



Chronologic evolution and prognostic implications of impaired coronary flow after chronic total occlusion angioplasty

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Background: Although vessels have the potential to recover following successful recanalization of chronic total occlusion (CTO), evidence is limited about the clinical significance of slow flow (SF) phenomenon after recanalization. The aim of this study was to evaluate the determinants, development and prognostic impact of SF after percutaneous coronary intervention (PCI) for CTO.

Methods: This was a retrospective cohort study, 500 patients were consecutively enrolled undergoing CTO PCI and consecutive follow-up angiography in Zhongshan Hospital, Fudan University, between 2015 and 2020. Coronary flow was assessed by corrected Thrombolysis in Myocardial Infarction (TIMI) frame count (CTFC). The association between SF and outcomes of CTO PCI was evaluated by analyzing the clinical, angiographic, and procedural characteristics.

Results: SF was observed in 29 (5.8%) patients immediately after CTO PCI. Prior myocardial infarction, right coronary artery (RCA) revascularization and lack of bilateral collaterals were independent predictors of SF. SF was associated with increased risks of periprocedural myocardial infarction (PMI) [adjusted odds ratio (adOR): 4.12; 95% confidence interval (CI): 1.68–10.07; P=0.002] and target lesion restenosis (adOR: 2.50; 95% CI: 1.10–5.72; P=0.030). In patients with baseline left ventricular ejection fraction (LVEF) ≤60%, systolic improvement was compromised in the SF group (LVEF: 55.4%±9.6% in follow up *vs.* 52.1%±9.4% before CTO PCI, P=0.147) compared with that of the normal group (LVEF: 55.7%±9.3% *vs.* 51.6%±8.5%, P<0.001).

Conclusions: SF has a significant influence on the prognosis of patients undergoing CTO PCI. Achieving normal coronary flow is essential in CTO revascularization.

Keywords: Chronic total occlusion (CTO); slow flow (SF); percutaneous coronary intervention (PCI); prognosis

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Introduction

Background

At present, chronic total occlusion (CTO) revascularization is the most challenging task in percutaneous coronary intervention (PCI). With improvements in equipment, innovative techniques and operating experience, the success rate of PCI for CTO has substantially increased (1,2). However, the incidence of target lesion failure remains high even with the deployment of drug-eluting stents (3,4). Controversial results on the outcomes of PCI for CTO have been recently reported (5-7). The prognostic importance of CTO recanalization is still a subject of debate. Methods of ensuring the benefits of PCI for CTO are needed.

Rationale and knowledge gap

The slow flow (SF) phenomenon has been frequently reported after PCI, thus leading to myocardial injury and poor prognosis (8). In previous publications, impaired coronary flow after PCI for CTO was correlated with an increased risk of adverse cardiovascular events (9,10). Increasing coronary flow through procedural perfection or medical therapy seems promising for ameliorating a poor long-term prognosis. Notably, the mechanisms underlying SF in vessels distal to total occlusion probably differ from non-total lesions, while few data exist. Some studies

have demonstrated that lumen diameter, blood flow and microvascular function recover over a series of months after successful CTO recanalization (11,12). This implies that coronary flow is likely to be in a dynamic condition after PCI for CTO. However, large-scale studies investigating the chronological evolution and prognostic significance of SF do not exist.

Objective

In this study, we aimed to investigate the incidence, influence factors and evolution of SF after CTO revascularization, and to reveal the prognostic implications of SF in the long term. We present this article in accordance with the STROBE reporting checklist (available at <https://cdt.amegroups.com/article/view/10.21037/cdt-23-161/rc>).

Methods

Population and data collection

Between 2015 and 2020, 514 patients who underwent a successful PCI for CTO and consecutive angiography at Zhongshan Hospital, Fudan University, were consecutively included. Follow-up angiography after a period of 9 to 12 months was routinely recommended after successful recanalization. Among the included patients, 14 patients whose angiograms were unsuitable for caIMR (coronary angiography-derived index of microcirculatory resistance) measurement were excluded, and 500 patients were ultimately included in the final cohort (*Figure 1*). Demographic, angiographic and procedural data were prospectively collected through an electronic medical record system and analyzed retrospectively. This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (No. B2016-018) and conducted in accordance with the guidelines of the Declaration of Helsinki (as revised in 2013). All participants provided written informed consent at the time of hospitalization.

Angiography and intervention

PCI for CTO was performed by a single or double access site from the radial and/or femoral artery according to current algorithms (13,14). Tactics, strategy, use of device and concurrent treatment of non-total lesions were left to the discretion of the operators. In this study, the hybrid strategy was defined as a combination of antegrade and

Highlight box

Key findings

- Coronary angiography derived-index of microcirculatory resistance was elevated in patients with slow flow (SF) phenomenon, indicating impaired microvascular function after chronic total occlusion (CTO) revascularization. Old myocardial infarction, right coronary artery intervention and bilateral collateral circulation were independent predictors of SF.

What is known and what is new?

- Vessels distal to a total occlusion have the potential to recover after successful recanalization. However, coronary slow flow would still increase the risk of restenosis and compromise cardiac systolic function recovery.

What is the implication, and what should change now?

- Interventional cardiologists ought to pay more attention to the restoration of microvascular function besides recanalization to improve the outcomes of CTO percutaneous coronary intervention (PCI). Further studies are needed to confirm the long-term prognostic impact of SF after PCI for CTO in a larger population.

