Comparison of pathology of chronic total occlusion with and without coronary artery bypass graft

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Aims
The aim of our study was to investigate chronic total occlusion (CTO) in human coronary arteries to clarify the difference between CTO with prior coronary artery bypass graft (CABG) and those without prior CABG.

Methods and results
A total of 95 CTO lesions from 82 patients (61.6 ± 14.0 years, male 87.8%) were divided into the following three groups: CTO with CABG (n = 34) (CTO+CABG), CTO without CABG—of long-duration (n = 49) (LD-CTO) and short-duration (n = 12) (SD-CTO). A histopathological comparison of the plaque characteristics of CTO, proximal and distal lumen morphology, and negative remodelling between groups was performed. A total of 1127 sections were evaluated. Differences in plaque characteristics were observed between groups as follows: necrotic core area was highest in SD-CTO (18.6%) (LD-CTO: 7.8%; CTO+CABG: 4.5%; P = 0.02); calcified area was greatest in CTO+CABG (29.2%) (LD-CTO: 16.8%; SD-CTO: 12.1%; P = 0.009); and negative remodelling was least in SD-CTO [remodelling index (RI) 0.86] [CTO+CABG (RI): 0.72 and LD-CTO (RI): 0.68; P < 0.001]. Approximately 50% of proximal lumens showed characteristics of abrupt closure, whereas the majority of distal lumen patterns were tapered (79%) (P < 0.0001).

Conclusion
These pathological differences in calcification, negative remodelling, and presence of necrotic core along with proximal and distal tapering, which has been associated with greater success, help explain the differences in success rates of percutaneous coronary intervention in CTO patients with and without CABG.

Keywords
Chronic total occlusion • Coronary artery bypass graft • Percutaneous coronary intervention • Negative remodelling • Calcification

Introduction
Coronary chronic total occlusion (CTO) is a common finding with a reported prevalence of 18.4% in patients undergoing non-urgent coronary angiography in the absence of previous coronary artery bypass or those presenting with acute myocardial infarction.1 Revascularization of CTO is associated with the improvement of cardiac function and long-term clinical outcome.2,3 Although the success rate of percutaneous coronary intervention (PCI) for revascularizing CTOs was low (51–74%) up to 2009,4 recent technological advances and interventional strategies have improved the success rate of PCI of CTO. The introduction of stiffer guidewires, microcatheters, tapered guidewires, and retrograde approach has contributed to the incremental improvements in success rates of >85%.5–7 On the other hand, PCI for CTO with prior coronary artery bypass graft (CABG) remains a challenge.8,9 Since approximately half the patients with prior CABG have CTO1 and the patients with saphenous vein graft often develop recurrent symptoms,10 the need to revascularize CTO with prior CABG is high. Furthermore, since the short- and long-term outcomes of PCI of saphenous vein graft are poor with drug-eluting stents as well as with bare-metal stents,11–13 PCI of coronary CTO following CABG is, therefore, likely to result in more favourable outcome. However, the success rate for CTO with prior CABG is still lower (80%) than those without CABG (88%) even though newer techniques are being utilized.9

The pathological understanding of CTO from human autopsy studies has contributed to significant refinements of PCI techniques leading to improved results of revascularization. Histological correlates of angiographic CTOs have shown the influence of the duration of total occlusion on the presence of calcification, inflammation, and...
neovascularization. Another important finding in angiographic CTOs was the absence of complete occlusion on histological examination (78%) and, therefore, higher success rate is not surprising. Furthermore, the presence of microchannel diameter of 160–230 μm in human pathological study has encouraged the development of smaller diameter guidewires. In the present study, we sought to further investigate the extent of calcification, necrotic core size, remodelling, and proximal and distal lumen shape to understand better the differences in CTO characteristics in patients with and without CABG.

Methods
We interrogated the CVPath registry of sudden coronary death and CABG to select cases with CTO. The clinical records were also reviewed. In most cases, coronary arteries had been removed from the heart following perfusion fixation in 10% neutral buffered formalin. The major epicardial coronary arteries were radiographed and decalcified in EDTA. The arteries were sequentially cut at 3 mm intervals, labelled, dehydrated, and embedded in paraffin. The right coronary artery (RCA), left anterior descending (LAD), and left circumflex (LCx) were divided into proximal and mid to distal regions as previously described.

