Predictors and Prognostic Implications of Well-Matured Coronary Collateral Circulation in Patients with a Chronic Total Occlusion (CTO)

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Summary

The predictors and prognostic implications of well-matured collaterals in those with a chronic total occlusion (CTO) are unknown. We sought to identify the determinants of collateral maturation and to determine its effects on procedural outcomes and prognosis.

Patients presenting for CTO percutaneous coronary intervention (PCI) between April 2010 and July 2019 were included. Patients with a previous coronary artery bypass (CABG) to the CTO and those with only bridging collaterals were excluded. The degree of collateral maturation was determined by the Rentrop grading classification. Demographic, biochemical, and anatomical factors and procedural and longer-term outcomes were identified.

A total of 212 patients were included in the study. Patients with well-matured collaterals were more likely to be females (29.7% versus 15.2% versus 0%, \( P < 0.005 \) for Rentrop grade 3, 2, and 0 or 1, respectively), less likely to have chronic kidney disease (CKD) (8.8% versus 4.5% versus 19.2%, \( P < 0.05 \)) and less likely to have had a prior CABG (15.6% versus 18.7% versus 19.2%). Patients with well-matured collaterals had lower neutrophil-to-leukocyte ratio (NLR) (2.8 versus 4.0 versus 5.7, \( P < 0.0001 \)). Patients with well-matured collaterals were more likely to have procedural success (90.5% versus 62.5% versus 34.6%, \( P < 0.0001 \)). The degree of collateral maturation was not associated with longer-term mortality.

Improved collateral maturation was associated with female sex and lower rates of CKD and CABG and a lower NLR. Those with well-matured collaterals had a significantly higher rate of procedural success but not improved prognosis.

Key words: Coronary artery disease (CAD), Rentrop, Percutaneous coronary intervention (PCI)

A chronic total occlusion (CTO) of the coronary circulation is defined as complete or near-complete occlusion of an epicardial vessel, present for at least 3 months,11 angiographically appreciated via opacification of the distal vessel via the collateral circulation. The prevalence of a CTO identified during coronary angiography is estimated to be between 30 and 50%,2,3 with 6.6% of patients presenting with an ST elevation myocardial infarction also having a CTO in a non-infarct-related artery.17

The presence of well-developed coronary collaterals has been associated with improved prognosis in most studies in the setting of stable disease,5,6 however, studies have used conflicting definitions of a “sufficient” collateral circulation.5 While the presence of well-developed collaterals is often described as “benign” and an indication to avoid either percutaneous or surgical revascularization,1 conflicting studies have suggested that well-developed collaterals in patients with a CTO may be associated with increased ventricular arrhythmia and greater appropriate defibrillator therapy.40

Similarly, in the setting of an acute coronary syndrome, the ability to acutely recruit collaterals to supply the myocardial territory subtended by the culprit vessel has been associated with improved outcomes,49 although one study suggested better developed collaterals associated with poorer outcomes.40

Furthermore, while there have been correlations between patient demographics, culprit vessel characteristics, and circulating angiogenic mediators,11 the predictors of the coronary collateral recruitment and maturation remain uncertain.

Given the uncertainty of the factors associated with collateral recruitment, as well as prognostic implications of the degree of collateral maturation, we sought to determine the demographic, anatomic, and biochemical determinants of collateral maturation in patients presenting for planned CTO percutaneous coronary intervention (PCI).
We also sought to determine the impact of the coronary collateral circulation on procedural outcomes as well as prognosis.

Methods

All patients presenting for CTO PCI at our dedicated tertiary center between April 2010 and July 2019 were included in the review. Patients with a CTO of a vessel supplied by a coronary artery bypass graft (CABG) or a CTO of a bypass graft were excluded from the study as this may impact on the ability to recruit collaterals of the native circulation. To standardize definition of collateral maturation, all angiograms were reviewed to determine the degree of collateral formation, scored based on the Rentrop classification, whereby grade 0 is defined as no filling of collaterals or recipient vessel, grade 1 as filling of side branches of the recipient artery via collaterals without visualization of the epicardial segment, grade 2 as filling of the epicardial segment via collateral channels, and grade 3 as complete filling of the epicardial segment of the recipient artery via collateral channels. Reviewers were blinded to the outcome of the CTO PCI procedure.

For the analysis, patients were grouped as Rentrop grade 3 collaterals, Rentrop grade 2 collaterals, or Rentrop grade 0 or 1 collaterals. We also conducted analysis of those with Rentrop grade 3, which we defined as complete collaterals, and those with Rentrop grade 0, 1, or 2 collaterals which we defined as incomplete collaterals.

