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Original article

Incremental diagnostic value of whole-heart dynamic computed tomography perfusion imaging for detecting obstructive coronary artery disease

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ABSTRACT

Background: This study aimed to evaluate the incremental diagnostic value of dynamic myocardial computed tomography (CT) perfusion (CTP) imaging for detecting obstructive coronary artery disease (CAD) in comparison with coronary CT angiography (CTA).
Methods: Thirty-eight patients who had undergone coronary CTA and pharmacological stress dynamic CTP before invasive coronary angiography (ICA) were selected retrospectively. Using ICA, obstructive CAD was defined as the presence of severe (≥70%) or moderate (50–69%) stenosis with fractional flow reserve (FFR) <0.75. For CT evaluations, coronary vessels with any stenosis ≥50%, ≥70% or unassessable lesions were considered significantly stenotic. Dynamic CTP was assessed quantitatively using CT-derived myocardial blood flow (CT-MBF). Receiver operating characteristic (ROC) curve analysis determined the cut-off value of CT-MBF for identifying obstructive CAD. The diagnostic performances of CTA alone and integrated CTA and CTP assessments for detecting obstructive CAD were compared.
Results: Using ICA and FFR, 24 of 114 vessels had obstructive CAD. The cut-off value of CT-MBF for detecting obstructive CAD was 1.26 mL/g/min. The sensitivity, specificity, and positive and negative predictive values (PPV and NPV) at the vessel level were 96%, 57%, 37%, and 98% for CTA, and 83%, 93%, 77%, and 95% for integrated CTA and CTP assessment using cut-off 50% stenosis on CTA, respectively. The sensitivity, specificity, and PPV and NPV at the vessel level were 79%, 69%, 40%, and 93% for CTA, and 71%, 97%, 85%, and 93% for integrated CTA and CTP assessment using cut-off 70% stenosis on CTA, respectively. The area under the ROC curve for CTA and CTP was significantly higher than that for CTA alone (0.96 vs. 0.84, $p < 0.05$).
Conclusions: Stress dynamic myocardial CTP is feasible to detect hemodynamically obstructive CAD in patients with high pre-test likelihood and helps for improving diagnostic performance in comparison with coronary CTA alone.

Introduction

Functional assessments of coronary artery disease (CAD) are important for therapeutic decision-making and patients' outcomes [1,2]. Fractional flow reserve (FFR) is a functional parameter acquired using invasive coronary angiography (ICA) that measures pressure differences across a coronary artery stenosis, and it determines the likelihood that a stenosis is obstructive CAD [3]. Myocardial perfusion imaging, including single-photon emission computed tomography (SPECT), cardiac magnetic resonance imaging (MRI), and positron emission tomography, is a non-invasive investigative technique used to assess myocardial ischemia before ICA [4–6]. Although the diagnostic performance of coronary computed tomography angiography (CTA) is high for the detection of coronary artery stenoses assessed by ICA [7,8],

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morphological coronary artery stenoses do not necessarily cause myocardial ischemia [9,10]. Recently, advances in computed tomography (CT) technology have enabled myocardial CT perfusion (CTP) imaging to be used as an alternative means of assessing myocardial perfusion, and single center and multicenter trials showed that diagnostic performance of CTP for evaluating myocardial ischemia was comparable to SPECT and MRI [11,12]. Moreover, dynamic CTP imaging enables quantitative assessments of myocardial perfusion by using CT-derived myocardial blood flow (CT-MBF) with high levels of objectivity and reproducibility [13]. We reported that CT-MBF derived from every-beat CTP data provided high diagnostic performance for detecting myocardial perfusion abnormality assessed by SPECT and MRI [14]. The purpose of this study was to evaluate the incremental diagnostic value of quantitative CTP assessment for detecting obstructive CAD in addition to coronary CTA.

Methods

Study population

This retrospective study was approved by the organization's institutional review board. Informed consent was obtained from all patients. We identified 38 patients who underwent coronary CTA and stress dynamic CTP prior to ICA between January 2013 and March 2015. Patients were screened for CAD because of effort or resting angina diagnosed by electrocardiogram (ECG) change, relief of symptoms upon administration of nitroglycerin, or multiple coronary risk factors. The attending physician determined the indications for cardiac CT and ICA. The exclusion criteria were a history of acute/old myocardial infarction, cardiomyopathy, a left ventricular ejection fraction $<$20%, atrial fibrillation, a greater than first degree atrioventricular block, a left complete bundle branch block, valvular heart disease, and a history of percutaneous coronary intervention or a coronary artery bypass graft. The radiation dose was calculated from the dose-length product with a conversion factor of 0.014 as described previously [15].

