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ORIGINAL PAPER

Assessment of factors associated with measurability of fractional flow reserve derived from coronary computed tomography angiography in type 2 diabetic patients with intermediate coronary artery stenosis

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Abstract

Recently, fractional flow reserve (FFR) derived from coronary computed tomography angiography (CCTA) (FFR_{CT}) has been developed. However, FFR_{CT} cannot be calculated for all patients from CCTA datasets. The purpose of the present study, therefore, was to evaluate the predictors that results in cases being inappropriate for FFR_{CT} processing. This study was a sub-analysis of the TRACT trial, from which 50 patients were divided into 2 groups according to FFR_{CT} measurability (measurable [group M] or not measurable [group N]) using CCTA examination at baseline. Thirty-nine (78%) patients comprised group M and 11 (22%) comprised group N. Heart rate at CCTA examination (72 beats/min vs. 63 beats/min; $p = 0.007$) and Agatston score (665 vs. 33; $p = 0.002$) in group N were significantly higher than those in group M. Multivariate logistic regression analyses revealed that heart rate at CCTA examination (OR 1.348 [95% CI 1.167–1.556]; $p < 0.001$) and Agatston score (OR 1.002 [95% CI 1.000–1.003]; $p = 0.004$) were significant, independent factors associated with non-measurability of FFR_{CT}. The frequency of poor image quality was highest in patients with heart rate > 65 beats/min and Agatston score > 400 ($p < 0.0001$). In conclusions, high heart rate at the time of CCTA examination and higher Agatston score were associated with poor image quality that resulted in cases being inappropriate for FFR_{CT} processing. Heart rate control at CCTA examination is necessary to acquire good-quality images required for computing FFR_{CT}.

Keywords Agatston score · Coronary atherosclerosis · Coronary computed tomography angiography · Fractional flow reserve · Heart rate

Introduction

Fractional flow reserve (FFR) has been shown to be a useful tool for detecting lesion-specific myocardial ischemia and assessing the functional significance of coronary artery disease (CAD) [1]. In addition, invasive FFR-guided decision-making regarding percutaneous coronary intervention improves event-free survival compared with coronary angiography-guided decisions alone [2]. Thus, FFR measurement during invasive coronary angiography is considered the gold standard for functional ischemia as well as decisions pertaining to lesion-specific coronary revascularization [3].

The use of coronary computed tomography angiography (CCTA) for noninvasive anatomical detection or exclusion of CAD is increasing [4, 5]. However, stenosis severity evaluated using CCTA overestimates the severity of atherosclerotic obstructions [6], particularly in the presence of calcification [7]. Thus, the diagnostic performance of stenosis severity evaluated using CCTA is hampered by

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beam-hardening and blooming artifacts due to the presence of calcified plaque [5, 8, 9] and does not correlate with functional ischemia assessed using invasive FFR [10].

Recently, a method using computational fluid dynamics to calculate coronary blood flow, pressure, and FFR using routinely acquired CCTA datasets (FFR_{CT}) has been developed [11, 12]. Although FFR_{CT} provides high diagnostic performance compared with stenosis assessment using CCTA for the diagnosis of ischemic lesions of intermediate stenosis severity [12–14], FFR_{CT} cannot be computed for all patients. The purpose of the present study, therefore, was to evaluate the predictors of poor image quality that results in rejection for FFR_{CT}.

