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E-mail: jzus@zju.edu.cn

A pilot study on diagnosis of coronary artery disease using computed tomography first-pass myocardial perfusion imaging at rest

Qi WANG[1], Jing QIN[2], Lu-yue GAI[†‡1], Yun-dai CHEN[1], Wei DONG[1], Zhi-wei GUAN[3], Zhi-guo WANG[1], Zhi-jun SUN[1], Jia-he TIAN[3]

([1]*Department of Cardiology, Chinese PLA General Hospital, Beijing 100853, China*)

([2]*Department of Ultrasound, Chinese Armed Police General Hospital, Beijing 100039, China*)

([3]*Department of Nuclear Medicine, Chinese PLA General Hospital, Beijing 100853, China*)

[†]E-mail: luyuegai301@yahoo.com.cn

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Abstract: Background: Although computed tomography coronary angiography (CTCA) can identify coronary stenosis, little data exists on the ability of multislice computed tomography (MSCT) to detect myocardial perfusion defects at rest. Methods: In 33 patients with diagnosed or suspected coronary artery disease (CAD), CTCA using retrospective electrocardiography (ECG) gating at rest and invasive coronary angiography (ICA) was performed. The 2D myocardial images were reconstructed in diastolic and systolic phases using the same raw data for CTCA. CT values of the myocardium were used as an estimate of myocardial enhancement, which were shown by color mapping. Myocardial ischemia was defined as a pattern of transient endocardial hypo-enhancement at systole and normal enhancement at diastole. The results of ICA were taken as the reference standard. Results: When a diameter reduction of more than 50% in ICA was used as diagnostic criteria of CAD, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CT first-pass myocardial perfusion imaging (MPI) at rest were 0.85, 0.67, 0.92, and 0.50 per patient, respectively, and 0.58, 0.93, 0.85, and 0.76 per vessel, respectively. Conclusions: CT first-pass MPI at rest could detect CAD patients, which could become a practical and convenient way to detect ischemia, consequently offering the ability for MSCT to act as a "one stop shop" for the diagnosis of CAD.

Key words: Coronary artery disease, Myocardial ischemia, Perfusion, Multislice computed tomography
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1 Introduction

In recent years, noninvasive assessment of coronary artery anatomy has become possible with the introduction of multislice computed tomography (MSCT). CT coronary angiography (CTCA) has emerged as an accurate and robust imaging technique that is able to detect the presence of atherosclerosis in coronary artery, rule out the presence of significant coronary artery disease (CAD) accurately, and help to guide the process of coronary intervention (Mollet *et al*., 2005; Raff *et al*., 2005; Henneman *et al*., 2008; Li *et al*., 2010). However, the physiological significance of the coronary lesion can be uncertain (Meijboom *et al*., 2008). Treatment strategies for CAD also remain uncertain in the case of a positive CTCA result as hemodynamic information is needed.

More recently, animal models of stenosis and preliminary human studies have shown that MSCT could also detect myocardial ischemia under adenosine-induced stress (Kurata *et al*., 2005; George *et al*., 2006; 2007; Blankstein *et al*., 2009). However, the process of stress CT perfusion imaging is inconvenient and time-consuming, and is difficult to carry out in clinical practice.

[‡] Corresponding author

During the 1990s, physiological studies showed the influences of coronary flow and myocardial perfusion at systolic phase (Goto *et al*., 1991; Iwanaga *et al*., 1995). Some studies demonstrated that myocardial ischemia could influence the myocardial microvascular resistance, with the effects most prominent in the subendocardium during systole and in the subepicardium during diastole (Sabbah and Stein, 1982; Chilian, 1991). The capillary microvessels show a greater phasic change in microvascular resistance (Toyota *et al*., 2002; Pugliese *et al*., 2006). Consequently, the increase in subendocardial resistance induced by ischemia causes a decrease in the capacitance of microvessels during systole.

So, taking advantage of this theory, using CT first-pass myocardial perfusion imaging (MPI) may be a convenient and noninvasive way to detect myocardial ischemia at rest (Kurata *et al*., 2005; George *et al*., 2007; Kido *et al*., 2008). We sought to determine the diagnostic accuracy of CT first-pass MPI at rest in detection of CAD using invasive coronary angiography (ICA) as the reference standard.

2 Subjects and methods

2.1 Study population

The present study samples were derived from consecutive patients from May to October 2009 diagnosed or strongly suspected as CAD by clinical signs. All subjects were recommended the examination of CTCA and gave informed consent. The entry criteria were as follows: effort or rest angina, documented ST-T change on electrocardiography (ECG), pain relieved by administration of nitroglycerin, asymptomatic patients with a high probability of CAD or many risk factors, and abnormal findings on stress test.

