Diagnostic performance of coronary computed tomography (CT) angiography derived fractional flow reserve (CTFFR) in patients with coronary artery calcification: insights from multi-center experiments in China

Ying Tao[1], Yulong Gao[1], Xiangyu Wu[1], Yutong Cheng[1], Xianliang Yan[1], Yun Gao[1], Yuqi Liu[2], Yida Tang[3], Zhizhong Li[1]

[1]Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China; [2]Shenzhen Escope Technology Co., Ltd., Shenzhen, China; [3]Department of Cardiovascular Medicine, Peking University Third Hospital, Beijing, China

Contributions: (I) Conception and design: Y Tao; (II) Administrative support: Y Gao; (III) Provision of study materials or patients: X Wu, Y Cheng; (IV) Collection and assembly of data: X Yan, Y Gao, Y Liu; (V) Data analysis and interpretation: Y Tang, Z Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Zhizhong Li. Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China. Email: lzzeagle2@sina.com.

Background: Coronary computed tomography angiography (CCTA) is affected by calcification artifacts, which reduces its diagnostic efficacy. CT-derived fractional flow reserve (CTFFR) based on CCTA has been proven to be accurate in the diagnosis of non-calcified patients, but its clinical use in patients with calcified coronary artery disease remains to be investigated. The purpose of this study was to determine the effect of coronary artery calcification on CTFFR.

Methods: CCTA, coronary angiography, and FFR were performed on 128 patients in three clinical medical centers. Local investigators performed an assessment of stenosis for CCTA and the core laboratory performed the CTFFR calculations. CTFFR ≤0.8 and diameter stenosis ≥50% for CCTA was identified as lesion-specific ischemia. The diagnostic performance of CTFFR in identifying the diagnostic sensitivity, specificity, and accuracy was analyzed using an invasive FFR ≤0.8 as the gold standard. We compared the diagnostic performances between CTFFR and CCTA according to the level of calcification. We divided patients into four groups based on the coronary artery calcification score [coronary artery calcification score (CACS) =0, >0 to <100, ≥100 to <400, and ≥400].

Results: The Youden index indicated an optimal threshold of 0.80 for CTFFR to identify functionally ischemic lesions. The sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), and area under receiver operating characteristic curve (AUC) for CTFFR on a per-patient basis were 90% (80–96%), 98% (92–99%), 94% (89–97%), 98% (91–99%), 92% (83–97%), and 96.9% (94.2–99.6%), respectively. Compared to CCTA, CTFFR had a higher specificity, accuracy, PPV, NPV, and AUC in both the low to intermediate calcification group and the high calcification group. The diagnostic efficacy of CTFFR was higher than that of CCTA without the influence of calcification.

Conclusions: This Chinese multi-center study showed that CTFFR based on novel computational fluid dynamics (CFD) modeling demonstrated very high diagnostic efficacy compared to the invasive measurement of FFR in all lesions suspected coronary artery disease (CAD). Of particular note are the high specificity, sensitivity, and accuracy of CTFFR, even in patients with calcification, which were significantly better than previous CCTA assessments.

Keywords: CT-derived fractional flow reserve (CTFFR); computed tomography angiography (CTA); coronary artery calcification

Submitted May 26, 2022. Accepted for publication Jul 13, 2022.
doi: 10.21037/atm-22-3180
View this article at: https://dx.doi.org/10.21037/atm-22-3180

Introduction

Owing to its non-invasive assessment tools, coronary computed tomography angiography (CCTA) has been widely used in coronary artery disease (CAD) screening. The negative predictive value of CCTA facilitates the exclusion of coronary stenosis and the avoidance of non-essential invasive coronary angiography (ICA) tests (1). However, CCTA only provides an imaging assessment of the degree of stenosis and has several limitations in assessing the physiological function of the lesion, often underestimating or overestimating the functional severity of the lesion. Also, calcification artifacts significantly reduce the positive predictive value (PPV) of CCTA in calcified lesions (2).

Fractional flow reserve (FFR) is the "gold standard" for the functional assessment of coronary lesions (3). Recent study has applied a FFR ≤0.80 as a guide to interventional treatment and a predictor of prognosis (4). Although the clinical significance of FFR has been further confirmed, the need for invasive procedures and the side effects of adenosine have limited its clinical use, and only 10–20% of clinical revascularizations are performed based on FFR.

Fractional flow reserve derived from CT-derived fractional flow reserve (CTFFR) is a new technique that is performed by applying advanced hydrodynamic analytical methods based on CCTA data. In recent years, CTFFR has been applied to obtain a combination of anatomical and functional information in a single examination, without additional image acquisition and administration of loading drugs, and has become a new hot spot in clinical research (5-7). This non-invasive tool has the potential to replace other traditional modalities recommended in clinical guidelines as a long-term gatekeeper to guide hemodynamic reconstruction.