Methods

Study design

The present study was a sub-analysis of the Treatment of Alogliptin on Coronary Atherosclerosis Evaluated by Computed Tomography-Based Fractional Flow Reserve (TRACT) trial which was a prospective, multicenter, observational trial to evaluate the effects of 48-week alogliptin treatment on coronary atherosclerosis using CCTA in patients with type 2 diabetes. Details of the study design have been reported previously [15]. Inclusion criteria of the TRACT trial were as follows: (1) type 2 diabetes mellitus; (2) intermediate coronary artery stenosis as evaluated by CCTA (diameter stenosis < 70%); (3) judged by physician to administer alopgliptin; (4) age more than 20 years. Exclusion criteria of the TRACT trial were as follows: (1) required to perform percutaneous coronary intervention (PCI); (2) acute coronary syndrome; (3) past history of myocardial infarction; (4) past history of PCI or coronary artery bypass grafting; (5) complex congenital heart disease; (6) body mass index > 35 kg/m^2; (7) past history of heart failure, (8) past history of ketoacidosis or diabetic coma; (9) hepatic disorder; (10) renal dysfunction; (11) severe infection, before or after operation, or serious trauma; (12) allergy to alogliptin; (13) pregnant or lactating women; or (14) ineligible in the opinion of the investigator [15]. Necessity of coronary angiograpy or PCI was judged by the physicians based on the results of CCTA examination as well as symptoms of the subjects. A total of 51 patients were enrolled in the TRACT trial. One patient was lost to follow-up. Therefore, for the present study, a total of 50 patients from the TRACT trial were divided into 2 groups according to FFR_{CT} measurability (measurable [group M] or non-measurable [group N]) using CCTA examination at baseline. The determination of FFR_{CT} measurability was judged at core laboratory based on image quality of CCTA. Baseline patient characteristics, risk factor control, Agatston score, and volumetric analysis in the 3 coronary arteries were compared between the 2 groups. Significant factors related to poor image quality that resulted in cases being inappropriate for FFR_{CT} processing were identified.

The TRACT trial was conducted in accordance with the Declaration of Helsinki and with the approval of the institutional ethical committees of the 3 participating institutions. The TRACT trial has been registered with the University Hospital Medical Information Network (UMIN; UMIN ID: 000015381). Written informed consent was obtained from each patient enrolled in the study.

CCTA examination and image acquisition

The details of the CCTA examination have been described previously [15]. Each center performed CCTAs in accordance with the Society of Cardiovascular Computed Tomography (SCCT) guidelines on performance of CCTA using a variety of different computed tomography scanner platforms [16]. CCTA was performed using 64 detector row CT scans. Sublingual nitrates were administered before scanning in all patients. If necessary, beta-blockers were orally or intravenously administered targeting a heart rate of < 60 beats/min. During acquisition, 80–100 mL of contrast material was injected intravenously, followed by a saline flush. Helical or axial scan data were obtained with retrospective or prospective electrocardiographic gating, respectively. Image acquisition was prescribed to include the coronary arteries, left ventricle, and proximal ascending aorta.

CCTA core laboratory analysis

CCTA images recorded on DVD were transmitted to the core laboratory (HeartFlow Inc., Redwood City, CA, USA) for computational analysis of FFR_{CT}. The determination of FFR_{CT} measurability was judged at core laboratory based on image quality of CCTA. Image quality was scored using a quantitative scale reflecting the combined effect of CT artifacts on lumen interpretability for all vessel segments > 2.0 mm in diameter taking into consideration the length of vessel affected by artifacts or un-interpretability [17]. A pre-defined image quality score was used to select cases appropriate for FFR_{CT} analysis. Computation of FFR_{CT} was performed in a blinded manner. The FFR_{CT} was calculated after semi-automated segmentation of the coronary arteries and left ventricular mass [11]. Briefly, three-dimensional blood flow simulations in the coronary vasculature were performed using proprietary software with quantitative image quality analysis, image segmentation, and physiological modelling using computational fluid dynamics. Coronary blood flow and pressure were calculated under conditions simulating maximal hyperemia. The FFR_{CT} was obtained by dividing the mean pressure distal to the coronary stenosis by

the mean aortic pressure. The results provided a complete spatial distribution of FFR_{CT} in the coronary arteries.

