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Myocardial CT perfusion imaging and atherosclerotic plaque characteristics on coronary CT angiography for the identification of myocardial ischaemia

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AIM: To investigate the value of myocardial computed tomography (CT) perfusion imaging (CTP) and atherosclerotic plaque characteristics (APCs) identified on coronary CT angiography (CCTA) for the detection of myocardial ischaemia by using single-photon-emission CT (SPECT) as a reference.

MATERIALS AND METHODS: Thirty-six patients (63.9% males) undergoing combined stress dynamic CTP and CCTA were enrolled and analysed. Myocardial blood flow (MBF) from CTP was quantified and compared between normal and abnormal segments. The ability of CTP and APCs to detect ischaemia was compared to that of SPECT.

RESULTS: Nineteen patients with 78 segments had perfusion abnormalities on CTP. A significant difference was seen in MBF values between normal (118.51±27.86 ml/100 ml/min) and hypoperfused (79.60±21.35 ml/100 ml/min) segments (t=15.832, $p<0.05$). The sensitivity and specificity for identifying ischaemia were 90.91% and 94.97%, respectively, on a per-segment basis, resulting in a r value of 0.737 ($p<0.05$). On a per-vessel basis, the sensitivity and specificity for detecting ischaemia were 86.67% and 84.62%, respectively, for CTP; 93.33% and 58.97%, respectively, for CCTA; and 86.67% and 87.18%, respectively, for CTP combined with CTA, with an area under the receiver-operator characteristic curve (AUC) being 0.87 ($p<0.05$) and 0.887 ($p<0.05$) for CTP and its combination with CTA, respectively. On CCTA, 55 vessels with APCs were detected, with an AUC of 0.737 ($p<0.05$) for APCs combined with CCTA stenosis and 0.802 ($p<0.05$) for APCs combined with CTP.

CONCLUSIONS: Dynamic stress CTP shows good correlation with SPECT for the detection of ischaemia. Additionally, combining APCs with CCTA stenosis has the ability to discriminate ischaemic stenosis.

Introduction

Coronary computed tomography (CT) angiography (CCTA) is an established, reliable diagnostic test[1] used in the

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management of coronary artery disease (CAD), with a high sensitivity and negative predictive value (NPV); however, it is limited in its ability to assess whether a stenosis causes ischaemia, which is clinically important, as ischaemia-causing lesions warrant medical intervention. Because anatomical lesion severity is a poor predictor of haemodynamic significance, functional evaluation of stenoses is recommended for therapeutic decision-making.[2,3]

Dynamic stress myocardial CT perfusion (CTP) is a non-invasive imaging technique recently introduced to quantify myocardial blood flow (MBF)[4] that can provide functional information. Although previous studies have illuminated the diagnostic value of CTP in myocardial ischaemia, many of these studies were static protocols.[5,6] Recently, atherosclerotic plaque characteristics (APCs) detected from CCTA have been proven to have associations with acute coronary syndrome (ACS) and to predict future cardiovascular events[7–9]; these characteristics include positive remodelling (PR), low attenuation plaque (LAP), napkin ring sign (NRS), and spotty calcium (SC), but little is known about the significance of these findings in terms of myocardial ischaemia.

Currently, there is no study assessing ischaemia using CTP and APCs together. The purpose of this investigation was to examine the diagnostic performance of dynamic CTP and APCs in detecting myocardial ischaemia, using single-photon-emission CT (SPECT) as a reference.

Materials and methods

Study population

The local medical ethics committee approved the present study and all patients provided written informed consent. The enrolled patients were those suspected or known to have a diagnosis of CAD who were scheduled for CCTA. They underwent both CTA and stress CTP. Consenting patients meeting the inclusion criteria were also prospectively scheduled for stress myocardial perfusion imaging (MPI) by SPECT. In all 36 patients, the procedures were performed within 2 weeks, from June 2013 to February 2015. Exclusion criteria were prior percutaneous coronary intervention; prior coronary artery bypass graft surgery; suspicion of or recent ACS; prior pacemaker or defibrillator placement; contraindication to adenosine; significant arrhythmia; allergy to iodinated contrast medium; serum creatinine level >1.5 mg/dl; evidence of active clinical instability or life-threatening disease; or inability to hold breath for 30 seconds.