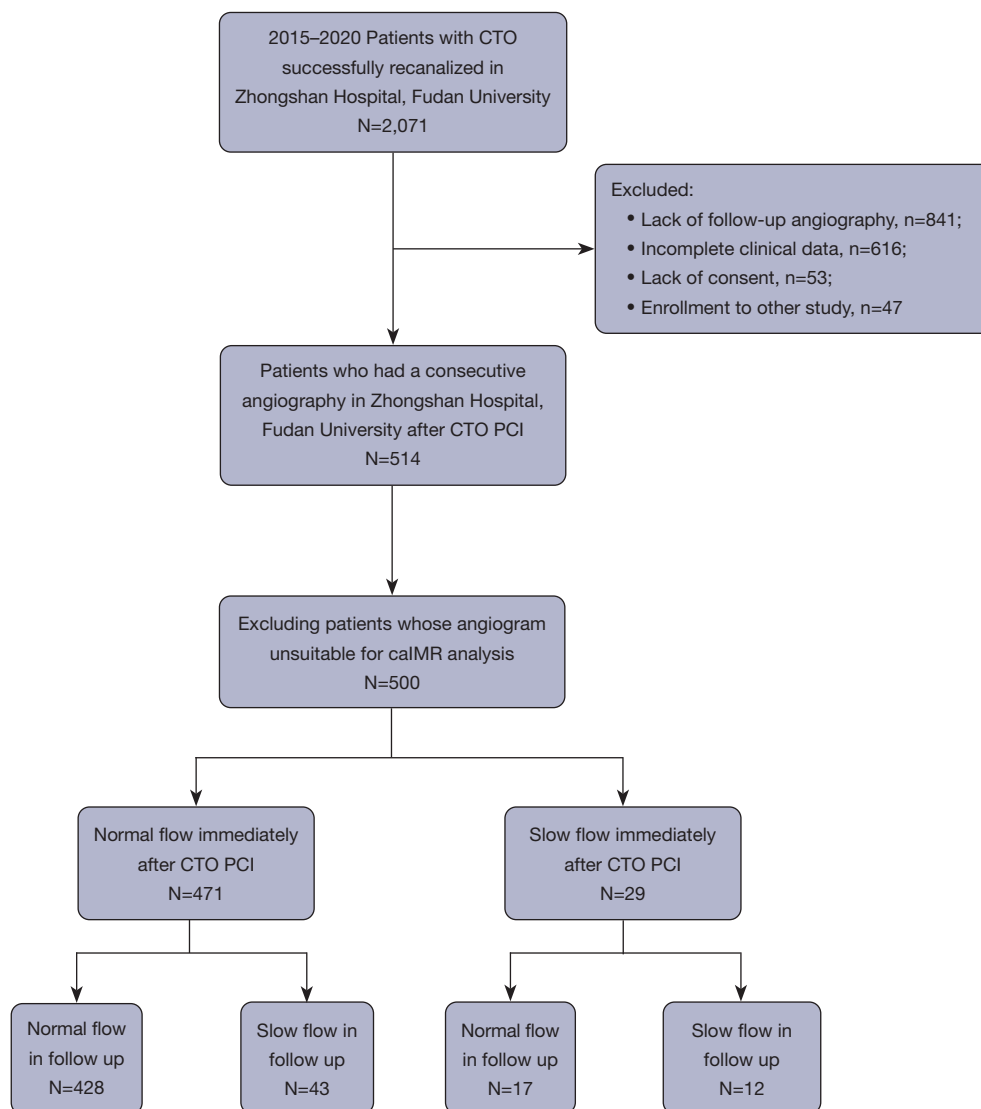


Figure 1 Flowchart of the study. CTO, chronic total occlusion; PCI, percutaneous coronary intervention; caIMR, coronary angiography-derived index of microcirculatory resistance.

retrograde approaches, which was not identified until the retrograde wire successfully crossed collaterals. Angiograms at the first hospitalization and follow-up were reviewed by at least two qualified cardiologists at the angiographic core laboratory. Images recorded at different frame frequencies were standardized to 30 frames per second. The Thrombolysis in Myocardial Infarction (TIMI) frame count was calculated from the first frame when contrast fully entered the ostium of the artery to the frame when contrast opacified the distal target branch. The distal target branches were defined as follows: the distal bifurcation of the left anterior descending artery (LAD); the distal bifurcation

of the longest branch in the left circumflex artery (LCX); and the first branch of the posterolateral artery in the right coronary artery (RCA). Films reviewed for TIMI flow assessment and TIMI frame count were taken after the vasodilator was given. Frame counts in the LAD were divided by 1.7 to correct for its longer length (15).

Study definitions

CTO was defined as 100% occlusion of a coronary artery with TIMI 0 flow for a duration of ≥ 3 months based on clinical, angiographic, or electrocardiographic criteria (16).

Old myocardial infarction (OMI) indicated prior myocardial infarction at least one month before the index procedure, which not specifically occurred in the CTO territory. The perfusion of the occluded artery segment was assessed using the Rentrop classification (17). The J-CTO (Multicenter CTO Registry in Japan) score was calculated by assigning 1 point to each of the following factors: blunt proximal cap, presence of calcification, bend $>45^\circ$, occlusion length ≥ 20 mm, and previously failed attempt (18). Side-branch occlusion was identified as TIMI flow grade ≤ 1 in branches ≥ 1.5 mm. Periprocedural myocardial infarction (PMI) was defined according to the fourth universal definition of myocardial infarction (UDMI) (19). Binary restenosis was defined as stenosis $>50\%$ in the target lesion. Technical success, defined as residual stenosis $<30\%$ within the target lesion, residual restenosis $<50\%$ in the target vessel and TIMI flow grade ≥ 2 , was achieved in all cases immediately after CTO PCI, and patients were further classified according to CTFC. Angiograms immediately after PCI for CTO and at the follow up were assessed. A corrected TIMI frame count (CTFC) >27 was defined as SF (15). According to the status of blood flow (normal or slow) on the two consecutive angiographies, patients were further classified into four groups: consistent normal flow, normal-to-slow flow, slow-to-normal flow and consistent SF.

caIMR measurements

Technical advances enable us to derive an index of microcirculatory resistance from angiography with high accuracy compared with conventional methods (20,21). caIMR was calculated retrospectively in an independent core laboratory using commercial software (FlashAngio, Rainmed Ltd., Suzhou, China) (22). The coronary mean flow velocity in diastole is assumed to be proportional to that in hyperemia. Therefore, caIMR was estimated in the following steps. First, a 3-dimensional mesh model was built from the ostium to the distal segment of the target coronary artery to determine the path length and lumen size using at least two angiographic views separated by at least 30° . Second, resting flow velocity was determined using the TIMI frame count method, and the mean aortic pressure recorded during the operation was input to the FlashAngio console. Pd_{hyp} (mean arterial pressure at the distal segment during hyperemia) was estimated by computational pressure-flow dynamic simulation. $V_{diastole}$ (flow velocity during hyperemia) was computed in FlashAngio software based on resting flow velocity and proprietary parameters.

Finally, caIMR was calculated using the following equation:

$$caIMR = Pd_{hyp} \frac{L}{K \cdot V_{diastole}} \quad [1]$$

L represents the vessel length between the inlet and the distal segment of the target vessel. K was the constant used to adjust the difference in hyperemic flow velocity under different states of illness (20).