Along with Rentrop classification, all angiograms had calculation of the Japan-CTO (J-CTO) score performed. Patients with only bridging collaterals, that is, no collaterals providing retrograde filling via a different epicardial vessel, were excluded from the analysis. PCI success was based on operator self-reporting. Electronic medical records were reviewed to identify biochemical and hematological blood tests, taken within 4 weeks prior to CTO PCI procedure, procedural characteristics, and inhospital course along with longer-term outcomes and biochemical results. Chronic kidney disease (CKD) was defined by an eGFR < 45 mL/minute/m².

Statistical analysis: Continuous variables were presented as means (± standard deviation) or as medians and interquartile ranges, if the distribution of data was not normal. Categorical variables were reported as percentages. The baseline characteristics, PCI procedural findings, and inhospital outcomes were compared between differing degrees of collateral formation. Comparisons between groups were performed using Pearson’s chi-square test for categorical variables for normally distributed and the Kruskal-Wallis H test for categorical variables which were not normally distributed. The analysis of variance (ANOVA) test was used for comparing continuous variables or the independent student’s t-test when comparing two groups. Cumulative event rates were calculated according to the Kaplan-Meier method and compared using the Breslow generalized Wilcoxon score. All tests were two-sided, and a P < 0.05 was considered statistically significant. All analyses were performed using SPSS (version 24, IBM, New York, New York).

Results

A total of 212 patients were included over the study period, of which 39 (18.4%) were females with a mean age of 69.2 (± 10.2). Within the study population, 26 patients (12.3%) had Rentrop 0 or 1 collaterals, 112 (52.8%) had Rentrop grade 2 collaterals, and 74 (34.9%) had Rentrop grade 3 collaterals. With respect to the culprit vessel, the RCA was the commonest (56.1%) followed by the LCx, 48 (22.6%), and the LAD 45 (21.1%).

Patients with well-matured collaterals were more likely to be female (29.7% versus 15.2% versus 0%, P < 0.005 for Rentrop grade 3, 2, and 0 or 1, respectively), although there was no difference in age or BMI. Cardiovascular risk factor profiles were similar between the three groups, although those with well-matured collaterals had lower rates of CKD (8.8% versus 4.5% versus 19.2%, P < 0.05). Patients with well-developed collaterals were also less likely to have a history of a previous CABG (15.6% versus 18.7% versus 19.2%, P < 0.05). Median ejection fraction, previous acute myocardial infarction, and medication usage at baseline were similar between all groups. Similarly, disease complexity, as assessed by the syntax score, was similar between all groups (Table I).

With respect to hematological blood results, patients with well-matured collaterals had a higher leukocyte concentration (1.9 × 10⁹/L versus 1.6 × 10⁹/L versus 1.9 × 10⁹/L, P < 0.01) and a lower NLR (2.8 versus 4.0 versus 5.7, P < 0.0001) (Table I). Other full blood count parameters were similar between the three groups. Similarly, there was no difference with respect to baseline biochemical results between either group (Table II).

Patients with well-matured collaterals had a higher PCI success rate as compared to those with poorer developed collaterals (90.5% versus 62.5% versus 34.6%, P < 0.0001) and were more likely to have successful CTO PCI performed via the retrograde approach (32.8% versus 18.6% versus 0%, P < 0.05). Patients with well-developed collaterals were less likely to use adjunctive intravascular imaging as compared to those with poorer developed collaterals (2.7% versus 5.4% versus 19.2%, P < 0.05). Other procedural characteristics were similar between both groups. The second-generation drug-eluting stents and total contrast volume used during the procedure were similar in both groups (Table III).

We subsequently reviewed electronic medical records to determine the impact on prognosis with respect to the degree of collateral maturation. The mean follow-up for patients were similar between the three groups: 686.8 days for Rentrop grade 3, 680.1 days for Rentrop grade 2, and 692.2 for Rentrop grade 1 or 0 (P = 0.99).

There was no difference in longer-term survival when analyzing patients by degree of collateral maturation with respect to mean survival in the overall population (2574.6 days versus 2387.5 days versus 1955.2 days, P = 0.50) (Figure 1). When grouping patients as those with complete collaterals (Rentrop grade 3) compared to incomplete collaterals (Rentrop grade 0, 1 or 2), there was a trend toward a reduction in longer-term mortality (2574.6 days versus 2372.5 days, P = 0.24) (Figure 2). After excluding patients who underwent successful CTO PCI pro-
cEDURE, we again analyzed the longer-term impact of the degree of collateralization on mortality. While there was a trend toward worse outcomes in those with complete collaterals compared to incomplete collaterals, there was no difference with respect to mean survival (1659.1 days versus 2124.1 days, \( P = 0.06 \)) (Figure 3).

