Characteristics of coronary artery calcium and its relationship to myocardial ischemia in Chinese patients with suspected coronary artery disease

Xiao L. Shao[1*] **MD,**
Yue T. Wang[1*]**, MD**
Jian F. Wang[1] **MD,**
Rui J. Zhou[2*] **MD**
Hai Y. Ke[2] **MD,**
Yan S. Yang[1] **MD**

**Xiao L. Shao and Yue T. Wang are the first co-authors*

1. Department of Nuclear Medicine, The Third Affiliated Hospital of Soochow University, Changzhou, 213003, China
2. Department of Cardiology, The Third Affiliated Hospital of Soochow University, Changzhou, 213003, China

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Corresponding author:
Yue T. Wang MD,
Tel: +86013852040196,
Fax: 86-519-86621235,
yuetao-w@163.com
Rui J. Zhou MD,
Tel: +86013961291586,
Fax: 86-519-86621235,
rjzhou0131@126.com

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Abstract

Objective: This study was aimed to investigate the characteristics of coronary artery calcium (CAC) in Chinese population with suspected coronary artery disease (SCAD). **Subjects and Methods:** We studied 205 Chinese patients with SCAD who were subjected to combined MPI and CAC score (CACS) study on a hybrid single photon emission tomography/computed tomography (SPET/CT) scanner. **Results:** a) Among the 205 patients 132 (64.3%) had CACS=0 and 73 (35.6%) had CACS>0. Of those with CACS>0, 58 (28.3%) had CACS of 1~399 and 15 (7.3%) had CACS ⩾400. b) The prevalence of CAC and CACS increased significantly with age (P<0.05). c) Age and hypertension were independent risk factors for CAC. d) The incidence of ischemic MPI for all 205 patients was 10.6% (14/132), 19.0% (11/58) and 33.3% (5/15). For patients with CACS=0, of 1~399 and ⩾400, respectively, showing significant difference (P=0.034), and significantly increased with CACS increasing (P=0.010). The incidence of ischemic MPI increased with increasing CACS from 10.6% (CACS=0) to 33.3% (CACS⩾400). e) CACS was weakly correlated or not correlated. The value of the correlation coefficient was very small, P value was less than 0.05 with ischemic MPI (r=0.164, P=0.019) but the accuracy of the presence of CAC for detecting ischemic MPI was only 65.4% (134/205). f) The area under the ROC curve was 0.615 (P<0.05, 95% CI: 0.500~0.729). **Conclusion:** Compared with western populations, the prevalence of CAC and absolute CACS in Chinese population with intermediate likelihood of CAD was low. CACS was weakly correlated with ischemic MPI, the accuracy of the presence of CAC for predicting ischemic MPI was low. CACS was not a reliable screening tool prior to MPI in Chinese patients with SCAD.

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Introduction

Coronary artery calcium (CAC) is a specific marker of coronary atherosclerosis [1], its extent reflects the burden of atherosclerotic plaques [2, 3]. According to current clinical studies, CAC score (CACS) conducted by the spiral computed tomography (CT) is a reliable noninvasive qualitative and quantitative tool for evaluating the extent of CAC and myocardial perfusion imaging (MPI) is an accurate noninvasive diagnostic tool for patients referred for detection of myocardial ischemia [4, 5]. Previous studies on western populations showed that the possibility for people with CACS<100 to have myocardial perfusion abnormalities in MPI was less than 2% [6, 7] and to have significant coronary stenosis (>50%) was less than 3% [8, 9], prompting that there was certain correlation between CACS and myocardial ischemia in MPI. The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) 2007 clinical expert consensus document [10] stated that for symptomatic patients with suspected CAD, CACS could be used as a beneficial filter before stress MPI or invasive coronary angiography (ICA).

Currently in China, hybrid single photon emission tomography/CT (SPET/CT) has become the mainstream imaging equipment in nuclear medicine, which allowed the combined assessment of MPI and coronary atherosclerosis. If low CACS could obviate the need for subsequent stress MPI in Chinese patients with suspected CAD, radiation exposure suffered by the patients with low CACS would be reduced. However, the multiethnic study of atherosclerosis (MESA) [11] showed significant racial differences in CACS and also showed that the prevalence and the extent of CAC in Chinese-Americans was lower than in whites. Thus, it is necessary to explore the characteristics of CACS and its correlation with MPI in Chinese population with SCAD, and explore whether CACS can be a good screening tool prior to MPI.

