Original Article

Impact of nitroglycerin on machine-learning fractional flow reserve in coronary computed tomography (CT)-angiography

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Background: Nitroglycerin administration prior to examination improves stenosis assessment of coronary computed tomography (CT) angiography (CCTA). However, whether nitroglycerin influences CT-derived fractional flow reserve (FFR, CT-FFR) evaluation remains unclear. This study aimed to investigate the effect of nitroglycerin on diagnostic performance of CT-FFR.

Methods: In this single-center retrospective study, 107 consecutive patients suspected of coronary artery disease (CAD) with nitroglycerin administration prior to CCTA in 2019 were matched to 107 patients without nitroglycerin in 2016 from Fuwai Hospital. All patients underwent CCTA and invasive FFR in a month. Vessel-based and patient-based accuracy and diagnostic performance of CT-FFR were compared between the two groups, as well as image quality, coronary artery diameter and evaluability. Quantitative variables were compared by Kruskal-Wallis H test. Categorical variables and rates were compared by χ^2 test or Fisher exact test.

Results: A total of 214 patients (56.1±8.9 years, 155 male) with 237 target lesion vessels were analyzed, including 120 vessels in nitroglycerin and 117 vessels in non-nitroglycerin group. Per-vessel based accuracy of CT-FFR was higher in nitroglycerin group {80.0% [95% confidence interval (CI): 71.7–86.7%] *vs.* 68.4% (59.1–76.7%), P=0.041}. On a per-patient basis, nitroglycerin administration improved the accuracy [83.2% (74.7–89.7%) *vs.* 68.2% (58.5–76.9%), P=0.01], specificity [82.7% (69.7–91.8%) *vs.* 61.9% (48.8–73.9%), P=0.01], positive predictive value (PPV) [83.6% (73.6–90.4%) *vs.* 58.6% (50.0–66.9%), P=0.004], and area under the curve (AUC) [0.83 (0.75–0.89) *vs.* 0.71 (0.61–0.79), P=0.03] of CT-FFR. Vessel diameters (left main arteries: 4.3 *vs.* 3.8 mm, P<0.001; left anterior descending arteries: 3.1 *vs.* 2.9 mm, P=0.001; left circumflex arteries: 2.9 *vs.* 2.7 mm, P=0.01; right coronary arteries: 3.7 *vs.* 3.4 mm, P=0.001) and number of evaluable coronary arteries (11.0 *vs.* 8.0, P<0.001) were larger in nitroglycerin group.

Conclusions: Nitroglycerin administration prior to CCTA has positive effects on diagnostic performance of CT-FFR.

Keywords: Coronary artery disease (CAD); computed tomography angiography (CTA); fractional flow reserve (FFR); myocardial ischemia; nitroglycerin

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Introduction

Computed tomography (CT) derived fractional flow reserve (FFR, CT-FFR) is a non-invasive technique utilized for evaluating hemodynamic alterations in coronary artery disease (CAD) (1,2). Previous clinical trials have confirmed the efficacy of CT-FFR in identifying ischemia (3), and recent guidelines recommend its use in patients with acute chest pain who have coronary artery stenosis of 40% to 90% based on coronary CT-angiography (CCTA) (4). One of the most critical steps in calculating CT-FFR is to construct an accurate coronary artery anatomy model based on high-quality CCTA images, especially to accurately identify luminal boundaries and stenoses (5). Previous evidence shows that sublingual nitroglycerin improves the image quality and stenosis assessment of CCTA (6). And routine nitroglycerin administration before CCTA scan has been recommended in the 2016 guidelines (7).

Theoretically, nitroglycerin-induced vasodilation may affect CT-FFR values and diagnostic performance (8). Previous studies have reported that CT-FFR values increased in both post-lesion and distal vessel after nitroglycerin administration (9), and CT-FFR diagnostic specificity increased (10). However, it has not been systematically proven. Further clarification regarding nitroglycerin's impact on CT-FFR is essential for its future clinical translation and widespread use. Therefore, we designed a single-center retrospective study to investigate the effect of preprocedural nitroglycerin administration on the calculation and diagnostic performance of machine learning CT-FFR, with invasive FFR as the reference standard. We present this article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1212/rc).

Methods

Study design and participants

From January 2019 to December 2019, we enrolled 107 consecutive patients with suspected CAD from Fuwai Hospital, who underwent CCTA with nitroglycerin administration priorly. We retrospectively matched 107 patients undergoing CCTA without nitroglycerin administration from the electronic medical database between January 2016 and December 2016 from Fuwai Hospital. Inclusion and exclusion criteria were the same for both groups. Inclusion criteria were (I) aged ≥18 years; and (II) at least one coronary artery lesion with 50–90% diameter stenosis according to CCTA; and (III) perform invasive coronary angiography (ICA) and FFR within one month. Exclusion criteria were as follows: (I) previous coronary revascularization; (II) previous myocardial infarction; (III) implanted cardiac devices; (IV) complex congenital heart disease; and (V) cardiomyopathies and valvular heart disease. Matching accounted for age, and body mass index (match tolerance =1.05). A total of 214 patients with 237 target lesion vessels, which contained coronary artery lesions with 50% to 90% diameter stenosis, were finally included in the study.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College/National Center for Cardiovascular Diseases (No. 2018-0074). 107 consecutive participants provided written informed consent, and for the retrospectively matched participants, written informed consent was waived.