Reasons for exclusion included unstable clinical status, severe left ventricular dysfunction (left ventricular ejection fraction <20%), chronic atrial fibrillation, acute myocardial infarction, deteriorated renal function, and known allergy to iodinated contrast.

Taking the exclusion criteria into account, 33 patients were enrolled in the current study and underwent contrast-enhanced MSCT and ICA within two weeks. During the two weeks' interval, no coronary events such as acute myocardial infarction or drug refractory angina requiring emergency intervention occurred.

2.2 MSCT scan protocol

A 64-row MSCT scanner within a positron emission tomography (PET)/CT device (Discovery VCT, GE Healthcare, USA) was used with the following scan parameters: retrospective ECG gating, 64 channel detectors along the *Z*-axis, tube voltage 120 kV, tube current 550–900 mA (depending on patient size), scan field of view (FOV) 50 cm, gantry rotation 0.35 s/rotation, matrix 512×512, and slice width 0.625 mm. A single oral dose of 25–75 mg metoprolol was administered 2 h before the scan if the patient's heart rate was more than 70 beats/min.

Patients were scanned in a fasting and asymptomatic state in the supine position. After scout images were obtained, contrast timing was determined with the use of a test bolus 10 to 15 ml of contrast (350 mg/ml Omnipaque). The true scan was obtained with an intravenous injection of 60–80 ml (depending on the patient's body weight) of contrast at a rate of 4 to 5 ml/s.

2.3 ICA analysis

All ICA images were sent to two experienced physicians, who blindly determined the percent stenosis of each coronary segment by quantitative coronary assessment (QCA). Significant stenosis was defined as a reduction in diameter of more than 50%.

2.4 CTCA reconstruction

The raw data were transferred to a dedicated workstation (Advantage Workstation 4.3, GE Healthcare) for post-program. Images reconstructed at 75% of the cardiac cycle length were most usually used. A preciously described 15-segment American Heart Association model of the coronary tree was employed (Austen *et al*., 1975). The technologies of maximum intensity projection (MIP), multiplanar reconstruction (MPR), and volume reconstruction (VR) were used for the CTCA reconstruction. Lesions were classified using the maximal luminal diameter stenosis seen in any plane. Significant stenosis was defined as a reduction in diameter of more than 50%.

2.5 CT first-pass MPI reconstruction

The same dedicated workstation and the same

raw data used for CTCA were used to create long-axis and short-axis images via reconstruction at 45% and 75% of the cardiac cycle length for systole and diastole, respectively. If the motion artifacts were found to be severe, the images could be reconstructed at 40%–50% and 70%–80% of the cardiac cycle. Assignment of the left ventricular segments was based on the American Society of Nuclear Cardiology/ American Heart Association (ASNC/AHA) statement (Cerqueira *et al*., 2002).

We reconstructed 2D long, vertical-long, and short-axial myocardial images in end-diastolic and end-systolic phases (Fig. 1). A previous study about the analysis of myocardial ischemia using MSCT demonstrated that the subendocardial intensity for ischemia was significantly lower than that for non-ischemia at systole, whereas there was no significant difference at diastole (Nagao *et al*., 2008). Accordingly, we defined a pattern of transient systolic hypo-enhancement in the predominant endocardium at systole and normal perfusion at diastole as the ischemic pattern on CT first-pass MPI, and a pattern of hypo-enhancement both in the systolic and the diastolic phases as infracted myocardium. Perfusion imaging is shown by color maps coding with CT value. They do not represent true perfusion imaging, but provide a surrogate of perfusion and demonstrate perfusion defects more clearly. The color scales were classified into five steps using the CT value as follows: 0–40 Hounsfield unit (HU), blue; 40–60 HU, green; 60–80 HU, yellow; 80–100 HU, orange; and 100–200 HU, red. The warm colors represent hyper-enhancement areas with high CT values, while the cold colors represent hypo-enhancement areas with low CT values. We evaluated the variation in myocardial enhancement at systole and diastole for segments. One slice of CT first-pass MPI offers a view of systolic and diastolic phases in the same myocardial section. And, we also measured the mean CT value using a 10-mm^2 circle in the normal and abnormal perfusion segments both at systole and diastole in triplicate.