There are relatively a few studies on the effect of calcification on the diagnostic efficacy of CTFFR (8). A study has shown that CTFFR exhibited improved discrimination of ischemia compared with CCTA alone in lesions with mild-to-moderate calcification (9). The main objective of this study was to investigate the effect of calcification on the diagnostic accuracy of CTFFR based on a new artificial intelligence algorithms. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3180/rc).

Methods

Study population

This diagnostic Chinese multicenter study enrolled consecutive patients with suspected or known CAD who underwent CCTA at three Chinese medical centers (Beijing Anzhen Hospital, Capital Medical University; Peking University Third Hospital; Fuwai Hospital) between January 1, 2021, and May 1, 2021. Subjects who met the exclusion criteria or had completed CCTA (image quality met the requirements) at the study center within 15 days prior to ICA were screened for CCTA, followed by ICA and FFR with pressure guidewire measurement.

The general exclusion criteria were as follows: (I) patients aged <18 or >80 years; (II) pregnant or lactating women; (III) patients with allergies to the contrast agent and adenosine; (IV) patients with previous myocardial infarction within 30 days prior to the CCTA examination; (V) patients with previous coronary artery bypass grafting (CABG), stent, pacemaker placement, implantable cardioverter defibrillator or prosthetic valve; (VI) patients with hypertrophic obstructive cardiomyopathy or severe heart failure (NYHA ≥III); (VII) patients with body mass index >35 kg/m^2; and (VIII) patients who did not sign the informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by each of the Ethics Committees of the included medical centers (Anzhen Hospital, No. 2019-0511; Peking University Third Hospital, No. D2020143; Fuwai Hospital, No. 2019-1161) and all patients provided written informed consent.

CCTA

All patients underwent CCTA at baseline and follow-up using at least a 64-level spiral CT machine (Somatom Definition, Aquilion One, Toshiba, Otawara, Japan; Optima CT660, GE Healthcare, Boston, USA). All patients were scanned for coronary artery calcification and then underwent prospective cardiac-gated CCTA. The scan parameters were as follows: tube voltage 100–120 kV, tube current 100–300 mAs, collimator width 128×0.625 mm, X-ray tube speed 0.27 s/revolution, and matrix 512×512; 50–70 mL of non-ionic contrast agent (iophorol, 370 mg/mL, Jiangsu Hengrui, Lianyungang, China) was injected at a flow rate of 4–5 mL/s, followed by 50 mL of saline at the same flow rate. The delay time was triggered by artificial intelligence, and the ascending aorta at the level of the main pulmonary window was set as the dynamic monitoring area. The scan was automatically triggered by a 6s delay after the CT value reached 150 HU.

CTFFR calculation

A FFR calculation software system with computational fluid dynamic (CFD) principle was developed and provided by CAscope (EScope Ltd., Shenzhen, China). Core laboratory investigators performed the CTFFR calculation in a blinded manner according to the following steps: (I) establishment of three-dimensional (3D) coronary anatomical models simulating maximal hyperemia; (II) definition of the luminal centerline and boundary; and (III) CTFFR calculation. The CTFFR values of target vessels were obtained at the position recorded during the FFR evaluation procedure. A CTFFR ≤0.80 was identified as a flow-limiting lesion.

ICA and FFR

ICA and FFR measurement were performed according to the standard guidelines (10). Intracoronary FFR measurements were carried out using the FFR measurement system from St. Jude Medical Supply, Inc. FFR was assessed as at least one vessel with a diameter ≥2.0 mm or greater and stenosis ≥30% during ICA. Intracoronary (40–60 μg/kg·min) or intravenous (140–180 μg/kg·min) adenosine infusion was used to induce a maximal state of coronary hyperemia at the discretion of the operator. The FFR value was automatically obtained by calculating the ratio (Pd/Pa) between the mean pressure (Pd) and the mean aortic pressure (Pa) in the distal part of the stenotic vessel, as measured by the pressure guidewire and guiding catheter, respectively. FFR ≤0.8 was used as the threshold value to determine myocardial ischemia. All images and FFR signals were interpreted by two experienced interventional cardiologists who were blinded to the CCTA and CTFFR results.