All patients stopped the ingestion of caffeinated foods and medications including theophylline, β-receptor inhibitors, dipyridamole, and diazepam for 24 hours before the stress test. Double venous channels were established in the double forearm vein with 18 and 22 needles placed for the injection of contrast medium and ATP, respectively. Every patient was trained to hold their breath for 30 seconds. After the examination, the patients were observed for 30 minutes.

CCTA and CTP acquisition

CCTA and CTP were obtained using a DSCT system (Somatom Definition Flash, Siemens Medical Solutions, Forchheim, Germany). After injecting 70 ml of iodinated contrast medium (iopamidol-370) at rates of 5 ml/s, CCTA images were obtained using a prospective electrocardiography (ECG)-triggered protocol. Scanning parameters were as follows: collimation 2×64 row detector×0.6 mm, 280 ms gantry rotation time, 100 kV tube potential, and 320 mAs per rotation tube current–time product. The systolic and diastolic phase images were reconstructed with a section thickness of 0.75 mm (interval 0.50 mm).

Eight minutes later, stress CTP images were acquired after ATP infusion (0.14 mg/kg/min for 3 min) using injection of 50 ml of contrast medium and dynamic acquisition mode. Data were acquired during end systole (250 ms after the R-peak at every other R-R interval), with the table shuttling back and forth between the two positions covering a 73 mm anatomical range. A standardised acquisition time of 30 seconds was required for the dynamic scan.

During the stress examination, patients were monitored, including evaluation of electrocardiogram, heart rate, blood pressure, and symptoms. The test was terminated based on the development of the following conditions: arrhythmia, continuous decrease in heart rate, decrease in blood pressure >40 mmHg, acute chest pain, and new elevation or depression in the ST segment.

CCTA analysis

CCTA datasets were transferred into a post-processing workstation (Syngo.via VB10, Siemens, Forchheim, Germany) for further analysis. Transverse sections and automatically generated curved multiplanar reformations were assessed. All evaluable coronary segments were assessed for the presence of stenosis and plaque by two experienced readers who were blinded to all patient and clinical data. The severity of luminal stenosis was determined by visual estimation using the Coronary Artery Disease-Reporting and Data System (CAD-RADS) classification as follows: 1, none or minimal (0–24% stenosis); 2, mild (25–49% stenosis); 3, moderate (50–69% stenosis); 4, severe (70–99% stenosis); and 5, total occlusion (100%). Myocardial ischaemia was defined as ≥50% luminal narrowing (CAD-RADS classification ≥3).

APCs analysis

In each vessel with plaque, a qualitative assessment of APCs was performed, and was considered positive with the presence of at least one of the following features: LAP, NRS, PR, and SC. LAP[10] was plaque with a mean CT attenuation value of <30 HU. NRS[11] was defined as a ring-like peripheral higher CT attenuation surrounding a core with lower CT attenuation. The remodelling index was defined as the ratio of the outer vessel diameter of the lesion area to the average of the diameters of its proximal and distal area. PR[12] was considered when the index was ≥1.1. SC[13] was defined as the presence of a small calcified plaque with a diameter <3 mm in any direction.

CTP analysis

CTP datasets reconstructed with a 2-mm section width were transferred to the corresponding post-processing software (Syngo VPN, Siemens Healthcare). "Myocardial" was selected in "Body PVCT" for analysis. Dynamic CTP studies were qualitatively interpreted visually, using the same 17-segment model as SPECT. On both short-axis and transverse images, the presence of a myocardial perfusion defect was considered when hypoperfusion appeared on two consecutive sections. For quantitative analysis, the MBF values were evaluated, except for the region 1 mm adjacent to the left ventricle and the pericardium. When CCTA was combined with CTP, ischaemia was defined as the presence of at least one area with ≥50% stenosis by CTA with an associated abnormal myocardial perfusion on CTP. All CT studies were independently evaluated by two experienced radiologists blinded to clinical history and other results. All discordant cases were resolved by a consensus reading.