Subjects and Methods

Subjects

A total of 205 inpatients with SCAD between January 2011 and January 2015 in our hospital were enrolled in the study. These patients had a mean age of 61.9±9.7 years old. Of them, 51.7% (106/205) were male. Patients were excluded if they had: a) acute coronary syndrome with myocardial infarction and elevated ST-segment or non-elevated ST segment, or with unstable angina; b) plasma troponin test positive; c) unstable hemodynamics; d) post-CAD PCI or bypass surgery; e) too severe arrhythmia to complete CACS or gated MPI; f) cardiomyopathy; g) age <18 years old; and h) pregnancy. All patients signed an informed consent and the study was approved by the Medical Ethics Committee of our hospital.

Imaging

A "one-stop shop" SPET/CT imaging programme of the gated radionuclide MPI combined with CACS was applied. Patients without exercise stress contraindications were subjected to exercise stress MPI using the Bruce protocol or the modified Bruce protocol, and patients with exercise stress contraindications were subjected to pharmacological (adenosine triphosphate, ATP) stress MPI. In brief, ATP was intravenously (i.v.) infused at 0.14mg/kg·min for 5min, and the imaging agent techentium-99m methoxyisobutylisonitrile (^{99m}Tc-MIBI) (radiochemical purity >95%, injected dose of 555~740MBq) was i.v. injected at 3min after ATP injection. Myocardial perfusion imaging was carried out 60~90min after i.v. injection of the imaging agent. Once CACS was finished, CT was immediately performed. Rest MPI was performed with the same dose and acquisition conditions without performing the CACS scan. The imaging equipment used was the SPET/CT scanner (Symbia T16, Siemens, Germany) supplemented with a high-resolution low-energy collimator. No attenuation correction was applied.

Myocardial perfusion image acquisition

Images of MPI were acquired using dual-head detector with angle of 90° and 6° step 180° rotation, (from the right anterior oblique of 45° to the left posterior oblique of 45°), with acquisition matrix of 128x128, magnification of 1.45, and 20% window centered on the 140keV peak energy.

Coronary arteries calcium score by the CT scan

Axial unenhanced CACS scan was performed using retrospective electrocardiography (ECG)-gated technology, and data were collected during the period of 60%~80% RR, at tube voltage of 120kV, tube current of 100mAs, and thickness of 3mm and scan range from the plane underneath the tracheal carina to the place 1~2cm below heart diaphragmatic surface.

Image processing and analysis

Myocardial perfusion image processing and analysis

Reconstruction of MPI was performed using the filtered back projection method (Butterworth filter with cutoff frequency of 0.35 and order of 5). The images were quantitatively analyzed using the quantification software (Cedars QPS/QGS 2009, Cedars-Sinai Medical Center, Los Angeles, USA) and evaluated using the 5-point scale system based on the 17 segment model recommended by the AHA. Points of 0, 1, 2, 3, and 4 indicated normal, mild defect, moderate defect, severe defect, and absence of detectable uptake, respectively. The summed stress score (SSS), summed rest score (SRS) and summed difference score (SDS) were calculated. Myocardial perfusion imaging with SSS⩾4 and and SDS⩾2 was considered abnormal and ischemic, respectively [12, 13].

Coronary arteries calcium score image processing and analysis

The CACS images were processed using Agatston automatic analysis software to record the calcification score of each coronary artery and the total CACS. Patients were divided into non-calcification (CACS=0) and calcification (CACS>0) groups based on their total CACS. Patients in the calcification group were further divided into CACS of 1~399 group and CACS⩾400 group, as recorded previously [7, 14].

Statistical analysis

Data were analyzed using SPSS 22.0 statistical software. Semiquantitative data were expressed as mean±standard deviation (SD) ($\bar{x}$ ±s) or median (P25, P75). The difference between two sets of quantitative data was compared using independent t-test or Mann-Whitney u rank sum test and the differences among multiple sets of quantitative data were compared using ANOVA. Count data were expressed as frequencies and percentages, and compared using x^2 test. The incidence of ischemic MPI in different CACS groups was compared using chi-square analysis. Multivariate analysis of categorical variables was performed using logistic regression analysis. The correlation of CACS to ischemic MPI was analyzed using Spearman correlation analysis. A P<0.05 was considered as statistically significant.

Results

General information of the subjects

Table 1 lists the general information of the studied population.