Comprehensive CT scan protocol

A comprehensive cardiac CT protocol was used with a 256-slice multidetector row CT unit (Brilliance iCT, Philips Healthcare, Cleveland, OH, USA) and an automatic dual injector (Stellant DualFlow; Nihon Medrad KK, Osaka, Japan), as described previously [14]. Briefly, a calcium scan was performed, then the scan timing was determined from a test scan that involved the administration of a 20% solution of the contrast medium, iopamidol (370 mg iodine/mL) (Bayer Yakuhin Ltd., Osaka, Japan), diluted with saline (5.0 mL/s for 10 s), followed by a saline chaser (5.0 mL/s for 4 s) at the ascending aorta. Stress dynamic CTP was performed to obtain a dataset comprising 30 consecutive heartbeats with the breath held in the expiration position by using the intravenous administration of adenosine triphosphate (ATP) (Adetphos-L Kowa; Kowa Company Ltd., Tokyo, Japan) at a rate of 0.16 mg/kg/min, which began at least 3 min before and continued during the scan, and contrast medium (5.0 mL/s for 10 s) followed by a saline chaser (5.0 mL/s for 4 s). The scan parameters were as follows: detector collimation: 64 $\times$ 1.25 mm; tube voltage: 100 kV; tube current-time product: 80 mAs; tube-rotation-time: 270 ms; prospective ECG-gated dynamic mode; and targeting phase: 40% of the RR interval. Subsequently, sublingual nitroglycerin (0.6 mg) was administered routinely, and a beta-blocker, namely, landiolol hydrochloride (0.125 mg/kg) (Corebeta; Ono Pharmaceutical Co., Osaka, Japan), was administered to patients with fast heart rates ($>$70 beats/min). Coronary CTA was performed using contrast medium (5.0 mL/s for 10 s) followed by a saline chaser (5.0 mL/s for 4 s). The scan parameters were as follows: detector collimation: 2 $\times$ 128 $\times$ 0.625 mm with a dynamic z-focal spot; tube voltage: 120 kV; tube current-time product: 30–1576 mAs; pitch factor: 0.14; prospective or retrospective ECG-gated scan mode for heart rates of $\leq$65 or $>$65 beats/min, respectively; and, targeting phase for dose modulation: 75% of the RR interval.

Coronary CTA and dynamic CTP assessments

Two experienced radiologists (one with 9 years and the other with 17 years of experience in cardiac CT), who were blinded to the other data, assessed the coronary CTA and dynamic CTP images. To assess the coronary CTA images, axial images with 0.8-mm slice thicknesses and 0.4-mm section intervals were reconstructed with a medium cardiac kernel (CB). First, the dataset from the 75% RR interval was assessed for image quality. If the image quality was suboptimal with the retrospective ECG-gated scan, the neighboring image datasets at $\pm$5% RR interval increments were repeatedly explored from 0 to 95% of the RR-interval until the highest image quality was obtained. The Society of Cardiovascular Computed Tomography guidelines and a six-point scale, where normal = no stenosis; minimal = 1–24% stenosis; mild = 25–49% stenosis; moderate = 50–69% stenosis; severe = 70–99% stenosis; and occluded stenosis, were used to assess the coronary CTA images of each vessel [16]. If a segment (vessel) had multiple lesions, the severity of the stenosis in the segment (vessel) was defined based on the worst lesion. A coronary lesion with $\geq$50% stenosis was defined as significant stenosis. If a vessel included unassessable segments, it was assumed to have significant stenosis. The coronary lesions were categorized according to their locations in three vessels, namely, the left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery. Discrepancies were resolved by consensus.

To assess the dynamic CTP images, a series of CTP images with 1.25-mm slice thicknesses were reconstructed using a 360° reconstruction algorithm. Using a dedicated workstation (IntelliSpace Portal; Philips Healthcare), elastic registration was applied for motion compensation, and a spatio-diffusion filter was applied to reduce noise spikes over time. Contiguous 8-mm-thick short-axial sections were generated from the apex to the base of the left ventricle without spatial and temporal gaps, and three representative short-axial CTP images (basal, mid, and apical) were selected according to the 16-segment model, which excluded the apex [17]. The two regions of interest were positioned in the middle layer of each 30–50 mm^2 myocardial segment. The CT-MBFs (mL/g/min) were calculated by using deconvolution analysis [14]. We evaluated the mean CT-MBF values per segment and per vessel. The cut-off value of CT-MBF for the detection of obstructive CAD was determined based on the results of ICA and FFR.