SPECT acquisition and analysis

ATP was injected intravenously at 140 mg/kg/min for 5 min. After 3 minutes, 1,110 MBq technetium-99m methoxyisobutylisonitrile (99mTc-MIBI) was injected intravenously; 30–60 minutes later, ECG-gated myocardial perfusion images were obtained by double detector γ-ray. The left ventricular short axis, vertical long axis, and horizontal long axis images were obtained by SPECT-MPI and the perfusion analysis of 17 segments was performed.[14] All SPECT-MPI studies were analysed by two experienced nuclear medicine physicians who were blinded to CTA and CTP results. When the result was inconsistent, a consensus result was obtained after discussion.

Statistical analysis

All continuous data are expressed as mean ± standard deviation, and categorical variables are expressed as percentages. Differences of MBF in hypoperfusion and non-hypoperfusion segments were assessed using Student's *t*-test. The correlations between CTP, APCs, and SPECT in detecting myocardial ischaemia were evaluated by Spearman's correlation coefficient. Qualitative estimations of CTP, CTA, APCs, and their respective combinations were compared and the corresponding sensitivity, specificity, positive predictive value (PPV), and NPV for the detection of myocardial ischaemia were determined. The diagnostic efficiencies of these values were calculated using the receiver-operator characteristic (ROC) curve. Data analysis was performed using SPSS for Windows (version 17.0, SPSS, Chicago, IL, USA). A *p*-value of <0.05 was considered statistically significant.

Results

Patient characteristics

Clinical characteristics of the study population are presented in Table 1. The DLP of CTP protocol was (610±114.3) mGy·cm and CCTA (262.1±43.57) mGy·cm, resulting in a total dose of (876.4±92.1) mGy·cm. The dose of contrast agent was 135 ml combined with 110 ml of saline.

CCTA and APC findings

On CCTA, 27 of 36 patients with 60 vessels were diagnosed as having ≥50% stenosis (CAD-RADS ≥3). APCs were analysed in each vessel on a vessel basis. In the 108 vessel regions, 55 vessels were detected with APCs, with 21, 7, 26, and 25 vessels showing PR, NRS, LAP, and SC, respectively. Thirty-six vessels were detected with only one APC, 15 with two APCs, three with three APCs, and one vessel with four APCs.

CTP findings using SPECT as reference

CTP showed that 19 patients (19/36) had various degrees of hypoperfusion. There were 38 regions (38/108) and 78 segments (78/612) with abnormal perfusion on a per-vessel and per-segment basis, respectively. The mean MBF of all myocardial segments at dynamic stress CTP was 98.32±30.67 ml/100 ml/min. There was a significant difference in MBF values between normal (118.51±27.86 ml/100 ml/min) and hypoperfused (79.60±21.35 ml/100 ml/min) myocardial segments (t=15.832, $p<0.01$). SPECT detected abnormal myocardial perfusion in 55 segments in 16 cases. On a per-vessel and per-segment basis, the r between CTP and SPECT were 0.669 ($p<0.05$) and 0.737 ($p<0.05$), respectively (Fig. 1a,c).

Diagnostic accuracy of CTA, CTP, and their combination

On a per-patient basis, the sensitivity, specificity, PPV, and NPV were 93.75%, 40%, 55.56%, and 88.89% for CTA; values were 87.5%, 75%, 73.68%, and 88.24% for CTP. Values for CTP combined with CTA were 87.5%, 80%, 77.78%, and 88.89%. Table 2 shows the sensitivity, specificity, PPV, and NPV for CTA, CTP, and CTA combined with CTP on a per-

Table 1
Baseline characteristic of the study population.

Age (years)	62.8±10.2
Male (%)	63.9 (23/36)
Weight (Kg)	64.8±8.2
Height (cm)	172.8±17.6
Body mass index (kg/m2)	23.4±4.8
Heart rate (bpm)	65.7±13.2
Diabetes *n* (%)	47.2 (17/36)
Hypertension *n* (%)	86.1 (31/36)
Dyslipidaemia *n* (%)	41.7 (15/36)
Family history of CAD *n* (%)	38.9 (14/36)
Tobacco abuse *n* (%)	52.8 (19/36)

CAD, coronary artery disease.

