Pathology of Coronary Chronic Total Occlusion

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ABSTRACT
There is an increasing need for percutaneous revascularization procedures of coronary Chronic Total Occlusion (CTO), because many patients with severe coronary artery disease have limited options for revascularization. Although the success rate of percutaneous revascularization of CTOs was unsatisfactory from the 1990s to the 2000s, recent technological advances in interventional strategies have improved the success rate to 85%. Detailed histological assessment of human autopsy studies of CTO has contributed significantly to the refinement in Percutaneous Coronary Intervention (PCI) techniques and device development. We have recently reported the pathological findings and characteristics of CTOs that occur in different clinical scenarios. In this review, we discuss the pathology of CTOs to facilitate greater understanding of revascularization strategies for CTOs.

1. Introduction
There is growing need for percutaneous revascularization of coronary Chronic Total Occlusion (CTO) as clinical studies have had a beneficial impact on patient outcome following revascularization (1, 2). The British Cardiovascular Intervention Society reported that successful CTO Percutaneous Coronary Intervention (PCI) of at least 1 CTO was significantly associated with improved survival (hazard ratio: 0.72; 95% confidence interval: 0.62 to 0.83; P < 0.001) compared to unsuccessful CTO (1). Furthermore, although the success rates of percutaneous revascularization of CTOs were not satisfactory, as they ranged from 51 to 74% up to 2009 (3), recent technological advances and interventional strategies have improved the success rate to 85% (4-6).

On the other hand, human autopsy studies of CTO have contributed significantly to the refinement of PCI techniques and device developments. Presence of microchannel from recanalization of CTOs described in human pathological studies (7, 8) encouraged the development of smaller diameter guidewires (9). Additionally, the concept of “Loose tissue tracking” was developed from a more fundamental understanding of CTO histopathology (10). Recently, our group reported the pathological definition and characteristics of various types of CTOs (11). In this review, we discuss the pathology of CTOs to further facilitate a greater understanding of revascularization strategies.
absence of fibrin in all sections of CTO, with negative remodeling (11). Short-duration CTO, on the other hand, was predominantly composed of proteoglycan with or without recanalization and inflammation, but fibrin had to be identified in at least one of the mid-sections (Figure 2) (11).

Figure 1. The Diagram Illustrates Definition of Chronic Total Occlusion Together with Adjacent Proximal and Distal Segments Studies. Reproduced with Permission from Sakakura et al. (11)

3. Components of CTO
CTO of different durations showed substantial variability in the underlying plaque morphology, such that short-duration CTO showed an organized or organizing thrombus and presence of necrotic core, whereas the predominant component of long-duration CTO was fibrous tissue (11).

Figure 2. Representative Images of Long-Duration Chronic Total Occlusion and Short-Duration Chronic Total Occlusion without Coronary Artery Bypass Graft

(A and C) Low-power images of long-duration and short-duration chronic total occlusion without coronary artery bypass graft. (B and D) High-power images of boxed areas in (A) and (C), respectively. The matrix is predominantly made up of collagen type I in (B). In (D), the matrix predominantly consists of proteoglycan and fibrin. CTO, chronic total occlusion. Reproduced with permission from Sakakura et al. (11).
Microchannels consist of small recanalization or thrombi with micro-capillaries. Indeed, approximately 50% of angiographically determined CTOs show recanalization (8). Katsuragawa et al. reported that the size of small microchannels at autopsy were 160 - 230 μm, when present (7), and were observed in 4 out of 10 CTOs (7). Microchannels were only observed in CTOs, which had a tapered proximal lumen pattern, whereas they were absent in CTOs, which had an abrupt proximal lumen pattern (7). In contrast, we reported that small recanalized channels of > 200 μm were infrequent among different histological CTOs (11). One potential explanation for this discrepancy is because autopsy studies were initially performed on CTOs that were defined by angiography, which also included incomplete occlusions. Indeed, one quarter of lesions reported by Srivatsa et al. were histologically sub-occlusive (90 – 95% stenosis) (8), which is not in agreement with our current definition of CTO. We used a much stricter definition of CTO; i.e., at least one section of CTO (cut at 3 mm intervals) had to have a total occlusion (> 99% stenosis) or 2 sections with > 95% stenosis. Nevertheless, microchannels are likely an important guide for the future device improvement, such as small-diameter guidewires or dedicated catheters aimed at crossing CTO lesions. However, it is unlikely that successful recanalization of CTO lesions is based on effective wire passage of microchannels in the range of 20 – 40 μm, but rather on targeted penetration of soft tissue, which is composed of proteoglycans, type III collagen, and fibrin within the body of the CTO. Furthermore, micro-capillaries in CTO lesions may connect to the adventitia rather than penetrate through the CTO, but this is not frequent (8). Inflammation also plays an important role in the development of CTO, where densities of macrophages are generally higher in occlusion of < 1-year duration compared to > 1-year duration (Figure 3) (12). Lymphocytes and macrophages play an active role in angiogenesis as well as atherosclerotic lesion progression by producing various mitogenic and angiogenic factors that influence the extent of recanalization (13, 14).

