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ORIGINAL PAPER

Feasibility and diagnostic performance of fractional flow reserve measurement derived from coronary computed tomography angiography in real clinical practice

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Abstract Non-invasive fractional flow reserve measured by coronary computed tomography angiography (FFR_{CT}) has demonstrated a high diagnostic accuracy for detecting coronary artery disease (CAD) in selected patients in prior clinical trials. However, feasibility of FFR_{CT} in unselected population have not been fully evaluated. Among 60 consecutive patients who had suspected significant CAD by coronary computed tomography angiography (CCTA) and were planned to undergo invasive coronary angiography, 48 patients were enrolled in this study comparing FFR_{CT} with invasive fractional flow reserve (FFR) without any exclusion criteria for the quality of CCTA image. FFR_{CT} was measured in a blinded fashion by an independent core laboratory. FFR_{CT} value was evaluable in 43 out of 48 (89.6%) patients with high prevalence of severe calcification in CCTA images [calcium score (CS) >400: 40%, and CS > 1000: 19%). Per-vessel FFR_{CT} value showed good correlation with invasive FFR value (Spearman's rank correlation = 0.69, $P < 0.001$). The area under the receiver operator characteristics curve (AUC) of FFR_{CT} was 0.87. Per-vessel accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 68.6, 92.9, 52.4, 56.5, and 91.7%, respectively. Even in eight patients (13 vessels) with extremely severely calcified lesions (CS > 1000), per-vessel FFR_{CT} value showed a diagnostic performance similar to that in patients with CS ≤ 1000 (Spearman's rank correlation = 0.81, $P < 0.001$). FFR_{CT} could be measured in the majority of consecutive patients who had suspected significant CAD by CCTA in real clinical practice and demonstrated good diagnostic performance for detecting hemodynamically significant CAD even in patients with extremely severe calcified vessels.

Keywords
Fractional flow reserve-computed tomography angiography · Fractional flow reserve · Coronary computed tomography angiography

Abbreviations

AUC	Area under the receiver operator characteristics curve
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CS	Calcium score
FFR	Fractional flow reserve
FFR_{CT}	Fractional flow reserve measured by coronary computed tomography angiography
NPV	Negative predictive value
PCI	Percutaneous coronary intervention
PPV	Positive predictive value

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Introduction

Coronary computed tomography angiography (CCTA) is a noninvasive diagnostic testing for detecting coronary artery disease (CAD) and is used with increasing frequency in real clinical practice [1]. CCTA images provide anatomic information of CAD such as location and severity of stenosis, disease burden and characteristics of atherosclerotic plaque [2–5]. However, despite its high sensitivity for detecting CAD, CCTA often overestimate the coronary stenosis severity, leading to increased referral of patients without obstructive CAD to invasive coronary angiography [6–8].

Fractional flow reserve measured by computed tomography angiography (FFR_{CT}) is a novel technology developed to noninvasively identify functional myocardial ischemia. Previous clinical studies showed the excellent diagnostic accuracy of FFR_{CT} in detecting CAD with invasive fractional flow reserve (FFR) as the reference standard [9–11]. However, the previous studies mostly enrolled selected patients with CCTA images suitable for FFR_{CT} measurement. The feasibility and diagnostic performance of FFR_{CT} have not been yet fully evaluated in unselected population in real clinical practice.

The aim of the current study, therefore, is to evaluate the feasibility and diagnostic performance of FFR_{CT} in consecutive patients who had suspected significant CAD by CCTA in real clinical practice, where a large population of patients might have inadequate CCTA image quality due to image artifacts and severe calcification.

Methods

Study design

The REAL-FFRCT (Real-world fEAsibiLity of noninvasive Fractional Flow Reserve derived from coronary Computed Tomography angiography) study was a prospective cross-sectional study comparing FFR_{CT} with invasive FFR, intended to enroll consecutive patients who had suspected significant CAD by CCTA and undergoing invasive coronary angiography within 60 days after acquisition of CCTA in real clinical practice. Suspected significant CAD by CCTA was defined as all significant coronary stenosis in CCTA and clinically suspected CAD with non-significant coronary stenosis in CCTA. There were no exclusion criteria for the quality of CCTA images influenced by various artifacts, such as coronary motion, opacification of coronary artery lumen by calcified plaque, and misregistration. Exclusion criteria about patients clinical characteristics were the same as in the prior FFR_{CT} clinical studies [9, 12, 13]; We excluded those patients with characteristics unsuitable for CCTA and invasive FFR, including contraindication to beta blockers, nitrates, or adenosine advanced bradycardia, severe tachyarrhythmia, severe hypotension, severe asthma, chronic obstructive pulmonary disease, congenital heart disease, previous artificial device implantation such as pacemaker or prosthetic valve, previous percutaneous coronary intervention (PCI) with coronary stents, previous coronary artery bypass grafting, serum creatinine level greater than 1.5 mg/dL with or without hemodialysis, allergy to iodine contrast, pregnant state, acute coronary syndrome requiring emergency coronary angiography, recent myocardial infarction within 30 days before CCTA or coronary angiography, life expectancy less than 2 years, and inability to adhere to the study procedures.

The current study protocol was approved by the ethics committee in Kyoto University Hospital and written informed consent was obtained from all the patients.

CCTA acquisition and analysis

CCTA was performed using single-source CT scanners with 320-slice detector rows (Aquilion ONE: Toshiba Medical systems, Tokyo, Japan) in Kyoto university hospital and double-source CT scanners with 64-slice detector rows (SOMATOM Definition: Siemens Healthcare, Erlangen, Germany) in Morishita private CT clinic, in accordance with the recommendations of the Society of Cardiovascular Computed Tomography guidelines [14, 15].