Histopathological identification of chronic total occlusions
Since angiographically total occlusion does not correspond to histologically total occlusion, histological definition of CTO was defined, when the lumen area was occupied by proteoglycan and/or collagen with or without neovascularization and chronic inflammation. Furthermore, for the histological definition of CTO, see Figure 1. The final length of the CTO lesion was calculated by multiplying individual 3 mm segment lengths by the total number of consecutive CTO sections. The CTO with bypass graft was defined as having an arterial or venous bypass graft that was anastomosed distal to the CTO, and the duration of graft had to be >2 years. The CTO without bypass graft was further divided into the long-duration CTO (LD-CTO) (morphologically the matrix had to be made up predominantly of collagen and no fibrin was identified in any section of CTO) or short-duration CTO (SD-CTO) (matrix consisting predominately of proteoglycan with fibrin present in at least one mid-section of the CTO) (Figure 2).

Lesion analysis
Various components of the CTOs were measured and analysed using image analysis software (IP Lab for Mac OS X, Scanalytics, Rockville, MD, USA) as previously described. The one section with the maximum per cent organized thrombus, necrotic core, and calcification area was utilized as representative of the CTO. The number of microvascular channels with diameters >200 μm were analysed in each CTO section.

Analysis of negative remodelling
Negative remodelling of CTO lesions was determined for all cases except ostial CTO lesions, which inherently do not have proximal reference segment and, therefore, it was not possible to determine remodelling. The largest proximal IEL dimension (P-3, P-2, or P-1) was used as the reference section to determine remodelling. The remodelling index (RI) was defined as the ratio of IEL area in CTO divided by the largest IEL area in

Figure 1  The diagram illustrates the method utilized for the examination of histological sections as well as definition of chronic total occlusion together with adjacent proximal and distal segments studies. CTO, chronic total occlusion.
one of the proximal reference section. Chronic total occlusion sections
demonstrating RI < 0.75 were classified as negative remodelling.18
Chronic total occlusion IEL was corrected for the influence of normal
tapering (1.2 mm²/cm),18 when CTO length was >10 mm. The
diagram of the definition of negative remodelling is shown in Figure 3.

Proximal and distal lumen patterns

The lumen pattern was classified as abrupt lumen when the proximal (or
distal) segments fulfill one of the following abrupt pattern criteria: (i) the
proximal or distal most section closest to CTO (P-1 or D-1, respectively)
had to have narrowing of <75% area stenosis, and the change from the
proximal to mid-section (P-2 or D-2) or between mid to distal (P-3 or
D-3) had to be <25% area stenosis change; (ii) bifurcation branch in
P-1 or D-1; and (iii) ostial type CTO. The lumen pattern was defined as
tapered lumen when the proximal (or distal) segments did not fulfill any
abrupt pattern criteria.

Statistical analysis

Results for continuous variables with normal distribution were expressed
as mean ± SD. Normality of distribution was tested with the Wilk–
Shapiro test. Variables with non-normal distribution were expressed as
median and inter-quartile range (IQR). Statistical comparisons of
normally distributed measurements were performed by linear general-
ized estimating equation (GEE) modelling with an assumed Gaussian dis-
tribution, an identity link function, and an assumed exchangeable
structure for the within-cluster correlation matrix in consideration of
the clustered nature of one or more individual measurements from
one patient. Non-normally distributed variables were logarithmically
transformed before entering GEE. Categorical data were compared
using the χ² test. All analyses were performed with the SPSS software
(version 19; Chicago, IL, USA) and JMP 5 (SAS Institute, Cary, NC,
USA). All reported P-values were determined by two-sided analysis
and values of <0.05 were regarded as statistically significant.

Results

From CVPath autopsy registry (from 2005 to 2011), 125 CTO lesions
were reviewed. A total of 30 CTOs were excluded (17 lesions due to
lack of adjacent proximal or distal sections to CTO, and another 13
CTOs were from recent CABG). A total of 95 CTO lesions from 82
patients [mean age was 61.6 ± 14.0 years, the majority of them were
males (87.8%)] were analysed. The case demographics and lesion
characteristics are shown in Table 1. In >80% of cases, the cause of
death was coronary related. Evidence of healed myocardial infarction