4. Negative Remodeling
One of the major differences between acute thrombotic occlusion and longer duration CTO is the extent of vascular remodeling. Acute thrombi from plaque rupture are associated with positive vascular remodeling (15). Based on animal studies, it is clear that organization of an acute occlusive thrombus leads eventually to vessel remodeling from organization consisting of inflammation, angiogenesis, and Smooth Muscle Cell (SMC) infiltration. SMCs lay down of proteoglycan matrix and collagen type III and I. The type I collagen cross-links with resulting shrinkage of the vessel; i.e., negative remodeling (16). Long-duration CTOs are composed predominantly of type I collagen and exhibit negative remodeling, while short-duration CTOs are composed mostly of MCs, proteoglycan, and fibrin in the absence of negative remodeling (11). The relatively high failure rate of recanalization procedures of long-duration CTOs can be explained on the basis of extensive negative

![Figure 3. Role of Inflammation in Formation of Neoangiogenesis in CTO](image-url)
remodeling and is the likely source for failure of guidewire penetration (17). Morphologic characteristics of CTO have been shown in Figure 4 (12).

5. Proximal and Distal Lumen Pattern
   It is well known that proximal lumen pattern (tapered or abrupt) is strongly associated with successful antegrade revascularization of CTO (18, 19). Tapered lumen pattern is associated with successful guidewire penetration, whereas abrupt lumen pattern with failure of successful wire passage (18, 19). In contrast, distal lumen pattern is difficult to judge owing to the difficulty in assessing distal lumen morphology during angiography. We reported that the prevalence of tapered pattern was significantly more frequent in distal lumen compared to proximal lumen (11). The utilization of retrograde approach is one of the main advances in revascularization techniques during CTO procedures and is responsible for the incremental success rates (6, 20).

6. CTO with Coronary Artery Bypass Graft (CABG)
   PCI procedures of CTO following long-term CABG are associated with a significantly higher rate of unsuccessful revascularization (21, 22). It is reported that approximately half of the patients with prior CABG have native coronary CTO (23). Although conduits in combination with the internal mammary artery have partly replaced the use of saphenous veins during CABG procedures, graft patency rates remain overall unsatisfactory (24). Moreover, short- and long-term outcomes of PCI in saphenous vein graft are poor with drug-eluting stents as well as bare-metal stents (25, 26). Therefore, the need to revascularize native coronary CTO with prior CABG is high. We recently reported the pathological characteristics of CTO with prior CABG, in which we showed that severe calcification was a common finding in CTO segments as well as in the proximal and distal adjacent segments (11) (Figure 5). The high failure rate of revascularization attempts in these highly calcified CTO coronary arteries (19) is likely explained by the difficulty encountered during passing of guide wires, even by highly experienced operators. In fact, calcification of CTO segments has been reported to be a significant determinant of unsuccessful CTO PCI patients with prior CABG, and CTO represents a cohort at high risk for adverse cardiovascular outcomes.

7. Summary
   Since prior histopathological studies were based on angiographically defined CTO, more accurate histological definition of CTO is an important step for determining better predictors of success and failure following PCI. Histologically, CTO lumen area, if occluded by proteoglycan and/or collagen with or without neovascularization, and chronic inflammation, with the luminal stenosis greater than 95%, have greater chances of PCI success when there is no negative remodeling and there is tapering of proximal non-CTO segments. On the other hand, in long-duration CTO, defined as having a matrix predominately composed of type I collagen and absence of fibrin identified in any histological section of CTO with negative remodeling, the success rates are less and retrograde approach is more likely to be successful. Severely calcified CTO, which

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**Figure 4. Morphologic Characteristics of CTO**

(A) Acute plaque rupture is shown, with luminal thrombus resulting in CTO. (B) Inflammation with early thrombus organization is shown. Note early recanalization accompanied by proteoglycan matrix (green) in the area of Total Occlusion (TO). (C) The late chronic phase of healed TO is shown, with deposition of collagen type I where the cross-linking of collagen promotes negative remodeling of the vessel. (D) Physiological recanalization is accompanied by restoration of normal flow distally, thus preventing negative remodeling. Reproduced with permission from Finn et al. (12)
The radiograph (left) shows severe calcification of the vein graft as well as a right coronary artery. P-1 is a proximal segment and D-1 is the distal segment. Serial CTO images show severe calcification. Note: The rate of area calcification in CTO-1 is 70% and CTO-5 shows five channels >200 μm in size. The proximal and distal sections to CTO show 54% and 48% area calcification, respectively. PRC, proximal right coronary artery; MRC, middle right coronary artery; RMB, right marginal branch; DRC, distal right coronary artery; PD, posterior descending artery; CTO, chronic total occlusion; P-1, proximal first section; D-1, distal first section. Reproduced with permission from Sakakura et al. (11).

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Authors’ Contribution
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References


