Additional diagnostic value of first-pass myocardial perfusion imaging without stress when combined with 64-row detector coronary CT angiography in patients with coronary artery disease

Corresponding author:

Toru Miyoshi, MD, Department of Cardiovascular Therapeutics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

Address: 2-5-1 Shikata-cho, Okayama 700-8558, Japan.

Phone: +81-86-235-7351; Fax: +81-86-235-7353; E-mail: miyoshit@cc.okayama-u.ac.jp

Kazuhiro Osawa, MD[1], Toru Miyoshi, MD[2], Yasushi Koyama, MD[3], Katsushi Hashimoto, MD[1], Shuhei Sato, MD[4], Kazufumi Nakamura, MD[1], Nobuhiro Nishii, MD[1], Kunihisa Kohno, MD[1], Hiroshi Morita, MD[2], Susumu Kanazawa, MD[4], Hiroshi Ito, MD[1]

[1]Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

[2]Department of Cardiovascular Therapeutics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

[3]Cardiovascular Center, Sakurabashi-Watanabe Hospital, Umeda, Kita-ku, Osaka, Japan

[4]Department of Radiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

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Abstract

Objective: Multi-detector coronary computed tomography angiography (CCTA) can detect coronary stenosis, but it has a limited ability to evaluate myocardial perfusion. We evaluated the usefulness of first-pass CT-myocardial perfusion imaging (MPI) in combination with CCTA for diagnosing coronary artery disease (CAD).

Methods: A total of 145 patients with suspected CAD were enrolled. We used 64-row multi-detector CT (Definition Flash, Siemens). The same coronary CCTA data were used for first-pass CT-MPI without drug loading. Images were reconstructed by examining the signal densities at diastole as color maps. Diagnostic accuracy was assessed by comparison with invasive coronary angiography.

Results: First-pass CT-MPI in combination with CCTA significantly improved diagnostic performance compared with CCTA alone. With per-vessel analysis, the sensitivity, specificity, positive predictive value, and negative predictive value increased from 81% to 85%, from 87% to 94%, from 63% to 79%, and from 95% to 96%, respectively. The area under the receiver operating characteristic curve for detecting CAD also increased from 0.84 to 0.89 ($p = 0.02$). First-pass CT-MPI was particularly useful for assessing segments that could not be directly evaluated due to severe calcification and motion artifacts.

Conclusion: First-pass CT-MPI has an additional diagnostic value for detecting coronary stenosis, in particular in patients with severe calcification.

What is already known about this subject?

Pharmacological adenosine stress CT myocardial perfusion imaging is an established method for detecting coronary artery disease. However, the results of studies evaluating the usefulness of first-pass myocardial perfusion imaging without drug loading have not been consistent.

What does this study add?

We evaluated the feasibility and diagnostic accuracy of first-pass myocardial perfusion imaging without drug loading in combination with CT angiography for diagnosing coronary artery disease.

How might this impact on clinical practice?

In this study, first-pass myocardial perfusion imaging in combination with CT angiography significantly improved diagnostic performance compared with CT angiography alone. This technique may complement CT angiography for diagnosing coronary artery disease.

INTRODUCTION

Coronary computed tomography angiography (CCTA) using 64-row detector CT is a feasible noninvasive modality for detecting coronary artery disease (CAD).[1] Despite this excellent performance, CCTA has limitations in cases of severe calcified coronary arteries and has substantial motion artifacts. To overcome these problems, stress single-photon emission computed tomography (SPECT) [2], stress echocardiography [3], and magnetic resonance imaging [4] have been used simultaneously. Recent studies demonstrated that pharmacological adenosine stress CT myocardial perfusion imaging (MPI) is a promising method for the detection of CAD [5]; however, this method requires additional contrast medium and radiation exposure.

A previous study showed that myocardial perfusion without stress is affected by coronary stenosis.[6] Coronary capillary microvessels autoregulate their hydrostatic blood pressure to maintain homeostasis. With moderate levels of coronary stenosis, the epicardial coronary pressure remains constant by increasing capillary resistance in the corresponding myocardial territory.[7] In individuals without myocardial infarction, when coronary stenosis becomes severe, the decrease in myocardial blood volume becomes prominent because a large amount of the perfusion bed shuts down, which is seen attenuation of myocardial perfusion on first-pass CT-MPI.

