Feasibility of Stress-Alone Cardiac CT for Detecting Hemodynamically Significant Coronary Stenosis in the Presence of High Coronary Calcium Score and Coronary Stents

Shiro Nakamori¹, Kakuya Kitagawa², Takashi Tanigawa¹,
Kaoru Dohi¹, Hiroshi Nakajima¹, Masaki Ishida²,
Kiyotaka Watanabe¹, Toshiki Sawai¹, Jun Masuda¹,
Motonori Nagata², Yasutaka Ichikawa², Norikazu Yamada¹,
Hajime Sakuma², Masaaki Ito¹

¹Departments of Cardiology and Nephrology, ²Radiology, Mie University Graduate School of Medicine, Tsu, Japan

Objective: Coronary computed tomographic angiography (CTA), including rest and stress myocardial perfusion computed tomography (CTP), allows for comprehensive assessment of flow-limiting coronary artery disease (CAD). In patients with severe coronary calcification or prior coronary stents where rest CTA had limited accuracy, stress CTP with coronary artery assessment on the same stress CTP dataset (stress-alone CTP/CTA) without rest CTA may be a valuable protocol. We assessed the diagnostic performance of stress-alone CTP/CTA with 320-slice CT compared to a combination of stress CTP/CTA and rest CTA/CTP using invasively determined fractional flow reserve (FFR) as the reference standard.

Materials and Methods: Thirty-five patients with a high calcium score, stratified according to >400 Agatston units and/or prior stents, underwent CT examination starting with stress CTP/CTA and followed by rest CTA/CTP and invasive angiography. FFR <0.80 or luminal stenosis >90% was considered hemodynamically significant.

Results: Fifty-six coronary vessels had flow-limiting stenoses. In our vessel-based analysis, integration of rest CTA/CTP with stress CTP/CTA significantly improved diagnostic performance to 82% sensitivity and 96% specificity, with an area under the receiver operator characteristic curve (AUC) of 0.94, compared with 0.90 for stress-alone CTP/CTA. However, according to our per-patient level analysis, stress CTP/CTA yielded its highest diagnostic performance with an AUC of 0.97, which was not an improvement on the integration of rest CTA/CTP. Mean radiation for stress-alone CTP/CTA and combined stress-rest CTA/CTP was 8.0 and 12.7 mSv, respectively. These were relatively high doses but were performed on a first-generation 320-slice CT scanner.

Conclusion: A stress-alone CTP/CTA protocol can provide excellent diagnostic performance for predicting flow-limiting CAD in patients with a high calcium score and coronary stents, omitting the need for radiation and contrast medium required for rest CTA/CTP.

Key words Myocardial perfusion imaging · Computed tomographic angiography · Fractional flow reserve · Myocardial · Coronary artery disease · Calcium · Stents.

Received: November 7, 2016

Revised: November 21, 2016

Accepted: November 23, 2016

Corresponding author

Kakuya Kitagawa, MD
Department of Radiology,
Mie University Graduate
School of Medicine, 2-174 Edobashi,
Tsu, Mie 514-8507, Japan
Tel: 81-59-231-5029
Fax: 81-59-232-8066
E-mail: kakuya@clin.medic.mie-u.ac.jp

INTRODUCTION

Coronary computed tomographic angiography (CTA) provides high sensitivity and negative predictive value (NPV) for the detection of obstructive coronary artery disease (CAD) in patients with low to intermediate pretest probability of disease [1,2]. However, its diagnostic accuracy is severely affected by calcification and previous stent placement [3,4]. With recent advances in cardiac computed tomography (CT) technology, cardiac CT examination has changed from a tool for anatomical imaging only to a combination of both anatomical and functional imaging of coronary stenosis for a single study session, using stress myocardial perfusion computed tomography (CTP) [5-8].

Although many stress CTP studies have prioritized the assessment of coronary artery morphology with rest coronary CTA and considered stress CTP to be an optional test, this strategy might be change in the presence of a high calcium score and coronary stents, where coronary CTA accuracy is limited. We hypothesized that stress myocardial perfusion assessment and coronary artery morphology using stress CT images (stress CTP/CTA) without rest CTA/CTP provide sufficient information to identify those who require invasive coronary angiography (ICA) in the above-mentioned patient population, thereby omitting radiation, contrast medium, and the time required for conducting

rest CTA/CTP. Accordingly, the aim of this study was to assess the diagnostic performance of stress CTP/CTA with 320 detector-row CT compared with a combination of stress CTP/CTA and rest CTA/CTP (combined stress-rest CTA/CTP), using invasively determined fractional flow reserve (FFR) as the reference standard, in patients with coronary artery calcium score >400 Agatston units and who had prior coronary stents.