Fig. 1 presents the diagnostic algorithm for the comprehensive CT assessments. Vessels with both significant stenoses on CTA images and myocardial ischemia on CTP images were considered positive findings in the integrated CTA and CTP assessments.

ICA assessments

ICA was performed using 4-Fr or 6-Fr coronary catheters, and the results were interpreted by a cardiologist with 18 years of experience in ICA who was blinded to the other data and used the 15-segment model [18]. The severity of the stenoses was assessed using commercially available quantitative coronary angiography (QCA) software (Pie Medical Imaging BV, Maastricht, Netherlands). The attending physician determined the indications for FFR, and FFRs were measured using pressure-monitoring guidewires (Verrata; Philips North America Corporation, Andover, MA, USA,

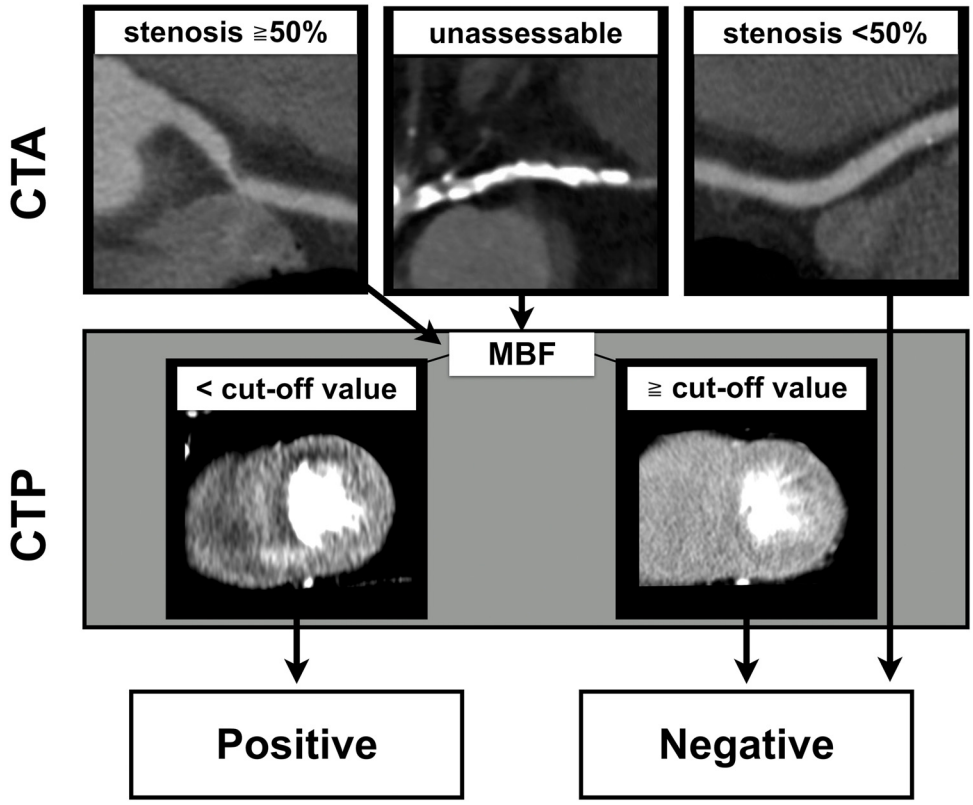

Fig. 1. Diagnostic algorithm for integrated assessments with computed tomography angiography and computed tomography perfusion. CTA, computed tomography angiography; CTP, computed tomography perfusion; MBF, myocardial blood flow.

or Aeris; Abbott Vascular, Temecula, CA, USA) during hyperemia induced by the intravenous administration of ATP at a rate of 0.16 mg/kg/min, as described previously [19]. The coronary lesions were categorized according to their locations in the three vessels, as described previously. Severe (≥70%) or moderate (50–69%) stenoses with FFRs <0.75 were defined as obstructive CAD [20,21]. Patients with at least single obstructive CAD were classified as positive, while patients having no obstructive CAD in all three vessels were classified as negative.