Study endpoints

The primary study endpoint was the per-patient diagnostic performance of CTFFR, as assessed by the sensitivity, specificity, and the area under the receiver operating characteristic (ROC) curve (AUC) of CTFFR for the diagnosis of hemodynamically significant stenosis, with invasive FFR (FFR ≤0.80) as the reference standard. Furthermore, the diagnostic performances of CTFFR in 128 patients with coronary calcification were compared using the Agatston calcium scores (11). Using a calcification score of 400 as the grouping threshold, the patients were divided into groups a low to intermediate calcification group (<400) and a high calcification group (≥400).

Statistical analysis

The Kolmogorov-Smirnov test was used to assess the normality of the quantitative data. Continuous variables with normal distribution were expressed as the mean ± standard deviation (SD), while non-normally distributed variables were presented as the median and quartiles. The accuracy, sensitivity, specificity, PPV, and negative predictive value (NPV) of CTFFR and CCTA were compared using the McNemar and chi-square tests. With invasive FFR (threshold 0.80) as the reference standard, the AUC, which was obtained by ROC curve analysis, was calculated and compared according to the method proposed by DeLong *et al.* (12). Spearman test correlation analysis and Bland-Altman analysis were used to test the correlation of CTFFR. A two-tailed P<0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS software version 22.

Results

Patient characteristics

The patients' demographic characteristics are listed in *Table 1*. Of the 160 patients screened for the study, a total of 32 patients were excluded based on the inclusion and exclusion criteria (*Figure 1*). Therefore, a total of 128 patients (median age: 58 years, IQR: 51 to 65 years; 65.5% men) who had undergone CCTA were available for analysis. The Agatston score (AS) was calculated in 128 patients evaluated by CCTA, including 13 [coronary artery calcification score (CACS) =0, 10.2%], 35 (CACS >0 to <100, 27.3%) mild calcification patients, 39 (CACS ≥100 to <400, 29.7%) moderate calcification patients, and 41 (CACS ≥400, 32.0%) high calcification patients (*Table 2*). The median coronary calcium scores were 212.0 (IQR: 59–626) at the

Table 1 Baseline characteristics of the included patients and the procedural results

Characteristics	Values
Age, years	58 [51–65]
Male, n (%)	84 (65.5)
Body mass index, kg/m^2	23.8 (21.7–26)
Cardiovascular risk factors, n (%)	
Diabetes	38 (30.2)
Hypertension	69 (53.8)
Tobacco abuse	45 (35.0)
Dyslipidemia	73 (50.7)
Lesion characteristic	
Location	
LM/LAD, n (%)	95 (74.2)
LCX, n (%)	10 (7.8)
RCA, n (%)	23 (18.0)
FFR ≤0.80, n (%)	57 (44.5)
FFR value	0.82 (0.71–0.88)
CCTA parameters	
30–49%/50–69%/70–90%	32/58/38
CTFFR ≤0.80, n (%)	62 (48.4)
CTFFR value	0.81 (0.71–0.87)
CACS	212 [59–626]

Values are n (%) and median (ranges). LM, left main artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; FFR, fractional flow reserve; CCTA, coronary computed tomography angiography; CTFFR, fractional flow reserve derived from coronary computed tomography angiography; CACS, coronary artery calcification score.

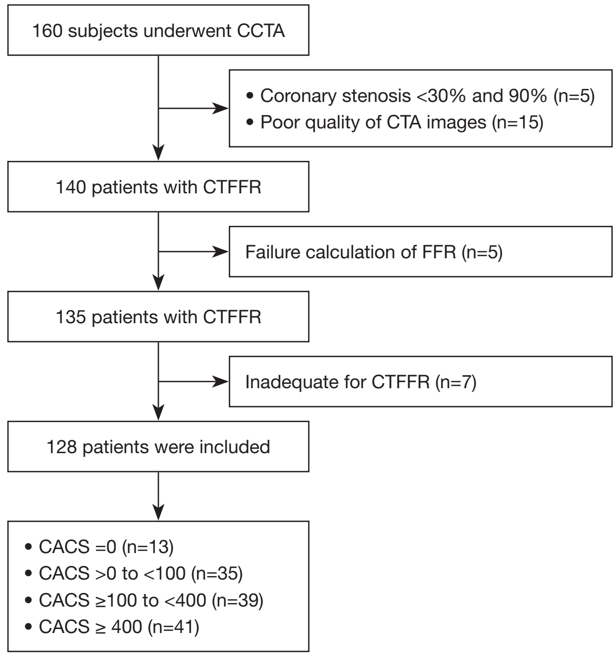

Figure 1 Flow chart of this study. CCTA, coronary computed tomography angiography; CTA, computed tomography angiography; CTFFR, fractional flow reserve derived from coronary computed tomography angiography; FFR, fractional flow reserve; CACS, coronary artery calcification score.

per-patient level. Invasive FFR identified the presence of hemodynamically significant stenosis (FFR ≤0.80) in 57 patients (44.5%). CTFFR determined the presence of hemodynamically significant stenosis (CTFFR ≤0.80) in 62 patients (48.4%) (*Table 1*).