CCTA acquisition

CCTA examination was performed by second- or third-generation dual-source CT scanners (Somatom Definition Flash/Force, Siemens Healthcare, Forchheim, Germany), and the images were collected according to the cardiovascular CT protocol (7). Nitroglycerin 0.5 mg (11) (0.5 mg per press; Nitroglycerin Aerosol, Bencao Pharmacy, China) sublingually has been administered 5 minutes before the scan since January 2017. Before that, nitroglycerin was not routinely used for patient in our clinical center. Beta-blockers were administered if a patient had a heart rate ≥75 beats/min. Electrocardiogram-triggered prospective step-and-shoot acquisition was performed at 35–75% of R-R interval. The scan parameters were as follows: detector collimation, 64×2×0.6/96×2×0.6 mm; gantry rotation time, 280/250 ms; tube voltage, 100 kV (<60 kg) or 120 kV

(>60 kg); tube current, automatic tube current modulation. All image data sets were reconstructed with a slice thickness of 0.75 mm and an increment of 0.5 mm. Reconstructions were performed according to dual-source CT scanner specifications. Iterative reconstruction (SAFIRE® with a strength level of 3) and medium smooth kernel (I26f) were used for Definition Flash data sets. Iterative reconstruction (Admire® with a strength level of 3) and medium soft convolution kernel (Bv40) were used for Force data sets. A triple phase contrast protocol was used as follows: the first injection of 60–65 mL iodinated contrast agent (Ultravist 370 mgI/mL, Bayer Schering Pharma; Germany) with flow rate 4–6 mL/s, followed by 30 mL contrast agent/saline mixture (mixing ratio 3:7) (4–6 mL/s), followed by injection of 30 mL saline (4 mL/s).

CCTA image assessments and analysis

All data were sent to a dedicated workstation (Syngo.Via, Frontier, Siemens, Germany). Image quality was assessed by two independent observers with five-year experience in a double-blind manner.

Coronary segments were evaluated using an 18-segment coronary model (12). For semiquantitative image quality assessment, we used a four-scale: 4 = excellent, no visible artifacts; 3 = good, artifacts exist in less than 20% of coronary segments; 2 = acceptable, artifacts exist in 20–40% of segments; and 1 = poor, artifacts exist in more than 40% of coronary segments. When two observers disagreed, they decided through mutual consultation. In order to obtain quantitative image quality assessment, two circular regions of interest with ≥1.5 cm^2 were placed within the aortic root and subcutaneous adipose tissue of the chest to calculate the signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR). Image noise was measured using the standard deviation of pixel values. Averaged values measured by two observers were used to minimize bias. The SNR and CNR were calculated using the following formulas: SNR = mean aortic root attenuation value/image noise, CNR = (mean aortic root attenuation value – mean subcutaneous adipose tissue attenuation value)/image noise.

The diameter of coronary artery was measured using the centerline-derived multiplanar reconstruction images. The luminal diameters of the left main artery (LM), left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), and right coronary artery (RCA) were measured within 1 cm from the ostia while avoiding plaques. The average measurement values of the two observers were also obtained to minimize bias. Coronary artery calcification (CAC) scores were assessed by one experienced radiologist with 3 years of clinical experience using the Agatston method in non-enhanced scanning (13).

CT-FFR analysis

CT-FFR was performed on dedicated software cFFR 3.2.2 (Syngo.Via, Frontier, Siemens, Germany) (not for clinical use) by a radiologist with five-year experience who was blinded to FFR values. CT-FFR values were calculated based on CCTA images as follows: (I) three-dimensional anatomical model construction of coronary trees; (II) centerline definition; (III) boundary condition; (IV) stenosis definition; and (V) CT-FFR calculation (14). The CT-FFR value of the target lesion vessel was obtained at 1–2 cm distal to the stenosis. CT-FFR ≤0.80 was considered lesion-specific ischemia. The number of evaluable coronary artery arteries including branches extracted for anatomical model construction during the CT-FFR calculation procedure was recorded.

ICA and FFR measurements

ICA was performed and FFR was determined according to standard practice (15) by senior cardiovascular physicians. Target coronary stenosis severity was categorized into 0 (0%), 1 (1–24%), 2 (25–49%), 3 (50–69%), or 4 (70–99%).

FFR was performed on target lesion vessels deemed clinically indicated for evaluation except the lesions with diameter stenosis >90%. A pressure-sensor-tipped guidewire (St Jude Medical, Minneapolis, Minn, USA) was advanced 1–2 cm distal to the stenosis. Intravenous adenosine (140–180 µg/kg/min) was administered to obtain maximal coronary hyperemia. Then slowly retract the guide wire and record the FFR value during the whole process. FFR ≤0.80 was considered hemodynamically significant. And the difference between CT-FFR and FFR was calculated as follows: ΔFFR=CT-FFR value – FFR value.