In Kyoto university hospital, CT scans were performed with bolus tracking method during end-inspiratory breath-hold after injection of iodine contrast media at 24.5 mgI/kg/sec and prospective electrocardiographic-gating was used for scan data. Scanning parameters included volume scan (without patient table sliding), 275 milliseconds gantry rotation time, 120 kVp (100 kVp for extremely low body weight below 40 kg and 135 kVp for extremely high body weight above 100 kg) tube voltage and 350–800 mA tube current. CCTA images were reconstructed in 0.5-mm axial slices with area-detector CT, using reconstruction kernel of FC04 with iterative reconstruction of AIDR 3D in ZIOSTATION 2.

In Morishita private clinic, CT scans were performed with timing bolus method during end-expiratory breath-hold after injection of iodine contrast media at 25.9 mgI/kg/sec and retrospective electrocardiographic-gating was used for scan data. Scanning parameters included heart-rate-dependent pitch (0.20, 0.22 and 0.26), 330 milliseconds gantry rotation time, 120 kVp (100 kVp for extremely low body weight below 40 kg or no calcification) tube voltage and 360–436 mA tube current. CCTA images were reconstructed in 0.75-mm axial slices with dual source CT, using reconstruction kernel of B36 HeartView medium ASA without iterative reconstruction in Aquarius iNtuition Edition version 4.4.7.

Nitroglycerin (0.3 mg) were administered to get coronary vasodilation using a sublingual tablet in Kyoto university or sublingual spray in Morhishita private clinic, with or without intravenous beta-blocker (landiolol) targeting a heart rate of <60 beats/min in both facilities. Coronary calcium scores were assessed according to the Agatston method [16], based on CT images which were scanned with prospective electrocardiographic-gating and reconstructed in 3 mm axial slices.

Experienced local physicians assessed luminal diameter stenosis in each vessels of reference vessel diameter ≥2 mm. Coronary stenosis was categorized as 0, 25, 50, 75, 90, 99, or 100 % to AHA classification [17]. Significant stenosis was defined as lumen reduction ≥75 %.

FFR_{CT} measurement

CCTA images were transmitted to the core laboratory (HeartFlow Inc, Redwood City, California) and FFR_{CT} value was measured in a fashion blinded to the results of invasive FFR value. Coronary blood flow and pressure were computed under conditions simulating maximal hyperemia using the most recent generation of FFR_{CT} analysis software. The results of FFR_{CT} measurement were provided throughout 3-dimensional coronary artery trees. FFR_{CT} value at the target vessel was defined as the FFR_{CT} value at the most distal location of each target vessel that could be measured in the core laboratory. Cut-off value of FFR_{CT} for hemodynamically significant stenosis was defined as ≤0.80.

Invasive FFR measurement

Invasive FFR measurement was performed using 6 French guiding catheter and a 0.014-inch pressure wire (Certus G7, Certus G8 or Aeris G8, St. Jude Medical Inc. and PrimeWire PRESTIGE PLUS, Volcano Inc.) by experienced interventional cardiologists, who are blinded to the results of FFR_{CT} measurement. Maximum hyperemia was induced by intravenous adenosine 150 μg/kg/min after crossing of the pressure wire through the target vessel. Invasive FFR value was defined as minimum FFR value within 3 min after adenosine infusion. FFR measurement was performed in all vessels with significant coronary stenosis detected by CCTA and other vessels with ≥50 % coronary stenosis detected by invasive coronary angiography excluding angiographically 99 % stenosis with delayed coronary flow and totally occluded lesions. Invasive FFR value ≤0.80 was regarded as hemodynamically significant stenosis [18–21].

Endpoints and statistical analysis

The main outcome measure of the current study was the per-vessel correlation between FFR_{CT} and invasive FFR, which was assessed by Spearman's correlation coefficients and Bland–Altman analysis. Diagnostic performance of FFR_{CT} was assessed by the area under the receiver operator characteristics curve (AUC) of FFR_{CT} for detecting hemodynamically significant coronary stenosis (invasive FFR ≤0.80 as a reference standard) on per-vessel basis. In AUC analysis, we adopted FFR_{CT} value rounded off to one decimal place. Diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also evaluated with diagnostic cutoff value for hemodynamically significant CAD defined as FFR_{CT} value ≤0.80 and invasive FFR value ≤0.80.

Pretest likelihood of CAD was evaluated with updated Diamond-Forrester model from typical chest pain, age and gender [22, 23]. After completing all the FFR_{CT} and invasive FFR measurements, all statistical analyses were performed at the study center (Kyoto University Hospital) independently from the FFR_{CT} core laboratory. All statistical analyses were performed using JMP 10 (SAS Institute Inc, Cary, NC) software. All the statistical analyses were two-tailed. P values <0.05 were considered statistically significant.

Results

Study population

Between May 2014 and June 2015, CCTA was performed in 450 patients for suspected CAD in Kyoto university hospital or Morishita private CT clinic. After excluding 109 patients with clinical exclusion criteria and 281 patients without significant coronary artery stenosis detected by CCTA, 60 patients who were planned to undergo invasive coronary angiography were eligible for the current study (Fig. 1). After further exclusion of 9 patients who did not undergo invasive FFR measurement, and 3 patients who refused to participate in the current study, the current study population consisted of 48 consecutive patients who underwent invasive FFR measurements for the target vessels within 60 days after CCTA.

Baseline characteristics reflected the real clinical practice, including high prevalence of advanced age (70.8 ± 7.8 years of age), hypertension, dyslipidemia, and diabetes mellitus (Table 1). Median score for the pretest likelihood for CAD in this population was 55.5 and 39 patients (81.3 %) had intermediate score (20–80 %) (Table 1).