Diagnostic performance of CTFFR

The diagnostic performances of CCTA and CTFFR in all patients are shown in *Table 3*. The Youden index indicated an optimal threshold of 0.80 for CTFFR to identify functionally ischemic lesions. The diagnostic sensitivity, specificity, accuracy, PPV, and NPV for CTFFR were 90% (80–96%), 98% (92–99%), 94% (89–97%), 98% (91–99%), and 92% (83–97%), respectively. This study showed that the diagnostic performance of CTFFR was higher than that of CCTA alone. Also, ROC curve analysis revealed that CTFFR had a superior diagnostic power [AUC =0.969 (95% CI: 0.942–0.996), P<0.001] (*Figure 2*).

Diagnostic performance of CTFFR versus coronary CCTA

The diagnostic performances of CTFFR and CCTA according to the level of calcification are summarized in *Table 4*. At the per-patient level, the sensitivity, specificity, accuracy, PPV, and NPV of CTFFR in detecting lesion-specific ischemia did not differ significantly between the low to intermediate CACS group and the high CACS group. The AUC comparison showed that CTFFR had a superior diagnostic performance compared to CCTA in both the low to intermediate CACS group [0.954 (95% CI: 0.913–0.995) *vs.* 0.617 (95% CI: 0.499–0.735), P<0.001] and the high CACS group [0.981 (95% CI: 0.942–0.998) *vs.* 0.505 (95% CI: 0.326–0.684), P<0.001] (*Figure 2*). The diagnostic

Table 2 Coronary artery calcification score categories in vessels

Variables	CACS =0	0< CACS <100	100≤ CACS <400	CACS ≥400
N (%)	13 (10.2)	35 (27.3)	38 (29.7)	41 (32.0)
FFR	0.84 (0.69–0.87)	0.84 (0.77–0.92)	0.79 (0.72–0.88)	0.80 (0.62–0.87)
CTFFR	0.88 (0.77–0.91)	0.83 (0.77–0.88)	0.80 (0.69–0.87)	0.76 (0.65–0.83)
CACS	0	56 .0 (26.2–72.9)	254.4 (168.9–316.0)	927 [656–1,415]
FFR ≤0.8 (%)	5 (38.5)	13 (37.1)	18 (46.2)	21 (51.2)
CTFFR ≤0.8 (%)	5 (38.5)	15 (42.9)	20 (51.3)	22 (53.4)
CCTA ≥50% (%)	10 (76.9)	26 (74.3)	12 (30.8)	8 (19.5)

Values are n (%) and median (ranges). FFR, fractional flow reserve; CTFFR, fractional flow reserve derived from coronary computed tomography angiography; CACS, coronary artery calcification score; CCTA, coronary computed tomography angiography.

Table 3 Diagnostic performances of CTFFR and CCTA in all patients

All patient (n=128)	CCTA, %	CTFFR, %	P value
Sensitivity	84 [72–93]	90 [80–96]	0.016
Specificity	32 [22–45]	98 [92–99]	<0.001
Accuracy	55 [46–64]	94 [89–97]	<0.001
PPV	50 [40–60]	98 [91–99]	<0.001
NPV	72 [53–86]	92 [83–97]	<0.001

Values are displayed as % [95% confidence interval]. CTFFR, fractional flow reserve derived from coronary computed tomography angiography; CCTA, coronary computed tomography angiography; PPV, positive predictive value; NPV, negative predictive value.

efficacy of CTFFR was higher than that of CCTA without the influence of calcification.

Correlation of CTFFR to FFR

There was a moderate correlation between the CTFFR and FFR values in all lesions (r=0.861; 95% CI: 0.815–0.903; P<0.001), as well as calcified lesions with r values of 0.830 (P<0.001) and 0.909 (P<0.001). Bland-Altman analysis showed a slight difference between the FFR and CTFFR values (mean difference 0.001; 95% limits of agreement: −0.196 to +0.196) (*Figure 3*).

Discussion

This Chinese multicenter study showed that CTFFR based on a novel CFD model had a very high diagnostic efficacy in calcified lesions compared to the invasive measurement of FFR. Our study provides evidence that coronary artery calcification does not significantly affect the diagnostic performance of CTFFR-based CFD and is superior to CCTA alone, even in the presence of severe calcification.