Statistical analysis

MedCalc version 18.2 (MedCalc Software) and SPSS version 22.0 (IBM SPSS Statistics, USA) were used for statistical analysis. Quantitative variables were expressed as mean ± standard deviation (SD) and compared using one-way analysis of variance (ANOVA) test if normally distributed (tested by Kolmogorov-Smirnov method), otherwise the median and interquartile range were used and compared by Kruskal-Wallis H test. Categorical variables were represented by numbers and percentages. The χ^2 test or Fisher exact test, as appropriate, were used for comparison of categorical variables and rates. Spearman correlation and Bland-Altman analysis were conducted for the correlation and consistency of CT-FFR and FFR. The correlation coefficient values were interpreted as follows: 0.00 to 0.09 considered negligible, 0.10 to 0.39 considered weak, 0.40 to 0.69 considered moderate, 0.70 to 0.89 considered strong, and 0.90 to 1.00 considered very strong (16). The accuracy and performance characteristics [sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC)] of CT-FFR in identifying ischemia on per-vessel and per-patient levels were assessed in nitroglycerin and non-nitroglycerin groups, with FFR as the reference standard. Receiver operating characteristics curves of CT-FFR in the two groups were performed and compared by DeLong method (17). Statistical significance was assumed at a P<0.05 (two-tailed).

Results

Baseline characteristic

Initially, 197 consecutive patients with clinically suspected CAD in 2019 were screened. Seventy-two patients with coronary stenosis <50% (n=64) or >90% (n=8) based on CCTA were excluded, not suitable for FFR. Eighteen patients were further excluded because of failure of FFR operation (n=18). Meanwhile, 224 patients undergoing CCTA with 50–90% stenosis from January to December 2016 were retrospectively collected from electronic database. Forty-six patients were excluded due to the history of previous coronary intervention or coronary bypass surgery (n=12), previous myocardial infarction (n=10), implanted cardiac devices (n=5), cardiomyopathies and valvular heart disease (n=11), or missed FFR measurements (n=8).

After patient matching, a total of 214 patients with 237 target lesion vessels were enrolled in this study, including 120 vessels in nitroglycerin group and 117 vessels in non-nitroglycerin groups (Flow chart displays in *Figure 1*). Of these patients, 155 (72.4%) were male and 59 (27.6%) were female, with an average age of (56.1±8.9) years. There was no statistically significant difference in the age, sex ratio, high-risk factors of CAD between nitroglycerin and non-nitroglycerin groups. Additionally, no significant differences were found in dual-source CT specifications and their heart rates during CCTA scans between two groups (*Table 1*).

Most (95.4%, 226/237) of the target lesion vessels had stenosis degree ≥50%, and particularly (38.0%, 90/237) of them was flow-limiting (FFR ≤0.8). The Baseline characteristics of the patients and target lesion vessels are listed in *Table 1*. *Figure 2* list two patients in nitroglycerin and non-nitroglycerin groups.

The correlation and difference of CT-FFR and FFR in nitroglycerin and non-nitroglycerin groups

The Spearman correlation between CT-FFR and FFR was moderate (r=0.606, P<0.001) in all target vessels. Subgroup analysis showed that the nitroglycerin group had a higher correlation coefficient (r=0.664, P<0.001) compared to the non-nitroglycerin group (r=0.548, P<0.001) (*Figure 3*).

Bland-Altman plots was used for the agreement of CT-FFR and FFR values (*Figure 4*). The biases of CT-FFR and FFR were as follows: nitroglycerin group [mean difference =−0.01, 95% limits of agreement (LOA): −0.25 to 0.24], and non-nitroglycerin group (mean difference =−0.05, 95% LoA: −0.32 to 0.21). And accordingly, significantly larger bias of CT-FFR was observed in non-nitroglycerin group (−0.05±0.13) than nitroglycerin group (−0.01±0.12) (P=0.007). It was also noticed the underestimation of CT-FFR compared to FFR in the two groups.

The effect of nitroglycerin on CT-FFR diagnostic performance

In total, the diagnostic sensitivity, specificity, PPV, NPV, accuracy, and AUC of CT-FFR identifying lesion-specific ischemia were 78.6%, 70.9%, 67.5%, 81.2%, 74.3%, 0.78 on a per-vessel level and 80.8%, 71.3%, 70.8%, 81.2%, 75.7%, 0.77 on a per-patient level, respectively.

The vessel-based and patient-based diagnostic performance of CT-FFR identifying ischemia in nitroglycerin and non-nitroglycerin groups is displayed in *Table 2* and *Figure 5*. On a per-vessel level, the accuracy of CT-FFR in nitroglycerin group [80.0% (71.7–86.7%), 96/120] was significantly higher than non-nitroglycerin group [68.4% (59.1–76.7%), 80/117] (P=0.041). While no major difference was found in the sensitivity [80.7% (68.1–90.0%) *vs.* 76.1% (61.2–87.4%), P=0.37], specificity [79.4% (67.3–88.5%) *vs.* 63.3% (51.1–74.5%), P=0.38], PPV [78.0% (68.2–85.4%) *vs.* 57.4% (48.8–65.6%), P=0.68], NPV [82.0% (72.5–88.7%) *vs.* 80.4% (70.3–87.6%), P=0.22], and AUC [0.82 (0.74–0.89)