General information of the subjects

Among the 205 patients with suspected CAD, 132 (64.4%) had no CAC (CACS=0) and 73 (35.6%) had CAC (CACS>0). Among the 73 patients with CAC, 58 (28.3%) had CACS of 1~399 and 15 (7.3%) had CACS ⩾400. According to patients' age, they were divided into 3 groups with age of <60, 60-69 and ⩾70 years old, respectively. Their CAC incidence was 17.7%, 30.9% and 75.6%, respectively, and had statistically significant difference (x^2=43.136, P<0.001). In addition, their corresponding CACS was 22.4±137.1, 87.0±464.4 and 356.0±737.9, respectively, and varied stati-

Table 1. *Characteristics of study population*

Age (years old)	61.9±9.7
Gender (male/female)	106/99
BMI (kg/m^2)	25.2±2.8
Risk factors	-
Smokers	53 (25. 9%)
Hypertension	131 (63.9%)
Diabetes mellitus	82 (40.0%)
Dyslipidemia	115 (55.1%)
Serum creatinine (mol/L)	72.1±20.3
Symptom class	-
Typical angina	36 (17.6%)
Atypical angina	65 (31.7%)
Non-angina pain	49 (23.9%)
Other symptoms	55 (26.8%)
Pre-test likelihood of CAD (%)	43.6±18.8
CACS	121.2±486.7

stical significantly (F=7.513, P=0.001). Furthermore, the prevalence of CAC and CACS were higher in male than in female, that was 40.6% vs 30.3% for the former and 164.1±626.9 vs 75.2±260.6 for the latter, but not significantly (x^2=2.352, P=0.125 for the former, and t=-1.342, P=0.182 for the latter).

Univariate analysis with CAC as a single variable showed that age, male, BMI, hypertension, diabetes, hyperlipidemia, serum creatinine level and symptoms of angina (including typical and atypical angina) were the risk factors for CAC (Table 2). Logistic multivariate regression analysis of those factors with significance in univariate analysis showed that age and hypertension are independent risk factors for CAC (Table 3).

Correlation and predictive value of CACS with ischemic MPI

Of the 205 patients with suspected CAD, 30 (14.6%) had myocardial ischemia in MPI and their SSS and SDS were 7.3±4.5 and 4.9±2.1, respectively; 175 (85.4%) had normal MPI and their SSS and SDS were 0.8±1.0 and 0.5±0.8, respectively. The incidence of ischemic MPI was 12.7%, 13.6% and 20.0% for patients at age of <60, 60-69 and ⩾70 years old, respectively, showing no significant differences(x^2=1.356, P=0.508). The median CACS was 3.1 (0,159.7) for patients with ischemic MPI and 0 (0,16.7) for patients with normal MPI, showing significant difference (Z=-2.34, P=0.019). The incidence of isc-

Table 2. *Information of patients with CAC and without CAC*

Characteristics	CAC (n=73)	No CAC (n=132)	P value
Age (years)	67.3±8.1	58.9±9.2	<0.001
Male (%)	58.9	47.7	0.125
Smokers (%)	31.5	22.7	0.169
BMI	25.1±2.9	25.2±2.7	0.829
Hypertension (%)	80.8	54.5	<0.001
Diabetes mellitus (%)	52.1	33.3	0.009
Serum creatinine (μmol/L)	69.2±17.5	77.6±23.8	0.005
Dyslipidemia (%)	50.7	59.1	0.246
Angina (%)	45.2	51.5	0.387

Table 3. *Multivariate analysis of risk factors for CAC*

Variables	Regression coefficient	Odds ration (OR)	95% Confidence interval (CI)	P value
Age	0.111	1.117	1.068~1.168	<0.001
Hypertension	0.934	2.545	1.182~5.479	0.017
Diabetes mellitus	0.577	1.781	0.887~3.578	0.105
Serum creatinine	0.015	1.015	0.997~1.033	0,102

hemic MPI was 21.9% (16/73) for patients with CAC (CACS> 0) and 10.6% (14/132) for patients with no CAC (CACS=0), showing significant difference (x^2=4.814, P=0.028). The incidence of ischemic MPI was 10.6% (14/132), 19.0% (11/58) and 33.3% (5/15) for patients with CACS of 0, 1~399 and ⩾ 400, respectively, showing significant differences (x^2=6.784, P=0.034). With CACS increasing, the incidence of ischemic MPI showed a significantly increased trend (x^2=6.550, P=0.010) (Figure 1).