3 Results

3.1 Baseline characteristics

Among the 33 patients, the average age was (61.6±11.9) years, 81.8% were male, 45.5% had hypertension, 21.2% had diabetes, and 27.3% had hypercholesterolemia. There was a high prevalence of CAD: 66.7% had documented history of angina, 30.3% had chest distress, 9.1% had a prior myocardial infarction, and 21.2% had a prior revascularization (Table 1).

Table 1 Baseline characteristics of patients

Parameter	Value*
Risk factors	
Age (year)	61.6±11.9
Proportion of men	27 (81.8%)
Hypertension	15 (45.5%)
Diabetes mellitus	7 (21.2%)
Hypercholesterolemia	9 (27.3%)
Family history of CAD	9 (27.3%)
Smoking	9 (27.3%)
Obesity (BMI>30 kg/m^2)	9 (27.3%)
Prior medical history	
Angina pectoris	22 (66.7%)
Chest distress	10 (30.3%)
Old myocardial infarction	3 (9.1%)
Prior coronary revascularization	7 (21.2%)
Baseline medications	
Aspirin	19 (57.6%)
β-Blocker	18 (54.5%)
Statin	17 (51.5%)
ACEI	19 (57.6%)
Heart rate (beat/min)	70.3±7.7

* Values are expressed as mean±SD or *n* (%). Total number of patients is 33. CAD: coronary artery disease; BMI: body mass index; ACEI: angiotensin-converting enzyme inhibitor

3.2 ICA analysis

ICA detected 29 (87.9%) patients had ≥50% stenosis in at least one coronary vessel. Among the 33 study participants, 11 (33.3%) patients had single-vessel disease, 10 (30.3%) patients had double-vessel disease, and 8 (24.2%) patients had triple-vessel disease. On a per-vessel basis, 55.6% of the 99 vessels studies had ≥50% stenosis.

3.3 CTCA reconstruction

Among the 33 patients, 7 (21.2%) patients had at least one nonevaluable segment. The most common reason for limited evaluation was the presence of extensive calcium. When the nonevaluable segments were considered to be a severe disease, 25 (75.8%) patients were categorized as having severe CAD. The sensitivity, specificity, positive predictive value

(PPV), and negative predictive value (NPV) were 0.89, 0.67, 0.92, and 0.57, respectively, for detecting ≥50% stenosis.

3.4 CT first-pass MPI at rest

Figs. 2 and 3 illustrate examples of CT first-pass MPI at rest and how they correlate to stress/rest myocardial perfusion scintigraphy (MPS).

CT perfusion defects at rest were identified for 25 of 33 patients (75.8%) and 27 of 99 vascular territories (27.3%). Of the 52 segments with perfusion defects at systole, 37 (71.2%) were graded as nontransmural, whereas the remaining 15 (28.8%) segments were graded as transmural. Of the 27 vascular territories with abnormal perfusion at systole, 2 (7.4%) were fixed, 16 (59.3%) were fully reversible at diastole, and 9 (33.3%) were partially reversible at diastole.

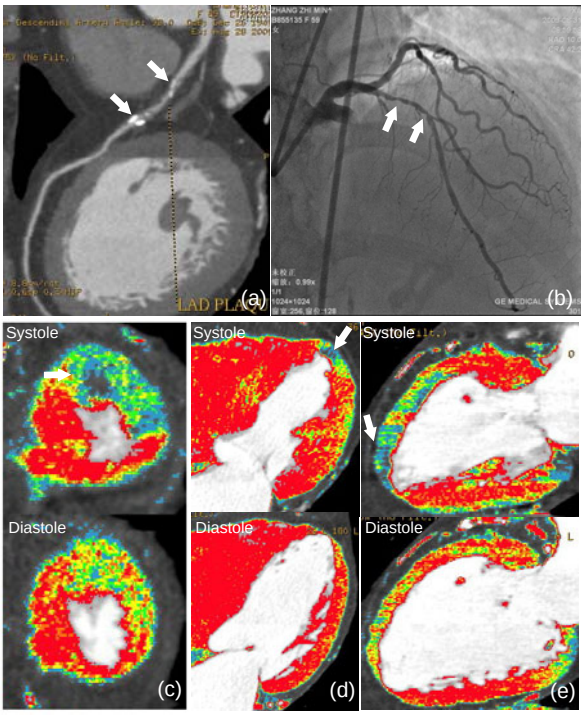

Fig. 2 Lesion in left anterior descending branch (LAD)
A 59-year-old woman complained of paroxysmal chest pain for one month. CTCA showed a large soft and mixed plaque in the proximal and middle LAD (arrows) (a), while CT first-pass MPI at rest showed perfusion defects at systole in apex and anterior walls from short (c), long (d), and vertical-long (e) views (arrows) while filling well at diastole. ICA in the right anterior oblique cranial view showed severe stenosis in the proximal and middle LAD (arrows) (b)

In the patients with myocardial ischemia detected by CT first-pass MPI, the mean CT value of perfusion defect segment at systole was lower than that of normal perfusion segment significantly ((4.3±15.9) HU vs. (96.9±17.8) HU, $P<0.001$), but at diastole, there was no significantly difference between them ((73.8±14.9) HU vs. (88.0±10.1) HU, $P>0.05$).