MATERIALS AND METHODS

Study population

The study protocol was approved by the Institutional Review Board of Mie University, and informed consent was obtained from each patient. A total of 104 patients agreed to undergo comprehensive cardiac CT examination starting with adenosine stress CT perfusion and followed by rest coronary CTA from March 2010 to December 2011. Inclusion criteria for the comprehensive cardiac protocol consisted of patients over 40 years old who were clinically referred for coronary CTA with known or suspected CAD with intermediate to high pretest likelihood. Our exclusion criteria were cardiac arrhythmia [atrial fibrillation (n=2) and second- or third-degree atrioventricular block (n=1)], previous coronary artery bypass grafting (n=4), unstable angina (n=1), renal insufficiency (defined as a glomerular filtration rate

Fig. 1. Flowchart of coronary vessel enrollment. (A) Flow diagram of patient recruitment. (B) Study flowchart. CT: computed tomography, CAD: coronary artery disease, CABG: coronary artery bypass grafting, AVB: atrioventricular block, FFR: fractional flow reserve, CACS: coronary artery calcium score, ICA: invasive coronary angiography, QCA: quantitative coronary angiography, RCA: right coronary artery.

<30 mL/min, $n=1$), and known allergy to iodine contrast media ($n=1$). Among the 94 patients, we retrospectively identified 42 patients with invasive angiography and FFR assessment within two months after CT examination. After we excluded subjects with a calcium score ≤ 400 Agatston units and/or no prior stent placement, 35 patients comprised the study population (Fig. 1A).

Cardiac computed tomography acquisition

Prior to arrival, subjects were asked to refrain from caffeine for 12 hours. Baseline blood pressure, heart rate, and ECG were acquired prior to CT examination. Oral metoprolol was given if the resting heart rate was >60 beats per minute. Intravenous access was obtained in the right and left antecubital veins to administer the iodinated contrast and adenosine, respectively. Patients were placed in a supine position in a 320 detector-row CT scanner (Aquilion One; Toshiba Medical Systems, Otawara, Japan) and attached to a rhythm and automated blood pressure monitor. In this study, three sequential imaging series were performed in a single CT study session: 1) coronary artery calcium scoring, 2) stress CTP/CTA imaging, and 3) rest CTA/CTP imaging. Stress CTP/CTA imaging was performed during the intravenous infusion of adenosine ($140 \mu\text{g/kg/min}$) with a 50 mL iopamidol bolus and an injection rate of 4–5 mL/sec (Iopamiron 370, Bayer) using prospectively ECG gated volume CT scanning that was initiated 7 seconds after reaching a threshold of 250 Hounsfield units (HU) in the descending aorta. Scan parameters were tube current, 550 mA; tube voltage, 120 kV; field of view, 200 mm; temporal resolution, 175 ms; and reconstruction kernel of FC03. Rest CTA/CTP imaging was performed after 20 minutes following stress CTP/CTA with the same scan and reconstruction parameter settings. A sharper FC05 kernel was used to evaluate coronary CTA to reduce artifacts from coronary calcification and stents. All contrast-enhanced images were reconstructed using beam hardening correction and the phase with least coronary and myocardial motion. The effective radiation dose was estimated for cardiac CT examination using a conversion factor of 0.014 mSv/mGy cm [9].

Stress perfusion computed tomography image analysis

Using multi-planar reformations, stress and rest perfusion images were arranged in the cardiac short axis with a slice thickness of 8 mm, and two independent blinded observers visually assessed the presence or absence of perfusion defects in each major coronary arterial territory, using a narrow window setting (typically width 200 HU, level 100 HU), with disagreements resolved by a third reader. Presence or absence of perfusion defect was determined by visually assessing stress CTP only and then both stress and rest CTP together. Overall image quality for the stress and rest images was scored for each vessel territory as excellent, good, fair, or poor according to the following defi-

nitions: excellent (of diagnostic image quality and is devoid of artifacts that would interfere with interpretation); good (of diagnostic quality with minimal artifacts, and any artifacts present are subtle and do not interfere with study interpretation); fair (of diagnostic quality, but there are significant artifacts limiting the interpretation of portions of the study); and poor (image quality is severely limited, making study uninterpretable). Myocardial territories that were non-evaluable due to poor stress-image quality were classified as positive for the presence of perfusion defects.

Coronary computed tomographic angiography analysis

CT angiographic images were transferred to a dedicated workstation (Vitrea Fx 6.2; Vital Images, Minnetonka, MN, USA) for analysis by a cardiologist and a radiologist who were blinded to all other data. All segments ≥ 1.5 mm were analyzed using a 19-segment model [10]. Each coronary segment was assessed visually for percent luminal stenosis, and a vessel was considered obstructive if there was at least one segment that had $\geq 50\%$ luminal stenosis or was otherwise non-evaluable (due to the presence of motion artifacts, calcification, stent, or a low contrast-to-noise ratio).