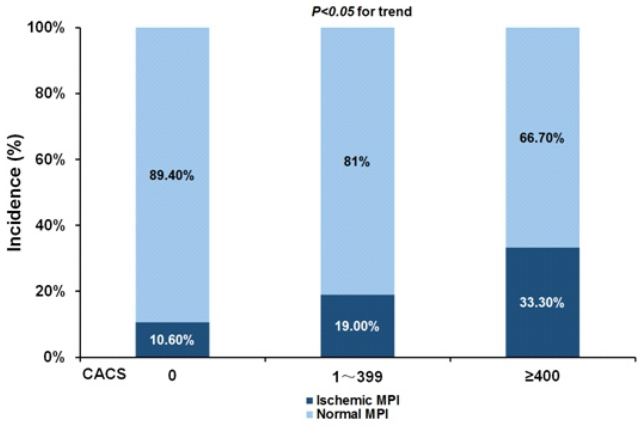

Figure 1. Bar graph illustrating the incidence of ischemic MPI by CACS.

However, there was only weak correlation between CACS and the incidence of ischemic MPI (r=0.164, P=0.019). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of the presence of CAC for detecting ischemic MPI were 53.3% (16/30), 67.4% (118/175), 21.9% (16/73), 89.4% (118/132) and 65.4% (134/205), respectively. The receiver operating characteristic (ROC) analysis of CACS for detecting ischemic MPI showed that the area under the curve was 0.615 (P<0.05, 95% CI: 0.500~0.729) (Figure 2).

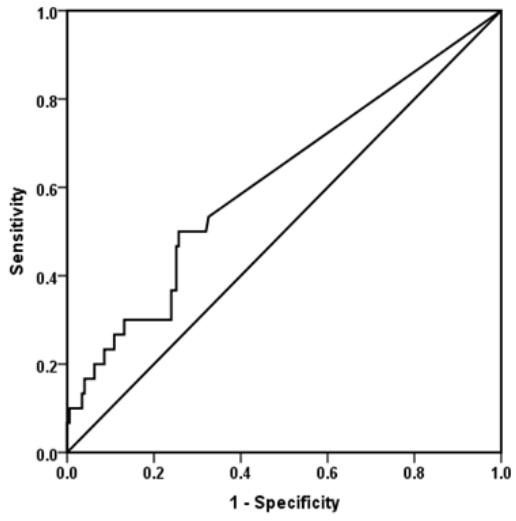

Figure 2. ROC curve representing the diagnostic accuracy of CACS for identifying ischemic MPI. The area under the curve was 0.615 (P<0.05, 95% CI: 0.500~0.729).

Discussion

Among the Chinese population with suspected CAD, the prevalence and extent of CAC significantly increased with patients' age increasing (P<0.05), consistent with previous aboard researches [11, 14, 15]. However, compared with the data in European and American populations, the extent of CAC was less in Chinese population, showing lower absolute CACS and a larger proportion of patients without CAC. Schenker et al. (2008) [14] studied 695 patients with intermediate likelihood of CAD at mean age of 60.9±13.1 years old and found that their mean CACS was 429±869 and only 34.3% had no CAC (CACS=0). In this study, among the 205 Chinese patients, their pretest likelihood of CAD was 43.6±18.8% and their mean age was 61.9±9.7 years old. The patients without CAC (CACS=0) accounted for 64.4% and had mean CACS of only 121.2±486.7. Therefore, the population of different regions due to different ethnic [11], diet and lifestyle [15] had different prevalence and extent of CAC.

Multiracial epidemiological data [16] indicated that the occurrence of CAC was related with multiple cardiovascular risk factors such as age, smoking, obesity, dyslipidemia, diabetes, hypertension, chronic kidney disease [17] and so on. Logistic regression analysis of the possible risk factors that may lead to CAC showed that in addition to age, hypertension is an independent risk factor for CAC. The underlying reasons may be related to the increased impact of coronary blood flow under hypertension, resulting in the injury of coronary artery intima, and subsequent inflammation and development of calcium deposition and plaque [18-20].

Coronary atherosclerosis induced coronary artery stenosis is the most common cause of myocardial ischemia [21] and CAC is a specific marker of atherosclerosis [1]. In symptomatic patients, with CACS rising, coronary atherosclerotic plaque burden increases and leads to increased possibility of obstructive CAD (coronary artery stenosis ⩾50% or 70%) [10] and the occurrence of myocardial ischemia shown in MPI. According to other researchers, if CACS was less than 100, the possibility for people with abnormal MPI was less than 2% [6, 7], suggesting that CACS could be used as a beneficial filter prior to MPI.

