initiatives have focused on improvement of wire technology (Table 2). Wires may be thought of as “coated” or “uncoated,” with the coating being a hydrophilic polymer. Hydrophilic wires move more easily through soft tissue, providing improved maneuverability in tortuous vessels and around sharp bends. However, the hydrophilicity also makes it easier to pass into false lumens or small side branches, which increase the risk of perforation. Much engineering has gone into improving the torgue capabilities, making newer guidewires more responsive. In addition, guidewire tips are available in varying weights with increasing power to penetrate more fibrocalcific tissue. Other wires have tapered tips, which can selectively penetrate microchannels and facilitate penetration of fibrous caps. The Steer-It™ (Cordis, Miami Lakes, FL) deflecting tip guidewire makes it possible to change the guidewire tip angle and thereby improve the chances of engaging difficult take-off angles, negotiating around tortuous bends, and steering away from dissection planes. In contrast to other tip deflection systems, the Steer-It provides bi-directional deflection capability, improved ergonomics, and longer in vivo deflection sustainability; however, this device is not yet approved for use in CTOs.

Adjunct Devices. Earlier adjunct catheter technology to treat CTOs, including ball-tipped guidewires, laser ablation, and vibrational ultrasound, demonstrated no significant improvement in procedural success and had higher complication rates. The Tornus® catheter (Asahi Intec, Japan) is a novel over-the-wire stainless steel penetration catheter designed to provide greater support and assist with penetration of the CTO (Figure 2). It is constructed of eight individual 0.007-inch wires stranded together to form the catheter, with a silicone coating on the inner and outer surfaces and a tapered tip. The device works via a screw-like mechanism through counterclockwise rotation. The Venture™ Wire Control Catheter (St. Jude Medical, Inc, St. Paul, MN) is a support catheter that also provides steering control through a deflectable tip (Figure 3). This enhances the ability to engage tortuous lesions or acute angle take-off lesions common in CTOs. Limitations include the 0.0175-inch internal diameter, which results in a low clearance for wire manipulation, the inability to change the guidewire tip angle when used with a stiffer wire, and the large profile of the device. The Crosser™ system (FlowCardia, Inc., Sunnyvale, CA) uses high-frequency vibrational energy (20 kHz ultrasound) transmitted through the tip of the catheter to facilitate mechanical recanalization (Figure 4). This system has a lower profile and is more deliverable than its predecessors. It is currently under clinical investigation.

Lumen Reentry Devices employ different technologies to return guidewires into the true lumen after they have created a dissection plane. The Pioneer® catheter (Medtronic, Minneapolis, MN) uses ultrasound guidance while the Outback® re-entry catheter (LuMend, Picataway, NJ) uses standard fluoroscopy. The Frontrunner® XP CTO Catheter (LuMend, Picataway, NJ) is a manually operated device that uses a hinged tip to spread tissue by blunt microdissection (22). It is supported by a probing and recanalization catheter. In pilot studies, the device showed success in penetrating refractory lesions (23). However, there are concerns regarding increased risk of perforation, particularly when navigating tortuous vessels. This technology is targeted for use in peripheral arterial applications and may also have a niche role for refractory in-stent CTOs (24).

Biological Agents. To modify plaque composition, biological agents have been evaluated in several studies. Small studies using intracoronary urokinase or tissue plasminogen activator infusion followed by angioplasty reported success ranging from 53% to 94%, but with increased bleeding complications, primarily at the entry site (25,26). A more recent study using pre-interventional intracoronary infusion of alteplase or tenecteplase showed a procedural success rate of 54% in CTOs in which previous crossing attempts had failed (27). The use of collagenase has shown promise in facilitating wire passage of CTOs in rabbit models, improving success rates by 33% in one study and facilitating passage in 100% in another (28,29).

Other new technologies in development that could be applied to the treatment of CTOs include remotely-guided, three dimensional magnetic navigation systems (stereotaxis), forward looking ultrasound, percutaneous in-situ coronary artery bypass, and percutaneous in-situ coronary venous arterialization (30).

Use of Non-invasive Imaging for CTOs

The heightened sensitivity and specificity of magnetic resonance imaging (MRI) has improved viability assessment, crucial in patient selection. MRI can also provide delineation of lesion pathways. Multi-detector cardiac computed tomography (CT) is being used to define lesion characteristics and to predict outcomes. In one study, lesion length and calcification identified on 16-slice CT were shown to be independent predictors of PCI outcome (11). Ongoing studies will evaluate the use of 64-slice CT in CTO assessment, and the next generation of scanners (256-slice) is on the horizon.