Statistical analysis

Statistical analysis was performed with R software (version 4.1.3) and SPSS version 25.0 (IBM, Armonk, New York, USA). Patients with missing data were excluded as shown in *Figure 1*. Discrete variables are presented as counts (percentage) and were compared by the chi-square test or Fisher's exact test. Normally distributed continuous variables were reported as the means \pm standard deviations (SD) and compared with Student's t -test; non-normally distributed continuous variables were summarized as the median with interquartile range (IQR) and compared with the Mann-Whitney U test. Paired tests were conducted using paired t -tests and Wilcoxon signed-rank tests, as appropriate. Comparisons among three groups were performed by analysis of variance (ANOVA) or the Kruskal-Wallis H test. The odds ratio (OR) was calculated by univariate and multivariate logistic regression. Correlations between continuous values and endpoints were evaluated using spline curve analysis. Two hypotheses were tested in this study, that is, there is no statistical difference in the long-term outcome between patient with and without SF after CTO PCI (H_0), and there is a significant difference between patient with and without SF in relation to the occurrence of PMI, target lesion failure or systolic dysfunction (H_1). A two-tailed, P value <0.05 was considered statistically significant.

Results

Baseline characteristics

Of the 500 patients included in the final cohort, 85.4% were male with a median age of 63.0 (IQR, 54.0–69.0) years (*Table 1*). TIMI flow grade ≥ 2 , residual stenosis within the target lesion $<30\%$ and residual stenosis in the target vessel $<50\%$ were achieved in all patients after CTO recanalization. Based on CTFC, 29 (5.8%) patients had SF immediately after PCI for CTO. Compared with the normal group, patients with SF were more likely to have a history of

Table 1 Demographic and clinical characteristics

Risk factors	Total (n=500)	Normal flow (n=471)	Slow flow (n=29)	P value
Age (years)	63.0 [54.0, 69.0]	63.0 [54.0, 69.0]	59.0 [50.0, 65.0]	0.062
Male	427 (85.4)	399 (84.7)	28 (96.6)	0.102
Hypertension	330 (66.0)	309 (65.6)	21 (72.4)	0.453
Diabetes mellitus	170 (34.0)	162 (34.4)	8 (27.6)	0.453
Smoking history	258 (51.6)	242 (51.4)	16 (55.2)	0.692
OMI	136 (27.2)	123 (26.1)	13 (44.8)	0.028*
Prior PCI	152 (30.4)	140 (29.7)	12 (41.4)	0.185
Prior CABG	19 (3.8)	17 (3.6)	2 (6.9)	0.369
Prior failed attempt	115 (23.0)	104 (22.1)	11 (37.9)	0.049*
Stroke	33 (6.6)	31 (6.6)	2 (6.9)	0.947
BMI (kg/m ²)	25.4 [23.4, 27.1]	23.3 [25.4, 27.1]	25.5 [23.6, 28.7]	0.514
Follow-up period (months)	13 [11, 17]	13 [11, 16]	13 [12, 17]	0.357
Presentation at the first admission				
Stable angina	392 (78.4)	370 (78.6)	22 (75.9)	0.732
Unstable angina	50 (10.0)	48 (10.2)	2 (6.9)	0.566
NSTEMI	47 (9.4)	43 (9.1)	4 (13.8)	0.404
STEMI	11 (2.2)	10 (2.1)	1 (3.4)	0.485
Presentation in follow up				
Stable angina	482 (96.4)	453 (96.2)	27 (93.1)	0.325
Unstable angina	13 (2.6)	13 (2.8)	1 (3.4)	0.572
NSTEMI	5 (1.0)	5 (1.1)	1 (3.4)	0.303
STEMI	0 (0.0)	0 (0.0)	0 (0.0)	–
Laboratory and auxiliary examinations				
Creatinine (μmol/L)	81 [71, 91]	81 [71, 91]	82 [74, 90]	0.646
hs-CRP (mg/L)	1.50 [0.60, 4.20]	1.50 [0.60, 4.18]	1.60 [0.50, 6.48]	0.905
White blood cell count (×10 ⁹ /L)	6.46 [5.48, 7.60]	6.43 [5.47, 7.57]	6.68 [5.41, 8.17]	0.389
Platelet (×10 ⁹ /L)	202 [165, 234]	202 [164, 234]	198 [166, 226]	0.876
Hemoglobin (g/L)	140 [130, 149]	139 [129, 148]	143 [139, 154]	0.010*
Total cholesterol (mmol/L)	3.64 [3.04, 4.45]	3.65 [3.02, 4.45]	3.56 [3.26, 4.29]	0.962
Low density lipoprotein (mmol/L)	1.87 [1.33, 2.56]	1.88 [1.31, 2.56]	1.80 [1.54, 2.46]	0.747
Triglyceride (mmol/L)	1.59 [1.12, 2.30]	1.57 [1.10, 2.30]	1.66 [1.23, 2.25]	0.758
High density lipoprotein (mmol/L)	0.96 [0.81, 1.12]	0.96 [0.80, 1.12]	0.96 [0.84, 1.09]	0.664
Lp (a) (mg/L)	179 [82, 439]	177 [79, 438]	192 [94, 671]	0.366
HbA1c (%)	6.0 [5.6, 6.8]	6.0 [5.6, 6.8]	5.9 [5.5, 7.1]	0.694
Pre-PCI hs-cTnT (ng/mL)	0.011 [0.008, 0.024]	0.011 [0.008, 0.024]	0.014 [0.009, 0.033]	0.570

Table 1 (continued)

Table 1 (continued)

Risk factors	Total (n=500)	Normal flow (n=471)	Slow flow (n=29)	P value
Post-PCI hs-cTnT (ng/mL)	0.072 [0.031, 0.183]	0.067 [0.030, 0.178]	0.133 [0.074, 0.331]	0.011*
Left ventricular ejection fraction (%)				
Baseline	59.9±9.2	60.0±9.2	58.4±10.4	0.336
Follow-up	60.5±8.2	60.6±8.2	59.0±8.9	0.282
Anti-platelet therapy at discharge				
Aspirin	455 (91.0)	429 (91.1)	26 (89.7)	0.794
Clopidogrel	379 (75.8)	358 (76.0)	21 (72.4)	0.661
Ticagrelor	121 (24.2)	113 (24.0)	8 (27.6)	0.661
Cilostazol	45 (9.0)	42 (8.9)	3 (10.3)	0.737

Data are shown as median [interquartile range], n (%) or mean ± standard deviations. *, P<0.05. OMI, old myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, body mass index; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; hs-CRP, high-sensitivity C-reactive protein; Lp (a), lipoprotein (a); HbA1c, hemoglobin A1c; hs-cTnT, high-sensitivity cardiac troponin T.