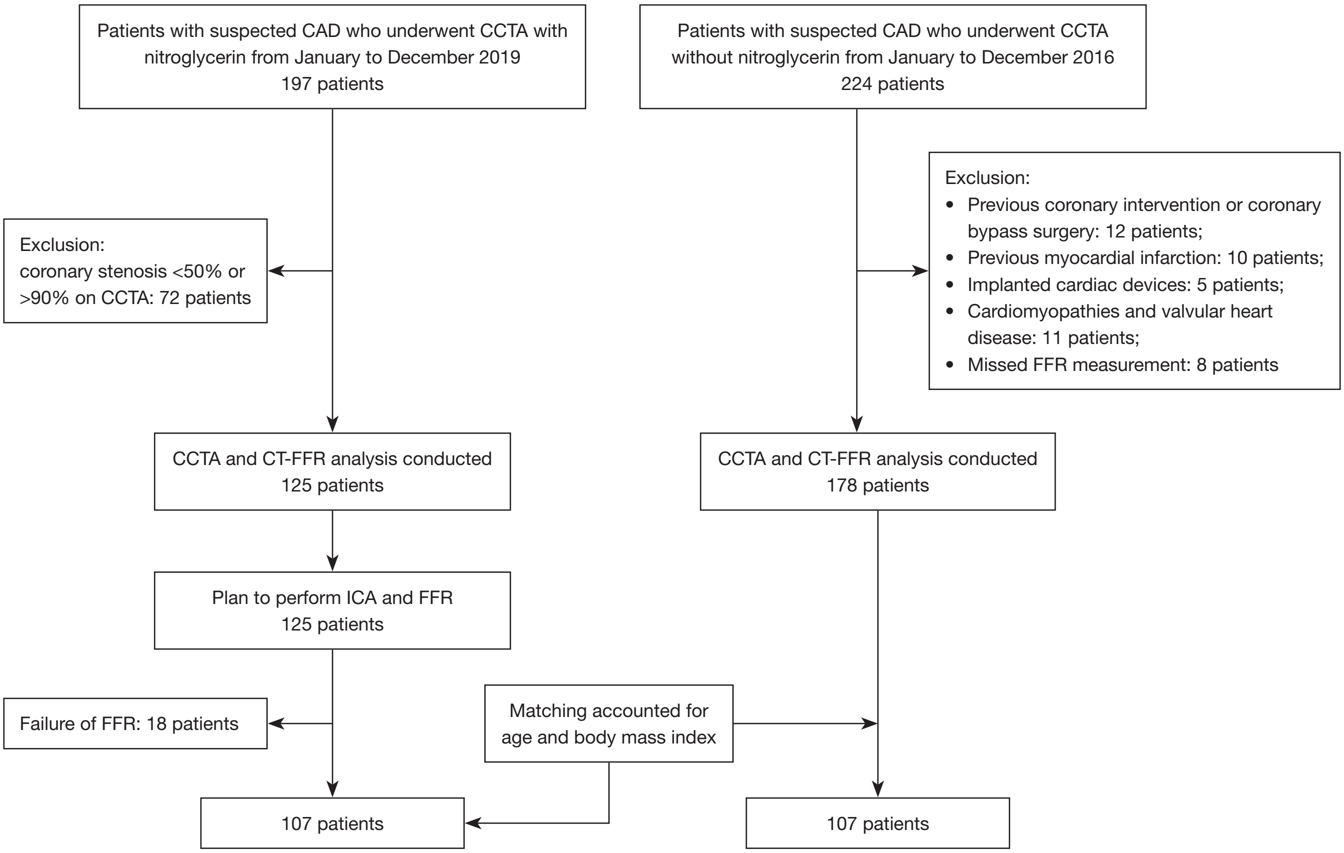

Figure 1 Flow chart of the study. CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CT-FFR, computed tomography derived fractional flow reserve; FFR, fractional flow reserve; ICA, invasive coronary angiography.

vs. 0.74 (0.65–0.83), P=0.13] of CT-FFR between the two groups. On a per-patient basis, nitroglycerin administration before CCTA significantly elevated the accuracy [83.2% (74.7–89.7%) *vs.* 68.2% (58.5–76.9%), P=0.01], specificity [82.7% (69.7–91.8%) *vs.* 61.9% (48.8–73.9%), P=0.01], PPV [83.6% (73.6–90.4%) *vs.* 58.6% (50.0–66.9%), P=0.004], and AUC [0.83 (0.75–0.89) *vs.* 0.71 (0.61–0.79), P=0.03] of CT-FFR. And the two groups possessed similar sensitivity [83.6% (71.2–92.2%) *vs.* 77.3% (62.2–88.5%), P=0.60] and NPV [82.7% (72.2–89.8%) *vs.* 79.6% (68.6–87.4%), P=0.85].

Assessments of image quality and coronary evaluability in nitroglycerin and non-nitroglycerin groups

The evaluation of image quality and coronary artery were conducted and compared in nitroglycerin and non-nitroglycerin groups (*Table 3*). The semiquantitative image quality assessment was mainly focused on the artifacts causing by various factors. Semiquantitative image quality comparison showed a higher score in the nitroglycerin group than non-nitroglycerin group (3.7±0.5 *vs.* 3.5±0.7, P=0.02). However, there was no significant difference found in quantitative assessment parameters (SNR: 27.6±22.0 *vs.* 28.9±30.5, P=0.72; CNR: 34.0±22.4 *vs.* 35.4±37.1, P=0.73) of CCTA image quality between the two groups.

