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Research paper

The evaluation of combined fractional flow reserve and dynamic SPECT in chronic total occlusion

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ABSTRACT

Background: Chronic total occlusion (CTO) is the most challenging subset in percutaneous coronary intervention (PCI), but the optimal selection of patients and indication for such procedures remain a subject of debate. We sought to investigate the role of physiological function in treatment decisions of CTO PCI by measuring fractional flow reserve (FFR) and Dynamic SPECT imaging in this study.

Methods: All the FFR of CTO vessel were measured before and immediately after CTO revascularization, and Dynamic SPECT imaging were detected before PCI in patients with an identified CTO.

Results: A total of 53 patients with single-vessel CTO lesions were included in this cohort study. The mean FFR value was 0.34 ± 0.09 at baseline. Immediately after successful CTO PCI, the FFR value significantly increased to 0.79 ± 0.11. The regional coronary flow reserve (CFR) of CTO vessels was 1.62 ± 0.64, which was significantly and positively correlated with the baseline FFR value ($r = 0.607$, $p = 0.005$). The area under the ROC curve of the baseline FFR for the detection of ischemia was 0.923 ($p < 0.001$). The diagnostic performance in terms of sensitivity and specificity was 83.3 % and 85.7 % for baseline FFR with a ROC-optimized cutoff value of 0.35.

Conclusions: A significant correlation was found between the CFR derived from dynamic SPECT and baseline FFR. An FFR of <0.35 before CTO PCI can be taken as the cutoff for the presence of inducible ischemia, which was a useful index for therapy options.

1. Introduction

Chronic total occlusion (CTO), defined as coronary artery occlusion with Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow and duration ≥3 months, occurs in as many as 18 %–26 % of patients with obstructive coronary artery disease (CAD) [1]. CTO remains one of the most challenging lesion subsets in percutaneous coronary intervention (PCI) because of the great technical difficulty and perceived procedural complexity. Over the past decade, with the development of interventional techniques and equipment and operator expertise, the success rate of CTO PCI has substantially improved. Although observational data have shown the symptomatic benefit of successful CTO PCI, the prognostic benefit of CTO PCI is still not well-established [2]. Therefore, the optimal selection of patients and indication for such procedures remain a subject of debate and research, especially in patients without severe symptoms or ischemia.

There is accumulating evidence that the functional significance of coronary stenosis determines the potential benefit of the coronary

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revascularization procedure in patients with stable CAD, and physiological and hemodynamic assessment of coronary lesions has become increasingly important. Fractional flow reserve (FFR), typically calculated as the distal-to-proximal pressure ratio across a coronary lesion by a pressure guidewire during invasive coronary angiography (CAG), is currently considered to be the gold-standard method for defining hemodynamically significant coronary lesions [3]. Although FFR-guided revascularization strategy has been proven to be associated with improved clinical outcomes compared to angiography-guided revascularization alone, the value and changes of FFR in CTO PCI are still unclear [4]. Single-photon emission computed tomography (SPECT) imaging is a useful and feasible tool to detect myocardial blood flow (MBF) and coronary flow reserve (CFR), especially for new cadmium zinc telluride (CZT)-based detectors [5]. In the present study, we sought to investigate the functional results of CTO PCI by measuring FFR and Dynamic SPECT imaging before and immediately after CTO revascularization to help treatment decision.

2. Methods

2.1. Study population

This single-center, prospective observational study was conducted from February 2019 to October 2021 at Zhongshan Hospital, Fudan University (ClinicalTrials.gov NCT03803020). A total of 286 patients with symptomatic stable angina scheduled for CTO PCI were consecutively enrolled. CTO was defined as a lesion with Thrombolysis In Myocardial Infarction (TIMI) grade 0 flow within the occluded segment and evidence of a duration ≥3 months. The duration of occlusion was estimated based on symptom onset, a history of angina, a previous myocardial infarction in the same territory, or a previously confirmed angiography. The exclusion criteria were as follows: 1) acute myocardial infarction within 1 month, 2) >1 CTO, 3) CTO lesion located in the vessel with a reference diameter < 2.5 mm, 4) presence of angiographic stenosis ≥50 % in non-CTO arteries and 5) presence of patent bypass grafts. All the patients provided informed consent for both the procedure and subsequent data collection and analysis for research purposes. The study was approved by the institutional review board.