Quantitative analyses of the coronary artery were performed at another independent core laboratory (Cardiocore Japan, Tokyo, Japan) in accordance with the SCCT guidelines on CCTA interpretation [16]. Details of core laboratory analyses have been reported previously [15]. Briefly, quantitative atheroma analyses were performed by independent, experienced observers who were blinded to the FFR_{CT} results and clinical data. All reconstructed datasets were transferred to an offline workstation to perform quantitative coronary atheroma volume analysis using dedicated software with a semi-automated three-dimensional contour detection algorithm (QAngioCT, vs. 2.1 RC4, MEDIS™, Leiden, The Netherlands) [18]. The reconstructed image was set at a window width of 740 and a window level of 220 for quantitative coronary artery assessment. All 3 coronary vessels > 2.0 mm in diameter were analyzed (QAngioCT, vs. 2.1 RC4, MEDIS™) according to an AHA 17 segment model. All plaques were characterized based on Hounsfield units (HU) into low-attenuation (< 30 HU), intermediate-attenuation (30–150 HU), and calcified plaque (> 150 HU) [19], and the volume of each component was measured.

Laboratory data

Hemoglobin A1c levels were measured using high-performance liquid chromatography (Adams A1c HA-8160, Arkray Inc., Kyoto, Japan), and plasma glucose levels were measured using the glucose oxidation method (chemical reagent and Glucose AUTO and STAT GA-1160 analyzer; Arkray Inc.). Serum levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, and high-density lipoprotein cholesterol were measured using standard enzymatic methods (AU2700, Beckman Coulter, CA, USA) and commercially available kits (Kyowa Medex, Tokyo, Japan). Serum levels of high-sensitivity C-reactive protein (hs-CRP) were measured at a central clinical laboratory (SRL, Inc., Tokyo, Japan).

Statistical analysis

Statistical analysis was performed using StatView, version 5.0 (SAS Institute, Cary, NC, USA). Results are expressed as mean ± standard deviation or median (range). Differences in continuous variables between the two groups were compared using the unpaired *t* test when the variables had a normal distribution and the Mann–Whitney *U* test when they did not. Categorical variables between the two groups were compared using the chi-squared test or Fisher's exact test. Univariate and multivariate logistic regression analyses were performed to assess the factors related to poor image quality that resulted in cases being inappropriate for FFR_{CT} processing. Statistical significance was set at $p < 0.05$.

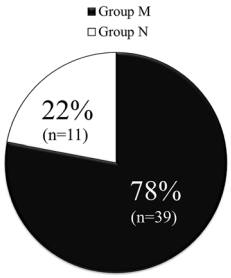

Fig. 1 Number of patients comprising the measurable (group M) and not measurable (group N) for FFR_{CT}. Thirty-nine (78%) patients comprised group M and 11 (22%) comprised group N

Table 1 Baseline characteristics of the subjects

	Group M (n = 39)	Group N (n = 11)	p value
Age (years)	71 ± 9	76 ± 6	0.08
Males	21 (54)	7 (64)	0.73
Body mass index (kg/m^2)	24.7 ± 3.4	24.6 ± 4.5	0.95
Hypertension	33 (85)	7 (64)	0.2
Dyslipidemia	24 (62)	9 (82)	0.29
Smoking	8 (21)	1 (9)	0.66
Statin	17 (44)	3 (27)	0.49
Ezetimibe	5 (13)	2 (18)	0.64
Antiplatelet	8 (21)	5 (45)	0.1
ACE inhibitor or ARB	17 (44)	6 (55)	0.52
Beta-blocker	8 (21)	2 (18)	> 0.99
Hypoglycemic medications			
DPP-4 inhibitor	21 (54)	7 (64)	0.73
Sulfonylurea	11 (28)	1 (9)	0.26
Biguanide	10 (26)	2 (18)	> 0.99
α-Glucosidase inhibitor	4 (10)	0 (0)	0.56
Glinide	2 (5)	1 (9)	0.53
Thiazolidine	1 (3)	1 (9)	0.4
Insulin	0 (0)	1 (9)	0.22

Data are expressed as mean ± SD or n (%)

ACE angiotensin-converting enzyme, *ARB* angiotensin-receptor blocker, *DPP*-4 dipeptidyl peptidase-4

Results

Thirty-nine patients (78%) comprised group M and 11 (22%) comprised group N (Fig. 1). Baseline characteristics of the patients are summarized in Table 1. There were no significant differences in male sex, frequency of hypertension and dyslipidemia, or medications between the two groups. Although mean age was slightly higher in group N, the difference was not statistically significant.