Invasive coronary angiography and FFR measurements

ICA was performed according to standard techniques, with a catheter inserted via the radial or brachial artery using a 5- or 6-F guiding catheter. All angiograms were analyzed by two experienced cardiologists for the presence of a significant coronary artery stenosis $>50\%$ on visual assessment.

FFR was measured with sensor-tipped 0.014-inch guidewire (Pressure Wire; Radi Medical Systems, Uppsala, Sweden) in every major coronary vessel with a luminal narrowing between 50% and 90% on visual analysis. After positioning the pressure sensor distal to the stenosis, maximal myocardial hyperemia was induced with a continuous intravenous infusion of adenosine ($140 \mu\text{g/kg/min}$) for a minimum of two minutes. During maximum hyperemia, FFR was calculated as the ratio of the mean distal pressure, measured by the pressure wire, to the mean proximal pressure, measured by the guiding catheter. Quantitative coronary angiography (QCA) was performed on all coronary arteries >1.5 mm in diameter using a 19-segment coronary model by two experienced cardiologists who were blinded to FFR and CT findings; disagreements were resolved by consensus (CAAS; Pie Medical, Maastricht, the Netherlands). A major coronary artery with an FFR value <0.80 , luminal narrowing $\geq 90\%$, or its side branch with $\geq 85\%$ stenosis on QCA was considered functionally significant. If more than one coronary artery stenosis was present within the same perfusion territory, the most severe stenosis was used for analyses.

Interpretation of imaging results

Analyses were performed on both a per-patient and a per-main-vessel basis. In CTP analysis, perfusion defects were assigned to three coronary artery territories according to well-established criteria [11]. In cases where the coronary arterial anatomy varied from the above criteria, the coronary CTA was used to reassign segments to the appropriate vessel territory, as previously described [12]. For the combined assessment of CTA and CTP, a patient or a vessel territory was considered positive only if the stenosis and perfusion defect were in the same vascular distribution.

Statistical analysis

Continuous variables were expressed as mean and standard deviation; categorical variables were expressed as numbers and proportions. Analyses were performed on both a patient and coronary territory basis by calculating the sensitivity, specificity, positive predictive value (PPV), and NPV to detect hemodynamically significant stenosis. Cohen's kappa statistic was used to assess intermodality and intra/interobserver agreements. The area under the receiver operating characteristic was calculated and compared for all diagnostic testing strategies for FFR <0.80. A p-value <0.05 was considered statistically significant. All anal-

Table 1. Patient characteristics

Characteristic	Value
Age, year	67±10
Women, n (%)	10 (29)
Body mass index, kg/m ²	24.4±2.9
Body weight, kg	63.3±12.2
Coronary risk factor (%)	
Hypertension	29 (83)
Dyslipidemia	31 (89)
Smoking	
Current smoker	7 (20)
Ex-smoker	5 (14)
Diabetes mellitus	11 (31)
Family history of CAD	8 (23)
Symptoms (%)	
Typical angina	18 (51)
Atypical angina	8 (23)
Dyspnea on effort	4 (11)
ECG abnormality	5 (14)
Previous percutaneous coronary intervention (%)	16 (46)
Previous coronary artery bypass graft (%)	0 (0)
Previous myocardial infarction (%)	9 (26)
Days between CT and ICA-Median (IQR)	9 (2–37)
CT data	
Heart rate during stress, beats/min	64±9
Heart rate during rest, beats/min	56±4
Agatston Calcium Score-Median (IQR)	738 (455–1244)
Any hemodynamically significant stenosis (%)	30 (86)
Single-vessel disease	11 (31)
Double-vessel disease	12 (34)
Triple-vessel disease	7 (20)
Angiographic data (per vessel, %)	
Luminal narrowing >50% in the major coronary artery	57/105 (54)
FFR measurement performed in vessels with 50–90% stenosis with a diameter >2 mm	25/105 (24)
Technical failure	2/25 (8)
Vessels with FFR >0.80	10/25 (40)
Vessels with FFR <0.80	13/25 (52)

Variables given are mean±SD or n (%) or median (interquartile range). CAD: coronary artery disease, ICA: invasive coronary angiography, FFR: fractional flow reserve, IQR: interquartile range

Fig. 2. (A) A true-positive case with a total Agatston calcium score of 2388. The proximal LAD and mid LCx were not evaluable due to severe calcifications on stress CTA images. Stress CTP images showed anterior and lateral myocardial perfusion defects (thick red arrows). Despite integration of rest CTA, lesions in the LAD and LCx territories could not be evaluated (thin red arrows). Coronary angiography showed tight or intermediate lesions in the LAD and LCx (thin red arrows). FFR measured in the LAD and LCx arteries was 0.69 and 0.71, respectively, confirming flow-limiting stenoses. (B) A case allowing simultaneous assessment of coronary stenosis and myocardial ischemia on CTP images alone. The patient's heart rate was <65 beats per minute during adenosine infusion. Stress CTP images showed severe stenosis in the proximal LAD and a perfusion defect in the anterior wall. CTP images provided simultaneous assessment of coronary stenosis and myocardial ischemia, potentially avoiding rest CTA and additional radiation exposure. LAD: left anterior descending artery, LCx: left circumflex artery, CTA: computed tomographic angiography, CTP: perfusion computed tomography, FFR: fractional flow reserve.