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.
was found in 90.3% of cases, and the majority of them were identified as transmural. Chronic total occlusions were most frequently located in RCA (57.9%), followed by LAD (22.1%) and least frequent in LCx (20.0%), with most located in the proximal (68.4%) regions. The median length of CTO was 15.0 mm (IQR: 12.0–30.0 mm). Of the 95 CTO lesions, 34 CTO lesions had long-term CABG (CTO + CABG), whereas 61 CTO were without bypass graft (12 lesions were from SD-CTO and 49 had LD-CTO). Of the 34 CTO + CABG lesions, 31 had vein graft and 3 had arterial. Although six vein grafts were obstructed (defined as ≥80% stenosis), the majority (82.4%) of bypass grafts were patent at the time of the autopsy, and no significant differences were observed between those with and without obstruction. The representative lesions of CTO + CABG, LD-CTO, and SD-CTO are shown in Figures 4–6, respectively.

A total of 1127 histological sections were analysed. A morphological comparison between CTO + CABG, LD-CTO, and SD-CTO lesions is shown in Table 2. CTO + CABG and SD-CTO were predominantly located in the proximal, whereas only half of LD-CTOs were located in the proximal. The median CTO lengths between CTO + CABG [15.0 mm (IQR: 11.3–30.0 mm)] and LD-CTO [15.0 mm (IQR: 9.0–25.5 mm)] were similar, whereas the median length of SD-CTO without CABG [31.5 mm (IQR: 15.0–49.5 mm)] was twice as long (P = 0.01). Vessel size (EEL and IEL) was similar in CTO + CABG and SD-CTO, but was smallest in LD-CTO. Microchannels with diameter ≤200 μm were infrequently observed in all three groups.

The comparison of plaque components between the three groups is shown in Table 3. The per cent organized thrombus area in CTO segments was highest in SD-CTO [36.9% (IQR: 25.9–48.0%)], followed by LD-CTO [27.7% (IQR: 19.8–35.4%)], and was smallest in CTO + CABG [23.2% (IQR: 15.1–33.2%)] (P = 0.02). The per cent necrotic core area in CTO segments was highest in SD-CTO [45.9% (IQR: 0–23.2%)], followed by LD-CTO [45.9% (IQR: 0–23.2%)], and lowest in CTO + CABG [4.5% (IQR: 0–23.2%)]. The per cent calcification area in CTO segments was highest in CTO + CABG [29.2% (IQR: 19.5–49.5%)], followed by LD-CTO [16.8% (IQR: 19.5–39.9%)], and smallest in SD-CTO [12.1% (IQR: 0.4–37.0%)]. Furthermore, the per cent calcified areas in proximal vs. distal segments was also significantly greater in CTO with CABG.

The comparison of proximal and distal lumen patterns of the three groups is shown in Table 4. Although the prevalence of the abrupt pattern in proximal lesions was not significantly different between groups, approximately half the lesions (51.6%) exhibited abrupt...
lumen patterns. Although the prevalence of the abrupt pattern in the distal lumen was also not significantly different between groups, the majority of the lesions exhibited tapered (78.9%) lumen patterns. In all CTOs, the prevalence of abrupt patterns in the proximal lumen was significantly more frequent than in the distal lumen ($P < 0.0001$). Furthermore, in CTO+CABG and LD-CTO, the prevalence of the abrupt pattern in the proximal lumen was significantly higher than that in the distal lumen ($P < 0.0001$ for CTO+CABG and $P = 0.02$ for LD-CTO). No significant difference between proximal and distal was observed for SD-CTO ($P = 0.41$). Representative images of abrupt and tapered patterns are shown in Figure 7.

Comparison of negative remodelling between the three groups is shown in Table 5. Negative remodelling was the lowest in SD-CTO [RI: 0.86 (IQR: 0.63–1.16)], followed by CTO+CABG [RI: 0.72 (IQR: 0.53–0.97)], and was the highest in LD-CTO [RI: 0.68 (IQR: 0.51–0.96)] ($P < 0.001$). We also classified all CTO sections ($n = 546$) into the following four types: organizing thrombus sections [$n = 46$ (8.4%)], proteoglycan-rich thrombus sections [$n = 82$ (15.0%)], calcified CTO (>10% calcification area) sections [$n = 186$ (34.1%)], and non-calcified CTO sections rich in collagen type I (<10% calcification area) [$n = 232$ (42.5%)]. The comparison of negative remodelling between four types of CTO sections is shown in Figure 8. Negative remodelling was least in sections containing organizing thrombus [RI: 0.99 (0.75–1.35)], followed by calcified CTO sections [RI: 0.79 (0.56–1.15)], proteoglycan-rich thrombus sections [RI: 0.77 (0.61–1.03)], and was the greatest in non-calcified CTO sections rich in collagen type I [RI: 0.63 (0.47–0.86)] ($P < 0.001$).