Risk factor control at CCTA examination and volumetric analysis data in the three coronary arteries are shown in Table 2. Serum lipid levels, markers of glucose metabolism, or hs-CRP did not differ between the two groups. However, heart rate at CCTA examination (72 ± 5 beats/min vs. 63 ± 10 beats/min; p = 0.007) and Agatston score (665 vs. 33; p = 0.002) in group N were significantly higher than those in group M. Furthermore, in group N, lumen volume was significantly smaller (433.7 ± 297.8 mm^3 vs. 608.6 ± 405.9 mm^3; p = 0.03) and percentage atheroma volume (PAV) was significantly greater (58.4 ± 9.0% vs. 52.9 ± 10.9%; p = 0.02) than those in group M.

Data from all 11 cases in group N are presented in Table 3. Motion artifact was the most significant cause of poor image quality that resulted in cases being inappropriate for FFR_{CT} processing; this was observed in 10 subjects. Blooming artifact was apparent in 4 cases and sub-optimal contrast timing was observed in 1 case.

Univariate logistic regression analyses revealed that heart rate at CCTA examination (OR 1.163 [95% CI 1.082–1.250]; p < 0.001), Agatston score (OR 1.001 [95% CI 1.000–1.002]; p < 0.001), lumen volume (OR 0.998 [95% CI 0.997–1.000]; p = 0.04), and PAV (OR 1.063 [95% CI 1.011–1.118]; p = 0.02) were significant, independent factors associated with inappropriate for FFR_{CT} processing. Multivariate logistic regression analysis revealed that heart rate at CCTA examination (OR 1.348 [95% CI 1.167–1.556]; p < 0.001), Agatston score (OR 1.002 [95% CI 1.000–1.003]; p = 0.004), and PAV (OR 1.157 [95% CI 1.036–1.291]; p = 0.009) were significant, independent factors associated with inappropriate for FFR_{CT} processing (Table 4). The frequency of poor image quality was highest in patients with heart rate > 65 beats/min and Agatston score > 400 (p < 0.0001). Few patients with heart rates ≤ 65 beats/min, irrespective of Agatston score, had poor image quality that resulted in cases being inappropriate for FFR_{CT} processing (Fig. 2).

Table 3 Case presentations that were inappropriate for FFR_{CT} processing

Case no.	Heart rate (bpm)	Agatston score	Reasons for inappropriate for FFR_{CT} processing
1	60	286	Sub-optimal contrast timing
18	71	900	Motion and blooming
21	71	479	Motion
23	77	1368	Motion
29	78	No data	Motion
33	64	1927	Motion
35	74	420	Motion and blooming
36	72	800	Motion and blooming
38	77	22	Motion
42	73	531	Motion and blooming
44	73	3757	Motion

FFR fractional flow reserve, *bpm* beats/min

Table 2 Risk factor control at CCTA examination and volumetric analysis in the three coronary arteries

	Group M (n = 39)	Group N (n = 11)	p value
Total cholesterol (mg/dL)	199 ± 30	197 ± 21	0.89
LDL cholesterol (mg/dL)	120 ± 31	121 ± 20	0.9
Triglycerides (mg/dL)	146 (36–442)	188 (51–330)	0.33
HDL cholesterol (mg/dL)	63 ± 15	57 ± 13	0.22
hs-CRP (ng/mL)	683 (65–8970)	405 (152–3050)	0.83
PG (mg/dL)	140 ± 46	150 ± 42	0.51
HbA1c (%)	7.1 ± 0.8	7.2 ± 0.7	0.71
SBP (mmHg)	139 ± 19	143 ± 25	0.58
DBP (mmHg)	83 ± 13	83 ± 17	0.95
HR (beats/min)	63 ± 10	72 ± 5	0.007
Agatston score	33 (0–3426)	665 (22–3757)	0.002
Vessel volume (mm^3)	1267.2 ± 728.7	1008.3 ± 631.0	0.09
Total atheroma volume (mm^3)	658.5 ± 390.5	574.6 ± 363.3	0.3
Lumen volume (mm^3)	608.6 ± 405.9	433.7 ± 297.8	0.03
PAV (%)	52.9 ± 10.9	58.4 ± 9.0	0.02