Fig. 2. (C) A true-negative case. Visual CTP analyses showed no perfusion defect, although the proximal LAD was not evaluable in either stress or rest CTA image (red arrow). The case was considered positive because of the presence of obstructive stenosis. FFR measured in the LAD was 0.88, corresponding to normal perfusion in CTP images. LAD: left anterior descending artery, LCx: left circumflex artery, CTA: computed tomographic angiography, CTP: perfusion computed tomography, FFR: fractional flow reserve.

yses were performed using SPSS software, version 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient demographics are summarized in Table 1. The mean Agatston score in 20 patients without stents was 1365 ± 708 , with a median of 1223 and a range of 695 to 3255. There were a total of 41 coronary stents in 24 vessels in 15 patients. The average stent diameter was 3.0 ± 0.4 mm with a range of 2.5–4.0

mm. Most stents were located in the proximal (11, 27%), mid-left anterior descending (7, 17%), or mid-right (10, 24%) coronary artery. The mean radiation dose was 1.1 ± 0.2 mSv for the calcium-scoring scan, 6.9 ± 4.3 mSv for the stress CTP/CTA, 4.7 ± 2.4 mSv for the rest CTA/CTP, and 12.7 ± 5.7 mSv for the entire cardiac CT examination. Visual analysis of ICA revealed 32 vessels with $\geq 90\%$ stenosis, 48 vessels with $\leq 50\%$ stenosis, and 25 vessels with 50–90% stenosis. We attempted FFR in all 25 vessels with intermediate stenosis, and the FFR values ranged from 0.47 to 0.90, with 13 vessels presenting with FFR < 0.8 .

Fig. 2. (D) A false-negative case. Stress CTA showed significant stenosis with severe calcification in the proximal LAD (red arrow); however, no definite perfusion defect was shown on stress CTP images because of subtle artifacts (red arrow). Potential explanations for the false-negative results include motion artifacts, inappropriate vasodilator stress, inadequate acquisition timing, the effect of beta-blocker on hyperemic myocardial blood flow, and limitations of FFR assessment. LAD: left anterior descending artery, LCx: left circumflex artery, CTA: computed tomographic angiography, CTP: perfusion computed tomography, FFR: fractional flow reserve.

Two vessels in which FFR measurement failed for technical reasons were considered hemodynamically significant. An additional 10 vessels were also considered significant because they had $\geq 85\%$ diameter stenosis in their major side branches (≥ 1.5 mm in diameter) according to QCA. Overall, 56 coronary vessel territories were found downstream of functional stenosis (Fig. 1B). There were five patients with no significant CAD, 11 patients with single-vessel disease, and 19 patients with multi-vessel disease.

Coronary CT angiography

Rest coronary CTA yielded 41 vessels with obstructive stenosis and 39 vessels without. A total of 25 coronary vessels (24%) in 18 patients were non-evaluable and considered to have obstructive stenosis for subsequent analysis. Rest CTA had a sensitivity of 96% (54/56), specificity of 71% (35/49), NPV of 95% (35/37), and PPV of 79% (54/68) for detecting hemodynamically significant coronary artery stenosis in vessel-based analysis and 100% (30/30), 40% (2/5), 100% (2/2), and 91% (30/33), respectively, in patient-based analysis.

Stress coronary CTA revealed 32 vessels with obstructive stenosis and 33 vessels without. A total of 40 coronary vessels (38%) in 21 patients were non-evaluable and considered to have obstructive stenosis for subsequent analyses. Stress CTA had a sensitivity of 96% (54/56), specificity of 59% (29/49), NPV of

94% (29/31), and PPV of 73% (54/74) in vessel-based analysis and 100% (30/30), 40% (2/5), 100% (2/2), and 91% (30/33), respectively, in patient-based analysis. Fig. 2A and B show representative cases in which integration of rest CTA into stress CTP/CTA provided no additional information. Rest and stress CTA had equivalent diagnostic performance when non-evaluable vessels were considered obstructive. The diagnostic accuracy values are summarized in Table 2 and 3.