Statistical analyses

The continuous variables are expressed as the means and the standard deviations or as the medians (25–75 percentiles), as appropriate. The scan heart rates were compared during stress and rest using a paired *t*-test. The interobserver variability was calculated using an interclass correlation coefficient for CT-MBF. The correlations between CT-MBF and FFR were evaluated using Spearman's rank correlation coefficient. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value of CT-MBF by using Youden's index, compared with ICA and FFR [22]. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for obstructive CAD detection were determined for CTA alone using a threshold of 50% and 70% lumen diameter reduction and for the integrated CTA and CTP assessments, by per-patient and per-vessel basis analysis respectively. The areas under the ROC curves (AUC) for CTA alone and for the integrated CTA and CTP assessments were compared using a previously described method with Bonferroni correction [23,24]. All the statistical data were reported with the 95% confidence intervals (CI). A value of $p < 0.05$ was considered statistically significant. The statistical analyses were performed using JMP software, version 12 (SAS Institute, Cary, NC, USA) and R version 3.2.1 (The R Foundation for Statistical Computing, Vienna, Austria; http://cran.r-project.org).

Results

Study population

Table 1 presents the patients' characteristics. Twenty-two patients (58%) had a coronary artery calcification (CAC) score ≥400. None of the patients experienced worsening angina or cardiac events during the imaging sessions. All the patients underwent successful whole-heart stress dynamic CTP imaging. The scan heart rate increased significantly from 62.7 ± 11.1 beats/min at rest to

Table 1
Patients' characteristics ($n = 38$).

Age, years	69.9 ± 8.6
Men, *n* (%)	27 (71)
Body mass index, kg/m^2	24.0 ± 3.5
Coronary risk factors	
Hypertension, *n* (%)	22 (58)
Dyslipidemia, *n* (%)	19 (50)
Diabetes mellitus, *n* (%)	13 (34)
Smoking habit, *n* (%)	21 (55)
Family history of coronary artery disease, *n* (%)	12 (32)
Chest pain, *n* (%)	30 (79)
Coronary artery calcium score	812 (209–1041)
1–99, *n* (%)	8 (21)
100–399, *n* (%)	8 (21)
≥400, *n* (%)	22 (58)
Interval between CT and ICA, days	25 (8–35)

The data presented are the numbers (percentages), means and standard deviations, or the medians (25–75 percentiles).
CT, computed tomography; ICA, invasive coronary angiography.

77.2 ± 11.7 beats/min during pharmacological stress ($p < 0.05$). A risk assessment, which was based on a 19-year follow-up study of a representative Japanese population [25], determined that the 10-year CAD death pretest probabilities were <0.5% ($n = 1$), 0.5–1% ($n = 2$), 1–2% ($n = 7$), 2–5% ($n = 11$), 5–10% ($n = 10$), and >10% ($n = 7$). Prospective and retrospective ECG-gated scans were performed on 21 patients (55%) and 17 patients (45%), respectively, during coronary CTA. The mean effective radiation doses for CTP and coronary CTA were 10.2 ± 1.2 mSv and 6.8 ± 5.8 mSv, respectively. A total amount of contrast medium was 108.8 ± 11.3 mL.

Characteristics of the coronary vessels assessed using ICA and FFR

Fig. 2 presents the flow diagram of the patients and the coronary vessels. Sixteen vessels were diagnosed with severe stenoses ≥70%. Twenty vessels with moderate stenoses were assessed using FFR, and eight vessels were diagnosed with hemodynamically significant stenoses (FFR < 0.75). Complementary diagnoses using ICA and FFR determined that 19 patients (50%) and 24 vessels (21%) had obstructive CAD. Fourteen patients had single-vessel and five patients had double-vessel disease.

Assessment of coronary CTA and CTP

Coronary CTA classified 114 vessels to severe stenoses (≥70%, $n = 17$), moderate stenoses (50–69%, $n = 15$), non-significant stenoses (<50%, $n = 52$), and unassessable vessels ($n = 30$). All the unassessable vessels had massive CACs. The mean CT-MBF for all the coronary artery vessel territories was 1.41 ± 0.23 mL/g/min. The interobserver variability for the CT-MBF assessed in randomly selected 10 patients (30 vessel territories) was 0.84, and we concluded that the reliability was satisfactory (>0.70). The CT-MBF significantly correlated with the FFR ($r = 0.66$, $p < 0.05$; Fig. 3).