2.2. CTO PCI and FFR measurements

All patients received optimal dual antiplatelet therapy (clopidogrel or ticagrelor + aspirin) before and after PCI. During the intervention procedures, patients received an initial bolus of unfractionated heparin at a dose of 100 U/kg; additional boluses were given to maintain an activated clotting time > 300 s, which was checked every 30 min. The choice of the PCI arterial route and CTO revascularization strategy was left to the operator's discretion, following the CTOCC algorithm [6]. All patients received drug-eluting stent implantation after successful recanalization. Technical success was defined as successful CTO recanalization with TIMI grade 3 anterograde flow and residual diameter stenosis ≤30 % by visual assessment on coronary angiography.

First, at baseline, after successful anterograde wire crossing or retrograde passing through the collateral branch, a microcatheter was introduced anterogradely or retrogradely for FFR measurement (Fig. 1). Before each measurement, 200 μg of intracoronary nitroglycerin was administered. A 0.014-in. coronary pressure wire (Abbott Vascular, Santa Clara, CA) was calibrated outside of the body and then equalized to the guiding catheter pressure with the sensor positioned just outside the ostium of the guiding catheter. Subsequently, the wire was advanced to the far distal portion of the CTO lesion through a microcatheter, and then in retrograde approach the microcatheter was pulled back to the donor artery. FFR was calculated as the ratio of the mean distal coronary pressure (Pd) to the mean aortic pressure (Pa) during maximal hyperemia. Maximal hyperemia was induced through intravenous administration of adenosine triphosphate (ATP) disodium at a rate of 140 μg/kg/min. Immediately after successful PCI, post-PCI FFR measurement for the target vessel was repeated with the pressure wire placed distally beyond the stented segment. After all recordings, a subsequent measure of the FFR value at the aorta site was conducted to check that drift did not occur routinely. If the value was beyond the range of 0.97–1.03, the FFR measurement was repeated.

2.3. Angiographic assessment

Quantitative coronary angiography was performed by two independent physicians, and discordance was settled by consensus with a third physician. The filmed catheter tip was used as a calibration device. The diameter of the normal segment proximal to the CTO lesion was used as the reference diameter. Lesion complexity was measured by the J-CTO score based on 5 selected factors: a previously failed lesion, a blunt stump type, bending, calcification, and an occlusion lesion longer than 20 mm [7]. The collateral grade was defined according to the Rentrop and collateral connections grading methods [8,9]. The anatomic pathway of the collateral supply was categorized as intramyocardial pathway (collateral channels *via* the myocardium, often through the intraventricular septum), epicardial pathway (collateral filling *via* connections on the epicardial surface), or coexistence pathway (both epicardial and intramyocardial pathways).

2.4. Dynamic SPECT imaging

Patients with an identified CTO on previous angiography underwent ^{99m}Tc-sestamibi (MIBI) SPECT imaging for assessment of myocardial ischemia within 3 days before CTO PCI. SPECT imaging by D-SPECT (Spectrum Dynamics, Caesarea, Israel) was performed according to a single-day rest/stress imaging protocol as previously described [10]. For rest imaging, prescanning was performed after the administration of an initial dose of approximately 1 mCi MIBI to enable positioning of the heart in the center of the field of view and establish the scanning region

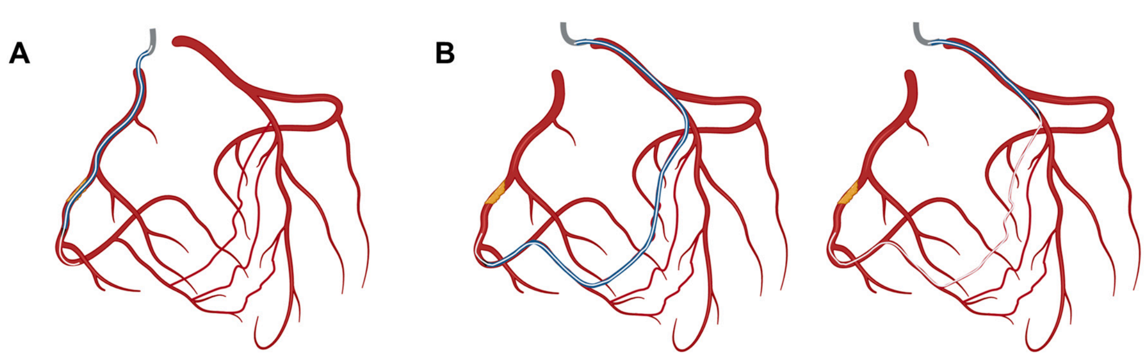

Fig. 1. The measurement of fractional flow reserve by a microcatheter anterogradely (A) or retrogradely (B).