Stress CTP alone and combined stress-rest CTP imaging

On visual analysis, 50 of 105 myocardial vascular territories had perfusion defects on stress CTP images. An additional 10 vascular territories (10%) were considered positive for perfusion defect due to uninterpretable poor-quality images caused by artifact presence, including motion ($n=4$), beam-hardening ($n=1$), reconstruction artifact ($n=2$), and poor contrast enhancement ($n=3$). Assessment of stress CTP alone had a sensitivity, specificity, NPV, and PPV of 84% (47/56), 73% (36/49), 80% (36/45), and 78% (47/60), respectively, in vessel-based analysis and 93% (28/30), 80% (4/5), 67% (4/6), and 97% (28/29) in the patient-based analysis. The likelihood ratio was 3.2 with an area under the receiver operator characteristic curve (AUC) of 0.79. There was good interobserver and intraobserver agreement, yielding kappa values of 0.87 (95% CI: 0.77–0.97) and 0.89 (95% CI: 0.80–0.98), respectively. All territories with perfusion

defects on stress CTP images were completely or partially reversible on rest CTP images. A combination of rest CTP and stress CTP had similar diagnostic performance to stress CTP alone (Table 2 and 3).

Combined assessment of rest CTA and stress-rest CTP (combined stress-rest CTA/CTP) imaging

Twelve of 14 vessel territories with false-positive rest CTA results had normal perfusion on stress-rest CTP images; thus, our combined test corrected these diagnoses (Fig. 2C). In contrast, eight of 54 vessel territories with true-positive rest CTA results had no perfusion defect on stress-rest CTP images, re-

sulting in incorrect classification. In per-vessel analysis, sensitivity, specificity, NPV, and PPV were 82% (46/56), 96% (47/49), 83% (47/57), and 96% (46/48), respectively, while the AUC was 0.94 (Table 2). In per-patient level analysis, sensitivity, specificity, NPV, and PPV were 93% (28/30), 100% (5/5), 71% (5/7), and 100% (28/28), respectively, with an AUC of 0.97 (Table 3).

Combined assessment of stress CTP and stress CTA (stress CTP/CTA alone) imaging

Fifteen of 20 vessel territories with false-positive stress CTA results had normal perfusion on stress CTP images (Fig. 2C). In contrast, eight of 54 vessel territories with true-positive visual

Table 2. Comparison of diagnostic parameters for predicting hemodynamically significant CAD

	Per-vessel					
	Rest CTA >50% (95% CI)	Stress-rest CTP (95% CI)	Rest CTA/stress-rest CTP (95% CI)	Stress CTA >50% (95% CI)	Stress CTP alone (95% CI)	Stress CTP/CTA (95% CI)
CAD (%)	53.3	53.3	53.3	53.3	53.3	53.3
Sensitivity (%)	96 (88–100) 54/56	84 (72–92) 47/56	82 (70–91) 46/56	96 (88–100) 54/56	84 (72–92) 47/56	82 (70–91) 46/56
Specificity (%)	71 (57–83) 35/49	73 (59–85) 36/49	96 (86–100) 47/49	59 (44–73) 29/49	73 (59–85) 36/49	90 (78–97) 44/49
PPV (%)	79 (68–88) 54/68	78 (66–88) 47/60	96 (86–100) 46/48	73 (61–83) 54/74	78 (66–88) 47/60	90 (79–97) 46/51
NPV (%)	95 (82–99) 35/37	80 (65–90) 36/45	83 (70–91) 47/57	94 (79–99) 29/31	80 (65–90) 36/45	82 (69–91) 44/54
LR (+)	3.4	3.2	20.1	2.4	3.2	8.1
LR (-)	0.05	0.22	0.19	0.06	0.22	0.20
AUC	0.84 (0.76–0.90)	0.79 (0.70–0.86)	0.94 (0.88–0.98)	0.78 (0.69–0.85)	0.79 (0.70–0.86)	0.90 (0.83–0.95)

Values for sensitivity, specificity, PPV, and NPV are presented with 95% CI. CAD: coronary artery disease, CTA: coronary computed tomographic angiography, CTP: perfusion computed tomography, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio, AUC: area under the receiver operator characteristic curve, CI: confidence interval

Table 3. Comparison of diagnostic parameters for predicting hemodynamically significant CAD