Diagnostic performances of CTA and integrated assessments using CTA and CTP

ROC curve analysis showed the cut-off value of CT-MBF was 1.26 mL/g/min for obstructive CAD detection assessed by ICA and FFR. Table 2 shows the patient-level diagnostic performances of CTA alone and of the integrated CTA and CTP. The integrated assessment of CTA and CTP improved specificity and PPV in comparison to CTA alone (32% vs. 95% and 59% vs. 95% for a threshold of 50% stenosis by CTA; 42% vs. 95% and 58% vs. 94% for a threshold of 70% stenosis by CTA, respectively). Table 3 shows the vessel-level diagnostic performances of CTA alone and of the integrated CTA and CTP. The integrated assessment of CTA and CTP improved specificity and PPV in comparison to CTA alone (57% vs. 93% and 37% vs. 77% for a threshold of 50% stenosis by CTA; 69% vs. 97% and 40% vs. 85% for a threshold of 70% stenosis by CTA, respectively).

The AUCs detecting obstructive CAD were 0.84 for CTA alone, and 0.96 for the integrated CTA and CTP, respectively. The AUC for the integrated CTA and CTP was significantly greater than those of CTA alone ($p < 0.05$; Fig. 4). Fig. 5 illustrates a representative case.

Discussion

This study's main findings showed that (1) the CT-MBF correlated significantly with FFR and (2) quantitative assessments of myocardial CTP significantly improved the diagnostic performance of CTA for obstructive CAD detection.

Assessments of CTA are often influenced by the CAC severity [26], and in this study, CAC hampered the coronary CTA assessments, which led to a low level of specificity and PPV for obstructive CAD detection. The quantification of coronary artery stenosis using CTA does not show robust reproducibility for the assessment of coronary artery stenosis on ICA [27], and the detection of obstructive CAD by CTA has not been accurate [28]. Therefore, noninvasive imaging modalities that precede ICA have been used to assess myocardial ischemia. Compared with SPECT, the spatial resolution of CTP is sufficiently high to facilitate multivessel disease assessments [29]. A recent multicenter prospective study reported that the diagnostic performance of CTA and static CTP was significantly higher than that by CTA alone [30]. In that study, additional static CTP improved specificity and PPV compared with coronary CTA alone, even though CTA could

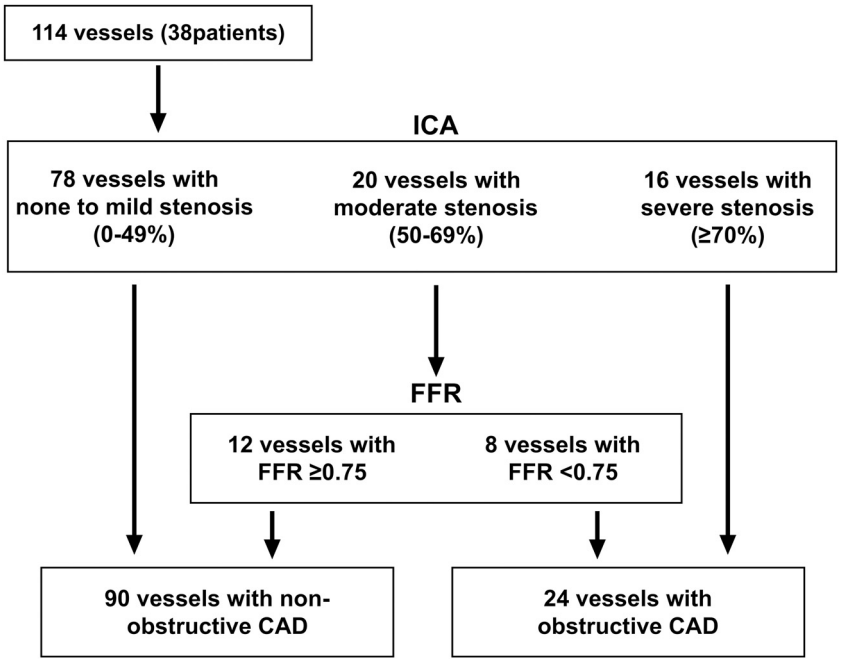

Fig. 2. Study flow chart for the patients and the vessels. ICA, invasive coronary angiography; FFR, fractional flow reserve; CAD, coronary artery disease.