Regarding CCTA acquisition characteristics, median heart rate was 65 bpm under control by beta-blocker use (Table 2). Nitrates were administered in all patients. Among 48 patients whose CCTA images were transmitted to the FFR_{CT} core laboratory, FFR_{CT} measurement in the core laboratory was feasible in 43 (89.6 %) patients. FFR_{CT} value

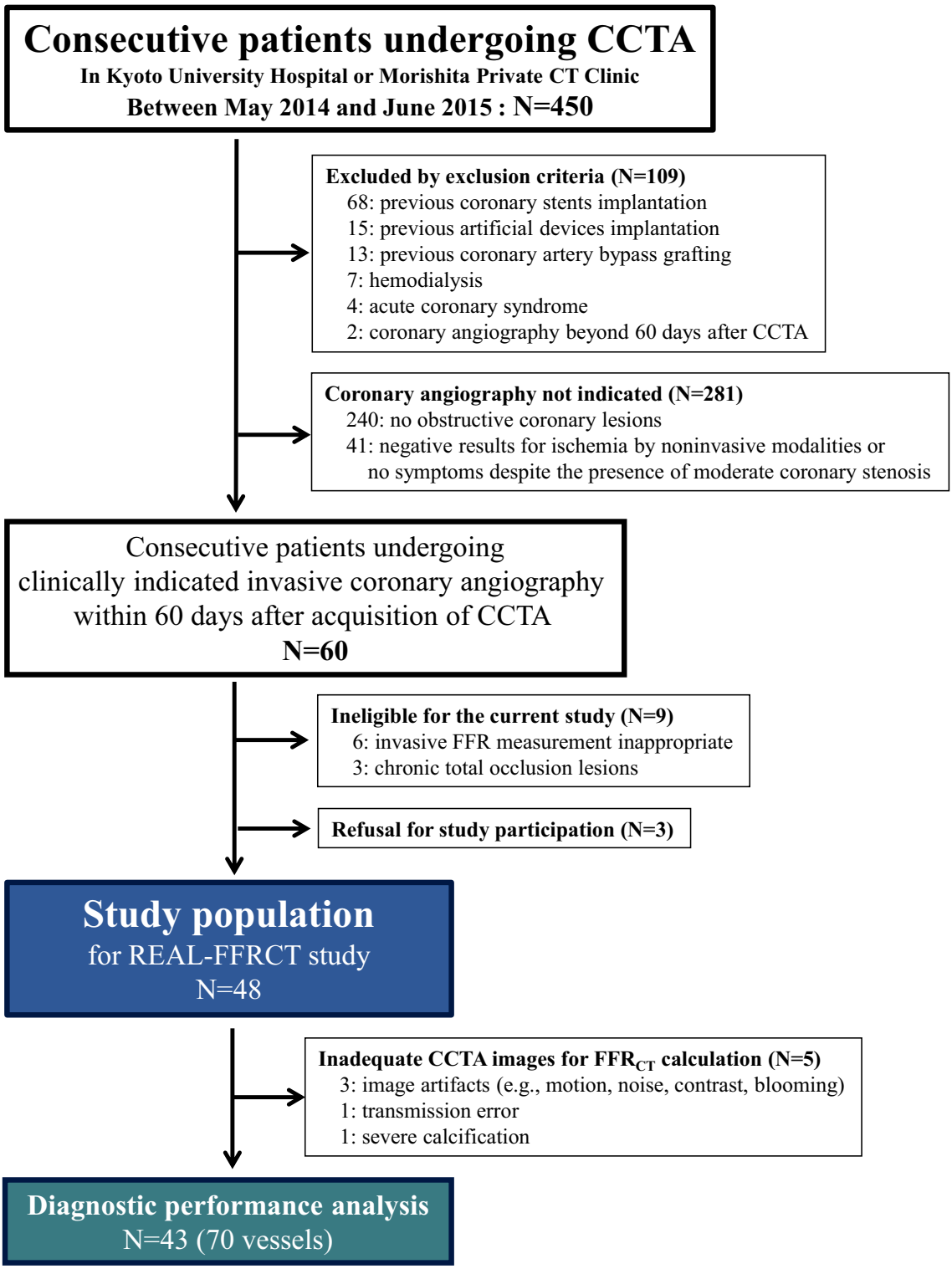

Fig. 1 Study flow chart. *CCTA* coronary computed tomography angiography, *FFR* fractional flow reserve, FFR_{CT} fractional flow reserve derived from computed tomography angiography

could not be measured in three patients with image artifacts (e.g., motion, noise, contrast, blooming), one with transmission error to the core laboratory and one with severe calcification (Fig. 1 and Supplementary Fig. 1).

In the 43 patients with evaluable FFR_{CT} value, CCTA images revealed high prevalence of severe calcification [median calcium score (CS): 285 [114–778], CS > 400: 40 %, and CS > 1000: 19 %] (Table 3). Significant coronary

Table 1 Baseline characteristics

Patient characteristics	All N = 48
Age (years)	70.8 ± 7.8
Male	31 (65 %)
Height	164.2 (156.2–168.4)
Weight	61.4 (53.3–71.9)
Body mass index (kg/m^2)	23.5 (21.5–25.9)
Hypertension	26 (54 %)
Dyslipidemia	35 (73 %)
Diabetes mellitus	17 (35 %)
Current smoke	5 (10 %)
Typical chest pain	13 (27 %)
Pretest likelihood of obstructive CAD	54.4 (43.7–69.2)
Intermediate (20–80 %) pretest likelihood	39 (81 %)