OMI and failed occlusion revascularization. The prevalence of other traditional risk factors, such as hypertension, diabetes, smoking and dyslipidemia, was comparable between the two groups. No significant difference was found concerning the presentation and high-sensitivity cardiac troponin T (hs-cTnT) at the first admission. However, hs-cTnT values after PCI were substantially elevated in the SF group [0.133 (0.074–0.331) vs. 0.067 (0.030–0.178) ng/mL, P=0.011].

Angiographic and procedural features

Although the Rentrop classification assessing the perfusion provided by collaterals was not significantly different between the two groups, bilateral collateral circulation was more prevalent in the normal flow group (46% vs. 24%, P=0.018) (Figure 2). The procedure was generally accomplished using an antegrade approach (78.4%) and the hybrid strategy (18.6%), accompanied by a wire escalation technique (81.7%). We did not find a significant difference in the strategy or tactics used in PCI for CTO. RCA was more commonly recanalized in the SF group (72.4% vs. 40.1%, P=0.003), while the percentage of PCI for LAD was lower (13.8% vs. 43.7%, P=0.002) (Table 2). The incidence of collateral perforation was higher (10.3% vs. 1.1%, P=0.008) in the SF group, but the differences in other complications (dissection/hematoma and side-branch loss) were not significant. After CTO PCI, patients with SF had

prominently increased microvascular resistance [32.2 (22.9–41.5) vs. 17.3 (13.2–22.5), P<0.001].

Predictors of SF

Univariate and multivariate logistic models were constructed to identify predictors of SF. As shown in Figure 3, OMI and recanalization in RCA were independent risk factors for SF, while bilateral collaterals were protective against SF following CTO PCI. To investigate the reason RCA was associated with increased risk of SF after the procedure, patients were regrouped according to the target vessel. Demographics and procedural characteristics are summarized in Tables S1,S2. It was demonstrated that in patients accepting RCA recanalization, the incidence of prior coronary artery bypass grafting (CABG) and prior failed attempts was higher (both P<0.05). In addition, procedures using wire escalation were less commonly performed (LAD: 82.9% vs. LCX: 91.3% vs. RCA: 76.7%, P=0.014), while more procedures were accomplished using reverse controlled antegrade and retrograde subintimal tracking (R-CART) (LAD: 5.7% vs. LCX: 1.3% vs. RCA: 9.0%, P=0.046). Stent length was substantially longer in RCA {LAD: 61 [42–71] mm vs. LCX: 45 [33–60] mm vs. RCA: 84 [64–108] mm, P<0.001}. Besides, dissection/hematoma occurred more frequently following PCI (LAD: 0.5% vs. LCX: 1.3% vs. RCA: 3.3%, P=0.030). Of note, the average stent diameter and minimal stent diameter were

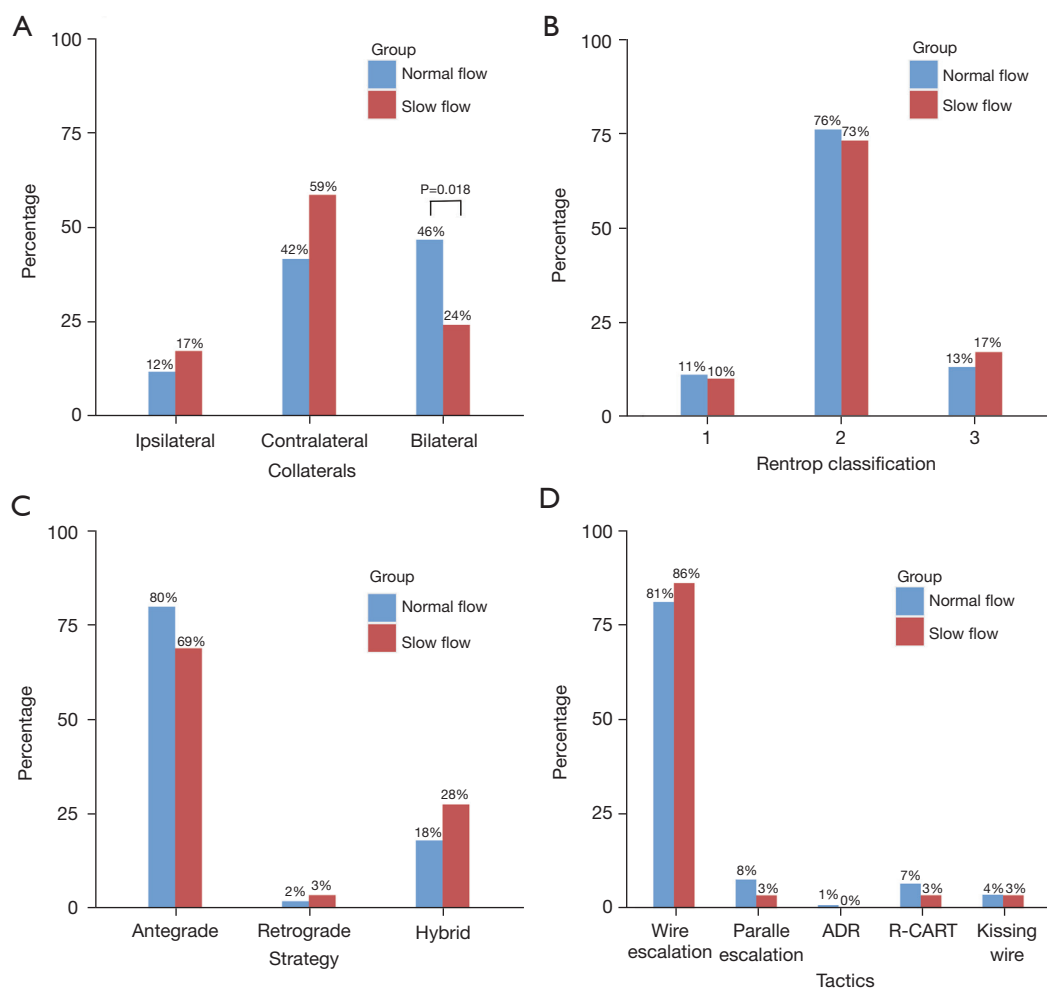


Figure 2 Angiographic and procedural characteristics. (A) Collateral circulation in patients with slow flow or not. (B) Rentrop grade of collaterals in patients with slow flow or not. The strategy (C) and wire crossing tactics (D) used in the procedure. ADR, antegrade dissection re-entry; R-CART, reverse controlled antegrade and retrograde subintimal tracking.

slightly larger (both $P < 0.001$).