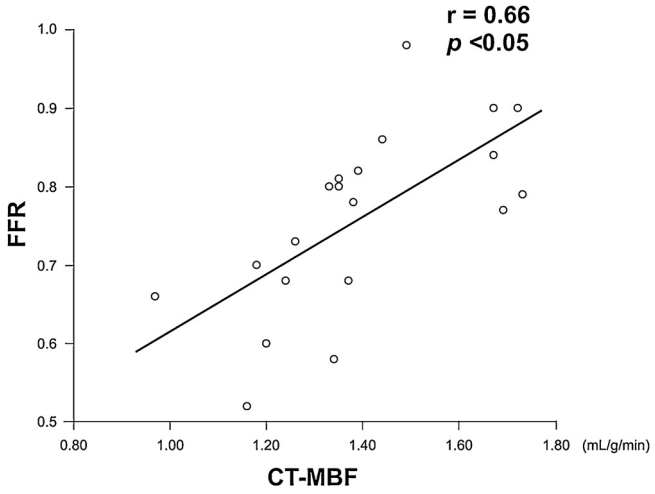

Fig. 3. The relationship between computed tomography-derived myocardial blood flow and fractional flow reserve. CT-MBF, computed tomography-myocardial blood flow; FFR, fractional flow reserve.

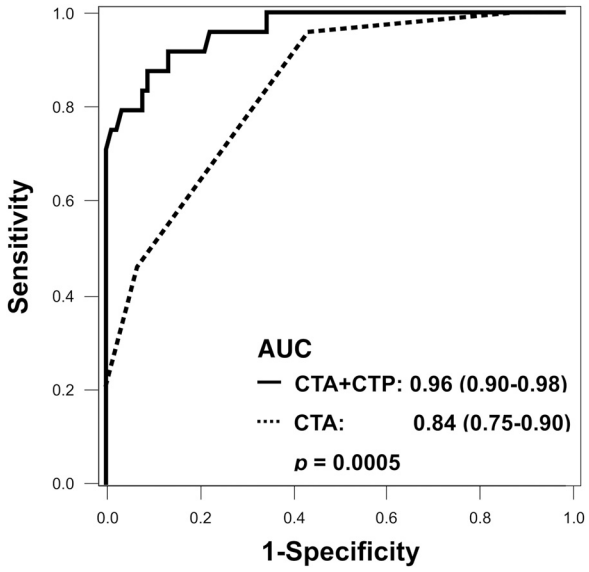

Fig. 4. Receiver operating characteristic curve analysis describing the diagnostic performances of computed tomography angiography (CTA) and integrated assessments using CTA and computed tomography perfusion (CTP) for the detection of obstructive coronary artery disease. AUC, area under the curve.

assess most of the coronary arteries. Dynamic CTP allows for quantification of myocardial perfusion which is advantageous for assessing the severity of myocardial ischemia and the treatment effect of revascularization therapy with high levels of objectivity and reproducibility [14,31]. In quantification of MBF, the CT-MBF in the present study was lower than that by ^{15}O-H_2O-positron emission tomography (PET) as a gold standard, of which the first-pass extraction fraction is stable even at increased blood flows [32]. However, the present results indicated that the optimized cut-off value of CT-MBF was feasible for detecting obstructive CAD, even though the value was lower than PET-MBF, as some studies previously reported [33,34]. Kikuchi et al. recently reported the feasibility of coronary flow reserve by CT-MBF using rest-stress dynamic CTP and the Renkin–Crone model [35]. Coronary (myocardial) flow reserve by CT-MBF may be a promising indicator for the assessment of not only CAD but also microvascular or myocardial disease.

In the present study, CT-MBF could be available in all patients, and CT-MBF correlated significantly with FFR. We speculate that robust quantification of CT-MBF was possible because we acquired every-beat dynamic whole-heart CTP data with wide-detector CT [36]. Although the study population had a median CAC score of 812.6 and considerable unassessable vessels, the integrated assessment of CTA and CTP improved the specificity and PPV compared with CTA alone using a threshold of 50% and 70% stenosis. Sharma et al. also described the incremental diagnostic value of CTP in patients with high CAC scores of ≥400 [37]. These results of the present study support the clinical robustness of integrated CTA and CTP assessments. When the threshold of 70% stenosis on CTA was applied, the integrated assessment of CTA and CTP also improved specificity and PPV, but conversely impaired sensitivity by overlooking obstructive CAD with moderate stenosis on CTA, compared to the integrated assessment of CTA and CTP using the threshold of 50% stenosis on CTA. The present study indicated that a threshold of 50% stenosis by CTA should be applied as first-line gatekeeper with high sensitivity and NPV and the following CTP assessment is useful for detecting obstructive CAD with myocardial ischemia.