**Discussion**

The present histopathological study of human CTOs demonstrated several important features to clarify the difference among three different types of CTOs. First, CTOs with CABG are characterized by severe calcification and moderate negative remodelling. Second, LD-CTOs without CABG are characterized by severe negative remodelling and moderate calcification. Third, SD-CTOs without CABG are characterized by abundant organizing thrombi and necrotic cores, and least negative remodelling. Furthermore, the prevalence of abrupt patterns in proximal and distal lumens is not different among the three types of CTOs; however, the prevalence of the
abrupt pattern in the proximal lumen is more frequent than that in the distal lumen.

Although the presence of coronary CTOs is commonly recognized during angiography, there are few existing reports in the literature describing the histological findings of the different types of CTO, especially in the presence of CABG. In one of the earliest correlative histopathological studies in the late 1990s, Srivatsa et al.14 investigated 96 angiographically proven CTO lesions where they recognized that angiographic CTO lesions were not always totally occluded at post-mortem studies with 90–95% stenosis observed in 25% of CTOs, 96–98% in 24% of CTOs, 99% in 29% of CTOs, and complete occlusion in 22%. Because the present study demonstrates that microchannels of adequate size (>200 μm) are infrequent, angiographic CTOs <95% must not be treated as CTOs. The importance of lesion morphology in defining treatment strategies for revascularizing CTOs was highlighted by Katsuragawa et al.15 They classified 10 CTO lesions with reference to the proximal segment lumens to help explain why the tapering type of occlusion and short-occluded segments have a favourable successful outcome following PCI. The findings indicated that the above morphology was associated with small microvessel recanalization with surrounding ‘loose fibrous tissue’ in the occluded segment and, therefore, such lesions were more amenable to PCI due to the ease of the wire to penetrate the lesion. However, there is no published histological study available to our knowledge that compares CTO with prior CABG with CTO without prior CABG.

**Chronic total occlusion with coronary artery bypass graft**

Our results demonstrated that CTOs with CABG have extensive calcification not only in the CTO segments but also in the adjacent proximal and distal segments. Since extensive calcification is associated with diffuse coronary atherosclerotic disease,19 CTO with CABG exhibited more advanced stable atherosclerosis than CTO without CABG. Although precise mechanism of atherosclerosis in CTO with CABG is unknown, several clinical studies reported that atherosclerotic progression occurs more rapidly in grafted arteries than in non-grafted arteries.20,21 Furthermore, the progression from severe atherosclerosis to total occlusion,
which is usually located proximal to the anastomosis, is common in grafted arteries.\(^{20,21}\) It is possible that blood stasis and low shear stress resulting from competitive flow between native and bypass graft may be the underlying mechanism of greater calcification in the grafted native arteries.\(^{20,22}\) It is also known that calcification is closely associated with difficulty in obtaining success during PCI in CTO.\(^{23,24}\) Therefore, it is likely that extensive and larger areas of calcification may be the most important explanation for lower success rate of PCI for CTO with prior CABG (\(>2\) years duration) compared with CTO without CABG.

### Short-duration chronic total occlusion without bypass graft

Although we defined CTO including organizing thrombus as short-duration CTO, it does not necessarily imply recent total occlusion. The time of complete organization of the thrombus in CTO is dependent on the length of CTO. As we have shown in Figure 6, both edges of CTO, which come in contact with flowing blood, are more likely to organize early, whereas the centre of CTO without blood contact remains unorganized. Furthermore, our data are consistent with the above concept as the length of SD-CTO lesions was significantly longer than in the other groups. Shorter length thrombotic CTOs are more likely to mature in a short time, whereas longer length CTOs will take a longer time to mature.