Stent length was not a significant factor influencing SF in binary logistic regression. Otherwise, spline curve analysis revealed that the relationship between stent length and the OR was not linear (Figure 3B). Deployment of a stent that was too long or too short would increase the risk of SF. Among the 14 patients who underwent percutaneous coronary angioplasty (PTCA) without stenting, 4 (28.6%) patients had SF. All 4 patients underwent RCA intervention with an average diameter less than 2.50 mm and an average length greater than 38.0 mm in the target lesions, and 3 of them had total reocclusion during follow up (data not shown).

Follow-up of coronary flow

The median interval of follow-up was 13 (IQR, 11–17) months. Fifty-five (11.0%) patients had SF at the follow-up. According to the blood flow on the two consecutive angiographies, patients were further classified into 4 groups: consistent normal flow ($n=428$, 85.6%), normal-to-slow flow ($n=43$, 8.6%), slow-to-normal flow ($n=17$, 3.4%) and consistent SF ($n=12$, 2.4%). Clinical, angiographic and procedural statistics are summarized in Tables S3,S4. In accordance with previous results, RCA was the dominant target vessel in patients with consistent SF and normal-to-

Table 2 Angiographic and procedural features

Risk factors	Total (n=500)	Normal flow (n=471)	Slow flow (n=29)	P value
Syntax score	22.5 [16.5, 27.0]	22.5 [17.0, 27.0]	20.0 [11.5, 25.5]	0.094
Target vessel				
Left anterior descending artery	210 (42.0)	206 (43.7)	4 (13.8)	0.002*
Left circumflex artery	80 (16.0)	76 (16.1)	4 (13.8)	0.738
Right coronary artery	210 (42.0)	189 (40.1)	21 (72.4)	0.003*
J-CTO score	2 [2, 3]	2 [2, 3]	2 [2, 3]	0.779
Dual angiography	249 (49.8)	233 (49.5)	16 (55.2)	0.551
Use of rotablator	7 (1.3)	6 (1.3)	1 (3.4)	0.344
Intra-stent occlusion	42 (8.4)	38 (8.1)	4 (13.8)	0.281
Stent length (mm)	62.5 [40.3, 86.0]	64.0 [44.0, 86.0]	56.0 [26.0, 73.5]	0.053
Average stent diameter (mm)	2.83 [2.64, 3.04]	2.84 [2.63, 3.03]	2.83 [2.60, 3.38]	0.284
Minimal stent diameter (mm)	2.50 [2.50, 2.75]	2.50 [2.50, 2.75]	2.75 [2.50, 3.00]	0.418
Side-branch loss	6 (1.2)	5 (1.1)	1 (3.4)	0.303
Dissection/hematoma	9 (1.8)	8 (1.7)	1 (3.4)	0.419
Collateral perforation	8 (1.6)	5 (1.1)	3 (10.3)	0.008*
Contrast volume (mL)	250 [200, 350]	250 [200, 350]	220 [180, 325]	0.368
Immediately after CTO PCI				
calMR	17.5 [13.3, 23.0]	17.3 [13.2, 22.5]	32.2 [22.9, 41.5]	<0.001*
CTFC	14 [10, 18]	13 [9, 16]	33 [28, 38]	<0.001*
Follow-up				
Binary target lesion restenosis	93 (18.6)	83 (17.6)	10 (34.5)	0.024*
Absolute diameter stenosis** (%)	17.74±34.35	16.95±33.69	30.69±42.25	0.047*
CTFC	16 [12, 20]	16 [12, 20]	24 [15, 39]	<0.001*

Data are shown as median [IQR 25, 75] or n (%) or mean ± standard deviations. *, P<0.05; **, the most severe residual stenosis in the target vessel after the procedure. CTO, chronic total occlusion; PCI, percutaneous coronary intervention; calMR, coronary angiography derived-index of microcirculatory resistance; CTFC, corrected Thrombolysis in Myocardial Infarction frame count; IQR, interquartile range.

slow flow (P<0.01).

Prognosis and SF

According to the fourth UDMI, 246 (49.2%) patients had PMI after PCI for CTO. After adjustment, SF was independently associated with PMI [adjusted odds ratio (adOR): 4.12; 95% confidence interval (CI): 1.68–10.07; P=0.002] (Table S5). Absolute diameter stenosis was significantly more severe in patients with impaired coronary flow (Table 2, Table S4). Overall, the incidence of binary restenosis in the target lesion was 18.6%. Notably, the rates

of binary restenosis in patients with baseline SF, normal-to-slow flow and consistent SF were 34.5%, 69.8%, and 66.7% in comparison with 17.6%, 12.6% and 11.8% in patients with baseline normal flow, consistent normal flow and slow-to-normal flow, respectively. The association between flow status and occurrence of restenosis was displayed in Figure 4. As shown in Table 3, SF (adOR: 2.50; 95% CI: 1.10–5.72; P=0.030), female sex (adOR: 2.19; 95% CI: 1.21–3.96; P=0.010), prior history of percutaneous or surgical revascularization (adOR: 2.08; 95% CI: 1.29–3.35; P=0.003) and low-density lipoprotein (LDL) levels at follow-up (adOR: 1.34; 95% CI: 1.02–1.75; P=0.034)