FFR-CT has been introduced as a useful tool for detecting obstructive CAD by post-processing of rest CTA image [38]. FFR-CT calculation necessitates several strict requirements such as high image quality of CTA, lesser coronary artery calcification, free from coronary stents, and motion artifacts. While CTP requires pharmacological stress and additional scan, it allows high diagnostic performance for detecting hemodynamically significant CAD comparable to FFR-CT [39] even in patients with unassessable CTA lesions, providing the estimation of the extent of ischemic area. Combined assessment of CTA and CTP can evaluate both CAD lesions and corresponding extent of myocardial ischemia in single modality.

For clinical applications, it is necessary to discuss how to use CTP in the diagnostic workflow and scan protocol. CTA should be performed initially for patients with intermediate pretest proba-

Table 2
Diagnostic performance of computed tomography angiography (CTA) and integrated assessments using CTA and computed tomography perfusion for obstructive coronary artery disease detection at a patient level.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cut-off of 50% stenosis on CTA				
CTA	100 (89–100)	32 (12–51)	59 (43–76)	100 (75–100)
CTA + CTP	95 (81–100)	95 (81–100)	95 (81–100)	95 (81–100)
Cut-off of 70% stenosis on CTA				
CTA	79 (61–97)	42 (22–62)	58 (40–75)	67 (43–90)
CTA + CTP	79 (61–97)	95 (81–100)	94 (78–100)	82 (66–98)

The data presented in parentheses are the 95% confidence intervals. The cut-off value of CTA is 50% stenosis.
CTA, computed tomography angiography; CTP, computed tomography perfusion; PPV, positive predictive value; NPV, negative predictive value.

Table 3
Diagnostic performance of computed tomography angiography (CTA) and integrated assessments using CTA and computed tomography perfusion for obstructive coronary artery disease detection at a vessel level.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cut-off of 50% stenosis on CTA				
CTA	96 (88–100)	57 (46–67)	37 (25–49)	98 (94–100)
CTA + CTP	83 (68–98)	93 (88–98)	77 (61–93)	95 (91–99)
Cut-off of 70% stenosis on CTA				
CTA	79 (63–95)	69 (59–78)	40 (27–54)	93 (86–99)
CTA + CTP	71 (54–88)	97 (92–100)	85 (69–100)	93 (87–98)

The data presented in parentheses are the 95% confidence intervals.
CTA, computed tomography angiography; CTP, computed tomography perfusion; PPV, positive predictive value; NPV, negative predictive value.