of interest. Full scanning was started immediately after the injection of the remaining dose of approximately 15 mCi MIBI, and dynamic images were acquired in list mode for over 6 min. For stress imaging, pharmacological stress was induced with an intravenous infusion of ATP at a rate of 140 μg/kg/min for 5 min, and 25 mCi MIBI was injected 3 min later from the start of ATP injection, followed by dynamic image acquisition. Images were analyzed by two experienced nuclear physicians who were blinded to the CAG and FFR results. Rest and stress MBF and CFR were calculated using Corridor 4DM software.

2.5. Statistical analysis

Categorical variables were described as numbers and percentages and were tested by Pearson's chi-squared. Continuous variables were presented as means ± SD and were compared by paired *t*-test. For all tests, a 2-sided alpha level of 0.05 was considered to indicate statistical significance, and $p < 0.05$ was defined as significant. Pearson correlation coefficients or Spearman correlation coefficients were used to clarify the relationship between 2 continuous variables. A receiver operating characteristic (ROC) curve analysis was performed using MedCalc version 18.2.1 to evaluate the accuracy of FFR in the diagnosis of myocardial ischemia detected by SPECT. Statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC), version 9.3.

3. Results

3.1. Baseline clinical and procedural characteristics

A total of 53 patients with single-vessel CTO lesions were included. The baseline clinical characteristics of the patients are summarized in Table 1. The mean age of the patients was 59.3 ± 21.1 years, 47 (88.7 %) were male, and the mean body mass index was 24.6 ± 2.5 kg/m2. With regard to coronary risk factors, 31 patients (58.5 %) had hypertension, 7 (13.2 %) had dyslipidemia, 20 (37.7 %) had diabetes mellitus, 16 (30.2 %) were current smokers, and 4 (7.5 %) had a familial history of premature CAD.

Table 1 shows the angiographic and procedural details. The left anterior descending artery (LAD) was the most commonly involved CTO vessel (50.9 %), followed by the right coronary artery (RCA), 43.4 %, and 3 patients (5.7 %) had circumflex artery involvement. The coexistence of intramyocardial and epicardial pathways was the most frequent anatomic pattern of the collateral supply. The mean J-CTO score was 1.75 ± 1.20. The retrograde strategy was used in 17 cases, with successful retrograde recanalization in 64.7 % of the cases. The mean procedure time was 118.8 ± 47.6 min, with an overall technical success rate of 96.2 %. Of the 2 failed cases, both retrograde and antegrade wires were unable to cross the CTO lesion due to severe calcification. These two cases were excluded from further analysis.

Table 1
Baseline clinical and procedural characteristics.

Demographic data ($n = 53$)	
Age, y	59.3 ± 12.1
Male, n (%)	47 (88.7)
Body mass index, kg/m^2	26.1 ± 5.1
Hypertension, n (%)	31 (58.5)
Dyslipidemia, n (%)	7 (13.2)
Diabetes mellitus, n (%)	20 (37.7)
Current smoking, n (%)	16 (30.2)
Familial history of premature CAD, n (%)	4 (7.5)
Previous myocardial infarction, n (%)	21 (39.6)
Previous PCI, n (%)	17 (32.1)
Previous CABG, n (%)	4 (7.5)
Previous stroke, n (%)	1 (1.9)
Chronic kidney disease, n (%)	2 (3.8)
LVEF, %	56.9 ± 10.3
Angiographic characteristics (n = 53)	
CTO vessel (LAD/LCx/RCA), n (%)	27 (50.94)/3 (5.66) /23 (43.40)
Reference diameter, mm	2.76 ± 0.54
Predominant donor vessel (LAD/LCx/RCA), n (%)	17 (32.08)/8 (15.09)/28 (52.83)
J-CTO score	1.75 ± 1.20
Rentrop collateral grade (1/2/3), n (%)	1 (1.9)/10 (18.9)/42 (79.2)
Collateral connection grade (1/2/3), n (%)	37 (69.8)/14 (26.4)/2 (3.8)
Anatomic collateral pathway (Intramyocardial/ Epicardial/Coexistence), n (%)	36 (67.9)/5 (9.4)/12 (22.6)
Procedural details (n = 53)	
Retrograde strategy, n (%)	12 (22.64)
Number of stents implanted	2.29 ± 0.98
Total stent length, mm	70.13 ± 29.94
Minimal stent diameter, mm	2.71 ± 0.29
Drug coated balloon, n (%)	3 (5.66)
Procedure time, min	94.53 ± 46.48
Technical success	51(96.2 %)

CAD: coronary artery disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; LVEF: left ventricular ejection fraction; CTO: chronic total occlusion; LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery.