Categorical data are presented as number of patients (prevalence). Continuous variables are presented as mean ± SD or median and interquartile range on the basis of their distributions

CAD coronary artery disease

Table 2 Coronary CT angiography acquisition characteristics

Coronary CT angiography acquisition characteristics	N = 48
Heart rate (beats/min)	64 (59–72)
Systolic blood pressure (mmHg)	132 (123–144)
Diastolic blood pressure (mmHg)	71 (65–79)
Administration of beta blockers before examination	32 (67 %)
Administration of nitrates before examination	48 (100 %)
Sublingual tablets	33 (69 %)
Sublingual spray	15 (31 %)

Categorical data are presented as number of patients (prevalence). Continuous variables are presented as median and interquartile range

CT computed tomography

stenosis (≥75 %) by CCTA image was present in 41 patients (95.3 %) with 52 vessels (74.3 %). The other 18 vessels (25.7 %) had 50 % stenosis detected by CCTA.

The mean interval from CCTA acquisition to invasive FFR measurement was 23.6 ± 15.5 days.

Diagnostic performance of FFR_{CT} in the entire cohort

All the results for FFR_{CT} and invasive FFR in the individual cases were presented in Supplementary Table 1. FFR_{CT} showed a good correlation with invasive FFR in per-vessel analysis (Spearman's rank correlation = 0.69, P < 0.001) (Fig. 2). The extreme outliers of the difference ≥0.30 between FFR_{CT} and invasive FFR values were found in 2 patients with 2 vessels (Fig. 3). FFR_{CT} value ≤0.80 was present in 35 patients (81.4 %) with 46 vessels (65.7 %), while invasive FFR value ≤0.80 was present in 21 patients (48.8 %) with 28 vessels (40.0 %) (Table 3).

There were 2 vessels of false negative and 20 vessels of false positive by FFR_{CT} (Fig. 2). Regarding the two false negative vessels, both invasive FFR values were the grey zone of 0.75–0.80 and both FFR_{CT} values were just above 0.80 (Supplementary Table 1). The mean differences between FFR_{CT} and invasive FFR in 20 false positive vessels were 0.13 ± 0.09 (range: 0.01–0.45). The AUC of FFR_{CT} (per-vessel) was 0.87 (95 % confidence interval 0.79–0.95)

Table 3 Patient and vessel characteristics on CCTA, FFR_{CT}, and invasive FFR

Patient characteristics	N = 43
Calcium score	285 (114–778)
Calcium score > 400	17 (40 %)
Calcium score > 1000	8 (19 %)
Significant obstruction in at least one vessel by CCTA	41 (95 %)
Functional ischemia in at least one vessel by FFR_{CT}	35 (81 %)
Functional ischemia in at least one vessel by invasive FFR	21 (49 %)
Vessel characteristics	**N = 70**
Target vessel	
Left anterior descending artery	37 (53 %)
Left circumflex artery	17 (24 %)
Right coronary artery	16 (23 %)
Significant obstruction by CCTA	52 (74 %)
Functional ischemia in at least one vessel by FFR_{CT}	46 (66 %)
Functional ischemia by invasive FFR	28 (40 %)

Categorical data are presented as number of patients (prevalence). Continuous variables are presented as median and interquartile range

CCTA coronary computed tomography angiography, *FFR* fractional flow reserve, *FFRCT* fractional flow reserve derived from coronary computed tomography angiography