### Negative remodelling

Negative remodelling is another important characteristic of CTO and is one of the determinants of success or failure of CTO lesions by PCI.\(^{25}\) In the rabbit femoral artery CTO model, Jaffe et al.\(^{26}\) reported negative remodelling of CTO. In their study, the SD-CTOs contained abundant proteoglycan extracellular matrix and low collagen density, whereas the longer duration CTOs contained less proteoglycan extracellular matrix and increased collagen density.\(^{26}\) In the present study, we demonstrated that least negative remodelling is
### Table 2  Comparison of vessel morphology between chronic total occlusion with coronary artery bypass graft, long-duration chronic total occlusion and short-duration chronic total occlusion without coronary artery bypass graft lesions

<table>
<thead>
<tr>
<th></th>
<th>CTO with CABG n = 34 (IQR)</th>
<th>Long-duration CTO n = 49 (IQR)</th>
<th>Short-duration CTO n = 12 (IQR)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vessel</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD/LCx/RCA, n (%)</td>
<td>7 (20.6)/8 (23.5)/19 (55.9)</td>
<td>13 (26.5)/9 (18.4)/27 (55.1)</td>
<td>1 (8.3)/2 (16.7)/9 (75.0)</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal/middle/distal/branch, n (%)</td>
<td>31 (91.2)/2 (5.9)/1 (2.9)/0</td>
<td>25 (51.0)/17 (34.7)/3 (6.1)/4 (8.2)</td>
<td>9 (75.0)/3 (15.0)/0/0</td>
<td>0.01</td>
</tr>
<tr>
<td>CTO length (mm)</td>
<td>15 (11.3–30)</td>
<td>15 (9–25.5)</td>
<td>31.5 (15–49.5)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Vessel size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal EEL area</td>
<td>12.99 (9.46–17.17)</td>
<td>10.02 (6.71–13.18)</td>
<td>11.68 (10.03–18.78)</td>
<td>0.001</td>
</tr>
<tr>
<td>CTO EEL area</td>
<td>9.58 (6.88–13.61)</td>
<td>6.48 (4.62–9.23)</td>
<td>10.20 (7.25–13.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distal EEL area</td>
<td>7.20 (5.01–12.34)</td>
<td>4.23 (3.01–6.84)</td>
<td>5.96 (2.47–8.85)</td>
<td>0.001</td>
</tr>
<tr>
<td>Proximal IEL area</td>
<td>10.05 (8.30–15.77)</td>
<td>8.62 (5.95–10.76)</td>
<td>9.09 (7.58–14.02)</td>
<td>0.002</td>
</tr>
<tr>
<td>CTO IEL area</td>
<td>8.31 (5.85–11.98)</td>
<td>5.71 (3.91–7.85)</td>
<td>8.52 (6.35–11.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distal IEL area</td>
<td>5.99 (4.11–9.77)</td>
<td>3.67 (2.38–5.75)</td>
<td>5.11 (1.79–7.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proximal % stenosis</td>
<td>76.0 (69.4–86.6)</td>
<td>79.5 (72.9–86.2)</td>
<td>76.1 (62.8–82.7)</td>
<td>0.62</td>
</tr>
<tr>
<td>CTO % stenosis</td>
<td>98.0 (95.8–99.2)</td>
<td>98.6 (97.3–99.2)</td>
<td>95.8 (90.6–97.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>Distal % stenosis</td>
<td>83.1 (76.5–88.6)</td>
<td>84.2 (79.9–88.6)</td>
<td>77.0 (70.2–84.4)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Microchannel (&gt;200 μm)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean number of microchannel in CTO</td>
<td>0.5 (0.3–0.8)</td>
<td>0.5 (0.3–0.8)</td>
<td>0.7 (0.5–0.8)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

EEL, external elastic lumen; IEL, internal elastic lumen; CTO, chronic total occlusion; CABG, coronary artery bypass graft; RCA, right coronary artery.

- †P < 0.05: CTO with bypass graft lesions vs. long-duration CTO without bypass graft lesions.
- ‡P < 0.05: CTO with CABG lesions vs. short-duration CTO without CABG lesions.
- §P < 0.05: long-duration CTO without CABG lesions vs. short-duration CTO without CABG lesions.