Conclusions

Progress in the treatment of CTOs has been much like attempts to cross the lesions themselves: slow, with promising beginnings sometimes leading to dead ends and with progress coming over time through the use of ingenuity and perseverance. Suboptimal durability of vessel patency after successful recanalization has been largely solved by the use of DES. Most innovation has focused on the most difficult part of CTO revascularization, i.e., crossing the lesion. While some promising ingenuity culminated in failed devices, dedicated engineering has led to the development of an armamentarium of specialized guidewires, support catheters, and adjunct devices. Still, there is much progress to be made. One could envision the future treatment of CTOs involving stereotactic wire tip manipulation with intravascular guidance and virtual lesion histology provided by forward looking ultrasound.

References

1. Stone GW, Kandzari DE, Mehran R, Colombo A, Schwartz RS, Bailey S, Moussa I, Teirstein PS, Dangas G, Baim DS, Selmon M, Strauss BH, Tamai H, Suzuki T, Mitsudo K, Katoh O, Cox DA, Hoye A, Mintz GS, Grube E, Cannon LA, Reifart NJ, Reisman M, Abizaid A, Moses JW, Leon MB, Serruys PW. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. *Circulation* 2005;112:2364-2372.
2. Kahn JK. Angiographic suitability for catheter revascularization of total coronary occlusions in patients from a community hospital setting. Am Heart J 1993;126:561-564.
3. Bourassa MG, Roubin GS, Detre KM, Sopko G, Krone RJ, Attabuto MJ, Bjerregaad P, Bolling S, Herman MV, Frye R. Bypass Angioplasty Revascularization Investigation: patient screening, selection, and recruitment. *Am J Cardiol* 1995;75:3C-8C.
4. Kandzari DE. The challenges of chronic total coronary occlusions: an old problem in a new perspective. *J Interv Cardiol* 2004;17:259-267.
5. Williams DO, Holubkov R, Yeh W, Bourassa MG, Al-Bassam M, Block PC, Coady P, Cohen H, Cowley M, Dorros G, Faxon D, Holmes DR, Jacobs A, Kelsey SF, King SB 3rd, Myler R, Slater J, Stanek V, Vlachos HA, Detre KM. Percutaneous coronary intervention in the current era compared with 1985–1986: the National Heart, Lung, and Blood Institute Registries. *Circulation* 2000;102:2945-2951.
6. Anderson HV, Shaw RE, Brindis RG, Hewitt K, Krone RJ, Block PC, McKay CR, Weintraub WS. A contemporary overview of percutaneous coronary interventions: the American College of Cardiology–National Cardiovascular Data Registry (ACC-NCDR). *J Am Coll Cardiol* 2002; 39:1096-1103.
7. Stone GW Reifart NJ, Moussa I, Hoye A, Cox DA, Colombo A, Baim DS, Teirstein PS, Strauss BH, Selmon M, Mintz GS, Katoh O, Mitsudo K, Suzuki T, Tamai H, Grube E, Cannon LA, Kandzari DE, Reisman M, Schwartz RS, Bailey S, Dangas G, Mehran R, Abizaid A, Moses JW, Leon MB, Serruys PW. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part II. *Circulation* 2005;112:2530-2537.
8. Han YL, Zhang J, Jing QM, Wang SL, Ma YY, Luan B, Li Y. Coronary intervention in 1148 patients with chronic total coronary occlusion. *Zhonghua Xin Xue Guan Bing Za Zhi* 2005;33:299-302[Article written in Chinese].
9. Srivatsa SS, Edwards WD, Boos CM, Grill DE, Sangiorgi GM, Garratt KN, Schwartz RS, Holmes DR Jr. Histologic correlates of angiographic chronic total coronary artery occlusions influence of occlusion duration on neovascular channel patterns and intimal plaque composition. *J Am Coll Cardiol* 1997;29:955-963.
10. Kumamoto M, Nakashima Y, Sueishi K. Intimal neovascularization in human coronary atherosclerosis: its origin and pathophysiological significance. *Hum Pathol* 1995; 26:450-456..
11. Mollet NR, Hoye A, Lemos PA, Cademartiri F, Sianos G, McFadden EP, Krestin GP, Serruys PW, de Feyter PJ. Value of preprocedure multi-slice computed tomographic coronary angiography to predict the outcome of percutaneous recanalization of chronic total occlusions. *Am J Cardiol* 2005;95:240-243.
12. Kinoshita I, Katoh O, Nariyama J, Otsuji S, Tateyama H, Kobayashi T, Shibata N, Ishihara T, Ohsawa N. Coronary angioplasty of chronic total occlusions with bridging