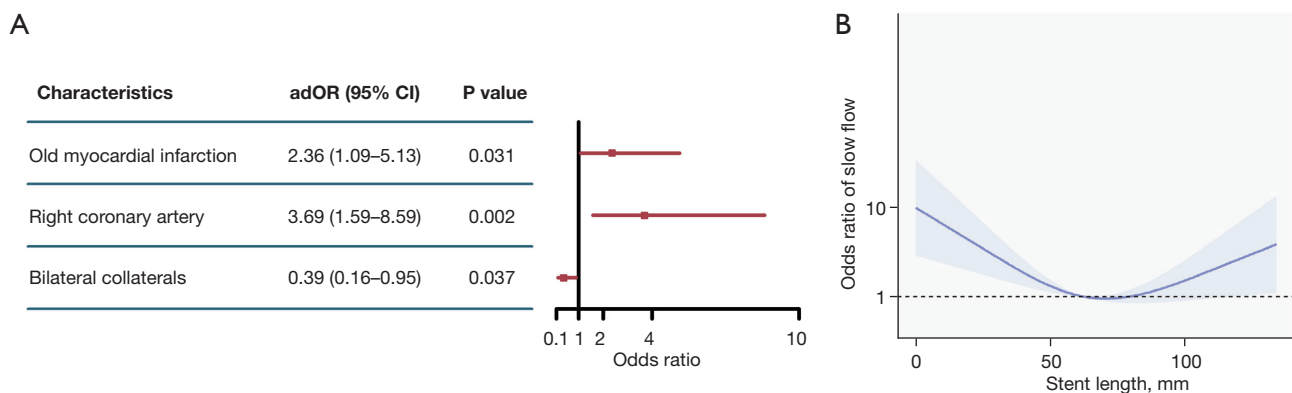


Figure 3 Risk factors for slow flow after CTO PCI. (A) Independent risk factors for slow flow after CTO PCI in multivariate logistic regression. (B) Spline curve analysis of the association between stent length and slow flow. The purple line represents the odds ratio, and the colored ribbon zone indicates the 95% confidence interval. adOR, adjusted odds ratio; CTO, chronic total occlusion; PCI, percutaneous coronary intervention.

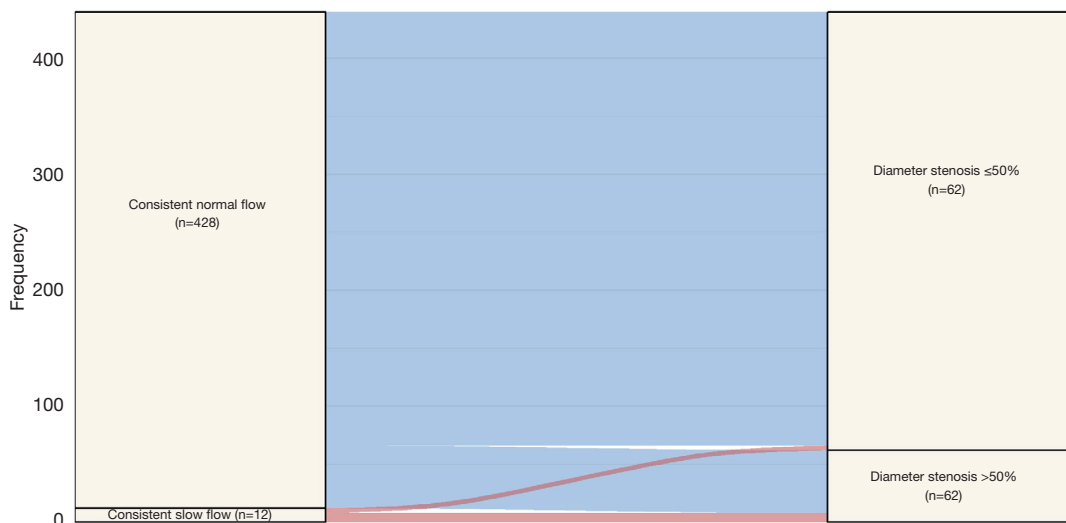


Figure 4 The association between slow flow and restenosis after CTO PCI. The Sankey diagram shows the association between flow status and target lesion restenosis. Among 12 patients who had consistent slow flow, 8 (66.7%) had target lesion restenosis. 428 patients had consistent normal flow, out of whom 54 (12.6%) had target lesion restenosis. CTO, chronic total occlusion; PCI, percutaneous coronary intervention.

were independent risk factors for restenosis. Of note, it was revealed that a >15% reduction in LDL from baseline values would decrease the risk of target lesion restenosis (OR: 0.59; 95% CI: 0.37–0.94; P=0.026).

It seems that echocardiographic parameters, such as the left ventricular ejection fraction (LVEF), did not substantially improve after CTO PCI and showed no difference between patients with or without SF. Herein, we conducted pairwise analysis including only those with a baseline LVEF ≤60%. In patients with normal flow

immediately after PCI for CTO, there was a significant improvement in LVEF (55.7%±9.3% vs. 51.6%±8.5%, P<0.001) in comparison with patients with SF (55.4%±9.6% vs. 52.1%±9.4%, P=0.147), mainly due to a decreased left ventricular end systolic diameter (LVESD) (36.3±7.2 vs. 39.3±6.8, P=0.006). Patients who had slow-to-normal flow did not benefit from CTO recanalization, and in patients with consistent SF, there was even a trend of decreased LVEF. In contrary, LVEF could still be improved in patients with normal flow after CTO PCI even if they developed SF

Table 3 Risk factors of target lesion restenosis in logistic regression

Risk factors	Unadjusted		Adjusted	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Female	1.96 (1.11–3.45)	0.020	2.19 (1.21–3.96)	0.010
Age	1.02 (1.00–1.04)	0.119	–	–
Hypertension	0.89 (0.56–1.42)	0.622	–	–
Diabetes mellitus	0.95 (0.59–1.52)	0.817	–	–
Smoking history	0.79 (0.50–1.24)	0.303	–	–
OMI	1.03 (0.62–1.70)	0.912	–	–
Prior revascularization*	2.01 (1.27–3.18)	0.003	2.08 (1.29–3.35)	0.003
Stent length (per 10 mm increase)	1.04 (0.97–1.12)	0.256	–	–
Attained target lesion residual diameter	1.01 (0.96–1.03)	0.664	–	–
Syntax score	0.98 (0.96–1.01)	0.208	–	–
Re-vascularizing strategy	1.23 (0.71–2.15)	0.460	–	–
Dissection/hematoma	3.56 (0.94–13.54)	0.062	–	–
Slow flow after the procedure	2.43 (1.09–5.40)	0.030	2.50 (1.10–5.72)	0.030
calMR after the procedure	1.01 (0.98–1.03)	0.513	–	–
LDL at follow-up	1.39 (1.07–1.81)	0.013	1.34 (1.02–1.75)	0.034

*, including percutaneous coronary intervention and surgical intervention. calMR, coronary angiography derived-index of microcirculatory resistance; CI, confidence interval; OMI, old myocardial infarction; LDL, low density lipoprotein.

at follow-up.