	Per-patient					
	Rest CTA >50% (95% CI)	Stress-rest CTP (95% CI)	Rest CTA/stress-rest CTP (95% CI)	Stress CTA >50% (95% CI)	Stress CTP alone (95% CI)	Stress CTP/CTA (95% CI)
CAD (%)	85.7	85.7	85.7	85.7	85.7	85.7
Sensitivity (%)	100 (88–100) 30/30	93 (78–99) 28/30	93 (78–99) 28/30	100 (88–100) 30/30	93 (78–99) 28/30	93 (78–99) 28/30
Specificity (%)	40 (5–85) 2/5	80 (28–100) 4/5	100 (48–100) 5/5	40 (5–85) 2/5	80 (28–100) 4/5	100 (48–100) 5/5
PPV (%)	91 (76–98) 30/33	97 (82–100) 28/29	100 (87–100) 28/28	91 (76–98) 30/33	97 (82–100) 28/29	100 (87–100) 28/28
NPV (%)	100 (16–100) 2/2	67 (22–96) 4/6	71 (29–96) 5/7	100 (16–100) 2/2	67 (22–96) 4/6	71 (29–96) 5/7
LR(+)	1.7	4.7	-	1.7	4.7	-
LR(-)	<0.01	0.08	0.07	<0.01	0.08	0.07
AUC	0.70 (0.52–0.84)	0.87 (0.71–0.96)	0.97 (0.84–0.99)	0.70 (0.52–0.84)	0.87 (0.71–0.96)	0.97 (0.84–0.99)

Values for sensitivity, specificity, PPV, and NPV are presented with 95% CI. CAD: coronary artery disease, CTA: coronary computed tomographic angiography, CTP: perfusion computed tomography, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio, AUC: area under the receiver operator characteristic curve, CI: confidence interval

stress CTA results had no perfusion defect on stress CTP images (Fig. 2D). The stress CTP/CTA alone protocol yielded sensitivity, specificity, NPV, and PPV values of 82% (46/56), 90% (44/49), 82% (44/54), and 90% (46/51), respectively, for per-vessel analysis, and the AUC was 0.90. For per-patient analysis, sensitivity, specificity, NPV, and PPV were 93% (28/30), 100% (5/5), 71% (5/7) and 100% (28/28), respectively, and the AUC was 0.97. Assessment with stress CTP/CTA alone yielded a per-patient diagnostic performance that was equivalent to assessment with combined stress-rest CTA/CTP (Table 2 and 3). Additionally, the stress CTP/CTA alone protocol provided better diagnostic performance (AUC of 0.97) than rest CTA (AUC of 0.70) according to per-patient analysis ($p < 0.05$). This trend was also observed in per-vessel analysis (rest CTA; 0.84, stress CTP/CTA; 0.90, $p = 0.10$) (Fig. 3).

The per-vessel accuracy for predicting hemodynamically significant CAD when non-evaluable vessels/myocardial territories were considered negative for stenosis/ischemia is shown in the Supplementary Material.

Accuracy when non-evaluable coronary/myocardial segments were considered as negative for stenosis/ischemia for analysis

If non-evaluable coronary/myocardial segments were considered as negative for stenosis/ischemia, for per-vessel level, sensitivity, specificity, NPV, and PPV were 59% (33/56), 84% (41/49), 64% (41/64), and 81% (33/41), respectively, for rest CTA, 45% (25/56), 88% (43/49), 58% (43/74) and 81% (25/31)

for stress CTA, 73% (41/56), 82% (40/49), 73% (40/55) and 82% (41/50) for stress CTP, 45% (25/56), 98% (48/49), 61% (48/79) and 96% (25/26) for combined stress-rest CTA/CTP, 38% (21/56), 100% (49/49), 58% (49/84) and 100% (21/21) for stress CTP/CTA alone (Supplementary Table 1 in the online-only Data Supplement).

Stress CTP/CTA alone protocol provided better diagnostic performance with AUC of 0.79, compared with rest CTA with AUC of 0.71 ($p < 0.05$). Integration of rest CTA/CTP into a stress CTP/CTA yielded small improvement with AUC of 0.83, however there was no statistical significance between both groups ($p = 0.13$) (Supplementary Fig. 1 in the online-only Data Supplement).

Comparative accuracy of stress-alone CTP/CTA in patients with or without chronic myocardial infarction

We also measured the diagnostic performance of stress-alone CTP/CTA in patients with chronic myocardial infarction (MI) versus those without chronic MI. In nine patients with chronic MI, the accuracy of stress CTP alone decreased to a sensitivity of 81% and a specificity of 64% with an AUC of 0.72 in per-vessel analysis, compared with an AUC of 0.81 in non-MI patients. However, the diagnostic performance of stress-alone CTP/CTA for detecting flow-limiting stenosis at vessel level was not significantly different, with sensitivity, specificity, and AUC of 81%, 82%, and 0.88, respectively, in patients with chronic MI, versus 83%, 92%, and 0.90 in non-MI patients.

Fig. 3. Receiver operating characteristic (ROC) curve comparisons. ROC curves and corresponding area under the curves (AUC) describing the diagnostic performance of rest CTA alone (blue line), stress CTP alone (green line), stress CTP/CTA (pink line), and combined assessment of rest CTA and stress-rest CTP (red line) to identify flow-limiting stenosis at the vessel level (A) and the patient level (B). CTA: computed tomographic angiography, CTP: perfusion computed tomography.