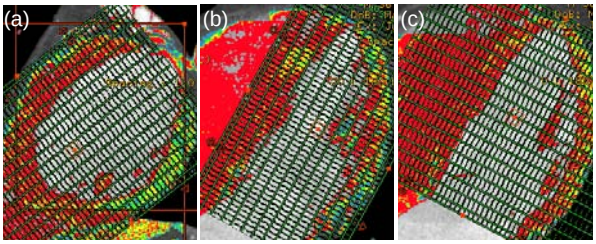

Fig. 1 Reconstruction for CT first-pass MPI
(a) Green lines for long axial reconstruction (in sagittal plane); (b) Green lines for vertical-long axial reconstruction (in coronal plane); (c) Green lines for short axial reconstruction (in coronal plane). Green curves between green lines showed the distance between two layers

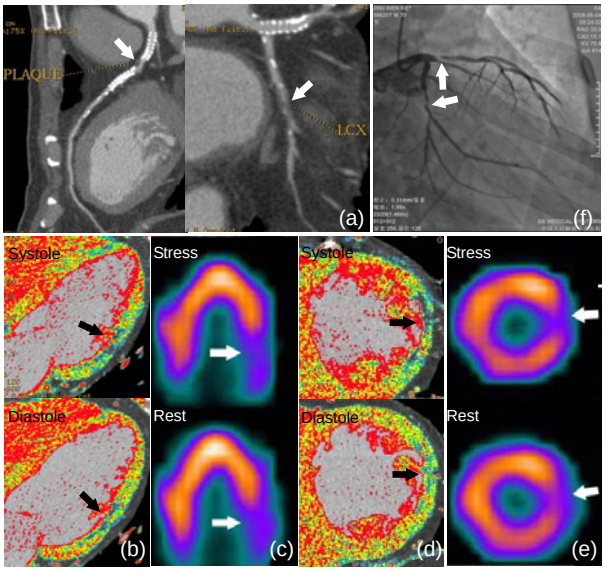

Fig. 3 Lesion in left anterior descending branch (LAD) and left circumflex coronary artery (LCX)
A 70-year-old man with two prior LAD stents complained of aggravating paroxysmal chest pain. CTCA showed a large plaque between the LAD stents (arrow) (left) and large mixed plaque in the mid LCX (arrow) (right) (a). CT first-pass MPI at rest showed partially reversible perfusion defect in the lateral wall from long (b) and short (d) axis views (arrows) where old infarcted myocardium and ischemia myocardium existed, which corresponded to the result of adenosine stress/rest myocardial perfusion scintigraphy (MPS) (arrows) (c, e). ICA in the right anterior oblique caudal view showed severe stenosis in proximal LAD and mid LCX (arrows) (f)

Table 2 shows the per-patient and per-vessel diagnostic accuracies of CT perfusion among the 33 subjects included in the study. When stenosis of ≥50% in ICA was used as the reference standard, the sensitivity, specificity, PPV, and NPV of CT first-pass MPI at rest were 0.85, 0.67, 0.92, and 0.50 per patient, respectively, and 0.58, 0.93, 0.85, and 0.76 per vessel, respectively.

Table 2 Per-patient and per-vessel accuracies of CT perfusion imaging*

Parameter	Value	
	Per-patient	Per-vessel
Invasive angiography		
≥50% (+)	23	23
≥50% (−)	4	17
<50% (+)	2	4
>50% (−)	4	55
Sensitivity	0.85	0.58
Specificity	0.67	0.93
PPV	0.92	0.85
NPV	0.50	0.76

* CT MPI vs. ICA stenosis ≥50%

4 Discussion

Nuclear perfusion imaging provides an accurate noninvasive method to detect physiologically significant CAD while simultaneously providing robust prognostic information that can help determine the need for further medical management or revascularization, which also plays the role of "door keeper" for ICA (Shaw *et al*., 1999). However, single photon emission computed tomography (SPECT) MPI has some limitations. Firstly, attenuation artifacts in SPECT can lead to false negative findings while balanced ischemia in the setting of three-vessel disease. Secondly, SPECT has a low spatial resolution, which cannot assess the ischemic area precisely, whether transmural or nontransmural. Thirdly, SPECT MPI could only provide physiological information but no anatomical information, which cannot rule out of the diagnosis of CAD. Although combined SPECT MPI and CTCA could provide physiological and anatomical information, the cost and procedure limited clinical application. Taking these into considerations, a test that can provide both coronary anatomical information and an accurate physiological assessment of perfusion simultaneously would be beneficial.