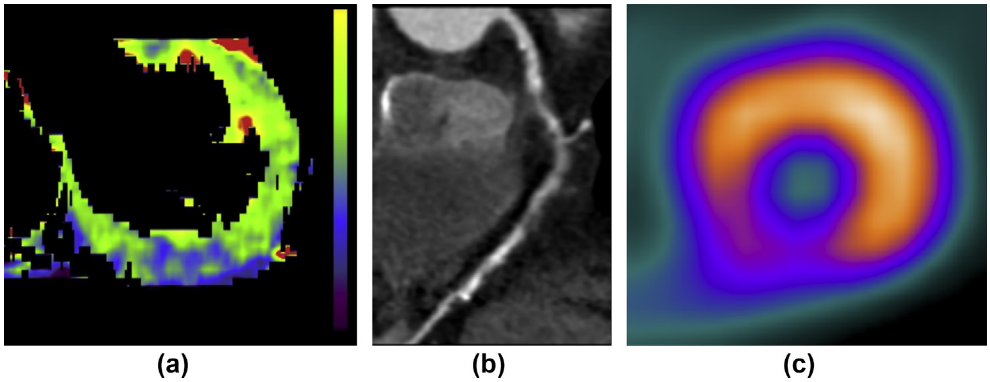

Figure 1 CTP, CCTA, and SPECT results from a 58-year-old woman with chest pain. (a) CTP shows inferior wall perfusion defect, the same result of SPECT (c). (b) CCTA shows diffuse calcification and non-calcification plaques in the RCA, with moderate stenosis.

vessel basis. The *r* of CTP and its combination with CTA correlated to SPECT were 0.669 ($p<0.05$) and 0.702 ($p<0.05$), respectively; the area under the ROC curve (AUC) of these were 0.870 (95% confidence interval [CI]: 0.749–0.992, $p<0.05$) and 0.887 (95% CI: 0.780–0.995, $p<0.05$), respectively (Figs 1 and 2a).

Diagnostic performance of APCs and APCs combined with CTA

Twenty-five APCs were identified in stenotic vessels on CCTA that had abnormal SPECT perfusion. The sensitivity, specificity, PPV, and NPV for CTA combined with APCs were 83.33%, 79.49%, 60.98%, and 92.54%, respectively. The AUCs of APCs and their combination were 0.666 (95% CI: 0.479–0.852, $p=0.09$) and 0.737 (95% CI: 0.575–0.900, $p<0.05$), respectively (Table 2, Fig 2b).

Diagnostic performance of the combination of CTP and APCs

Thirty-three vessels with APCs had hypoperfusion on CTP (Fig 3). The sensitivity, specificity, PPV, and NPV for CTP combined with APCs were 76.67%, 87.18%, 69.7%, and 90.67%, respectively, with an AUC of 0.802 (95% CI: 0.660–0.943, $p<0.05$; Table 2, Fig 2c).

Table 2
Diagnostic performance of CTA, CTP, and APCs (%).

	Sensitivity	Specificity	PPV	NPV
Per-patient				
CTA	93.75	40	55.56	88.89
CTP	87.5	75	73.68	88.24
CTA combined with CTP	87.5	80	77.78	88.89
Per-vessel				
CTA	93.33	58.97	46.67	95.83
CTP	86.67	84.62	68.42	94.29
CTA combined with CTP	86.67	87.18	72.22	94.44
APCs	83.33	61.54	45.45	90.57
CTA combined with APCs	83.33	79.49	60.98	92.54
CTP combined with APCs	76.67	87.18	69.7	90.67

CTA, computed tomography angiography; CTP, computed tomography perfusion; APCs, atherosclerotic plaque characteristics; PPV, positive predictive value; NPV, negative predictive value.

Discussion

As a non-invasive method, CCTA plays a very important role in the diagnosis of CAD, but with a high false-positive rate and inability to discriminate myocardial ischaemia. It is important to evaluate both coronary artery structural and functional information in patients with suspected or known CAD. The present study demonstrated that dynamic stress CTP correlates well with SPECT for detecting myocardial perfusion defects in patients with suspected or known ischaemic heart disease. The diagnostic accuracy of the integration of CTP and CTA for identifying ischaemia was improved compared to CTA and CTP alone, providing haemodynamic functional information of detected lesions. Additionally, when APCs were combined with CCTA stenosis, meaningful data for the detection of ischaemic stenosis was provided, which can serve as an adjuvant diagnostic technique.