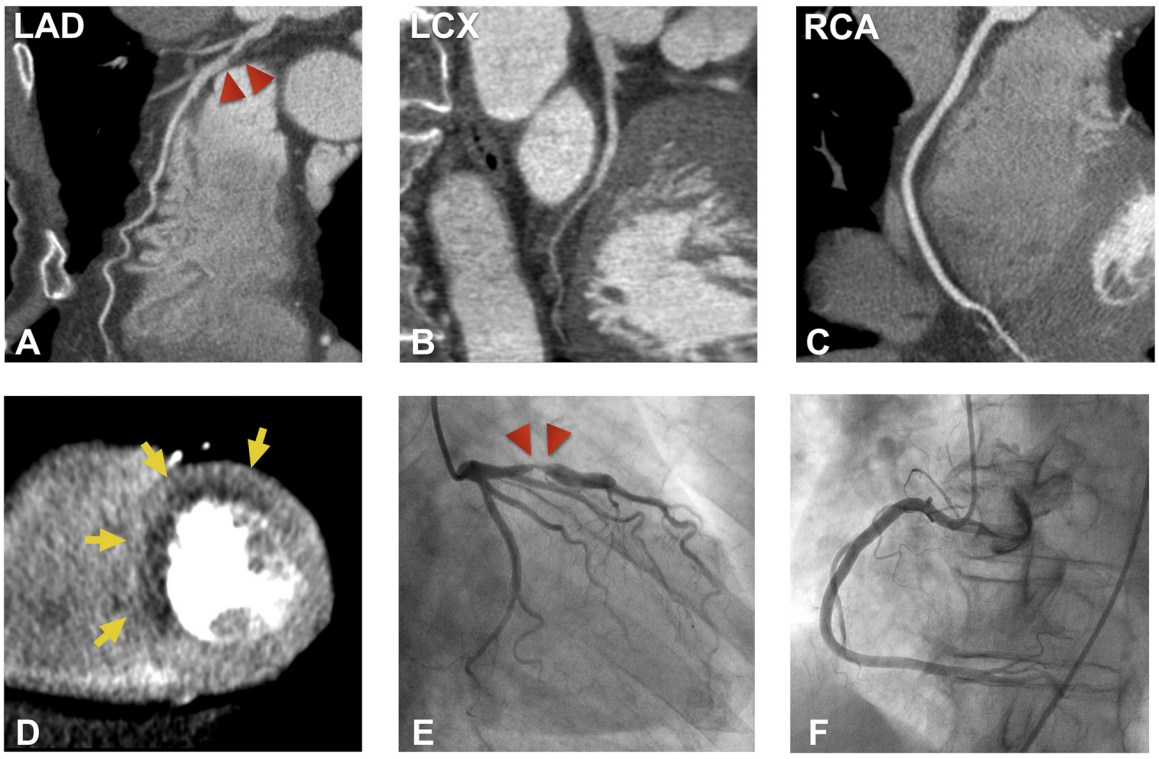

Fig. 5. A 63-year-old man with stable angina. Coronary computed tomography angiography showed severe stenosis in the proximal portion of the left anterior descending artery (LAD) (red arrowhead) (A), and no significant stenosis in the left circumflex artery (LCX) or right coronary artery (RCA) (B and C). Computed tomography perfusion imaging showed a subendocardial perfusion defect in the antero-septal left ventricle wall (yellow arrow) (D). A quantitative computed tomography perfusion assessment revealed that the mean computed tomography-derived myocardial blood flow (CT-MBF) in the LAD, LCX, and RCA territories were 0.85 mL/g/min, 1.67 mL/g/min, and 1.36 mL/g/min, respectively. The CT-MBF in the LAD territory was lower than the cut-off value (1.26 mL/g/min), and the patient was suspected of having myocardial ischemia. Invasive coronary angiography revealed severe stenosis in the proximal portion of the LAD (red arrowhead) (E), and no significant stenosis in the LCX or RCA.

bility of CAD, and additional CTP may be recommended according to the CTA results, as the recently published multi-society joint practice guidelines of coronary CTA [40]. Comprehensive CT protocol of CTA and CTP may be appropriate for patients with high pretest probability of CAD or in decision-making of coronary revascularization therapy. Further large multicenter studies are required to establish the role of dynamic myocardial CTP in the context of its incremental diagnostic value, influence on therapeutic strategies, patient outcomes, and cost-effectiveness.

This study has some limitations. First, the study population was small and it was obtained from a nonrandomized retrospective cohort. Second, the radiation dose associated with the comprehensive CT protocol was a concern. While we adopted a low kilovolt scanning protocol for the stress dynamic CTP imaging, reduced sampling and iterative reconstructions will also help to resolve this issue without impairing image quality and diagnostic performance [41]. Third, this study's comprehensive CT protocol comprised CTP scans followed by CTA scans because we were apprehensive about underestimating myocardial ischemia due to beta-blocker and contrast medium used in the preceding CTA scans [42]. Fourth, neither rest dynamic CTP nor late iodine enhancement image was obtained in terms of radiation dose and contrast medium in the present study. Myocardial infarction, viability, and coronary (myocardial) flow reserve are crucial for the assessment of not only CAD and microvascular disease but also other cardiac diseases. Thus, further study will be required to evaluate the feasibility of rest dynamic CTP study. Lastly, the registration between the coronary arteries and the myocardial segments was suboptimal. The study applied a commonly used per vessel analysis combined with the 16-segment model regardless of the anatomical position of coronary artery stenosis.

In conclusion, dynamic myocardial CTP provided an incremental diagnostic value for detecting obstructive CAD defined by ICA and FFR in addition to coronary CTA, and a comprehensive CT protocol for CTA and CTP is feasible for simultaneously obtaining morphological and functional information from patients with high pretest probabilities of CAD.

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Conflict of interest

The authors declare that there is no conflict of interest.

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