We applied this theory to CCTA. We reconstructed first-pass CT-MPI data that were simultaneously acquired during CCTA in patients with suspected CAD. The purpose of this study was to evaluate the feasibility and diagnostic accuracy of first-pass CT-MPI without stress for detecting clinically important coronary artery stenosis compared to invasive coronary angiography, which was the reference standard.

METHODS

Detailed methods are provided in the online supplement.

Study design and patient population

This study population consisted of consecutive patients with suspected CAD who therefore underwent CCTA at Okayama University Hospital between August 2011 and December 2012 (Figure 1). The following candidates were excluded: Patients with acute clinical instability, contraindications to iodinated contrast material (known allergy or serum creatinine level >1.5 mg/dl), non-sinus rhythm, previous myocardial infarction, evidence of Q waves on resting electrocardiography, previous coronary stent implantation, and previous coronary artery bypass graft surgery. In total, 145 patients were enrolled in this study. All patients underwent CCTA and invasive coronary angiography within 30 days. First-pass CT-MPI was simultaneously obtained during CCTA in all patients. Among the 145 patients, 35 also underwent a nuclear stress test within 30 days. This study was approved by the institutional ethics committee on human research. Written informed consent was given by all patients before the study. This study was conducted in accordance with the latest version of the Declaration of Helsinki.

Imaging acquisition

CT protocol

We obtained 128-slice CT scans using a DCT scanner (SOMATOM Definition Flash, Siemens Medical Solutions, Germany).[8]

First-pass CT-MPI

Retrospective image reconstruction was performed at 5% phase increments throughout the cardiac cycle. A total of 20 image data sets were reconstructed. The slice thickness was 3 mm. The short-axis images were reconstructed from 20 image data sets using the standard double

oblique method. The images were analyzed with a commercially available cardiac evaluation software program (Cardiac CT Image Report CIR-SV03, bundled software Vascular Volume Mapping [VVM], Siemens compatible version 1.0, ARGUS B.M.C., Ehime, Japan).

Nuclear stress testing

All stress and rest nuclear SPECT examinations were performed according to standard institutional clinical protocols with ^{99m}Tc or ^{201}Tl as the tracer using a dual detector cardiac gamma camera (DISCOVERY, NM/CT 670 GE Healthcare).

Invasive coronary artery angiography

Invasive coronary artery angiography was performed by one experienced senior cardiologist (H.K.) according to standard procedures using the transradial Judkin's technique. To visualize the left coronary artery, at least six projections were obtained; for the right coronary artery, at least four projections were obtained.

Image processing and interpretation

Reference standard: Quantitative coronary angiography

Quantitative coronary artery angiography analysis was performed to determine the percent stenosis in each coronary segment. Coronary artery stenosis was defined as "significant" if the mean luminal diameter narrowing exceeded 50%.

Coronary artery CT angiography: CCTA

The presence of coronary artery stenosis was defined as a luminal obstruction of greater than 50% of the diameter. All coronary artery segments were assessed for the presence of significant stenosis.

CT-MPI

The same raw data used for CCTA were used to create short-axis images via reconstruction at

the mid- to end-diastolic phase of the cardiac cycle and were finally expressed in a bulls-eye map. Assignment of the left ventricular segment was based on the 16 myocardial segment models, excluding the apical segment.[9] Perfusion imaging was expressed with color maps coded according to the CT value.

SPECT-MPI

Data were evaluated using short-axial, horizontal long-axial, and vertical long-axial source images. Gated SPECT data, if acquired, were also presented to the readers. Disagreements in data analysis between the two observers were resolved by consensus reading.

Matching of perfusion-based segments to the corresponding vascular territory

To ensure correct association of the myocardial segments with the correct vascular territory, angiographic visualization of vessel dominance was used to decide which vessel supplied the inferior and inferoseptal territories. Moreover, we also considered which vessel, diagonal branch, or obtuse marginal branch was dominant in the basal to mid-anterolateral wall.