CTFFR is an image post-processing technique that applies fluid dynamics to CCTA examinations and uses routinely standardized CCTA image data to assess hemodynamic differences in coronary artery stenoses (13). Heart Flow's CTFFR analysis (Heart Flow, Inc., USA) is currently the only commercially available software approved by the U.S. Food and Drug Administration (14). Most studies have applied CTFFR <0.8 as the threshold value (15). DISCOVER-FLOW was the first multicenter clinical trial to evaluate the diagnostic efficacy of CTFFR, which showed that the accuracy, specificity, and sensitivity of CTFFR were 84.3%, 81.6%, and 87.9%, respectively, for the vascular unit of analysis, and 87.4%, 81.6%, and 92.9%, respectively, for the patient unit of analysis. With the patient as the unit of analysis, the accuracy, specificity, and sensitivity of CTFFR diagnosis were 87.4%, 81.6%, and 92.6%, respectively. Also, CTFFR correlated well with FFR (correlation coefficient of 0.678) (16). The results of this study also support the high accuracy of CTFFR in the diagnosis of myocardial ischemia due to coronary artery stenosis, which is consistent with the results of previous studies (17-19).

Calcified plaque decreases the diagnostic accuracy of CCTA for coronary artery stenosis. Calcified plaques can appear as artifacts on CT images, manifesting as star-halo-like artifacts at the edges of high-density calcifications that obscure the normal coronary lumen, leading to an overestimation of luminal stenosis, which in turn affects diagnostic accuracy (20). Feldman *et al.* showed that

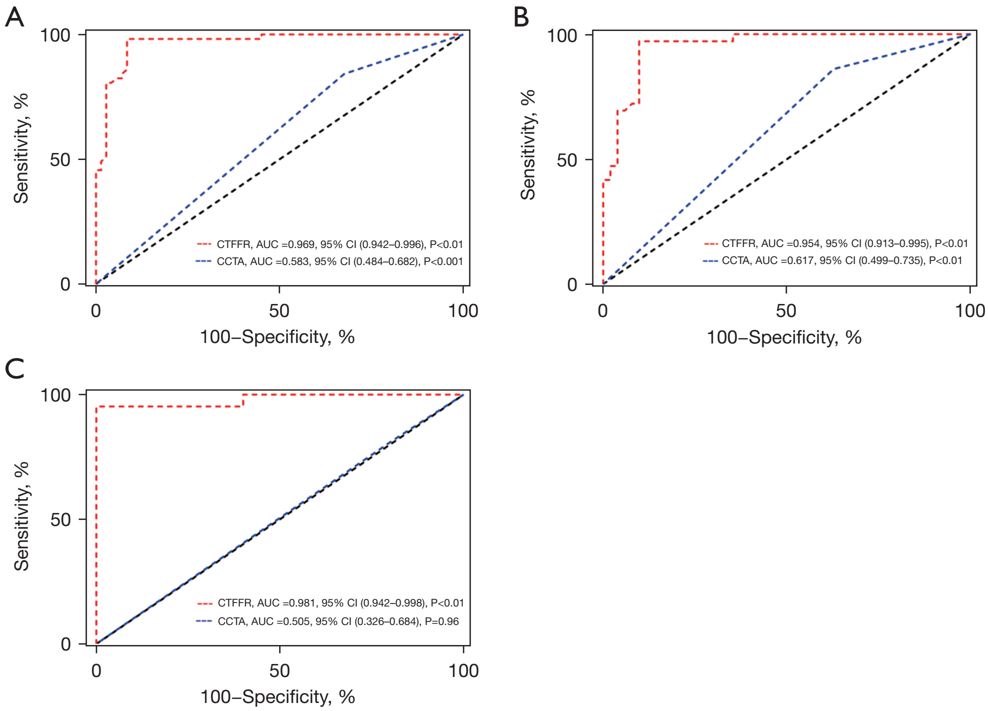

Figure 2 Receiver operating characteristic curve of the diagnostic performances of CTFFR and CCTA fractional flow reserve. AUC of the detection of ischemia with CTFFR (≤0.80) and CCTA (≥50% stenosis) using FFR as the reference standard. (A) Patients with all lesions; (B) patients with low calcification; (C) patients with high calcification. CTFFR, fractional flow reserve derived from coronary computed tomography angiography; AUC, area under the receiver operating characteristic curve; CCTA, coronary computed tomography angiography; FFR, fractional flow reserve; 95% CI, 95% confidence interval.