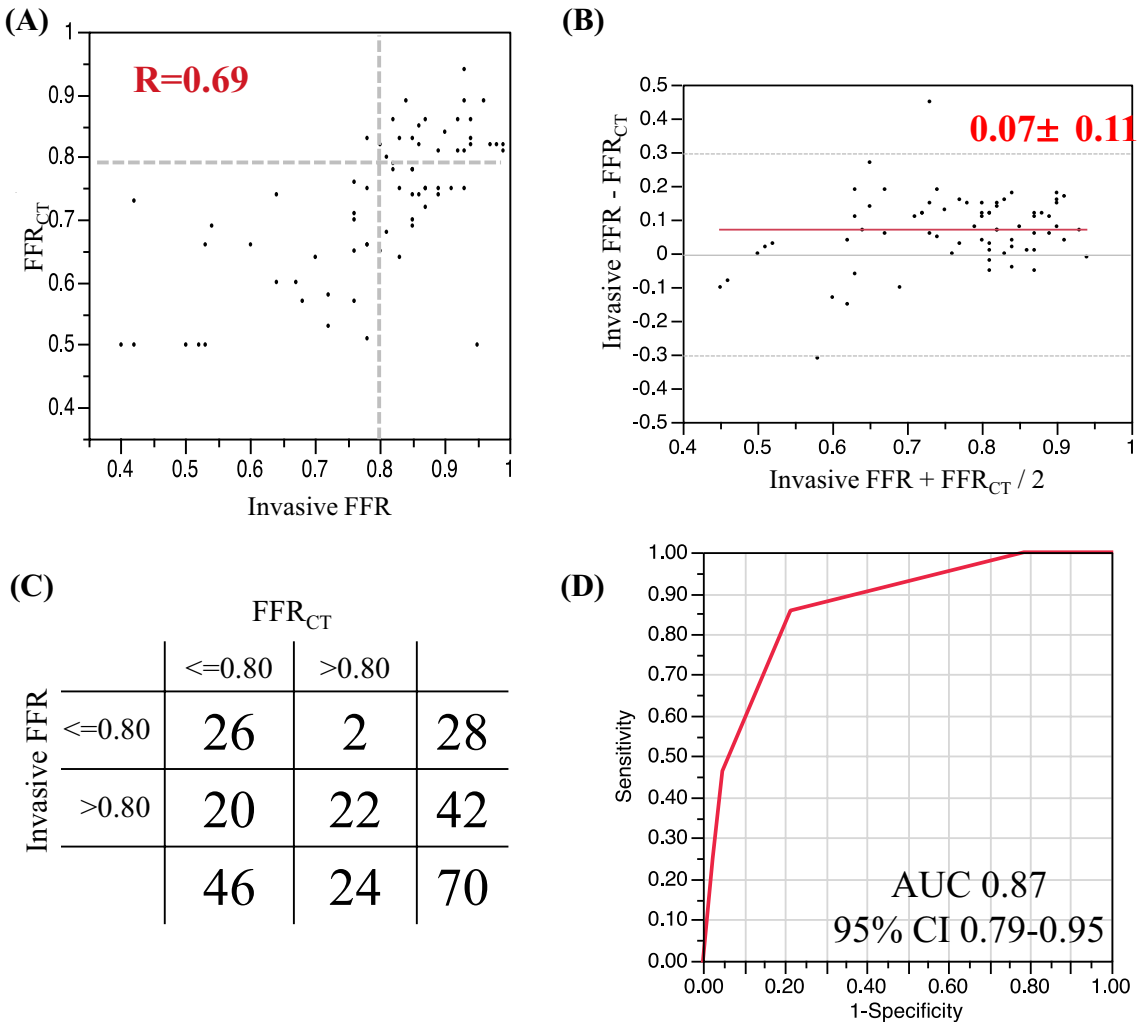

Fig. 2 Per-vessel diagnostic performance of FFR_{CT} for detecting hemodynamically significant CAD. **a** Correlation between FFR_{CT} and invasive FFR value. **b** Bland–Altman plot of FFR_{CT} and invasive FFR. **c** 2 by 2 tables for FFR_{CT} and invasive FFR (cutoff value: 0.80). **d** The area under the receiver operator characteristics curve (AUC) of FFR_{CT}. *CI* confidence interval

(Fig. 2). Per-vessel accuracy, sensitivity, specificity, PPV, and NPV were 68.6, 92.9, 52.4, 56.5, and 91.7 %, respectively (Fig. 4).

Diagnostic performance of FFR_{CT} in extremely severe calcified vessels

Among 43 patients with 70 vessels, 8 patients with 13 vessels had extremely severely calcified lesions as defined by CS > 1000. Good correlation between FFR_{CT} and invasive FFR was maintained even in patients with CS > 1000 (Spearman's rank correlation = 0.81, P < 0.001) (Fig. 4). Representative cases of extremely severely calcified vessels were presented in Fig. 5.

Per-vessel accuracy, sensitivity, specificity, PPV, and NPV were 76.9, 100, 62.5, 62.5, and 100 % in patients with severely calcified vessels, and 66.7, 91.3, 50.0, 55.2, and 89.5 % in patients without severely calcified vessels (Fig. 4).

Discussion

The main findings in the current study were as follows; (1) Measurement of FFR_{CT} was feasible in the majority of consecutive patients who suspected significant CAD by CCTA in real clinical practice; (2) FFR_{CT} showed a good correlation with invasive FFR, but tended to overestimate the functional significance of the stenosis compared with invasive FFR; and (3) FFR_{CT} showed good for detecting hemodynamically significant CAD defined as invasive FFR ≤0.80 regardless of existence of extremely severely calcified vessels.