Radiation dose estimates of CT

We calculated the effective radiation dose for each component of the cardiac CT examination by multiplying the dose-length product by a conversion coefficient for the chest (k = 0.014 mSV/mGy/cm).[8]

Statistical analysis

All continuous variables are presented as the mean ± SD, and categorical variables are expressed as frequencies or percentages. The inter-observer coefficient of variation was <5% as assessed in 20 randomly selected samples. With invasive coronary angiography as the primary reference, the diagnostic accuracies of CCTA, CT-MPI, CCTA plus CT-MPI, and SPECT-MPI were expressed in terms of sensitivity, specificity, positive predictive value (PPV), and negative

predictive value (NPV) for the detection of vascular territories with significant obstructive coronary artery stenosis. Diagnostic performance was calculated on a per-vessel and per-patient basis. The vessel-based analysis included the right coronary artery (RCA), left anterior descending artery (LAD), and left circumflex artery (LCX) in all patients. CCTA diagnosis was reclassified according to CT-MPI analysis (Figure 2). The area under the receiver operating characteristic (ROC) curve (C statistic) was calculated for all diagnostic testing strategies for which a reference standard was available. A p value <0.05 was considered statistically significant. The area under the ROC curve was compared using the ROCCOMP command (Stata 10; StataCorp, College Station, TX). Other statistical analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Study population

Clinical characteristics of the study population are shown in Table 1. Of the 145 study participants (mean age 65.7 ± 12.4 years, 61% men), 31% had diabetes mellitus and 24% were current smokers. The average volume of the contrast dose for CT-MPI and CCTA was 70 ± 12 ml. The average effective radiation dose for cardiac CT examination was 14.8 ± 2.9 mSV. The average radiation dose for stress SPECT was 4.5 ± 0.6 mGy with ^{99m}Tc (n = 31) and 26.3 ± 5.8 mGy with ^{201}Tl (n = 4).

Invasive coronary angiography

Invasive coronary artery angiography showed that 49 (34%) patients had more than 50% stenosis in at least one coronary artery. Of the 49 patients with stenotic vessels as determined with invasive coronary angiography, 19 (39%) had single-vessel disease, 18 (37%) had double-vessel disease, and 12 (24%) had triple-vessel disease. On a per-vessel basis, 91 of the 435 vessels had significant stenosis. Among the 91 stenotic vessels, 38 (42%) were in the LAD, 25 (27%) were in the LCX, and 28 (31%) were in the RCA.

Analysis in all patients

Representative images of CCTA, CT-MPI, stress SPECT-MPI, invasive of coronary angiography, and short-axial and long-axial left ventricular CT image are presented in the Figure 3 and 4.

With CCTA, luminal diameter narrowing of more than 50% was diagnosed in 69 (48%) patients and 118 (27%) vessels. Among them, 22 patients had at least one non-evaluable vessel, mainly due to severe calcification. First-pass CT-MPI showed that 48 patients (33%) had perfusion abnormalities, and among 435 vascular territories, 100 (23%) had perfusion

abnormalities. Among 21 (5%) vessels with moderate stenosis as seen with CCTA, CT-MPI revealed seven territory defects. Finally, CCTA plus first-pass CT-MPI identified 97 (22%) stenotic vessel territories in 435 vessel territories in 145 patients. Table 2 shows the diagnostic accuracy of CCTA, CT-MPI, and CCTA plus CT-MPI in all patients. CCTA plus first-pass CT-MPI yielded the following results for detecting vascular territories with more than 50% coronary stenosis (as determined with invasive angiography): sensitivity, 0.85; specificity, 0.94; PPV, 0.79; and NPV, 0.96. Per-patient results were as follows: sensitivity, 0.92; specificity, 0.89; PPV, 0.80; and NPV, 0.96. We observed a significant improvement in the area under the ROC curve for CCTA plus first-pass CT-MPI for distinguishing stenotic coronary arteries compared to CCTA alone, with an increase from 0.84 to 0.89 with per-vessel analysis ($p = 0.02$) and from 0.85 to 0.90 ($p = 0.04$) with per-patient analysis.

Analysis with three modalities—conventional coronary angiography, CCTA plus CT-MPI, and stress SPECT-MPI—in 35 patients

Thirty-five patients were assessed with all three modalities, invasive coronary angiography, CCTA plus CT-MPI, and stress SPECT-MPI (Table 3). In these patients, we investigated the diagnostic accuracy of CCTA plus first-pass CT-MPI compared with stress SPECT-MPI. With invasive coronary artery angiography, 23 (66%) patients had more than 50% stenosis in at least one coronary artery. On a per-vessel basis, 40 of 105 vessels had significant coronary stenosis. Among the 40 stenotic vessels, 18 (45%) were LADs, 11 (28%) were LCXs, and 11 (28%) were RCAs. First-pass CT-MPI showed perfusion abnormalities in 50 (48%) vascular territories among 105 vascular territories in 22 (63%) patients. CCTA plus first-pass CT-MPI showed that 54 (51%) among 105 vessels were identified as having significant stenosis in the coronary arteries. The area under the ROC curve for CCTA plus CT-MPI tended to increase from 0.64 to