Data are expressed as mean ± SD or median (range)

CCTA coronary computed tomography angiography, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *hs-CRP* high-sensitivity C-reactive protein, *PG* plasma glucose, *HbA1c* hemoglobin A1c, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *PAV* percentage atheroma volume

Table 4 Univariate and multivariate logistic regression analyses to predict poor image quality that resulted in cases being inappropriate for FFR_{CT} processing

	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
Heart rate	1.163	1.082–1.250	< 0.001	1.348	1.167–1.556	< 0.001
Agatston score	1.001	1.000–1.002	< 0.001	1.002	1.000–1.003	0.004
Lumen volume	0.998	0.997–1.000	0.04	0.999	0.997–1.001	0.37
PAV	1.063	1.011–1.118	0.02	1.157	1.036–1.291	0.009

FFR fractional flow reserve, *OR* odds ratio, *CI* confidence interval, *PAV* percentage atheroma volume

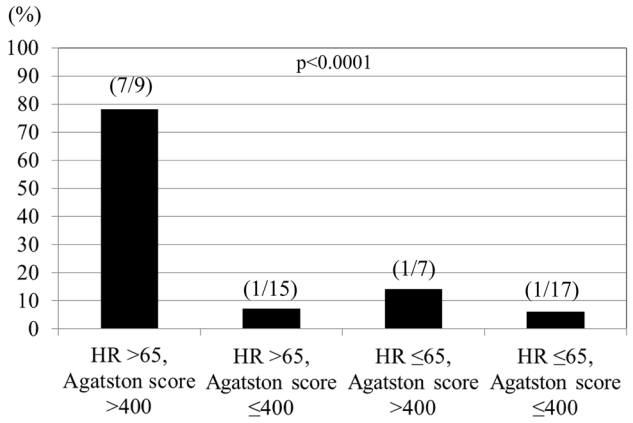

Fig. 2 The frequency of poor image quality that resulted in cases being inappropriate for FFR_{CT} processing according to heart rate (HR) and Agatston score. The frequency of poor image quality that resulted in cases being inappropriate for FFR_{CT} processing was highest in patients with HR > 65 beats/min and Agatston score > 400 ($p < 0.0001$)

Discussion

The major findings of the present study are as follows: FFR_{CT} could be measured in 78% of patients who underwent CCTA examination; high heart rate at CCTA examination, Agatston score, and PAV were significant factors associated with inappropriate for FFR_{CT} processing; and the frequency of poor image quality that resulted in cases being inappropriate for FFR_{CT} processing was highest in patients with heart rates > 65 beats/min and Agatston score > 400.

Noninvasive anatomical assessment using CCTA yields high diagnostic performance for the detection or exclusion of CAD [4, 5]. However, CCTA has only modest accuracy in the evaluation of stenosis severity, particularly in the presence of calcification. The presence of calcified coronary lesions often leads to overestimation of stenosis severity due to blooming and beam-hardening artifacts obscuring the vessel lumen [7]. Ong et al. reported that 64 detector row CCTA could accurately detect the presence of significant coronary stenosis with mild calcification, but became less reliable when the Agatston score exceeded 142 [9]. Budoff et al. reported that the diagnostic sensitivity of 64 detector row CCTA to detect coronary artery stenosis did not change; however, specificity was reduced in cases with Agatston score > 400 [8]. Thus, CCTA artifacts can be caused by an enlargement of the calcified plaque [5, 8, 9]. FFR_{CT} provides high diagnostic performance for the diagnosis of ischemia in intermediate stenotic lesions [12, 14]. It has been reported that the diagnostic accuracy and specificity of FFR_{CT} were significantly higher than for stenosis assessment using CCTA in patients with a high Agatston score [20]. These findings were in accordance with those observed in the Determination of Fractional Flow Reserve by Anatomic CTA (DeFACTO) trial [13]. Thus, although high Agatston score was a significant factor associated with poor image quality resulting in cases being inappropriate for FFR_{CT} processing in this study, FFR_{CT} is less affected by calcification than stenosis severity on CCTA [21].