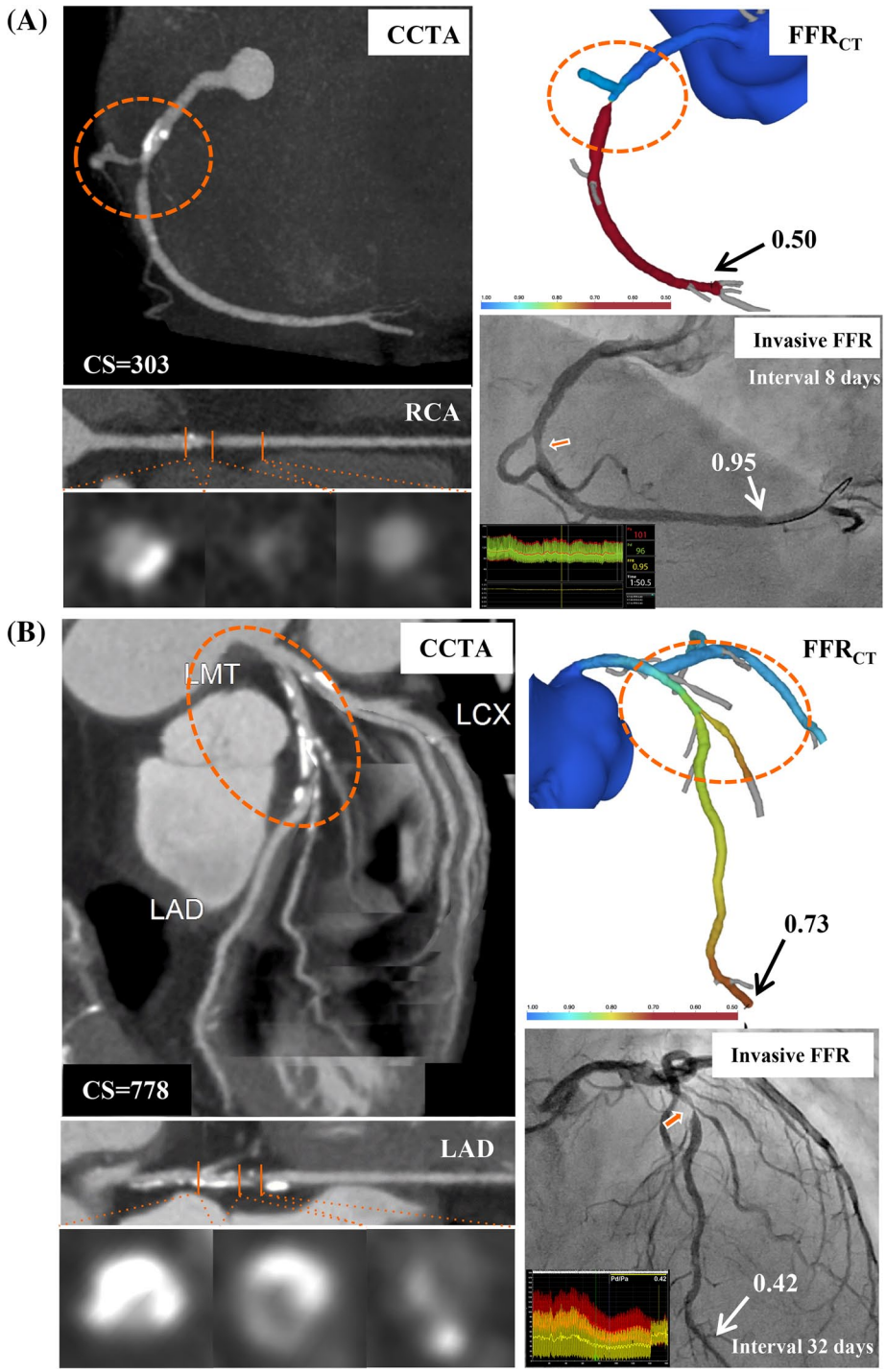

Fig. 3 Representative cases of extreme outliers. **a** Coronary computed tomography angiography (CCTA) performed by a single-source CT scanners with 320-slice detector rows with prescription of beta blocker and nitrate tablet (heart rate: 61 bpm), demonstrated sub-total lesion in mid right coronary artery (RCA). FFR_{CT} value in this case was 0.50 (*orange circle*). In invasive coronary angiography 8 days after CCTA acquisition, however, the target lesion in the mid RCA showed only moderate stenosis (*orange arrow*), and invasive fractional flow reserve (FFR) was 0.95 (*white arrow*). The difference of the severity of target lesion between CCTA/FFR_{CT} and invasive coronary angiography might be caused by inadequate vasodilation at the time of CCTA. **b** CCTA showed moderate-severe bifurcation lesion with severe calcification in mid left anterior descending artery (LAD) (*orange circle*). Total calcium score in this case was 778. FFR_{CT} value at the distal end of LAD was significant for functional ischemia (FFR_{CT} value: 0.73). In invasive coronary angiography 32 days after CCTA acquisition, the target lesion in mid LAD showed severe coronary stenosis. Invasive FFR value at distal LAD (*white arrow*) was also significant for functional ischemia, but much lower than FFR_{CT} value (FFR_{CT}: 0.73, and FFR: 0.42). This underestimation of the functional significance of the target lesion occurred during semi-automatic reconstruction of a 3-dimensional anatomic model from CCTA image, which emphasizes the need for manual correction. This case might indicate one of the most critical limitations of FFR_{CT}