For coronary artery evaluation, it included the assessment about the vessel diameter and the number of evaluable vessels including branches extracted for anatomical model construction during the CT-FFR calculation procedure. The vessel diameters of four main coronary arteries in nitroglycerin group were higher than the non-nitroglycerin group (LMs: 4.3±0.8 *vs.* 3.8±0.8 mm, P<0.001; LADs: 3.1±0.6 *vs.* 2.9±0.6 mm, P=0.001; LCXs: 2.9±0.7 *vs.* 2.7±0.6 mm, P=0.012; RCAs: 3.7±0.7 *vs.* 3.4±0.7 mm, P=0.001). Meanwhile, the number of evaluable coronary arteries was also significantly larger in nitroglycerin group than the non-nitroglycerin group [median:11.0 (interquartile range:

Table 1 Baseline characteristics of the patients and target vessels

Parameters	Full	Nitroglycerin	Non-nitroglycerin	P
No. of patients	214	107	107	
Age (years)	56.1±8.9	56.1±9.5	56.0±8.4	0.91
Male	155 (72.4)	83 (77.6)	72 (67.3)	0.18
Body mass index (kg/m^2)	25.7±3.2	26.0±3.2	25.4±3.2	0.08
Hypertension	125 (58.4)	65 (60.7)	60 (56.1)	0.57
Hyperlipidemia	184 (86.0)	92 (86.0)	92 (86.0)	>0.99
Diabetes	68 (31.8)	39 (36.4)	29 (27.1)	0.18
Smoker	110 (51.4)	53 (49.5)	57 (53.3)	0.68
Heart rate (beats/min)	66.7±11.4	67.8±11.6	65.8±11.2	0.12
CACs	48.3 (0, 188.5)	69.0 (10.5, 277.7)	38.0 (0, 138.0)	0.24
DSCT				0.48
Somatom definition flash	81 (37.9)	38 (35.5)	43 (40.2)	
Somatom force	133 (62.1)	69 (64.5)	64 (59.8)	
No. of vessels	237	120	117	
Target lesion vessel				0.20
Left anterior descending artery	173 (73.0)	87 (72.5)	86 (73.5)	
Left circumflex artery	30 (12.7)	19 (15.8)	11 (9.4)	
Right coronary artery	34 (14.3)	14 (11.7)	20 (17.1)	
Stenosis grade by ICA				0.71
0 (0%)	4 (1.7)	1 (0.8)	3 (2.6)	
1 (1–24%)	7 (2.9)	3 (2.5)	4 (3.4)	
2 (25–49%)	0 (0)	0 (0)	0 (0)	
3 (50–69%)	59 (24.9)	31 (25.9)	28 (23.9)	
4 (70–99%)	167 (70.5)	85 (70.8)	82 (70.1)	
FFR				0.26
<0.75	45 (19.0)	24 (20.0)	21 (17.9)	
0.75–0.8	45 (19.0)	20 (16.7)	25 (21.4)	
>0.8	147 (62.0)	76 (63.3)	71 (60.7)	

The continuous variables are expressed as mean ± standard deviation or median (interquartile range), and the categorical variables are expressed as number (percentage). CACs, coronary artery calcium score; DSCT, dual source computed tomography; ICA, invasive coronary angiography; FFR, fractional flow reserve.

9.0,14.0) *vs.* 8.0 (7.0, 10.0), P<0.001].

In addition, there was a weak correlation between CT-FFR and vessel diameter in LMs (r=0.203, P=0.003), LADs (r=0.274, P<0.001), LCXs (r=0.210, P=0.002), and RCAs (r=0.187, P=0.006) (as detailed in Appendix 1, Figure S1). However, no significant association was found between the semiquantitative image quality and CT-FFR (P=0.19) (as detailed in Appendix 1, Figure S2).