3.2. Dynamic SPECT data

Dynamic perfusion SPECT data were acquired in 20 patients before CTO PCI (Table 2). The baseline heart rate and blood pressure were significantly increased and decreased, respectively, during ATP administration. Pharmacological stress significantly increased global MBF and regional MBF of both CTO and non-CTO arteries. As expected, the regional CFR of the CTO vessels was lower than that of the non-CTO vessels, although the difference was not statistically significant (1.62 ± 0.64 *vs.* 1.81 ± 0.68, $p = 0.287$). However, an interesting finding was that even the regional CFR of non-CTO vessels was <2.0, which was reported to be suggestive of myocardial ischemia.

3.3. FFR data

Individual FFR changes before and after successful CTO PCI are detailed in Fig. 2. The mean FFR value was 0.34 ± 0.09 at baseline. Immediately after successful CTO PCI, the FFR value significantly increased to 0.79 ± 0.11, with 27 (52.9 %) patients having FFR <0.80 and 42 (82.4 %) patients having FFR <0.90. Both the FFR at baseline and immediately after PCI were similar among patients with Rentrop grade 1/2 and grade 3, as well as between subjects with collateral connection grade 0/1 and grade 2. A statistically significant negative correlation was found between the mean absolute FFR increase after PCI and the baseline FFR, suggesting that the patients with the lower baseline FFR had a greater net FFR increase after successful PCI. Consistently, there was a trend of higher baseline FFR in patients with LAD CTO than in those with RCA CTO (0.36 ± 0.08 *vs.* 0.32 ± 0.08, $p = 0.081$), while the trend was opposite after PCI (0.76 ± 0.11 *vs.* 0.82 ± 0.10, $p = 0.063$).

3.4. FFR correlation to SPECT data

As depicted in Fig. 3, the regional CFR of CTO vessels was significantly and positively correlated with the FFR value ($r = 0.607$, $p = 0.005$). ROC analysis was further performed to assess the value of baseline FFR for identifying patients with ischemia of CTO lesions characterized by regional CFR <2.0. The area under the ROC curve of the baseline FFR for the detection of ischemia was 0.923 ($p < 0.001$). The diagnostic performance in terms of sensitivity and specificity was 83.3 % and 85.7 % for baseline FFR with a ROC-optimized cutoff value of 0.35.

4. Discussion

In the present study, we performed a prospective trial to examine the

Table 2
Haemodynamic conditions and coronary low reserve estimates from dynamic SPECT.

	HR, bpm	BP, mmHg		Rate–pressure product	MBF, mL/min/g		
		Systolic	Diastolic		Global (n = 20)	CTO artery (n = 20)	Non-CTO artery (n = 40)
Rest	69.1 ± 10.1	133.4 ± 21.7	67.1 ± 14.1	9265.4 ± 2256.6	0.91 ± 0.40	0.83 ± 0.45	0.98 ± 0.46
Stress	78.4 ± 9.3	123.4 ± 19.2	60.4 ± 13.5	9652.0 ± 1718.7	1.55 ± 0.79	1.29 ± 0.74	1.74 ± 0.91
P value *	0.002	0.003	0.001	0.344	<0.001	0.001	<0.001
CFR					1.70 ± 0.54	1.62 ± 0.64	1.81 ± 0.68

HR: heart rate; BP: blood pressure; MBF: myocardial blood flow; CFR: coronary flow reserve.