0.77 with per-patient analysis (p = 0.06 vs. CCTA alone). Among the 35 patients, stress SPECT-MPI showed myocardial perfusion defects in 37 (35%) vascular territories of the 105 vascular territories in 24 (69%) patients. Vascular territories with a perfusion defect were seen in the LAD (n = 14), LCX (n = 11), and RCA (n = 12). We observed no significant difference in the area under the ROC curve between CCTA plus first-pass CT-MPI and stress SPECT-MPI (0.85 vs. 0.78 on a per-vessel basis, respectively, p = 0.23, and 0.77 vs. 0.70 on a per-patient basis, respectively, p = 0.61).

DISCUSSION

The main finding of this study is that first-pass CT-MPI in concert with CCTA significantly improved the area under the ROC curve for distinguishing stenotic coronary arteries compared to CCTA alone in patients without a history of CAD. A decrease in myocardial signal density during diastole suggests that the vascular volume of this myocardium was impaired because of significant stenosis of the epicardial coronary artery. We applied this theory and clearly demonstrated the incremental diagnostic value of first-pass CT-MPI obtained simultaneously with CCTA for assessing significant stenosis of coronary arteries in patients without myocardial infarction.

As intra-myocardial perfusion consists mostly of coronary capillaries [6], stenotic epicardial coronary flow fails to supply optimal coronary blood flow. As a result, capillary resistance increases to maintain capillary hydrostatic pressure, which results in a reduction in myocardial blood volume and perfusion attenuation. Thus, the main reason for impaired blood flow caused by more than 75% stenosis is due to capillary derecruitment rather than the stenosis itself. Several reports have investigated first-pass CT-MPI in a clinical setting. Nagao et al. showed that first-pass CT-MPI at systole alone shows excellent performance for identifying CAD patients with a sensitivity and specificity of 0.90 and 0.83, respectively, using pharmacological SPECT-MPI as the reference standard.[10] Yoshida et al. also reported that first-pass CT-MPI alone can detect reduced myocardial enhancement continued from early and late diastole, with a sensitivity and specificity of 0.76 and 0.99, respectively [11]. In the present study, we analyzed myocardial perfusion during diastole because it is less subject to motion artifacts. The result of the overall diagnostic performance of first-pass CT-MPI in combination with CCTA showed a sensitivity and specificity of 0.85 and 0.94, respectively (per-vessel analysis), which is in line

with previous studies. On the other hand, Spiro *et al*. reported no significant difference in CT perfusion between patients with or without obstructive CAD.[12] Several reasons for this difference are possible. Regarding technical issues, the timing of the scan with our methods may be later than that in their methods. In our protocol, the delay before the formal scan was calculated as the time to peak enhancement in the ascending aorta plus 3 s to ensure enhancement of the left ventricular myocardium. However, the protocol reported by Spiro *et al*. has no delay, which may cause insufficient enhancement, leading to poorer diagnostic accuracy of CT-MPI. Regarding patient characteristics, the body mass index in this study (23 ± 4 kg/m^2) was lower than that in their population (30 ± 8 kg/m^2). Obesity attenuates the X-ray beam, which may make detection of hypoperfusion more difficult.

Our results showed a lower diagnostic accuracy of CCTA than a previous study [13], especially in terms of the specificity and PPV in both patient-based analysis (0.71) and vessel-based analysis (0.63). This lower diagnostic performance may be explained by high coronary artery calcification in the patients in our study (Agatston score 455 [644], expressed as the median [interquartile range] in all 145 patients) that may negatively impact CCTA performance; however, the combination of CCTA and CT-MPI significantly improved the diagnostic performance. With per-vessel–based analysis, the specificity increased from 0.87 to 0.94, and PPV increased from 0.63 to 0.79. This diagnostic improvement may be caused by changes in diagnosis with CCTA alone of insufficiently evaluated lesions, which were considered to show significant stenosis owing to severe calcification or substantial banding artifact. Another reason for improvement in the diagnostic performance was due to changes from positive diagnosis in moderate stenotic lesions with CCTA to negative diagnosis with CCTA in combination with CT-MPI. In principle, first-pass CT-MPI showed a defect only with severe

stenosis, and first-pass CT-MPI can compensate when CCTA shows borderline stenosis.