Discussion

In this comparative, retrospective study, we investigated the

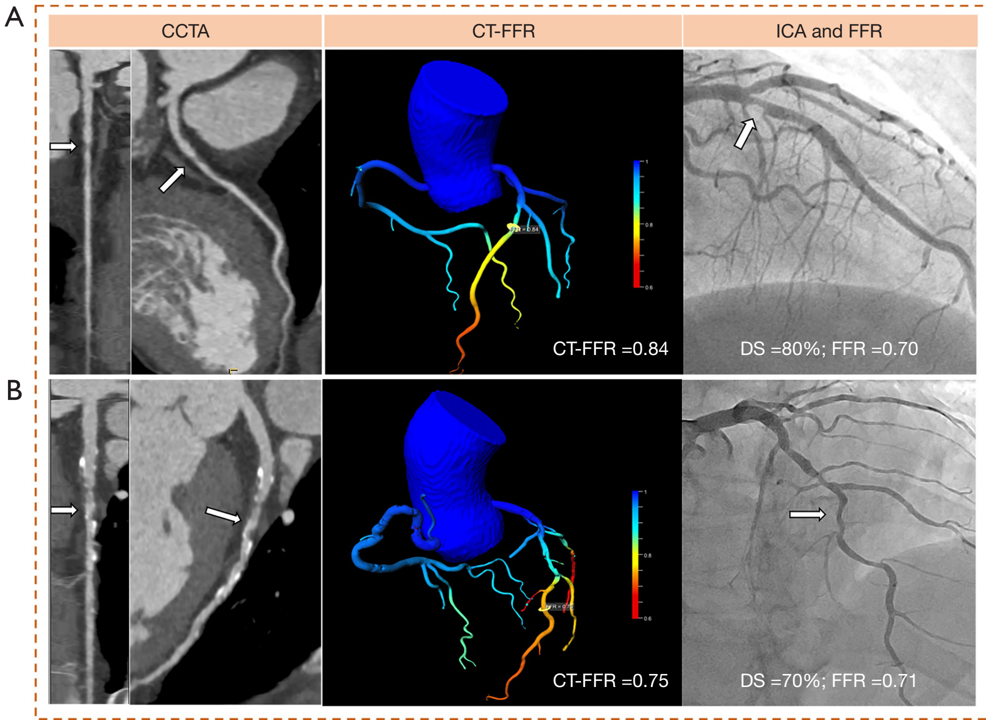

Figure 2 Representative cases in nitroglycerin and non-nitroglycerin groups. (A) A 50-year-old female with a mixed plaque causing 80% diameter stenosis in the middle LAD (arrows). No sublingual nitroglycerin was used prior to CCTA. The luminal diameter of LAD is 3.1 mm based on CCTA, and 7 coronary arteries including branches were derived for anatomical model construction of CT-FFR. The FFR and CT-FFR values distal to the lesion are 0.70 and 0.84. (B) A 70-year-old female with multiple mixed plaques causing 70% stenosis in middle LAD (arrows). Sublingual nitroglycerin was administered before CCTA examination. The luminal diameter of LAD is 3.6 mm on CCTA images, and 17 coronary arteries were derived for coronary model. Distal FFR and CT-FFR values of the lesion are 0.71 and 0.75. CCTA, coronary computed tomography angiography; CT-FFR, computed tomography derived fractional flow reserve; ICA, invasive coronary angiography; FFR, fractional flow reserve; DS, diameter stenosis; LAD, left anterior descending artery.

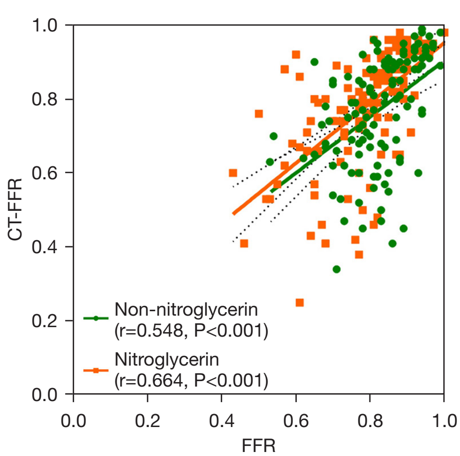

Figure 3 The correlation of CT-FFR and FFR in nitroglycerin and non-nitroglycerin groups. CT-FFR, computed tomography derived fractional flow reserve; FFR, fractional flow reserve.

impact of nitroglycerin administration on machine-learning based CT-FFR for identifying ischemia, with invasive FFR as the reference standard. The major findings of this study can be summarized as follows: (I) sublingual nitroglycerin administration before the CCTA scan improved diagnostic performance and reduced bias of CT-FFR. (II) A higher semiquantitative image score was obtained with nitroglycerin administration. (III) A larger vessel diameter and a higher number of evaluable coronary arteries were observed in the nitroglycerin group.

Currently, there have been limited studies investigating the effect of nitroglycerin on CT-FFR (9,10,18-20). Gao *et al.* (9) found the use of sublingual nitroglycerin was associated with increased post-stenosis and vessel distal CT-FFR values. Interestingly, Holmes *et al.* (19) found that different dosages of nitroglycerin (0.4 *vs.* 0.8 mg) did not alter CT-FFR values. However, none of the above studies

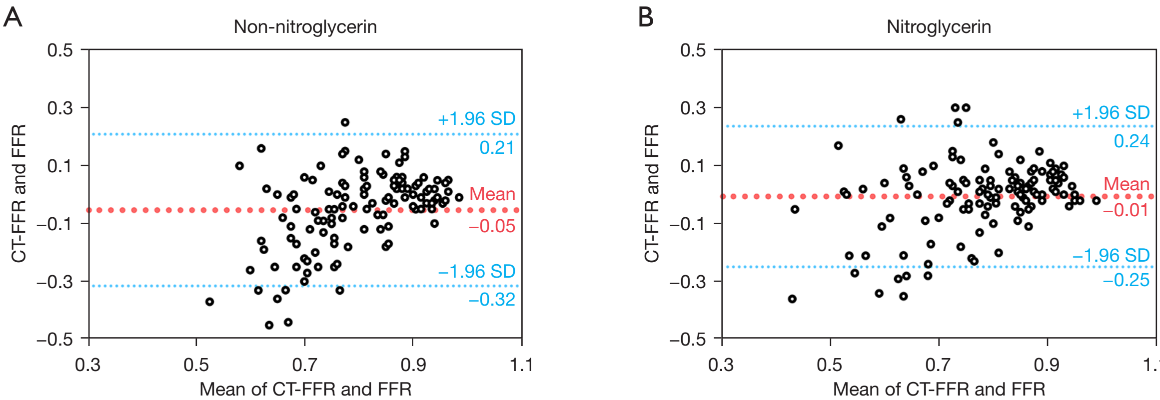

Figure 4 Bland-Altman plots of CT-FFR with FFR in vessels. The Bland-Altman plots in non-nitroglycerin (A) and nitroglycerin (B) groups. The bias of CT-FFR and FFR values was −0.01 (95% LoA: −0.25 to 0.24) in nitroglycerin group and −0.05 (95% LoA: −0.32 to 0.21) in non-nitroglycerin group. CT-FFR, computed tomography derived fractional flow reserve; FFR, fractional flow reserve; LoA, limits of agreement.