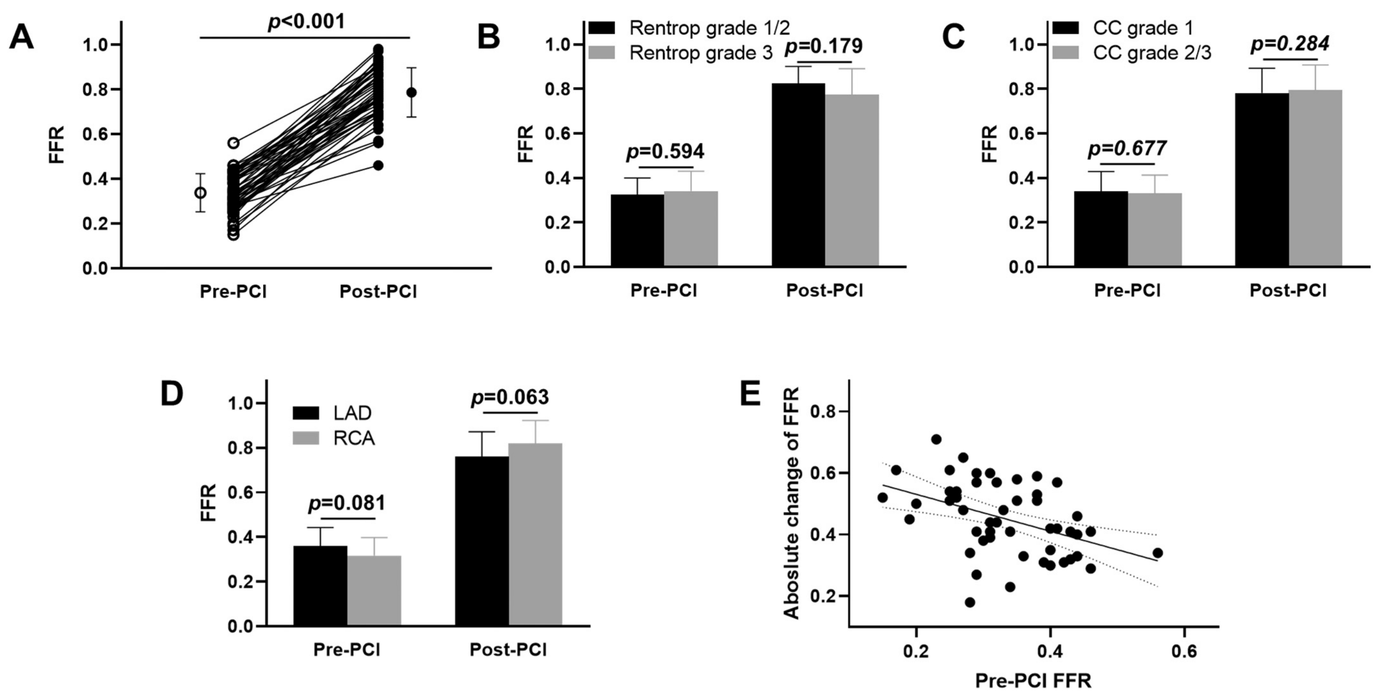

Fig. 2. Fractional flow reserve (FFR) changes before (Pre-PCI) and after (Post-PCI) successful intervention.

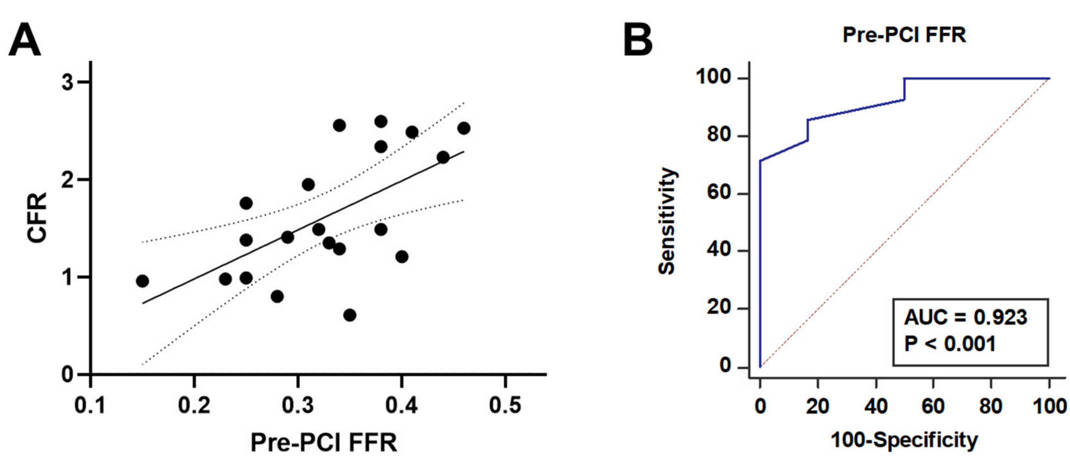

Fig. 3. The regional coronary flow reserve (CFR) of chronic total occlusion (CTO) vessels and fractional flow reserve (FFR) value before percutaneous coronary intervention (Pre-PCI).