### Discussion

In our single-center experience, the presence of well-developed collaterals was more common in females, those without a history of renal failure, and those without a prior coronary bypass graft. While other studies have suggested that older age reduces the likelihood of collateral recruitment, possibly due to reduced telomerase activity, we found no effect of age on the degree of collateral maturity.\(^{19}\)

The presence of renal impairment has previously been associated with poorer angiographically determined collateral recruitment.\(^{19,20}\) It has been suggested that the greater prevalence of endothelial dysfunction in patients with renal impairment may attenuate endothelial-derived nitric oxide pathways,\(^{11,22}\) with resultant reduction in collateral recruitment and maturation.

We found that patients who had a history of previous CABG were less likely to have well-developed collaterals. The presence of a bypass graft is associated with accelerated atherosclerotic disease process and greater risk of development of a CTO of a bypassed vessel.\(^{20}\) Early studies indicated that patients with occluded bypass grafts were able to recruit the same degree of collaterals as prior to the surgery,\(^{24,25}\) although other series have suggested that the ability to recruit collaterals to the bypassed vessel is reduced.\(^{20}\) As we excluded patients who had a previous bypass to the occluded vessel, the presence of a CABG itself appears to negatively impact on the collateral circulations’ ability to spontaneously mature.

The neutrophil-to-lymphocyte ratio (NLR) has been

| Table 1. Baseline Characteristics |
|----------------------------------|
|                                | Rentrop 1 (n = 26) | Rentrop 2 (n = 112) | Rentrop 3 (n = 74) | \( P \)-value |
| Age (years)                     | 70.9 (± 10.6)      | 69 (± 10.0)         | 68.9 (± 10.4)     | 0.65         |
| BMI (kg/m²)                     | 29.8 (± 5.2)       | 28.5 (± 5.9)        | 28.4 (± 5.5)      | 0.54         |
| Female sex (n) (%)              | 0 (0%)             | 17 (15.2%)          | 22 (29.7%)        | < 0.005      |
| CTO vessel (n) (%)              |                   |                     |                   | 0.83         |
| LAD                             | 6 (23.1%)          | 24 (21.4%)          | 15 (20.3%)        |             |
| LCx                             | 8 (30.8%)          | 24 (21.4%)          | 16 (21.6%)        |             |
| RCA                             | 12 (46.1%)         | 64 (57.1%)          | 43 (58.1%)        |             |
| Smoking history (%)             |                   |                     |                   | 0.91         |
| Current                         | 7.7                | 10.8                | 10.9              |             |
| Ex-smoker                       | 34.6               | 36.0                | 41.1              |             |
| Non-smoker                      | 57.7               | 53.1                | 47.9              |             |
| Hypertension (%)                | 80.8               | 76.8                | 79.2              | 0.85         |
| Hypercholesterolemia (%)        | 88.5               | 79.5                | 77.0              | 0.46         |
| Diabetes mellitus (%)           | 42.3               | 31.2                | 27                | 0.35         |
| Family Hx of CAD (%)            | 19.2               | 31.2                | 36.5              | 0.26         |
| Renal failure (%)               | 19.2               | 4.5                 | 8.8               | < 0.05       |
| Prior CABG (%)                  | 42.3%              | 18.7%               | 15.6%             | < 0.05       |
| LVEF (%)(median, IQR)           | 55 (50-60)         | 55 (50-60)          | 55 (40-60)        | 0.18         |
| LV impairment, n (%)            | 5 (22.7%)          | 21 (21.9%)          | 19 (32.8%)        | 0.31         |
| Previous AML, n (%)             | 17 (65.4%)         | 58 (51.8%)          | 38 (51.3%)        | 0.42         |
| Medications, n (%)              |                   |                     |                   |             |
| Aspirin                         | 22 (91.7%)         | 91 (87.5%)          | 65 (87.8%)        | 0.85         |
| P2Y12 inhibitor                 | 21 (87.5%)         | 90 (86.5%)          | 67 (93.0%)        | 0.38         |
| Beta blocker                    | 15 (65.2%)         | 68 (70.1%)          | 48 (73.8%)        | 0.72         |
| ACE-I/ARB                       | 15 (65.2%)         | 69 (71.9%)          | 39 (60.9%)        | 0.34         |
| Statin                          | 22 (95.6%)         | 81 (83.5%)          | 61 (93.8%)        | 0.07         |
| CTO of stented vessel (%)       | 7.7%               | 4.5%                | 6.8%              | 0.72         |
| Syntax score (median, IQR)      | 1.7 (1.2)          | 1.9 (1.2)           | 1.7 (1.1)         | 0.41         |