Table 4 Diagnostic performance of CTFFR versus CCTA according to the Agatston score categories

Patients (n=128)	Low to intermediate CACS (n=87)			High CACS (n=41)		
	CCTA, %	CTFFR, %	P value	CCTA, %	CTFFR, %	P value
Sensitivity	86 [71–95]	97 [85–100]	0.198	81 [58–95]	100 [84–100]	0.107
Specificity	37 [24–52]	90 [79–97]	<0.001	20 [6–44]	95 [75–98]	<0.001
Accuracy	57 [46–68]	93 [86–97]	<0.001	51 [35–65]	97 [87–99]	<0.001
PPV	49 [36–62]	88 [73–96]	<0.001	52 [34–69]	95 [77–100]	<0.001
NPV	79 [58–93]	98 [89–99]	0.014	50 [16–84]	100 [82–100]	<0.001

Values are displayed as % [95% confidence interval]. CTFFR, fractional flow reserve derived from coronary computed tomography angiography; CCTA, coronary computed tomography angiography; CACS, coronary artery calcification score; PPV, positive predictive value; NPV, negative predictive value.

the diagnostic efficacy of CCTA was higher in patients with a calcification score <600 compared to those with a calcification score >600, with an increase in diagnostic specificity from 44% to 90% and an increase in NPV from 50% to 83%, as well as a significant increase in the value of CCTA to exclude coronary artery disease. Therefore, for patients with severe coronary artery calcification, the diagnostic efficacy of CCTA is reduced, and the diagnostic false positive rate is higher, which can result in patients undergoing unnecessary invasive tests (21).

Recent studies have shown that CTFFR in combination with other hemodynamic indices such as flow shear stress

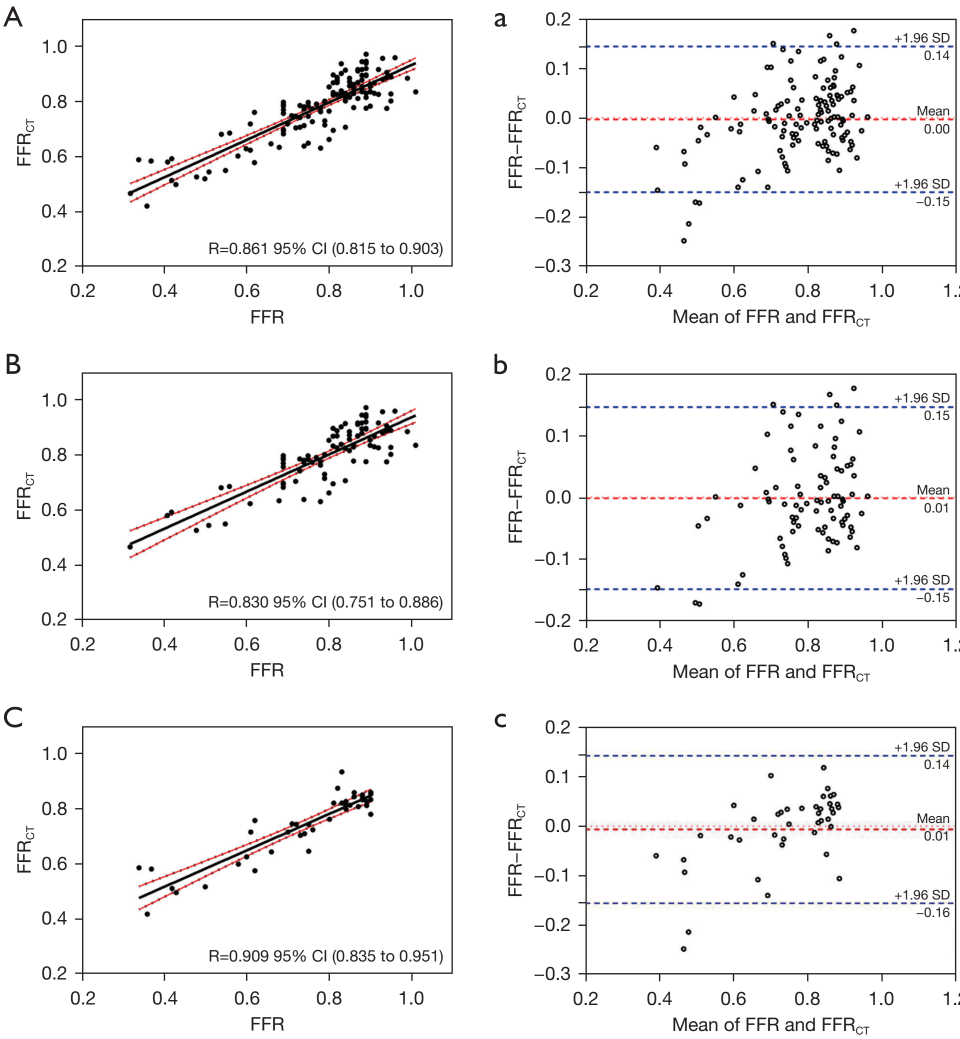

Figure 3 Bland-Altman and Scatter plots of the association between CTFFR and FFR. Bland-Altman plots (a-c) and correlation (A-C) of invasive FFR versus CTFFR. For all patients (n=128) (A,a); for patients with low calcification (B,b); for patients with high calcification (C,c). CTFFR, fractional flow reserve derived from coronary computed tomography angiography; FFR, fractional flow reserve; SD, standard deviation; 95% CI, 95% confidence interval.