validated the diagnostic accuracy of CT-FFR compared with the gold standard invasive FFR. Leipsic *et al.* (10) got a preliminary result that the diagnostic specificity of CT-FFR increased when using nitroglycerin, while there remained some interference effects of confounding factors such as patients' baseline characteristics on the results. In this study, we included two clusters of patients with similar baseline characteristics, so that the interference of potential baseline confounding factors could be excluded when exploring the effect of nitroglycerin. In addition, due to CT-FFR diagnostic performance varies for different degrees of stenosis (21), especially inadequate diagnostic accuracy within the "gray zone" range of 0.7–0.8 (3,22). Consequently, it is crucial to ensure that there are no disparities in the vessel stenosis grade and hemodynamic condition as determined by FFR between the two groups, thereby avoiding potential interference from inherent lesion characteristics. In addition to excluding potential bias in patient selection, differences in CT specifications and scan parameters may also affect CT-FFR calculations (23). In this study, there were no significant differences between the two groups in dual-source CT specifications and scan parameters.

Our study manifested that sublingual nitroglycerin administration was related to smaller bias of CT-FFR values than non-sublingual nitroglycerin group, in relation to the gold standard FFR. Higher diagnostic performance of CT-FFR was observed in nitroglycerin group on both per-vessel and per-patient levels, especially the improved specificity. Diagnosis of ischemia by CT-FFR is a dichotomous judgment with a single cut-off value of ≤0.8 (3,24). When the FFR value is around 0.8, a small measurement deviation of CT-FFR may lead to a change in diagnosis. It is also one of the reasons for the poor diagnostic accuracy of CT-FFR in "gray zone" (22,25). That is theoretically inevitable. But from a technical point of view, based on our study, the nitroglycerin administration may improve the diagnostic performance of CT-FFR in "gray zone" lesions by improving the accurate measurement. Further systematic study is necessary to confirm it. In addition, all the participants in this study came from real clinical practice, and CT-FFR showed 74.5% (68.8–79.7%) diagnostic accuracy. To some extent, it reflects the performance of CT-FFR in real world, which is consistent with a recent meta-analysis (3).

Precise CT-FFR measurement relies on accurate coronary artery model derived from high-quality CCTA image. There are many factors influencing CCTA image quality, including preprocedural preparation and patients' condition, which may influence the CT-FFR calculation (10,20,26). It's essential to understand the impact of nitroglycerin administration on CCTA image quality and coronary artery evaluability before interpreting the result above. Previous studies have reached different conclusions on the effects of nitroglycerin on subject and objective CCTA image quality (6,27). This study showed that nitroglycerin administration resulted in higher semiquantitative score (subjective quality), which meant less artifacts and more evaluable coronary segments. Besides, the lumen attenuation is also the basis of segmentation and quantization of CT technology (28). Xu *et al.* (20) indicated

Table 2 Diagnostic performance of CT-FFR in nitroglycerin and non-nitroglycerin groups

Analysis basis	Results				Diagnostic parameters											
					Sensitivity		Specificity		PPV		NPV		Accuracy		AUC	
	TP	TN	FP	FN	% (95% CI)	P	% (95% CI)	P	% (95% CI)	P	% (95% CI)	P	% (95% CI)	P	% (95% CI)	P
Per-vessel level						0.37		0.38		0.68		0.22		0.041*		0.13
All	81	95	39	22	78.6 (69.5–86.1)		70.9 (62.4–78.4)		67.5 (61.0–73.4)		81.2 (74.6–86.4)		74.3 (68.2–79.7)		0.78 (0.73–0.84)	
Non-nitroglycerin	35	45	26	11	76.1 (61.2–87.4)		63.3 (51.1–74.5)		57.4 (48.8–65.6)		80.4 (70.3–87.6)		68.4 (59.1–76.7)		0.74 (0.65–0.83)	
Nitroglycerin	46	50	13	11	80.7 (68.1–90.0)		79.4 (67.3–88.5)		78.0 (68.2–85.4)		82.0 (72.5–88.7)		80.0 (71.7–86.7)		0.82 (0.74–0.89)	
Per-patient level						0.60		0.01*		0.004*		0.85		0.01*		0.03*
All	80	82	33	19	80.8 (71.7–88.0)		71.3 (62.1–79.4)		70.8 (64.1–76.7)		81.2 (73.9–86.8)		75.7 (69.4–81.3)		0.77 (0.70–0.82)	
Non-nitroglycerin	34	39	24	10	77.3 (62.2–88.5)		61.9 (48.8–73.9)		58.6 (50.0–66.9)		79.6 (68.6–87.4)		68.2 (58.5–76.9)		0.71 (0.61–0.79)	
Nitroglycerin	46	43	9	9	83.6 (71.2–92.2)		82.7 (69.7–91.8)		83.6 (73.6–90.4)		82.7 (72.2–89.8)		83.2 (74.7–89.7)		0.83 (0.75–0.89)	

Data are presented as percentage (95% CI) or value (95% CI). *, statistical significance. CT-FFR, computed tomography derived fractional flow reserve; TP, true positive; TN, true negative; FP, false positive; FN, false negative; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; CI, confidence interval.