BMI indicates body mass index; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; CABG, coronary artery bypass graft; CTO, chronic total occlusion; LVEF, left ventricular ejection fraction; LV, left ventricle; AMI, acute myocardial infarction; P2Y12, clopidogrel, ticagrelor, or prasugrel; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and JCTO, Japan CTO.
An elevated neutrophil count is associated with survival in multiple subtypes of malignancies, and a higher ratio is associated with poorer cardiovascular outcomes. An elevated neutrophil count is associated with elevated levels of vascular endothelial growth factor (VEGF), which is a primary promotor of angiogenesis, but it is not believed to play a role in angiogenesis, the proposed mechanism by which collateral arteries mature. Patients with well-developed collaterals had significantly lower NLR and a higher leukocyte count than those with poorer developed collaterals. The process of arteriogenesis, whereby preexisting arteriolar connections between epicardial vessels mature, occurs as a result of elevated shear stress detected by mechanoreceptors within the endothelial cells. This results in downstream upregulation of proteins involved in monocyte activation and macrophage differentiation with subsequent adventitial proteolysis and vascular structural development. However, numerous animal studies have also suggested that T cells play an integral role in neovascularization from collaterals, particularly NK cells and CD-4+ cells. However, in a peripheral animal model, infusion of lymphotactin and subsequent T-cell accumulation did not increase arteriogenesis. The association between collateral maturation and NLR suggests that the relative increase in lymphocytes, rather than absolute increase, may be more relevant to increasing collateral maturation.

The presence of well-developed collaterals was associated with a significantly higher likelihood of procedural success, which has previously been associated with significantly improved prognosis. The most commonly used
Figure 1. Kaplan-Meier cumulative survival in all patients

Figure 2. Kaplan-Meier cumulative survival in all patients with complete (Rentrop grade 3) or incomplete (Rentrop grade 0, 1 or 2) collaterals
scoring tool for predicting successful CTO PCI, the J-CTO score,\textsuperscript{13} does not include the presence, maturity, or size of the vessel. The more recently described PROGRESS CTO score,\textsuperscript{38} while it includes the presence or absence of “interventional collaterals” defined as collaterals which are amenable to crossing with a guidewire and microcatheter. However, this does not consider filling of the distal vessel, which is exclusively assessed using the Rentrop grading system. We found that the degree of collateral filling of the distal vessel predicted successful anterograde and retrograde approach, suggesting that their predictive effect is not as an interventional tributary, but may reflect better distal opacification and hence visualization. The overall success rate of CTO PCI in the entire cohort was 68.9%, which is similar to the core lab adjudicated procedural success of 73\% in the EXPLORE trial\textsuperscript{39} and higher than the 59\% success rate from the National Cardiovascular Data Registry.\textsuperscript{40} While other clinical trials\textsuperscript{41,42} have shown higher success rates, these outcomes represent “real-world” data in patients presenting for CTO PCI using both anterograde and retrograde approaches.

In longer-term follow-up in patients presenting for CTO PCI, we found no difference in all-cause mortality rates in patients with well-developed collaterals as compared to those with poorer developed collaterals. Similarly, in those patients who had failed CTO PCI, we did not find any difference in rates of longer-term mortality between groups. Patients with well-developed collaterals are often not referred for invasive revascularization as it is felt that they have sufficient perfusion to prevent ischemia. Contrary to this often held belief, invasive flow studies have shown that the territory of myocardium subtended by a CTO is in a constant state of ischemia, irrespective of the degree of collateral formation.\textsuperscript{43} The absence of any prognostic benefit of the presence of well-matured collaterals in all patients, including those with failed CTO revascularization, suggests that angiographically well-matured collaterals should not be an indication to pursue medical management, but rather revascularization decision should be driven by the presence of anginal symptoms.

Limitations: This study in a single center, retrospective analysis of data, with which comes inherent limitations. While the overall numbers are small, we identified a number of factors associated with well-matured collaterals, including hematological factors. Given the proposed mechanism of collateral maturation and recruitment occurs based on monocyte and lymphocyte shift into the adventitial space, this provides clinical support for fundamental scientific theory. However, larger studies are required to confirm these findings and in particular to identify the molecular and cell signaling pathways by which this collateral recruitment occurs. Furthermore, we only included patients undergoing CTO PCI, and as such, patients treated with medical management or surgery were excluded, which may confound the results. However, this study also aims to assess whether collateral maturity predicts PCI success. Furthermore, we showed no benefit in prognosis in those with well-developed collaterals, which is often cited as a reason patients are not revascularized. These results will also require further larger dedicated studies to confirm.
Conclusion

Patients with well-matured collaterals are more likely to be females, with lower rates of renal dysfunction and history of prior CABG. A lower NLR and higher lymphocyte count are also associated with well-matured collaterals, underpinning the role of leukocytes in collateral development and maturation. While well-matured collaterals are a strong predictor of CTO PCI success, they do not seem to provide a survival advantage over those patients with less well-developed collaterals, and hence the decision to undertake CTO PCI should remain on the presence of symptoms. Newer scoring tools to predict the likelihood of successful CTO PCI may benefit from including these factors.

Disclosure

Conflicts of interest: None.

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