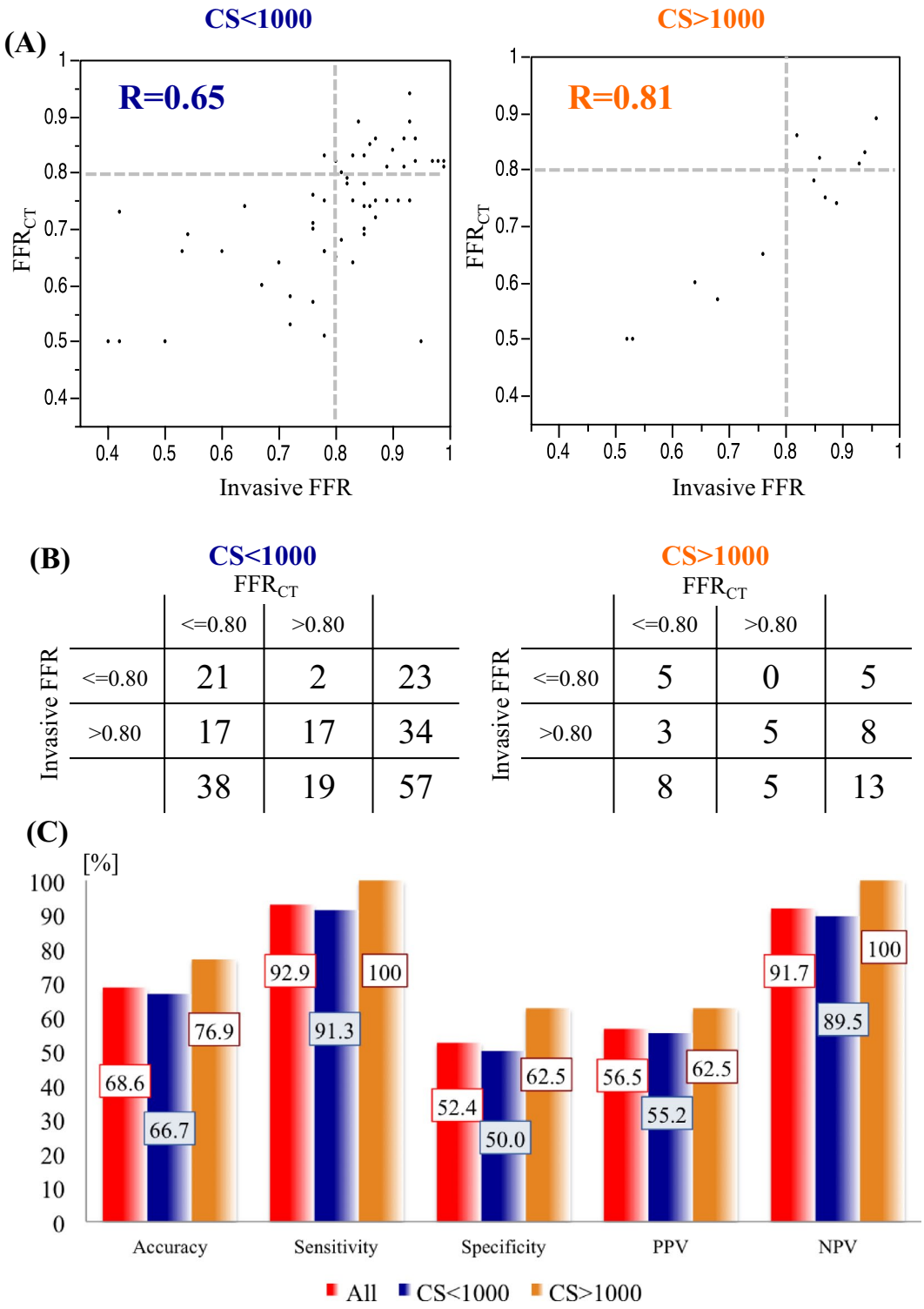

Fig. 4 Per-vessel diagnostic performance of FFR_{CT} for detecting hemodynamically significant CAD in patients with and without extremely severe calcified vessels [calcium score (CS) >1000]. **a** Correlation between FFR_{CT} and invasive FFR. **b** 2 by 2 tables for FFR_{CT} and invasive FFR (cutoff value: 0.80). **c** Diagnostic performance of FFR_{CT} in patients with and without extremely severe calcified vessels (CS > 1000). *PPV* positive predictive value, *NPV* negative predictive value

In the current study enrolling consecutive patients who were suspected significant CAD by CCTA, FFR_{CT} could be measured in the majority of cases despite inclusion of a significant proportion of patients with extremely severely calcified vessels (CS > 1000: 18.6%), revealing the feasibility of FFR_{CT} in daily clinical use. Furthermore, the