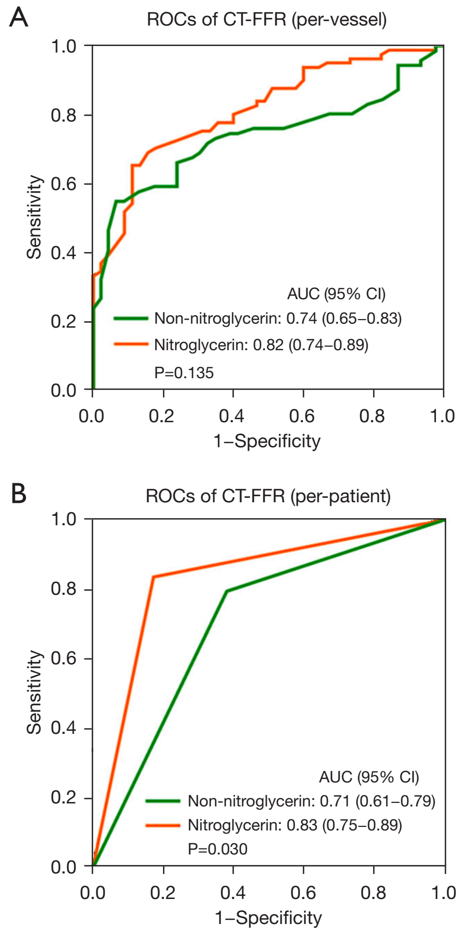

Figure 5 ROC curves of CT-FFR in identifying lesion-specific ischemia in nitroglycerin and non-nitroglycerin groups. (A) Vessel-based and (B) patient-based analysis revealed the superior performance of CT-FFR in nitroglycerin group, with significant difference on the per-patient level. ROC, receiver operating characteristic; CT-FFR, computed tomography derived fractional flow reserve; AUC, area under the curve; CI, confidence interval.

that intracoronary enhancement degree of 300–400 HU could be beneficial to accurate CT-FFR analysis. While no significant correlation was observed between the objective quantitative parameters of image quality and nitroglycerin in this study.

Additionally, improved coronary evaluability by nitroglycerin was also revealed in this study. Sublingual nitroglycerin administration resulted in significant coronary artery dilation and increased numbers of evaluable coronary arteries, consistent with previous studies (29-31). Klass *et al.* (31), and Okada *et al.* (29) even found a larger vessel diameter increase in the distal and peripheral segments

Table 3 Assessment of image quality and coronary artery in nitroglycerin and non-nitroglycerin groups

Parameters	Full (n=214)	Nitroglycerin (n=107)	Non-nitroglycerin (n=107)	P
Semiquantitative image quality	3.6±0.7	3.7±0.5	3.5±0.7	0.02*
Quantitative image quality				
Attenuation of aortic root (HU)	406.5±76.5	400.0±67.5	413.9±84.6	0.59
SNR	28.2±26.4	27.6±22.0	28.9±30.5	0.72
CNR	34.7±30.4	34.0±22.4	35.4±37.1	0.73
SD	16.6±4.2	16.3±3.3	16.8±4.9	0.33
Coronary artery diameter (mm)				
Left main artery	4.1±0.9	4.3±0.8	3.8±0.8	<0.001*
Left anterior descending artery	3.0±0.6	3.1±0.6	2.9±0.6	0.001*
Left circumflex artery	2.8±0.7	2.9±0.7	2.7±0.6	0.01*
Right coronary artery	3.5±0.7	3.7±0.7	3.4±0.7	0.001*
Number of evaluable coronary arteries	10.0 (8.0, 12.0)	11.0 (9.0, 14.0)	8.0 (7.0, 10.0)	<0.001*

Data are presented as mean ± standard deviation or median (interquartile range). *, statistical significance. HU, Hounsfield unit; SNR, signal-to-noise ratio; CNR, contrast-to-noise ratio; SD, standard deviation.

compared to the proximal ones. The nitroglycerin-induced vasodilation and improved coronary evaluability including distal segments and branches, greatly promote CT-FFR to simulate the maximum hyperemia flow of coronary (10). And CT-FFR measurement is closer to the real FFR value. In summary, nitroglycerin administration improved image quality and coronary evaluability, resulting in more accurate CT-FFR calculations. Sublingual nitroglycerin administration should be suggested in routine CT-FFR practice. Our study adds original evidence to standardize CT-FFR operation.

This study still has some limitations. Firstly, this is a retrospective study. Although there were no differences in baseline characteristics or scan parameters between the two groups, there may be some unknown confounding factors also present. Secondly, the study was conducted in a single clinic center and focused on the machine-learning CT-FFR. It's still unknown whether the results can be generalized to the real world and FFR with computational fluid hemodynamics. A multicenter prospective randomized study is necessary to verify the results, involving different CT scanner, scanning protocol, CT-FFR algorithms, and hospitals with different medical levels.

Conclusions

In conclusion, this study reveals that the sublingual nitroglycerin administration prior to CCTA has a positive effect on the diagnostic performance of CT-FFR, due to significant vessel dilation and improved evaluability of coronary arteries.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1212/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1212/coif). The 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). The study was approved by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College/National Center for Cardiovascular Diseases (No. 2018-0074). 107 consecutive participants provided written informed consent, and for the retrospectively matched participants, written informed consent was waived.

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