and blood flow velocity may avoid the over-evaluation of calcified plaques by CCTA (22). In an NXT subgroup study, Nørgaard *et al.* evaluated coronary calcification using the calcification score (AS) in 214 patients (grouped according to the quartile method) to assess the effect of calcification on the diagnostic efficacy of CTFFR. Their study showed that the differences in accuracy, sensitivity, and specificity of CTFFR were not statistically significant between each interval group; CTFFR had the same diagnostic efficacy (AUC: 0.86 and 0.92, respectively) in severe calcification load (AS: 416–3,599) and in low to moderate calcification score (AS: 0–415). Compared with conventional CCTA, CTFFR had higher diagnostic accuracy and specificity in each AS score interval (19). Our findings are similar to those of the NXT trial and the sub-studies of the MACHINE registry (8,23). We observed that the AUC value of CTFFR in identifying ischemia with CACS ≥400 was still high. Most high-grade stenoses detected by CCTA do not cause ischemia; therefore, the superior diagnostic performance of CTFFR compared with CCTA may improve the detection of ischemia and facilitate changes in the clinical decision tree for CAD management.

The above studies suggest that CTFFR has high diagnostic efficacy in calcified coronary lesions and is superior to conventional CCTA. Kamo *et al.* evaluated the diagnostic capability of CTFFR using the subtraction method (subtraction CTFFR) in patients with severe calcification. The sensitivity, specificity, PPV, and NPV of CTFFR versus subtractive CTFFR for detecting hemodynamically significant stenosis were 84.6% *vs.* 92.3%, 59.4% *vs.* 75.0%, 45.8% *vs.* 60.0%, and 90.5% *vs.* 96.0%, respectively. The AUC of subtractive CTFFR was significantly higher than that of CTFFR (0.84 *vs.* 0.70) (P=0.04). In patients with severe calcification, subtractive CTFFR showed a higher diagnostic value than CTFFR, increasing the specificity and PPV while maintaining the sensitivity and NPV, with high reproducibility (24). It is important to note that the proportion of patients with severe calcification (AS >1,000) included in these studies is relatively small at present, and more large-scale studies are needed to verify the impact of the diagnostic efficacy of CTFFR in severe calcification (25). Also, the impact of calcification severity on the discriminatory ability of CTFFR in clinical practice, especially for CACS ≥400 or ≥1,000, still needs to be explored.

The present study has some limitations that should be noted. Firstly, the sample size of patients with severe coronary artery calcification was relatively small. Although this is consistent with the real world, a larger study population with close attention to the real clinical situation, especially those with CACS ≥400 or even ≥1,000, is needed to confirm the results. Secondly, our experiment only recorded information on patient-based calcification and did not collect information on vascular-based calcification. Therefore, our article did not explore the vascular-based condition, which is the biggest limitation of our article.

In conclusion, this study showed that CTFFR has high accuracy in the diagnosis of myocardial ischemia due to coronary artery stenosis, and calcification does not affect the diagnostic accuracy of CTFFR within a certain range of calcification scores. Therefore, CTFFR can be used as an effective adjunct to CCTA in the assessment of coronary stenosis lesions and is expected to reduce unnecessary coronary angiography and hemodynamic reconstruction.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3180/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3180/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3180/coif). YL is from Shenzhen Escope Technology Co., Ltd. The other authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by each of the Ethics Committees of the included medical centers (Anzhen Hospital, No. 2019-0511; Peking University Third Hospital, No. D2020143; Fuwai Hospital, No. 2019-1161) and all patients provided written informed consent.