collateral vessels: immediate and follow-up outcome from a large single-center experience. *J Am Coll Cardiol* 1995;26:409-415.
13. Sirnes PA, Myreng Y, Molstad P, Bonarjee V, Golf S. Improvement in left ventricular ejection fraction and wall motion after successful recanalization of chronic coronary occlusions. *Eur Heart J* 1998;19:273-281.
14. Suero JA, Marso SP, Jones PG, Laster SB, Huber KC, Giorgi LV, Johnson WL, Rutherford BD.. Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: a 20-year experience. *J Am Coll Cardiol* 2001:38:409-414.
15. Aziz S. Percutaneous coronary intervention for chronic total occlusions: Improved survival for patients with a successful revascularization procedure compared to a failed procedure. Transcatheter Cardiovascular Therapeutics (TCT), Washington, DC. October 2005.
16. Olivari Z, Rubartelli P, Piscione F, Ettori F, Fontanelli A, Salemme L, Giachero C, Di Mario C, Gabrielli G, Spedicato L, Bedogni F; TOAST-GISE Investigators. Immediate results and one-year clinical outcome after percutaneous coronary interventions in chronic total occlusions: data from a multicenter, prospective, observational study (TOASTGISE). *J Am Coll Cardiol* 2003;41:1672-1678.
17. Lotan C. Chronic total occlusions (SICTO). Transcatheter Cardiovascular Therapeutics (TCT), Washington, DC. October 2004.
18. Abizaid A. WISDOM registry: one-year clinical outcomes and subset results. Transcatheter Cardiovascular Therapeutics (TCT) Washington, DC. October 2004.
19. Suttorp M. PRISON II. A prospective randomized trial of sirolimus-eluting and bare metal stents in patients with chronic total occlusions. Transcatheter Cardiovascular Therapeutics (TCT), Washington, DC. October 2005.
20. Hirokami M, Saito S, Muto H. Anchoring technique to improve guiding catheter support in coronary angioplasty of chronic total occlusions. *Catheter Cardiovasc Interv* 2006;67:366-371.
21. Colombo A, Mikhail GW, Michev I, Iakovou I, Airoldi F, Chieffo A, Rogacka R, Carlino M, Montorfano M, Sangiorgi GM, Corvaja N, Stankovic G. Treating chronic total occlusions using subintimal tracking and reentry: the STAR technique. *Catheter Cardiovasc Interv* 2005;64:407-411.
22. Whitbourn RJ, Cincotta M, Mossop P, Selmon M. Intraluminal blunt microdissection for angioplasty of chronic total occlusions. *Catheter Cardiovasc Interv* 2003;58:194-198.
23. Whitlow P, Selmon M, O'Neill W, Knopf W, Uruchurtu E, Colombo A, Grube E, Londero H, Sousa JE, Simpson J. Treatment of uncrossable chronic total coronary occlusions with the Frontrunner: multicenter experience. *J Am Coll Cardiol* 2002;90:29A[Abstract].
24. Yang YM, Mehran R, Dangas G, Reyes A, Qin J, Stone GW, Leon MB, Moses JW. Successful use of the Frontrunner catheter in the treatment of in-stent coronary chronic total occlusions. *Catheter Cardiovasc Interv* 2004;63:462-468.
25. Ruocco NA Jr, Currier JW, Jacobs AK, Ryan TJ, Faxon DP. Experience with low-dose intracoronary recombinant tissue-type plasminogen activator for nonacute total occlusions before percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1991;68:1609-1613.

26. Zidar FJ, Kaplan BM, O'Neill WW, Jones DE, Schreiber TL, Safian RD, Ajluni SC, Sobolski J, Timmis GC, Grines CL. Prospective, randomized trial of prolonged intracoronary urokinase infusion for chronic total occlusions in native coronary arteries. *J Am Coll Cardiol* 1996; 27:1406-1412.
27. Abbas AE, Brewington SD, Dixon SR, Boura JA, Grines CL, O'Neill WW. Intracoronary fibrin-specific thrombolytic infusion facilitates percutaneous recanalization of chronic total occlusion. *J Am Coll Cardiol* 2005;46:793-798.
28. Strauss BH, Goldman L, Qiang B, Nili N, Segev A, Butany J, Sparkes JD, Jackson ZS, Eskandarian MR, Virmani R.. Collagenase plaque digestion for facilitating guide wire crossing in chronic total occlusions. *Circulation* 2003;108:1259-1262.
29. Segev A, Nili N, Qiang B, Charron T, Butany J, Strauss BH. Human-grade purified collagenase for the treatment of experimental arterial chronic total socclusion. *Cardiovasc Revasc Med* 2005;6:65-69.
30. Oesterle SN, Reifart N, Hayase M, Hauptmann E, Low R, Erbel R, Haude M, Dirsch O, Schuler GC, Virmani R, Yeung AC. Catheter-based coronary bypass: a development update. *Catheter Cardiovasc Interv* 2003;58:212-218.