### Table 3  Comparison of plaque components between chronic total occlusion with coronary artery bypass graft, long-duration chronic total occlusion, and short-duration chronic total occlusion without coronary artery bypass graft lesions

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<th>Short-duration CTO n = 12 (IQR)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal segments plaque area (mm²)</td>
<td>8.10 (6.37–11.79)</td>
<td>6.53 (4.97–8.19)</td>
<td>6.90 (5.19–10.46)</td>
<td>0.006</td>
</tr>
<tr>
<td>CTO segments plaque area (mm²)</td>
<td>8.20 (5.59–11.58)</td>
<td>5.65 (3.80–7.50)</td>
<td>8.30 (5.92–10.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distal segments plaque area (mm²)</td>
<td>4.68 (3.41–8.03)</td>
<td>3.22 (1.90–4.90)</td>
<td>3.74 (1.54–6.63)</td>
<td>0.001</td>
</tr>
<tr>
<td>Proximal segments % organized thrombus area</td>
<td>9.3 (1.2–14.5)</td>
<td>5.0 (0–15.6)</td>
<td>7.0 (0–26.6)</td>
<td>0.67</td>
</tr>
<tr>
<td>CTO segments % organized thrombus area</td>
<td>27.7 (19.8–35.4)</td>
<td>23.2 (15.1–33.2)</td>
<td>36.9 (25.9–48.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Distal segments % organized thrombus area</td>
<td>11.2 (6.3–16.3)</td>
<td>9.0 (2.7–25.9)</td>
<td>12.7 (5.8–33.3)</td>
<td>0.81</td>
</tr>
<tr>
<td>Proximal segments % necrotic core area</td>
<td>1.1 (0–4.1)</td>
<td>2.4 (0–10.6)</td>
<td>8.7 (0–20.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>CTO segments % necrotic core area</td>
<td>4.5 (0–23.2)</td>
<td>7.8 (0–15.0)</td>
<td>18.6 (6.4–48.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Distal segments % necrotic core area</td>
<td>0 (0–5.6)</td>
<td>0 (0–1.7)</td>
<td>0 (0–4.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>Proximal segments % calcification area</td>
<td>31.5 (7.8–52.2)</td>
<td>12.1 (0–40.6)</td>
<td>0 (0–18.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>CTO segments % calcification area</td>
<td>29.2 (19.5–49.5)</td>
<td>16.8 (1.9–39.9)</td>
<td>12.1 (0.4–37.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>Distal segments % calcification area</td>
<td>28.8 (9.7–44.4)</td>
<td>1.2 (0–13.9)</td>
<td>0 (0–6.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CTO, chronic total occlusion; CABG, coronary artery bypass graft.

- †P < 0.05: CTO with CABG lesions vs. long-duration CTO without CABG lesions.
- ‡P < 0.05: CTO with CABG lesions vs. short-duration CTO without CABG lesions.
- §P < 0.05: long-duration CTO without CABG lesions vs. short-duration CTO without CABG lesions.
observed in an organizing thrombus which was seen in SD-CTO. Also, negative remodelling of a proteoglycan-rich thrombus was significantly less than that of non-calcified CTOs rich in collagen, which represents the late stage of CTOs without CABG. Our results suggest that negative remodelling of human CTOs occurs in two phases. In the early phase, a fibrin-rich organizing thrombus becomes a proteoglycan-rich thrombus. In the late phase, proteoglycan-rich thrombus becomes replaced by dense collagen within the CTO. Furthermore, negative remodelling in calcified CTOs was significantly less than negative remodelling in non-calcified collagen-rich CTOs. Severe calcification might play a role by providing a solid frame that prevents the CTO vessels from negative remodelling. Since CTO with CABG had highest calcification, severe calcification might be the explanation for the moderate negative remodelling in CTOs with CABG compared with the LD-CTOs without CABG that had the severest negative remodelling.

### Proximal and distal lumen patterns

When we look at lumens of coronary segments proximal and distal to CTOs to determine the nature of the lumen (i.e. abrupt or tapering), the reported prevalence of the proximal abrupt lumen pattern by angiography varies from 39.1 to 66.1%,23,27 which is comparable with our results of 51.6%. The prevalence of the proximal abrupt pattern was highest in CTO with CABG (58.8%), whereas the difference between groups was not significant [LD-CTO (46.9%) and SD-CTO (50%) without CABG, $P = 0.56$]. On the other hand, there are no reports describing the prevalence of the abrupt or tapering lumen pattern in the distal segments, since blood flow by collateral is not sufficient to judge the distal lumen pattern angiographically. The present results demonstrated that the majority of distal segments of CTO exhibited a tapered pattern and this would explain why true lumen placement of wire and devices is greater with retrograde approach. Also, the tapered pattern of CTO lumen is a better predictor of successful PCI based on a more favourable accessibility of guidewires27 into true lumens.