Previous studies[4–6,15] demonstrated the ability of CTP to detect ischaemia; however, many of these studies were static or not for whole heart perfusion. In this study, CCTA was first performed with the determination of the scan range of CTP. Although the detector coverage can satisfy the whole cardiac perfusion, there would be some misalignments for larger hearts or respiratory movement. Stress CTP was performed for 5 minutes in dynamic acquisition mode after CCTA, resulting in 8 minutes for flowing out of contrast medium, so that the influence of contrast medium would be weakened. In evaluation of the results, the first or second image could serve as a baseline.

MBF values were evaluated in the present study, with a significant difference between non-ischaemic and ischaemic myocardium. CTP showed a high sensitivity and specificity for the detection of myocardial perfusion abnormalities but with a high false-positive rate, which might be due to respiratory motion and hard beam artefacts, especially related to the septal wall at the base. Although one study[16] reported correction of hard beam artefacts, they cannot be completely removed. Moreover, the number of samples in this study was relatively small, and although it did meet the statistical requirements, a larger sample size is needed to obtain more reliable data.

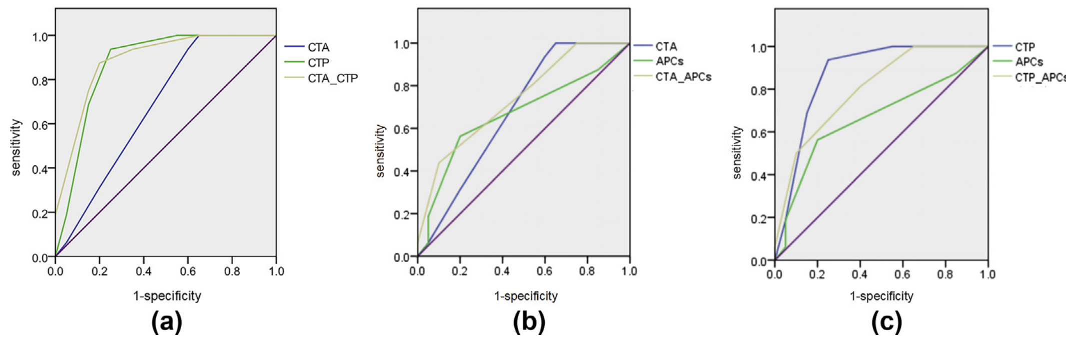

Figure 2 The ROC for discriminating myocardial ischaemia with CTA, CTP, and APCs on a per-vessel basis. (a) AUC for CTA, CTP, and their combination. The AUC for CTP (0.870; 95%CI: 0.749–0.992, $p<0.05$) was significantly higher than that of CTA (0.678; 95%CI: 0.503–0.853, $p=0.07$). It improved up to 0.887 (95%CI: 0.780–0.995, $p<0.05$) when CTA and CTP were combined. (b) AUC for CTA, APCs, and their combination. APCs (0.666; 95%CI: 0.479–0.852, $p=0.09$) alone did not have the ability to detect ischaemia; it was possible with the addition of CCTA stenosis, resulting in an AUC of 0.737 (95%CI: 0.575–0.900, $p<0.05$). (c) AUC for CTP, APCs, and their combination. A decreased AUC can be seen when CTP is combined with APCs (0.802; 95%CI: 0.660–0.943, $p<0.05$).

The present study showed that the sensitivity and specificity of CTP combined with CTA were 86.67% and 87.18%, respectively, which were similar to those reported by Bamberg *et al.*[17] who found a higher sensitivity (93%) and similar specificity (87%) using fractional flow reserve as a reference standard.

In the present study, CTP had better diagnostic value in detecting ischaemia than CCTA alone. After combination with CTP on a per-vessel basis, the specificity of CTA increased from 58.97% to 87.18% and the PPV increased from 46.67% to 72.22%, with the AUC improving from 0.678 to 0.887, which can rule out many false-positive CCTA results in clinical practice. Among the 32 stenotic vessels overestimated by CCTA, 16 vessels showed normal findings on CTP. For these patients, the addition of CTP could largely reduce unnecessary invasive procedures. The haemodynamic information obtained by CTP was a good supplement to CCTA, which provides only morphological data, suggesting the use of the comprehensive one-stop mode of CT for the diagnosis of myocardial ischaemia in CAD.