The high diagnostic performance of FFR_{CT} in the setting of coronary calcification is a result of the FFR_{CT} computation process. Luminal dimensions are assessed along the entire length of each vessel using segmentation methods that correct for calcium blooming and physiological models. Thus, segmental artifacts may not significantly influence the overall FFR_{CT} computation result [20]. In contrast, stenosis assessment using CCTA relies on identification of segmental reductions in lumen caliber, and thus, the presence of calcification may have greater impact on interpretation, and in turn, compromise diagnostic performance. This is supported by the findings of a sub-study from the Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve (DISCOVER-FLOW) trial, which demonstrated that even at lower levels of CCTA image quality, FFR_{CT} continued to provide significant diagnostic improvement compared with CCTA [22]. In this study, lumen volume was a significant factor related to poor image quality that resulted in cases being inappropriate for FFR_{CT} processing in univariate analysis, but not in multivariate analysis. On the contrary, PAV was a significant factor associated with inappropriate for FFR_{CT} processing in both univariate and multivariate analyses. Thus, FFR_{CT} may be less affected by luminal dimensions than PAV.

Another important result of this study was that poor heart rate control was a significant factor associated with inappropriate for FFR_{CT} processing. FFR_{CT} has been shown to be less sensitive to image quality than CCTA alone [22]. However, significant CT imaging artifacts may impair the diagnostic performance of FFR_{CT}. In fact, in the DeFACTO and Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT) trials, 11% and 13% of the patients, respectively, were not eligible for FFR_{CT} computation because of low image quality [21]. Low image quality can result from common CCTA artifacts, including motion/misalignment, high image noise, excessive calcium blooming, or low contrast-to-noise, which alone or in combination significantly compromised image quality [14]. Patient preparation for CCTA has been emphasized in the SCCT guidelines to help ensure satisfactory image quality and achieve optimal diagnostic accuracy [16]. Beta-blocker and sublingual nitroglycerin administration are recommended [16, 23, 24]. Similar to CCTA, the diagnostic performance of FFR_{CT} has been shown to improve with the adherence to best practices guidelines for image acquisition, particularly regarding heart rate control and the use of pre-scan nitroglycerin [25]. These data constitute evidence that guidelines-based CT acquisition and performance should be adhered to for optimal image quality and high acceptance rate for FFR_{CT}.

Study limitations

This study had several limitations. First, it was a post hoc sub-analysis of the non-randomized TRACT trial. Second, we included only diabetic patients with intermediate coronary artery stenosis; patients who required PCI were excluded. Thus, the results of this study cannot be generalized to all cardiac patients. Third, CT images were acquired using scanners from multiple manufacturers (Siemens Healthcare, GE Healthcare, and Toshiba). However, no differences were observed in performance of FFR_{CT} based on CT scanner manufacturer in the previous study [25]. Fourth, invasive FFR value was not measured in all subjects. Therefore we could not compare FFR_{CT} to invasive FFR value. Finally, the present study was limited by the relatively small number of patients. Further studies with larger sample sizes will be necessary to confirm our results and draw more definitive conclusions.

Conclusions

High heart rate at the time of CCTA examination and higher Agatston score were significant factors associated with poor image quality that resulted in cases being inappropriate for FFR_{CT} processing. Heart rate control at CCTA examination in accordance with SCCT guidelines is necessary to acquire good-quality images required for computing FFR_{CT}.

Compliance with ethical standards

Conflict of interest We declare that all authors have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in this study.

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