References

1. Leipsic J, Abbara S, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2014;8:342-58.
2. Dey D, Lee CJ, Ohba M, et al. Image quality and artifacts in coronary CT angiography with dual-source CT: initial clinical experience. J Cardiovasc Comput Tomogr 2008;2:105-14.
3. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery

disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. Eur Heart J 2015;36:3359-67.
4. Barbato E, Toth GG, Johnson NP, et al. A Prospective Natural History Study of Coronary Atherosclerosis Using Fractional Flow Reserve. J Am Coll Cardiol 2016;68:2247-55.
5. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA 2012;308:1237-45.
6. Chinnaiyan KM, Safian RD, Gallagher ML, et al. Clinical Use of CT-Derived Fractional Flow Reserve in the Emergency Department. JACC Cardiovasc Imaging 2020;13:452-61.
7. Fearon WF, Nishi T, De Bruyne B, et al. Clinical Outcomes and Cost-Effectiveness of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease: Three-Year Follow-Up of the FAME 2 Trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). Circulation 2018;137:480-7.
8. Tesche C, Otani K, De Cecco CN, et al. Influence of Coronary Calcium on Diagnostic Performance of Machine Learning CT-FFR: Results From MACHINE Registry. JACC Cardiovasc Imaging 2020;13:760-70.
9. Yu M, Li Y, Li W, et al. Calcification remodeling index assessed by cardiac CT predicts severe coronary stenosis in lesions with moderate to severe calcification. J Cardiovasc Comput Tomogr 2018;12:42-9.
10. Toth GG, Johnson NP, Jeremias A, et al. Standardization of Fractional Flow Reserve Measurements. J Am Coll Cardiol 2016;68:742-53.
11. Greenland P, Bonow RO, Brundage BH, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2007;49:378-402.
12. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-45.
13. Ko BS, Cameron JD, Munnur RK, et al. Noninvasive CT-Derived FFR Based on Structural and Fluid Analysis: A Comparison With Invasive FFR for Detection of Functionally Significant Stenosis. JACC Cardiovasc Imaging 2017;10:663-73.
14. Yoon YE, Choi JH, Kim JH, et al. Noninvasive diagnosis of ischemia-causing coronary stenosis using CT angiography: diagnostic value of transluminal attenuation gradient and fractional flow reserve computed from coronary CT angiography compared to invasively measured fractional flow reserve. JACC Cardiovasc Imaging 2012;5:1088-96.
15. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407-77.
16. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol 2011;58:1989-97.
17. Nørgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol 2014;63:1145-55.
18. Tang CX, Liu CY, Lu MJ, et al. CT FFR for Ischemia-Specific CAD With a New Computational Fluid Dynamics Algorithm: A Chinese Multicenter Study. JACC Cardiovasc Imaging 2020;13:980-90.
19. Nørgaard BL, Gaur S, Leipsic J, et al. Influence of Coronary Calcification on the Diagnostic Performance of CT Angiography Derived FFR in Coronary Artery Disease: A Substudy of the NXT Trial. JACC Cardiovasc Imaging 2015;8:1045-55.
20. Abdulla J, Pedersen KS, Budoff M, et al. Influence of coronary calcification on the diagnostic accuracy of 64-slice computed tomography coronary angiography: a systematic review and meta-analysis. Int J Cardiovasc Imaging 2012;28:943-53.
21. Feldman DI, Latina J, Lovell J, et al. Coronary computed tomography angiography in patients with stable coronary artery disease. Trends Cardiovasc Med 2021. [Epub ahead of print]. doi: 10.1016/j.tcm.2021.08.009.
22. Fu D, Xiao X, Gao T, et al. Effect of Calcification Based on Computer-Aided System on CT-Fractional Flow

Reserve in Diagnosis of Coronary Artery Lesion. Comput Math Methods Med 2022;2022:7020209.
23. Di Jiang M, Zhang XL, Liu H, et al. The effect of coronary calcification on diagnostic performance of machine learning-based CT-FFR: a Chinese multicenter study. Eur Radiol 2021;31:1482-93.
24. Kamo Y, Fujimoto S, Nozaki YO, et al. Incremental Diagnostic Value of CT Fractional Flow Reserve Using Subtraction Method in Patients with Severe Calcification: A Pilot Study. J Clin Med 2021;10:4398.
25. Kawaji T, Shiomi H, Morishita H, et al. Feasibility and diagnostic performance of fractional flow reserve measurement derived from coronary computed tomography angiography in real clinical practice. Int J Cardiovasc Imaging 2017;33:271-81.

(English Language Editor: A. Kassem)

Cite this article as: Tao Y, Gao Y, Wu X, Cheng Y, Yan X, Gao Y, Liu Y, Tang Y, Li Z. Diagnostic performance of coronary computed tomography (CT) angiography derived fractional flow reserve (CTFFR) in patients with coronary artery calcification: insights from multi-center experiments in China. Ann Transl Med 2022;10(14):788. doi: 10.21037/atm-22-3180