First-pass CT-MPI has other advantages. It may provide perfusion information without concerns about adverse reactions to the agents used in pharmacological stress testing. In addition, compared with pharmacological stress CT perfusion, first-pass CT-MPI does not require additional radiation doses or the use of contrast medium. Thus, first-pass CT-MPI is informative, although it does have some disadvantages. First, CT-MPI shows a potentially high rate of false positives. As first-pass CT-MPI data were obtained at the same time as CCTA, the time gap between attaining images of the epicardial coronary artery and capillary beds is an unsurpassable problem for the first-pass and a one-time image-acquiring protocol. Insufficient filtration of contrast medium into the myocardium may result in false-positive appearances. Second, first-pass CT-MPI cannot distinguish reversible myocardial ischemia from irreversible myocardial ischemia. The perfusion defects at the site of an old myocardial infarction are fixed and cannot be distinguished as a defect site that is or is not viable. This study excluded previous myocardial infarction and evidence of Q waves on resting electrocardiography; however, previous cohort studies using cardiac MRI showed the presence of unrecognized myocardial infarction.[14, 15] Thus, we cannot deny that a certain amount of patients with non-wave myocardial infarction may be included in the current study. Fat deposition in old myocardial infarction and/or decreased vascular blood volume in myocardial scare may substantially alter myocardial signal intensity in the current study. The interpretation of first-pass CT-MPI needs to be cautious in terms of this issue.

Limitations

There were several limitations in this study. First, this is a single-institution, non-randomized study with a small number of patients. Therefore, further investigations in a larger population are

needed to make solid conclusions regarding the value of first-pass CT-MPI. Second, the amount of radiation exposure in this study was relatively high. Our protocol of retrospective gating image acquisition may be an explanation. Our protocol could be improved by using strategies to reduce the radiation dose and electrocardiographically control modulation or prospective sequential scanning.[16] Third, we compared first-pass CT-MPI to stress SPECT-MPI as a non-invasive myocardial perfusion image. However, cardiac MRI may be a better reference standard because SPECT-MPI with poor spatial resolution cannot correctly assess the ischemic area. Fourth, β receptor–blocking agents and sublingual nitroglycerin were used before CT data acquisitions in all participants. β receptor–blocking agents may have no effect on the perfusion images, but sublingual nitroglycerin may make attenuated perfusion smaller.[17] These medications are generally essential for acquiring evaluable images. Even with these agents, our results demonstrated that first-pass CT-MPI was not inferior to stress SPECT-MPI in this study.

Conclusions

CCTA in combination with first-pass CT-MPI provided excellent diagnostic performance compared to CCTA alone, with invasive coronary angiography as the reference standard in patients without a history of CAD. First-pass CT-MPI makes it possible to evaluate not only the degree of epicardial coronary stenosis, but also the extent of impaired myocardium without additional stress, radiation exposure, or contrast injection. Thus, first-pass CT-MPI is complementary to CCTA, and the combination of these two diagnostic techniques is feasible in clinical practice.

Contributions: KO and TM designed the study, drafted the paper, and analyzed and interpreted data. YK, KH, and SS analyzed and interpreted the data. KN, NN, and KK designed the study.

HM, SK, and HI critically revised the manuscript.

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FIGURE LEGENDS

Figure 1

Flow diagram of patient recruitment

Figure 2

Reclassification Criteria. Before CT-MPI analysis, we defined any vessel that was non-evaluable with CCTA as positive for stenosis using the following criteria: those with no vessel wall definition owing to marked motion artifacts, significant structural discontinuity, or heavy calcification and high image noise–related blurring that precluded the acquisition of diagnostic information. After the CT-MPI analysis, non-evaluable vessels were considered positive for stenosis only if they corresponded to a CT-MPI defect in the same vascular distribution. Moderate stenoses (50–70%) on CCTA were reclassified as negative for stenosis if the CT-MPI showed no defect in the same distribution. CCTA stenosis was not reclassified when no stenosis <50% or >70% was apparent on CCTA.

Figure 3

An example of two-vessel disease identified by all modalities. A, Curved multiplanar reformatted CCTA image showed a large calcified plaque in the proximal RCA (white arrow) and significant stenosis in the middle RCA (black arrow). A stenotic lesion was also found in the proximal LAD with non-calcified and calcified plaques (red arrow). B, A CT perfusion image showed perfusion defects in the anterior (white arrow), inferoseptum (red arrow), and inferior walls (green arrow). C, The SPECT-MPI data showed a fully reversible defect throughout the anterior (white arrow) and inferior walls (black arrow). D, Invasive coronary angiography showed severe stenosis in the

proximal LAD (white arrow) and middle of the RCA (black arrow). E, Short-axial (left) and long-axial (right) left ventricular CT images. Short-axis images show impaired myocardial enhancement throughout the anterior (yellow arrow) and inferior walls (red arrow).