Discussion

Key findings

In the present study, we demonstrated that SF was a common phenomenon after PCI for CTO associated with OMI, RCA intervention and bilateral collateral circulation. Although coronary flow could recover over time, impaired flow immediately after the procedure was associated with increased risk of PMI, target lesion failure and cardiac systolic dysfunction.

Explanations of findings and comparison with previous researches

Over the past years, the clinical benefits of PCI for CTO have received increasing attention (5,6). Symptom relief seems to be the primary indication of PCI for CTO (23). However, Schumacher *et al.* reported that the magnitude of improvement in myocardial perfusion played a pivotal

role in the long-term outcomes of PCI for CTO (7). These differences inspire researchers to investigate methods of conducting the procedure in a beneficial way in respect of the excessive operative time and financial cost during CTO revascularization (24). SF frequently occurs after PCI and is correlated with poor outcomes (25). Ischemia-reperfusion injury, vessel wall damage and microembolization caused by plaque debris during angioplasty could contribute to impaired coronary blood flow (26). Overall, the antegrade, retrograde, or hybrid strategy nor specific wire crossing techniques significantly influenced coronary flow after the procedure in this study. This could be limited by the fact that only patients who had a consecutive follow-up angiography after PCI for CTO in our center were recruited rather than all patients who underwent PCI for CTO. However, this implied that not the specific techniques or guide wire entering the subintimal space, but controlling the length of false lumen and the preservation of the distal vessels were more crucial for the restoration of normal flow. Stent length and SF were correlated; that is, stents that were too short or too long would increase the risk of SF. Longer stenting and high prevalence of complications

would increase the risk of side-branch loss, vessel wall damage and plaque debris embolization, which could impair blood flow. The main reasons for implanting less stents were small vessels with long lesions and long segment in the false lumen. Impaired coronary flow without stenting was associated with a profoundly high rate of reocclusion (3 out of 4). While excessive stenting could impair small vessel function, partially due to side-branch loss and plaque debris embolization, and increase the risk of mismatch between the stents and the detracted vessel lumen.

In addition, there are unique features of the vessel distal to a total occlusion influencing coronary flow. Endothelial and smooth muscle cell dysfunction were observed in the coronary segment distal to a CTO, leading to compromised antegrade blood flow and was thus negatively correlated with the grade of collateral circulation (27). We found that caIMR was profoundly elevated in the SF group after PCI for CTO. However, this could be a consequence of both the complex intervention and intrinsic microvascular dysfunction. The ameliorated microvascular dysfunction by well-developed collaterals could account for our findings that bilateral collateral circulation was protective against SF after CTO PCI. From another point of view, these data implied that recanalization of a complex CTO unsuitable for stenting in the presence of low-grade collaterals could bear a high risk of SF and poor outcomes.

We collected the data about how SF was treated during the procedure. In our center, nitroglycerin intra-coronary injection was the most common treatment, followed by verapamil and nitroprusside intra-coronary injection. However, many patients received more than one drug treatment, making the assessment of which drug was more effective confounded. The efficacy of these drugs was not the focus of this study, and we aimed to analyze the long-term prognostic impact of SF.

Positive vascular remodeling and vascular function improvement could occur after successful PCI for CTO (11,12). In addition, collateral circulation would also regress over time (28). These results indicated that the recanalized vessel had great potential to recover on its own, which may reduce the demand for coronary flow immediately after CTO PCI. In this study, we demonstrated that SF was an independent risk factor for target lesion restenosis. Residual stenosis after PCI for CTO was slightly more severe in the SF group, but it was not significantly associated with the occurrence of restenosis. Further assessment found that more than half of the patients with baseline SF would

become normal in follow-up, and those with consistent SF were truly disposed to target lesion restenosis. The exact etiology between SF and target lesion failure was not fully understood, however, impaired shear stress, activation of inflammation reaction within the vessel could be part of the explanation.

Implications and actions needed

Coronary flow had the potential to recover after recanalization of CTO, however, this was far from enough to allow interventional cardiologists to tolerate the existence of impaired coronary flow. Evaluation of the echocardiography implied that improvement in systolic function (LVEF and LVESD) was compromised in the SF group. These results implied not merely the target lesion failure, but the function of microvascular circulation played a crucial role in the rehabilitation of the myocardium. Restoring normal vascular physiology could be more essential than solely achieving an open artery. Moreover, improvements in LVEF and LVESD were discovered among patients with a baseline LVEF $\leq 60\%$. This was an arbitrary cutoff value that indicated that perhaps patients with more severe systolic dysfunction, that is, more ischemic burden caused by CTO, would benefit from recanalization (29). The precise threshold needs to be validated in future, larger-scale studies.

Strengths and limitations

This study had several strengths. Compared with previous publications, our study included patients who had both the index and follow-up angiograph in our center, which guaranteed the quality of angiograms and precise assessment of coronary flow and the extent of restenosis. Besides, core laboratory were used in this study to ensure the objective review of angiograms. Third, the functional status of coronary microcirculation was evaluated by TIMI flow grade and caIMR, which made the results comprehensive and plausible.

There are some limitations of this study. First, this was a single-center retrospective study with a moderate sample size. As mentioned above, only patients who underwent consecutive surveillance angiography in our center were included, and the results need to be evaluated in a larger complex population. Second, in the present study, caIMR measurement could only be used in vessels with stenosis $< 50\%$. We did not report the results of caIMR during follow

up because data from patients with restenosis did not exist. Third, there were patients with a normal baseline flow who deteriorated into SF at follow-up. These patients had an increased incidence of restenosis, some of whom developed a severely narrowed lumen with substantially impaired coronary flow. However, in this group, we could not verify whether SF or restenosis occurred first or dominated in the pathogenesis due to the limitations of this study. In addition, patients with SF also had profound diameter restenosis. Whether SF (i.e., microvascular dysfunction) or stenosis played a causal role in impeding systolic function recovery requires further investigation. Moreover, pressure wire-based IMR is the gold standard to assess the function of microcirculation. caIMR we used in this study has been validated by prior publications, which prove to be accurate and reliable as a surrogate for conventional IMR. Still, it hasn't been broadly validated like the original method. Our findings would inspire prospective studies using pressure wire-based IMR in the future. Finally, we mainly used angiography and echocardiography to assess the prognostic benefits of PCI for CTO. Integration of more examinations, such as positron emission tomography perfusion imaging and cardiac magnetic resonance imaging, could provide more information, which also brings considerable expenses.