dynamic changes in FFR during CTO PCI and their role in the functional evaluation of CTO lesions. The main findings of our study can be summarized as follows. First, there was no obvious correlation between FFR and collateral grade at baseline. Second, the absolute increase of FFR immediately after successful recanalization was significantly and negatively correlated with the baseline FFR value. Third, compared with RCA CTO, LAD CTO was associated with higher baseline FFR and lower FFR immediately after CTO PCO. Finally, the baseline FFR of CTO vessels was significantly correlated with regional SPECT-derived CFR, which can reflect the functional significance of CTO lesions.

In the presence of CTO, coronary arteries provide not only their own myocardial territory but also the territory of the CTO vessel through collateral vessel supply. In contrast to non-CTO lesions, the physiological assessment of CTOs was substantially more affected by collateral circulation and donor vessels. In the present study, we excluded concomitant ≥50 % stenosis in non-target arteries to avoid, at least partially, the possible influence of donor vessels on FFR evaluation of CTO. Before PCI, collaterals are generally the only source of blood supply to the distal myocardium of CTO lesions. Our data confirmed that the perfusion of CTO territories measured by dynamic SPECT was closely correlated with baseline FFR measured before CTO recanalization. Therefore, the baseline FFR can represent collateral function and distal myocardial perfusion and be equivalent to collateral FFR (FFR_{coll}) [4,11]. Although anatomic methods of grading collaterals were preferably applied to assess collaterals development, it has been reported that angiographic assessment was not associated with collateral function in subjects with CTO and cannot be used to discern the functionality of collaterals. Consistently, we found that there was no significant relationship between Rentrop or collateral connection grade and baseline FFR, which was reported in the previous study [12]. In our study, however, it was interesting to find that baseline FFR in patients with LAD CRO was higher than that in patients with RCA CTO. The value of FFR has been demonstrated to be dependent on the amount of tissue perfused [13]. The myocardial mass in the territory of the LAD CTO is much larger than that of RCA CTO, which may explain the difference in baseline FFR observed between LAD and RCA CTO.

FFR is now considered to be the gold standard for evaluating ischemia in patients with intermediate coronary artery stenosis and for guiding clinical decision-making. FFR-guided revascularization, which has been demonstrated to be associated with a better outcome than revascularization based on angiographic stenosis severity alone, is given the highest recommendation in the guidelines [3]. Studies of FFR in CTO lesions were conducted in previous studies, which showed that the collateral FFR decreased after PCI, accompanied by myocardial and coronary FFR increased [14–16]. Our data suggested that subjects with lower baseline FFR obtained more benefit from revascularization therapy than those with higher baseline FFR; however, the cutoff value of FFR for the presence of myocardial ischemia in patients with CTO is still unclear. The study by Pijls et al. has suggested that pressure-derived collateral flow-index (CFI_P) <0.23 could be used as the cutoff for the presence of inducible ischemia, which was associated with more ischemic events [17]. The CFI_P was calculated as (P_{distal}-CVP)/($P_{proximal}$-CVP), where P_{distal} refers to pressure distal to the CTO, CVP refers to central venous blood pressure, and $P_{proximal}$ refers to aortic pressure. In addition, studies have reported that a $CFI_P < 0.25$ is an independent predictor of 10–15 years long-term cardiovascular mortality in patients with the single-vessel disease or no coronary disease [18,19]. Based on the change of electrocardiogram, Zimarino et al. found that coronary FFR <0.18 and collateral pressure index <0.38 could induce angina pain [15]. An FFR of <0.35 before CTO PCI was the threshold for ischemia in our study, which was different from other studies because of the diverse detection method.