In this study, the enrolled Chinese patients with suspected CAD were examined using SPET/CT imaging and the results suggested that CACS was weakly correlated with ischemic MPI (r=0.164, P<0.05), consistent with previous researches [6-7, 14]. In addition, patients with ischemic MPI had higher CACS than patients with normal MPI and the incidence of ischemic MPI in patients increased with CACS rising (P<0.05 for the trend). However, the incidence of ischemic MPI in patients without CAC was as high as 10.6%, and the accuracy of the presence of CAC for detecting ischemic MPI was only 65.4% (134/205), which verified that CACS was not a strong predictor of ischemic MPI in Chinese patients with suspected CAD. The possible reasons that can produce collateral circulation [22] to maintain adequate myocardial blood flow and avoid myocardial ischemia in MPI even in patients with a

high CACS (CACS⩾400) were long-term, chronic process of coronary atherosclerosis. Meanwhile myocardial ischemia in MPI was not only caused by atherosclerosis induced coronary artery stenosis, but also also involved a variety of mechanisms [23-25] including microvascular dysfunction (Figure 3), abnormal endothelial function, epicardial coronary artery stenosis and epicardial coronary spasm.

The study found that among patients with different age, the incidence of CAC and CACS was significantly different and increased with increasing age, but the incidence of abnormal MPI was not significantly different. The reasons for these phenomena may be that CAC usually occurs in the fibroatheroma and in the complicated plaque during the progression of atherosclerosis and often is the pathological manifestation of advanced atherosclerosis [1]. Thus, coronary plaque in younger patients is mainly composed of lipids

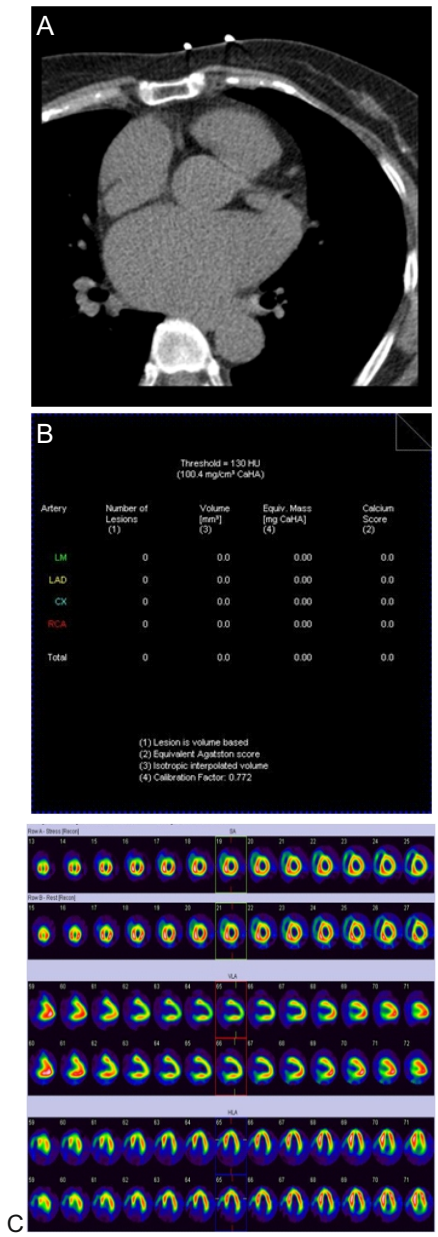

Figure 3 (A-C). Myocardial perfusion imaging of a 55 years old female patient who complained about chest stuffiness and palpitations. The patient was clinically diagnosed to have coronary microvascular disease and had myocardial ischemia on the anterior wall and apex of the left ventricle in MPI, although her CACS was zero.

or/and of fibers with lack of significant calcification [26]. This may also explain that despite the presence of myo-cardial ischemia in MPI, CACS is zero or lower in some pati-ents with angina.

Limitations

Although the study population was Chinese with suspected moderate CAD, their MPI positive rate was only 14.6% (30/205). The lower ischemic MPI rate may affect the results of different groups. In addition, the study was only a single-center study with smaller sample. Although it preliminary elaborated the characteristics of CACS and its relationship with abnormal MPI in Chinese population with suspected CAD, these results still need to be confirmed by a multi-center prospective study with larger sample size.

In conclusion, compared with western populations, the prevalence of CAC and CACS in Chinese population with intermediate likelihood of CAD is low. Age and hypertension are independent risk factors of CAC. CACS is only weakly correlated with myocardial ischemia in MPI. The incidence of ischemic MPI in patients without CAC was as high as 10.6%, and the accuracy of the presence of CAC for detecting ischemic MPI was only 65.4% (134/205). CACS is not a reliable screening tool prior to MPI in Chinese patients with suspected CAD.

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The authors declare that they have no conflicts of interest.

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