Conclusions

SF is a common phenomenon after PCI for CTO that holds profound prognostic significance. Adequate preoperative evaluation, optimized final coronary flow and restored vascular physiology would contribute to the improved prognosis of CTO recanalization.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (No. B2016-018) and conducted in accordance with the guidelines of the Declaration of Helsinki. All participants provided written informed consent at the time of hospitalization.

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References

1. Brilakis ES, Mashayekhi K, Tsuchikane E, et al. Guiding Principles for Chronic Total Occlusion Percutaneous Coronary Intervention. *Circulation* 2019;140:420-33.
2. Tajti P, Karmpaliotis D, Alaswad K, et al. The Hybrid Approach to Chronic Total Occlusion Percutaneous Coronary Intervention: Update From the PROGRESS

- CTO Registry. *JACC Cardiovasc Interv* 2018;11:1325-35.
3. Azzalini L, Dautov R, Ojeda S, et al. Procedural and Long-Term Outcomes of Percutaneous Coronary Intervention for In-Stent Chronic Total Occlusion. *JACC Cardiovasc Interv* 2017;10:892-902.
 4. Kwon O, Lee PH, Lee SW, et al. Retrograde approach for the percutaneous recanalisation of coronary chronic total occlusions: contribution to clinical practice and long-term outcomes. *EuroIntervention* 2019;15:e354-e361.
 5. Lee SW, Lee PH, Ahn JM, et al. Randomized Trial Evaluating Percutaneous Coronary Intervention for the Treatment of Chronic Total Occlusion. *Circulation* 2019;139:1674-83.
 6. Werner GS, Martin-Yuste V, Hildick-Smith D, et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J* 2018;39:2484-93.
 7. Schumacher SP, Stuijzand WJ, de Winter RW, et al. Ischemic Burden Reduction and Long-Term Clinical Outcomes After Chronic Total Occlusion Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* 2021;14:1407-18.
 8. Kawai Y, Hisamatsu K, Matsubara H, et al. Intravenous administration of nicorandil immediately before percutaneous coronary intervention can prevent slow coronary flow phenomenon. *Eur Heart J* 2009;30:765-72.
 9. Guan C, Yang W, Song L, et al. Association of Acute Procedural Results With Long-Term Outcomes After CTO PCI. *JACC Cardiovasc Interv* 2021;14:278-88.
 10. Wang Y, Zhao HW, Wang CF, et al. Incidence, Predictors, and Prognosis of Coronary Slow-Flow and No-Reflow Phenomenon in Patients with Chronic Total Occlusion Who Underwent Percutaneous Coronary Intervention. *Ther Clin Risk Manag* 2020;16:95-101.
 11. Keulards DCJ, Karamasis GV, Alsanjari O, et al. Recovery of Absolute Coronary Blood Flow and Microvascular Resistance After Chronic Total Occlusion Percutaneous Coronary Intervention: An Exploratory Study. *J Am Heart Assoc* 2020;9:e015669.
 12. Okuya Y, Saito Y, Takahashi T, et al. Novel predictors of late lumen enlargement in distal reference segments after successful recanalization of coronary chronic total occlusion. *Catheter Cardiovasc Interv* 2019;94:546-52.
 13. Galassi AR, Werner GS, Boukhris M, et al. Percutaneous recanalisation of chronic total occlusions: 2019 consensus document from the EuroCTO Club. *EuroIntervention* 2019;15:198-208.
 14. Harding SA, Wu EB, Lo S, et al. A New Algorithm for Crossing Chronic Total Occlusions From the Asia Pacific Chronic Total Occlusion Club. *JACC Cardiovasc Interv* 2017;10:2135-43.
 15. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 1996;93:879-88.
 16. Ybarra LF, Rinfret S, Brilakis ES, et al. Definitions and Clinical Trial Design Principles for Coronary Artery Chronic Total Occlusion Therapies: CTO-ARC Consensus Recommendations. *Circulation* 2021;143:479-500.
 17. Rentrop KP, Cohen M, Blanke H, et al. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 1985;5:587-92.
 18. Morino Y, Abe M, Morimoto T, et al. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. *JACC Cardiovasc Interv* 2011;4:213-21.
 19. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol* 2018;72:2231-64.
 20. Li J, Gong Y, Wang W, et al. Accuracy of computational pressure-fluid dynamics applied to coronary angiography to derive fractional flow reserve: FLASH FFR. *Cardiovasc Res* 2020;116:1349-56.
 21. Choi KH, Dai N, Li Y, et al. Functional Coronary Angiography-Derived Index of Microcirculatory Resistance in Patients With ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Interv* 2021;14:1670-84.
 22. Ai H, Feng Y, Gong Y, et al. Coronary Angiography-Derived Index of Microvascular Resistance. *Front Physiol* 2020;11:605356.
 23. Azzalini L, Karpaliotis D, Santiago R, et al. Contemporary Issues in Chronic Total Occlusion Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* 2022;15:1-21.
 24. Salisbury AC, Karpaliotis D, Grantham JA, et al. In-Hospital Costs and Costs of Complications of Chronic Total Occlusion Angioplasty: Insights From the OPEN-CTO Registry. *JACC Cardiovasc Interv* 2019;12:323-31.
 25. Ndrepepa G, Tiroch K, Fusaro M, et al. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. *J Am Coll Cardiol* 2010;55:2383-9.
 26. Piana RN, Paik GY, Moscucci M, et al. Incidence and

- treatment of 'no-reflow' after percutaneous coronary intervention. *Circulation* 1994;89:2514-8.
27. Brugaletta S, Martin-Yuste V, Padró T, et al. Endothelial and smooth muscle cells dysfunction distal to recanalized chronic total coronary occlusions and the relationship with the collateral connection grade. *JACC Cardiovasc Interv* 2012;5:170-8.
28. Lee JH, Kim CY, Kim N, et al. Coronary Collaterals Function and Clinical Outcome Between Patients With Acute and Chronic Total Occlusion. *JACC Cardiovasc Interv* 2017;10:585-93.
29. Mashayekhi K, Nührenberg TG, Toma A, et al. A Randomized Trial to Assess Regional Left Ventricular Function After Stent Implantation in Chronic Total Occlusion: The REVASC Trial. *JACC Cardiovasc Interv* 2018;11:1982-91.
28. Lee JH, Kim CY, Kim N, et al. Coronary Collaterals

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