DISCUSSION

In this study, we assessed the diagnostic performance of stress-alone CTP/CTA via 320-slice CT compared with integrated stress CTP/CTA and rest CTA/CTP, using invasively determined FFR as the reference standard, in patients with high coronary calcium score and/or coronary stents, who would benefit most from CTP. In our study population, integration of rest CTA/CTP into a stress CTP/CTA provided a minor improvement in specificity in per-vessel level analysis with the cost of increased scanning time, radiation exposure, and contrast medium for rest CTA/CTP, but there was no significant improvement in per-patient diagnostic performance for detection of flow-limiting stenosis. To our knowledge, this is the first study to demonstrate the feasibility of a stress CTP/CTA alone protocol for assessing both coronary stenosis and stress myocardial perfusion.

Our study results are consistent with a recent study by Rief et al. [13] in that integrating stress CTP into rest CTA improved CAD diagnostics and in-stent re-stenosis compared with rest CTA alone. However, in contrast with many previous studies that used a rest CTA first protocol and considered stress CTP as an optional test, we started our CT examinations with stress CTP and followed with rest CTA. Because it avoids contamination by contrast medium that would have been injected for rest CTA, the stress-first approach is preferable for assessing myocardial ischemia [14], and it can be argued that obtaining accurate stress CTP images is more important than rest CTA for this patient population in whom the use of CTA is generally considered unreliable or inappropriate.

In this study, simultaneous assessment of the coronary artery on stress CTP images could provide comparable diagnostic accuracy to rest CTA in detecting coronary luminal stenosis as a result of high rates of non-evaluable coronary artery segments on both rest and stress CTA images. Considering the limited value of rest CTA/CTP in stress-first comprehensive CT procedures in our study, routine acquisition of rest CTA/CTP after stress CTP/CTA is not justified in patients with high calcium score or who have stents. Therefore, in clinical settings, we suggest the use of stress-only CTA/CTP protocols if the patient's calcium score is >400 and/or if the patient has a stent. Meanwhile, a rest CTA/CTP first protocol can be followed by stress CTP if the patient's stenosis is within the range of 30–90%. We employed a first-generation 320-slice CT scanner, resulting in a relatively high dose of radiation. Now, with a newer generation of CT scanners, radiation doses can be much lower.

Stress myocardial CTP is not the only strategy for improving the accuracy of noninvasive evaluation of flow-limiting CAD. Recently, noninvasive FFR calculated using CTA (FFR-CT) has been demonstrated to be moderately accurate for detecting FFR in cases with significant stenosis [15,16]. With FFR-CT, the he-

modynamic significance of coronary artery stenosis can be assessed from rest CTA without performing stress CTP. Currently, several vendors provide on-site FFR-CT applications, which may increase the applicability of the technology in clinical and research settings [17,18]. However, computation of FFR-CT is dependent on CTA image quality [19], and further studies may be required, especially in the presence of heavily calcified plaques and prior stents.

Limitations

Several limitations of this study should be acknowledged. First, our sample size was small, and our study design was retrospective. Second, because CT accuracy was assessed in patients who had subsequently undergone ICA, there may be a selection bias in our study population. Third, patient- and vessel-based analyses were performed; however, the diagnostic accuracy of CTA should ideally be performed on a per-segment basis. In other words, it is not clear whether an anatomically significant stenosis according to coronary CTA is identical to an angiographic segment with an invasive FFR value <0.8 . We lack FFR measurements in vessels with luminal narrowing $\geq 90\%$ on ICA that were previously categorized as having functionally significant stenoses. Although these categorizations were based on reasonable assumptions, some patients might have had well-developed collaterals; thus, the true FFR, if measurable, might have been >0.8 . This issue would be relevant for patients with luminal stenosis $\geq 90\%$ in whom the CTP failed to show ischemia in this zone and, thus, were classified as false negatives. Additionally, beta-blockers may have hidden signs of ischemia in patients with significant CAD, because beta-blockers have been shown to increase hyperemic myocardial blood flow. The usefulness of stress-alone cardiac CT without rest scanning should not be generalized beyond this patient population. Stress-alone protocols might also be used in patients without heavy calcification or stents if stress CTP/CTA could be performed without obtaining motion artifacts. However, higher temporal resolution and further optimization of contrast enhancement protocol are necessary for a more robust evaluation of coronary arteries using stress CTP images. We employed prospective gating only to reduce radiation dose. Advantages of retrospective gating, such as providing alternative phases with fewer motion artifacts and combining analyses of wall motion abnormalities, may improve the diagnostic accuracy of stress CTP/CTA. Lastly, we did not evaluate the utility of stress CTA as a guide for revascularization therapy, which was beyond the scope of this study.