Pharmacologically induced stress CT could be a beneficial trail. Blankstein *et al*. (2009) found that an adenosine-induced CT scan alone could achieve CTCA and CT MPI simultaneously. Stress CT MPI had a sensitivity of 79% and a specificity of 80% for the detection of stenosis ≥50%. Although the study controlled the radiation dose to approximately 12.7 mSv, the protocol of that stress CT scan involving three steps was complicated, which would be carried out difficultly in clinical practice.

Nagao *et al*. (2008; 2009) performed a study that reconstructed the raw data of CTCA at systole and diastole, respectively, and defined myocardial ischemia as a pattern of transient systolic hypo-enhancement in the predominant endocardium and normal perfusion at diastole. Taking pharmacologically induced SPECT MPI as the reference standard, CT first-pass MPI at rest distinguished the ischemic patients with sensitivity, specificity, PPV, and NPV as 0.90, 0.83, 0.86, and 0.88, respectively.

Taking ICA as the reference standard, our study performed CT first-pass MPI at rest using contrast-enhanced 64-slice spiral CT to distinguish myocardial ischemia. Using the color map method, nontransmural or small perfusion defects could be clearly detected. The mean CT value of perfusion defect segment was significantly lower at systole, and increased at diastole. Because of the use of different mean CT value measuring methods, the disparity of mean CT value between perfusion defect and normal segment was higher than that of the reported value.

Taking stenosis ≥50% in ICA as the reference standard, the specificity and NPV of CT first-pass MPI at rest were lower (0.67 and 0.50). Motion artifacts occasionally occur, especially at systole and at the inferior wall, which can cause false positive cases. Decreasing the heart rate and reselecting the other phase during the corresponding period could decrease the artifact occurrence. In our study, the mean heart rate was fast ((70.3±7.7) beats/min), which affected the reconstruction quality, but the oral β-receptor blocker, which decreased the myocardial oxygen consumption, could also decrease the sensitivity for detecting myocardial ischemia. Next generation

MSCT may improve the spatial and temporal resolutions which could tackle with the referred issues.

We know that its inability to assess coronary artery stenosis in the presence of severe calcification is one of the biggest obstacles of CTCA (Raff *et al*., 2005; Ferencik *et al*., 2006; Pugliese *et al*., 2006). In our study, we could not accurately assess coronary stenosis in 21.2% of the patients due to severe calcifications using CTCA. While CT first-pass MPI at rest provides physiological information to assess myocardial perfusion status in the territory of a severely calcified coronary artery, it could also distinguish the culprit artery or lesion. CT first-pass MPI has the potential to address the limitations of CTCA, and elevate the diagnostic accuracy of CAD.

CT first-pass MPI at rest has many advantages. Firstly, CT first-pass MPI combined with CTCA at rest could make CT scan as "one stop shop" for diagnosis of CAD, providing anatomical and physiological information synchronously and simultaneously guiding the treatment strategy for CAD without any extra cost and any additional stress process. Secondly, in comparison to SPECT, MSCT has improved spatial resolution and may be better at detecting small areas of ischemia or infarction. And CT first-pass MPI also could offer improved accuracy for detecting multivessel disease. Thirdly, CT first-pass MPI at rest using the same raw data for CTCA with retrospective ECG gating, does not increase the radiation dose or contrast usage. The simple procedure and high cost-effectiveness would make it popular in clinical practice.

However, CT first-pass MPI at rest also has some limitations. Firstly, this is a small size and single-centre study; thus it would be important to validate these results in other centers with a larger sample size. Secondly, selection bias may be present in our design because recruited subjects generally had high-risk features on CTCA, which affects the diagnostic accuracy. A total of 18 (54.5%) patients had multivessel disease, which would explain why the NPV was so low.

Although our study only represents a limited experience, it suggests that MSCT could have an important role as a modality that would be able to simultaneously assess both anatomical CAD and its physiological consequences, which would be the "one stop shop" for diagnosis of CAD.

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