CFR, calculated as the ratio of the stress MBF to the rest MBF, is an index of CAD severity integrated epicardial coronary artery and coronary microcirculation, which can be measured non-invasively by positron emission tomography (PET), SPECT, and cardiac magnetic resonance (CMR) and invasively by Doppler flow velocity and thermodilution [20]. CFR by different measurements was used to evaluate CTO patients in a limited number of studies, and the value of CFR in CTO is uncertain. Intracoronary Doppler measured coronary flow velocity reserve (CFVR) after CTO PCI in an investigation. It showed that CFVR was <2 in 55 % of all patients, and 52 % of patients showed a CFVR <2 and an FFR ≥0.75 in subgroup study [21], and CFVR <2 and FFR ≥0.75 was observed in 24 (20 %) patients 5 months later [22]. In another study, collateral flow reserve of CTO ≥2.0 in only 7 % patients using Doppler flow velocity [23]. In a series of studies of CTO using PET, the CFR of CTO was 1.59 ± 0.55 before PCI and increased to >2 after PCI [24,25]. The average CFR of CTO vessels was 1.62 ± 0.64, with CFR of non-CTO coronary artery <2. The reasons may be related to the steal phenomenon caused by recruitment of the collateral channel from the non-CTO to CTO vessels during ATP stress. Neither CFR nor FFR alone is appropriate for assessing coronary physiology for CTO lesions.

In our study, dynamic perfusion SPECT was performed for the detection of myocardial ischemia. Different from traditional SPECT myocardial perfusion imaging, SPECT with high-sensitivity dedicated cardiac CZT camera allows dynamic acquisition of tomographic images suitable for quantitative perfusion assessment in terms of MBF and CFR. CFR quantitation using dynamic SPECT has been validated by a variety of studies [26], which was feasible and reliable compared to PET and invasive intracoronary measurements [5]. Although the cutoff value of CFR for detecting ischemia-causing CTO lesions has not yet been established, CFR ≥2 is taken as the normal cutoff in most clinical situations. Therefore, CFR <2 was used as the reference standard for the presence of ischemia in the present study [20]. Our results showed that a significant correlation was found between the CFR derived from dynamic SPECT and baseline FFR. To our knowledge, this is the first report to define a cutoff value for FFR indicating the presence of ischemia in patients with CTO. However, due to the absence of follow-up data, the benefit of FFR-guided revascularization in patients with CTO still needs further investigation.

4.1. Study limitations

There are several limitations that need to be considered when interpreting our results. First, it was a single-center observational study with a relatively small number of patients. The diagnostic performance of FFR in predicting ischemia may be influenced by the selection of the patient population. Second, circumflex CTO accounted for only 5.7 % of the included cases, which may cause potential bias. Third, quantitative coronary analyses and SPECT imaging analyses were not performed at an independent core laboratory. Fourth, myocardial perfusion SPECT imaging is not the gold standard of noninvasive CFR measurement. The validation of the method in hemodynamic assessment of CTO lesions has not been fully confirmed. Finally, the prognostic value of FFR for the outcome is still unclear due to the lack of long-term follow-up. The follow-up is ongoing, and the long-term results are promising. Further studies with larger samples and long-term follow-up are needed to establish the diagnostic and prognostic value of FFR in patients with CTO.

5. Conclusion

In summary, our data support the use of FFR and dynamic SPECT for hemodynamic assessment in patients with CTO. A significant correlation was found between the CFR derived from dynamic SPECT and baseline FFR. An FFR of <0.35 before CTO PCI can be taken as the cutoff for the presence of inducible ischemia. Based on the absolute change of FFR after successful CTO PCI, the benefit of revascularization was negatively correlated with the level of baseline FFR.

Ethical statement

We certify that this manuscript is original and has not been published and will not be submitted elsewhere for publication while being considered by *American Heart Journal Plus: Cardiology Research and Practice*. And the study is not split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time. No data have been fabricated or manipulated (including images) to support your conclusions. No data, text, or theories by others are presented as if they were our own.

The submission has been received explicitly from all co-authors. And authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.

CRediT authorship contribution statement

Shufu Chang: Writing – original draft, Project administration, Funding acquisition, Conceptualization. **Rende Xu:** Writing – original draft, Project administration, Conceptualization. **Hao Lu:** Project administration. **Yuxiang Dai:** Project administration. **Chenguang Li:** Project administration. **Jie Zhang:** Methodology. **Gang Zhao:** Project administration. **Juying Qian:** Project administration. **Jianying Ma:** Writing – review & editing, Project administration, Conceptualization. **Junbo Ge:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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