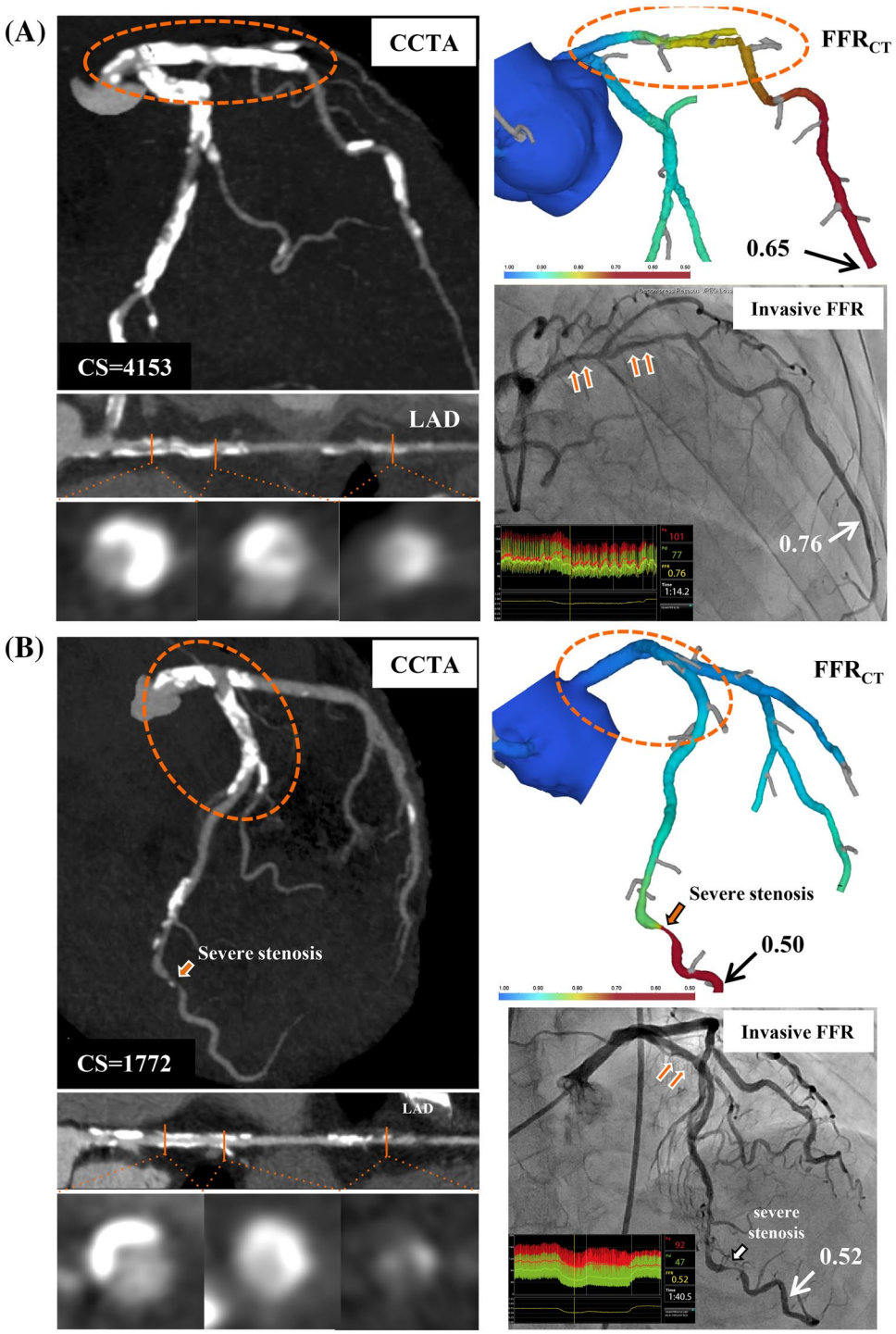

Fig. 5 Representative cases of extremely severe calcified vessels. **a** Coronary computed tomography angiography (CCTA) demonstrated diffuse severe calcified lesions in both proximal left anterior descending artery (LAD) and left circumflex coronary artery (LCx). Total calcium score (CS) was 4153. FFR_{CT} showed hemodynamically significant ischemia in LAD lesion and FFR_{CT} value at the distal end of LAD (*black arrow*) was 0.65. Invasive FFR also showed significant ischemia and invasive FFR value at the distal LAD (*white arrow*) was 0.77. **b** CCTA demonstrated severe coronary calcification from left main trunk to proximal LAD with severe stenosis in distal LAD. Total CS was 1772. FFR_{CT} value at distal end of LAD was 0.50, although major step up was observed only at distal severe LAD lesion (*orange arrow*). Coronary angiography revealed only moderate coronary stenosis in severe calcified lesions at proximal LAD (*orange arrow*). Invasive FFR value at the distal LAD was 0.51, and Step up was also observed at distal severe LAD lesion

diagnostic performance of FFR_{CT} in the current study enrolling unselected patients including those with heavily calcified vessels was acceptable, although that was lower than that in the prior clinical trials [9–11].

Considering the daily clinical use of FFR_{CT}, well understanding common reasons for the difference between FFR_{CT} and invasive FFR is important. According to the findings in the current study, FFR_{CT} tended to overestimate the functional significance of the stenosis compared with invasive FFR, leading to low false negative rate and relatively high false positive rate. One of the reasons for the smaller FFR_{CT} values as compared with invasive FFR might be that FFR_{CT} value indicated value at the most distal portion of the target vessels, whereas invasive FFR values are not usually measured at the most distal portion of the target vessel because of the gap between the tip and pressure censor in pressure wire. The lack of adequate vasodilation, furthermore, might cause the difference between FFR_{CT} and invasive FFR

value; timely administration of adequate dose of nitrate is essential for preventing vasoconstriction leading to overestimation of the functional significance of the stenosis by FFR_{CT} [24]. In the one of the two cases of extreme outliers in the current study, the severity of target lesion by CCTA was apparently more severe than that by coronary angiography, suggesting the possibility of inadequate vasodilation at the time of CCTA.

The existence of coronary calcification is known to be a major factor for decreasing diagnostic performance of conventional CCTA due to blooming and beam-hardening artifacts, which leads to overestimation of the severity of target lesions. Intuitively, in patients with severely calcified vessels, diagnosis of hemodynamically significant CAD using FFR_{CT} seems to be challenging. In the substudy of the Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT) trial, FFR_{CT} was reported to provide high diagnostic performance and discrimination for ischemia over a wide range of coronary calcification severity [10, 25]. In the NXT trial, however, the extent of coronary calcification seemed to be milder than that encountered in daily clinical practice. Indeed, extremely severe calcification of CS > 1000 was present in only 13 out of 214 (6 %) patients [10]. In the current study including consecutive patients without any exclusion criteria for the quality of CCTA image, the extent of coronary calcification was much greater than that in the NXT trial (median CS: 285, CS > 1000: 18.6 %). Even in the setting of patients with extremely severe calcified vessels (CS > 1000), good correlation between FFR_{CT} and invasive FFR was maintained in the current study, supporting the feasibility of using this new technology in the wide range of population in daily clinical practice. In symptomatic patients with a very high calcium score who might have a high odds of having a significant coronary stenosis, however, FFR_{CT} might not offer a sufficiently low NPV to avoid conventional coronary angiography. Further investigation is needed to clarify the role of FFR_{CT} in these patients.

Study limitations

The first and most important limitation in the current study was a small number of enrolled patients, although the current study is the first study evaluating utility of FFR_{CT} in consecutive CAD patients who were suspected significant CAD by CCTA. Considering a small number of enrolled patients and relatively low diagnostic accuracy in the current study, further large scale study would be needed to confirm the utility of FFR_{CT} in daily clinical practice. Second, the study results cannot generalize all the patients who receive CCTA because we enrolled only patients who were suspected significant CAD by CCTA and whose FFR_{CT} value could be measured by the core laboratory. However, this novel technology of FFR_{CT} may indicate patients who are suspected significant CAD by CCTA in daily clinical use, because conventional CCTA have an adequately high NPV for ruling out significant CAD. Third, it is possible that the nitrate protocol used in the current study may have led to incomplete vasodilation at the acquisition of CCTA in some patients. Finally, because the current study was performed in the university hospital and CT specialized clinic where high quality CCTA acquisition was achieved, generalizing these results in other settings should be done with caution.

Conclusions

FFR_{CT} could be measured in the majority of consecutive patients who had suspected significant CAD by CCTA in real clinical practice, and demonstrated good diagnostic performance for detecting hemodynamically significant CAD even in patients with extremely severely calcified vessels.

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Compliance with ethical standards

Conflict of interest This study was a collaborative study of Kyoto University Hospital with HeartFlow Inc. and C.A. The study was funded by the unrestricted grant of Kyoto University Hospital. FFR_{CT} was evaluated free of charge by HeartFlow Inc. C.A. Taylor is an employee and shareholder of HeartFlow Inc. All the other authors have no conflict of disclosures.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national 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 the study.

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