Recently, studies of the correlation between APCs and ACS have been reported. The predictive value of APCs was confirmed by Nadjiri[18] and Ferencik,[19] showing a higher risk of main adverse cardiac events in patients presenting with ACS than in stable patients; however, the diagnostic ability of APCs to detect myocardial ischaemia remains unclear. In the present study, integrating APCs and CCTA stenosis could improve discrimination of ischaemia (Fig 2b), with an AUC of 0.737 ($p<0.05$). This is similar to the study reported by Park,[20] which showed that the AUC gradually improved when APCs were combined with CTA stenosis. Bakhshi[21] indicated that APCs were independent predictors of ischaemia by SPECT. Although the present study showed that APCs alone or CTA alone did not have the ability to identify ischaemia (AUC=0.666, $p=0.09$ and AUC=0.678, $p=0.07$, respectively), their combination did. Considering its value in ACS and in ischaemia, the features of plaques should be taken into consideration during clinical evaluation.

The performance of CTP combined with APCs was also assessed, demonstrating an AUC of 0.802 ($p<0.05$), which was lower than that of CTP alone; however, the specificity and PPV of their combination showed slight increases, with specificity ranging from 84.62% to 87.18% and PPV ranging from 68.42% to 69.7%. In clinical decision-making, adding APCs to CTP would reduce the misdiagnosis rate if CTP was positive.

This study has some limitations. First, SPECT was used as the reference standard for ischaemia in CAD, which has a low sensitivity, and H_2O positron-emission tomography (PET) would be a preferable method. Second, the number of patients enrolled in the present study was relatively small,

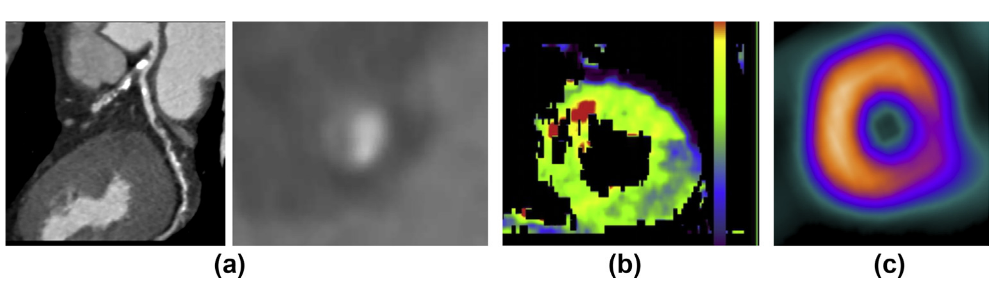

Figure 3 CCTA, CTP, and SPECT results in a 60-year-old man with chest pain. (a) CCTA shows diffuse calcification and non-calcification plaques in the circumflex artery, with moderate to severe stenosis. The NRS and low attenuation plaque can be seen in the middle segment (ai). (b) CTP shows an inferolateral wall perfusion defect, the same result of SPECT (c), with circumflex artery being the causative vessel (a).

and there was a high positive rate with possible selection bias that might influence the validity of the study. Large-scale multicentre trials are needed to validate the findings. Third, the total radiation dose of 12.27 mSv was relatively high, which may be solved by third-generation dual-source Force CT. In addition, artefacts might have influenced the evaluation of CTP images, leading to an increased false-positive rate. Lastly, only the qualitative features of plaques were evaluated, and integration with quantitative features is necessary in future studies.

In conclusion, dynamic stress CTP correlates well with SPECT for detecting myocardial perfusion defects in patients with suspected or known ischaemic heart disease. The combination of CTP and CTA proves to be a comprehensive anatomical–physiological approach, providing essential information for clinical decision-making in patients with ischaemic CAD and avoiding unnecessary invasive coronary angiography procedures in patients without myocardial ischaemia. In addition, adding APCs to CCTA stenosis has the ability to discriminate ischaemic stenosis.

Conflicts of interest

The authors declare no conflict of interest.

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