Figure 4

An example of one-vessel disease identified by all modalities A, A curved multiplanar reformatted image of CCTA showed heavy calcification in the proximal portions of the LAD (white arrow). B, The SPECT image showed reversible anterior defects throughout the anterior wall (white arrows). C, The CT-MPI data showed a perfusion defect in the anterior wall (white arrows). D, Invasive coronary angiography showed moderate stenosis in the proximal LAD (white arrow). E, Short-axial (left) and long-axial (right) left ventricular CT images. Short-axis images show impaired myocardial enhancement in the anterior wall (yellow arrows).

Table 1. Patient characteristics

Age (years)	65.7 ± 12.4
Male sex	88 (61)
Diabetes mellitus	45 (31)
Hypertension	87 (60)
Dyslipidemia	61 (42)
Body weight (kg)	61 ± 12
Body mass index (kg/m^2)	23.4 ± 3.6
Current smoking	35 (24)
Serum lipid biomarkers (mg/dl)	
Total cholesterol	190.2 ± 35.6
LDL cholesterol	112.6 ± 32.4
HDL cholesterol	55.7 ± 13.6
Serum triglycerides	153.4 (93.5)
Serum creatinine (mg/dl)	0.8 ± 0.2
Baseline medications (%)	
β-blockers	22 (15)
ACEIs/ARBs	58 (40)
Statins	38 (26)
Vital signs	
Systolic blood pressure (mmHg)	129.6 ± 23.4
Diastolic blood pressure (mmHg)	75.0 ± 12.4
Heart rate (beats/min)	68.9 ± 12.2

Data are the number (%) or mean ± SD. LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 2. Diagnostic accuracy of CCTA, first-pass CT-MPI, and CCTA in combination with first-pass CT-MPI for the detection of significantly stenotic coronary arteries in 145 patients

	CCTA		First-pass CT-MPI		CCTA + first-pass CT-MPI	
	Per vessel (n = 435)	Per patient (n = 145)	Per vessel (n = 435)	Per patient (n = 145)	Per vessel (n = 435)	Per patient (n = 145)
No. of results						
True positive	74	46	66	37	77	45
False negative	17	3	25	12	14	4
False positive	44	23	34	11	20	11
True negative	300	73	310	85	324	85
Statistical analysis (%)						
Sensitivity	81	94	73	76	85	92
Specificity	87	76	90	89	94	89
Positive predictive value	63	67	66	77	79	80
Negative predictive	95	96	93	88	96	96

value						
C statics	0.84 (0.80–0.89)	0.85 (0.80–0.90)	0.81 (0.76–0.86)	0.82 (0.75–0.89)	0.89 (0.86–0.93)	0.90 (0.85–0.95)

Table 3. Diagnostic accuracy of CCTA, CT-MPI, CCTA in combination with CT-MPI, and stress SPECT-MPI for detecting significantly stenotic coronary arteries in 35 patients

	CCTA		First-pass CT-MPI		CCTA + first-pass CT-MPI		Stress SPECT-MPI	
	Per vessel (n = 105)	Per patient (n = 35)	Per vessel (n = 105)	Per patient (n = 35)	Per vessel (n = 105)	Per patient (n = 35)	Per vessel (n = 105)	Per patient (n = 35)
No. of results								
True positive	33	22	28	18	34	22	28	19
False negative	7	1	12	5	6	1	12	4
False positive	17	8	15	4	20	5	9	5
True negative	48	4	50	8	45	7	56	7
Statistical analysis (%)								
Sensitivity	83	96	70	78	85	96	70	83
Specificity	74	33	77	67	69	58	86	58
Positive predictive value	66	73	65	82	63	81	76	79
Negative predictive value	87	80	81	62	88	88	82	64
C statistic	0.79 (0.72–0.87)	0.65 (0.50–0.79)	0.72 (0.64–0.81)	0.73 (0.56–0.89)	0.85 (0.78–0.920)	0.77 (0.62–0.92)	0.78 (0.70–0.86)	0.71 (0.54–0.871)