### Study limitations

In the present study, the results are representative of histologically proven CTO lesions, which may not reflect what it seen angiographically. Moreover, information about the precise age (i.e. duration) of the CTO was not available, as most of the CTO without CABG were from our sudden coronary death registry from individuals without prior history of CAD. Finally, although our study provides pathological insight supporting a retrograde approach for treating CTO, it is not our intention to recommend that only the retrograde strategy be used, since complications can be fatal28 and, therefore, CTO procedures should be performed by highly experienced interventional cardiologists.29,30

### Conclusions

A comparison between different types of CTOs with CABG, and LD-CTOs and SD-CTOs without CABG was performed in a large number of autopsy cases and showed that severe calcification is observed in CTOs with CABG, which may affect negatively on the success of PCI. Long-duration CTO without CABG demonstrated severe negative remodelling, whereas SD-CTO without CABG demonstrated abundant organized thrombus and larger necrotic core with least negative remodelling. These differences along with abrupt and tapering pattern of proximal and distal lumens likely affect the success rate of PCI in CTOs. Furthermore, the prevalence of the tapering pattern in the distal lumen was significantly higher than that in the proximal lumen, suggesting the advantage of retrograde approach.

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**Table 4** Comparison of proximal and distal lumen patterns between chronic total occlusion with coronary artery bypass graft, long-duration chronic total occlusion, and short-duration chronic total occlusion without coronary artery bypass graft lesions

<table>
<thead>
<tr>
<th></th>
<th>All, $n = 95$</th>
<th>CTO with CABG lesions, $n = 34$</th>
<th>Long-duration CTO, $n = 49$</th>
<th>Short-duration CTO, $n = 12$</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proximal lumen pattern</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abrupt</td>
<td>49 (51.6)</td>
<td>20 (58.8)</td>
<td>23 (46.9)</td>
<td>6 (50.0)</td>
<td>0.56</td>
</tr>
<tr>
<td>Tapered</td>
<td>46 (48.4)</td>
<td>14 (41.2)</td>
<td>26 (53.1)</td>
<td>6 (50.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Distal lumen pattern</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abrupt</td>
<td>20 (21.1)</td>
<td>4 (11.8)</td>
<td>12 (24.5)</td>
<td>4 (33.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>Tapered</td>
<td>75 (78.9)</td>
<td>30 (88.2)</td>
<td>37 (75.5)</td>
<td>8 (66.7)</td>
<td></td>
</tr>
<tr>
<td>P-value for proximal lumen pattern vs. distal lumen pattern</td>
<td>$&lt;0.0001$</td>
<td>$&lt;0.0001$</td>
<td>0.02</td>
<td>0.41</td>
<td></td>
</tr>
</tbody>
</table>

CTO, chronic total occlusion; CABG, coronary artery bypass graft.
Figure 7 (A) Representative images of the abrupt lumen pattern. Upper panels: adjacent proximal segment and chronic total occlusion segment of mid-left anterior descending. Per cent stenosis in P-3, P-2, and P-1 is 71, 80, and 71%, respectively, and was assigned to the abrupt lumen pattern. Lower panels: adjacent proximal segment and chronic total occlusion segment of mid-right coronary artery. Per cent stenosis in P-2 and P-1 is 69 and 81%, respectively. Because a large bifurcation branch is present in the P-1 section, this case was assigned to the abrupt lumen pattern. (B) Representative images of the tapered lumen pattern. Upper panels: adjacent proximal segment and chronic total occlusion segment of mid-right coronary artery. Per cent stenosis in P-3, P-2, and P-1 is 70, 91, and 90%, respectively; this case was assigned as tapered lumen pattern, because of gradual opening of the lumen. Lower panels: adjacent distal segment and chronic total occlusion segment of mid-left anterior descending. Per cent stenosis in D-3, D-2, and D-1 is 85, 91, and 95%, respectively; this case was assigned as tapered lumen pattern because of gradual opening of the lumen. CTO, chronic total occlusion.
Conflict of interest: none declared.

References
The results of CTO new technique for STandard procedure (CONQUEST) trial. J Invasive Cardiol 2008;20:571–577.