Conclusion

In patients with high calcium score and coronary stent, simultaneous assessment of myocardial ischemia and coronary arterial stenosis with stress CTP images alone yielded high diagnostic

accuracy and was more convenient because it offered lower radiation exposure and less need for contrast medium by eliminating rest CTA. Further studies are warranted to evaluate whether a stress CTP/CTA protocol without rest CTA can provide sufficient information about coronary morphology in patients who are scheduled for revascularization therapy.

Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.22468/cvia.2016.00094>.

Conflicts of Interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008;359:2324-2336.
2. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008;52:1724-1732.
3. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography: A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 2010;56:1864-1894.
4. Arbab-Zadeh A, Miller JM, Rochitte CE, Dewey M, Niinuma H, Gottlieb I, et al. Diagnostic accuracy of computed tomography coronary angiography according to pre-test probability of coronary artery disease and severity of coronary arterial calcification. The CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) International Multicenter Study. *J Am Coll Cardiol* 2012;59:379-387.
5. George RT, Silva C, Cordeiro MA, DiPaula A, Thompson DR, McCarthy WF, et al. Multidetector computed tomography myocardial perfusion imaging during adenosine stress. *J Am Coll Cardiol* 2006;48:153-160.
6. George RT, Jerosch-Herold M, Silva C, Kitagawa K, Bluemke DA, Lima JA, et al. Quantification of myocardial perfusion using dynamic 64-detector computed tomography. *Invest Radiol* 2007;42:815-822.
7. George RT, Arbab-Zadeh A, Miller JM, Kitagawa K, Chang HJ, Bluemke DA, et al. Adenosine stress 64- and 256-row detector computed tomography angiography and perfusion imaging: a pilot study evaluating the transmural extent of perfusion abnormalities to predict atherosclerosis causing myocardial ischemia. *Circ Cardiovasc Imaging* 2009;2:174-182.
8. Rochitte CE, George RT, Chen MY, Arbab-Zadeh A, Dewey M, Miller JM, et al. Computed tomography angiography and perfusion to assess coronary artery stenosis causing perfusion defects by single photon emission computed tomography: the CORE320 study. *Eur Heart J* 2014;35:1120-1130.
9. Bongartz G, Golding SJ, Jurik AG, Leonardi M, van Persijn van Meerten E, Rodríguez R, et al. European Guidelines for Multislice Computed Tomography. Funded by the European Commission. Contract number FIGM-CT2000-20078-CT-TIP.
10. Miller JM, Dewey M, Vavere AL, Rochitte CE, Niinuma H, Arbab-Zadeh A, et al. Coronary CT angiography using 64 detector rows: methods and design of the multi-centre trial CORE-64. *Eur Radiol* 2009;19:816-828.
11. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;105:539-542.
12. Ko BS, Cameron JD, Meredith IT, Leung M, Antonis PR, Nasir A, et al. Computed tomography stress myocardial perfusion imaging in patients considered for revascularization: a comparison with fractional flow reserve. *Eur Heart J* 2012;33:67-77.
13. Rief M, Zimmermann E, Stenzel F, Martus P, Stangl K, Greupner J, et al. Computed tomography angiography and myocardial computed tomography perfusion in patients with coronary stents: prospective intraindividual comparison with conventional coronary angiography. *J Am Coll Cardiol* 2013;62:1476-1485.
14. Techathit T, Cury RC. Stress myocardial CT perfusion: an update and future perspective. *JACC Cardiovasc Imaging* 2011;4:905-916.
15. Min JK, Leipsic J, Pencina MJ, Berman DS, Koo BK, van Mieghem C, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA* 2012;308:1237-1245.
16. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol* 2011;58:1989-1997.
17. Coenen A, Lubbers MM, Kurata A, Kono A, Dedic A, Chelu RG, et al. Fractional flow reserve computed from noninvasive CT angiography data: diagnostic performance of an on-site clinician-operated computational fluid dynamics algorithm. *Radiology* 2015;274:674-683.
18. Ko BS, Cameron JD, Munnur RK, Wong DT, Fujisawa Y, Sakaguchi T, et al. Noninvasive CT-Derived FFR based on structural and fluid analysis: a comparison with invasive FFR for detection of functionally significant stenosis. *JACC Cardiovasc Imaging* 2016 Oct 14 [Epub ahead of print]. <http://dx.doi.org/10.1016/j.jcmg.2016.07.005>.
19. Min JK, Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, et al. Effect of image quality on diagnostic accuracy of noninvasive fractional flow reserve: results from the prospective multicenter international DISCOVER-FLOW study. *J Cardiovasc Comput Tomogr* 2012;6:191-199.