Value of Coronary Artery Calcium Scoring in Iranian Patients Suspected to Coronary Artery Disease

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Abstract- Coronary artery calcium scoring (CACS) is a reasonable test for patients with the possibility of atherosclerosis. It can also be used for reclassifying the coronary artery disease (CAD) to the high-risk status by higher CACS and subsequently modifying the management of the patients.The purpose of this study was to investigate the association of CACS to the severity of coronary artery disease in the patients who were scheduled to perform coronary artery angiography (CAG) by tradition. CACS could be a simple, relatively cost-benefit, and noninvasive method for early screening of patients with obstructive coronary artery disease. Method: In the present study, CAC scoring was evaluated by non-enhanced Multi-Detector Computed Tomography (MDCT) in a total 239 patient suffering from coronary artery disease. Of them, 223 patients were planned to undergo CAG based on clinical examination or other noninvasive diagnostic methods (such as MPI, ETT, EKG or Echo). Results: Our results showed that 11 of 67 patients with a negative CACS (zero) had obstructive coronary artery disease derived from the results of CAG. We also found a significant correlation between high CACS (more than 400) and extensive obstructive CAD, except for the two patients who had only mild CAD. There was a linear correlation between CACS and the severity of CAD on the basis of Gensini score and the number of involved arteries (CC=0.507, PV<0.001). Despite fairly high sensitivity (86.6) of zero CAC among patients with a negative score (86%), zero CACS cannot rule out the existence of obstructive coronary artery disease. As we found, increased level of CACS (>400) might be a significant indicative of CAD in referring patients.

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Keywords: CACS; Obstructive CAD; Gensini score; Coronary Artery Angiography (CAG)

Introduction

According to the World Health Organization (WHO) CAD causes 16.7 million deaths in the world each year (1). Coronary artery calcium score (CACS) is a very simple and readily available test for identifying coronary artery disease (CAD) in asymptomatic patients to predict the risk of CAD incidence apart from routine cardiac risk factors (2).

Although mostly used for cardiovascular disease risk stratification, it seems that CACS may also have a diagnostic value to include or exclude patients in obstructive CAD. This group of patients has been demonstrated in the moderate to high-risk patients scheduled for coronary artery angiography. Multi-Detector Computed Tomography (MDCT) is able to diagnose obstructive coronary artery with 93% sensitivity and 98% specificity and is appropriate in patients with low and intermediate risk (3-8).

In this study, we tried to investigate the value of CACS in patients planned to undergo CAG in order to find a simple, cost –benefit, noninvasive way, beside the other diagnostic tests, in ruling in/out obstructive CAD.

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Materials and Methods

In a cross-sectional study, 239 patients were entered to undergo CAC after completing data sheets containing information on patients' history, physical examination, blood analysis, MPI findings, ETT, changes of ECG or Echo. All information was gathered from April 2011 to March 2012. 223 of 239 patients were also scheduled to undergo CAG along with an evaluation of CAC score. Patients who had renal failure, severe malignant disease, previously performed percutaneous coronary intervention (PCI), CABG and who did not satisfy to take part in the study, were not entered.

In all patients, we also measured weight, height, W/H, BMI, and ECG, supine systolic and diastolic blood pressure under standardized condition. The eligibility criteria for suspected patients were 1) cardiac symptoms including: typical chest pain, atypical chest pain, exertional chest pain, palpitation and DOE (Dyspnea on Exertion) 2) asymptomatic patients planned to non-cardiac surgery 3)patients with signs of cardiac disease such as: abnormal ETT and / or MPT results, EKG changes or echo results. Beside these indications for coronary artery angiography, peripheral vascular disease or multiple cardiovascular risk factors were also included.

Diabetes mellitus (DM) was defined using one of these indicators: FBS >126 mg/dl, HbA1c>6.9, the use of oral hypoglycemic agents or insulin.

The patients were grouped as smoking, current smoking, ex –smoking and nonsmoking. Then, the prior cardiovascular disease history was defined using clinical documents of patients in Iranian hospitals, physicians' offices or clinic registries. The history could also determine by means of studying the Q or QS pattern wave or LBBB in the baseline EKG and/or reduced EF or regional wall motion abnormality (RWMA) in echo.

Hyperlipidemia was defined as cholesterol >200, TG>150, LDL>100 mg/dl and/or treatment by the lipid-reducing agents. Positive family history was defined as the presence of obstructive CAD in the first relative of patients (55>male, 65>female). Hypertension (HTN) was defined as systolic and diastolic blood pressure BP>140/90.

EF (ejection fraction) was estimated by echo (eyeball method) which was evaluated at least by two experts.

All CAC scans were performed using non-enhanced MDCT (64-slice, American, General Electric).The electrocardiographic signal was used to trigger the data acquisition: A cine-segment mode with a 0.4 sec gantry rotation time was employed.

The following physical items were performed for coronary artery calcium detection 120kv tube voltage; 2.5 mm slice thickness and detector coverage 40 mm. The region of areas and areas of density were quantified by Agatston method and a standard of 130-170 attenuation thresholds.

ETT (exercise tolerance test) was performed by Bruce protocol with established criteria for performance and exercise discontinuation. One of the following items considered as criteria for ischemia: 1) more than 2 mm horizontal or downsloping ST segment depression, 2) more than1 mm ST segment elevation during exercise or at rest, 3) typical increasing angina during exercise. ETT was considered as a non-diagnostic investigation if it discontinued no evidence of ischemia before catching the 85% target heart rate.

Coronary artery angiography was performed using standard techniques with the assessment of the most severe obstruction from ≥2 orthogonal projections evaluated at least by two experts.

The maximum Lumen diameter stenosis >50% was considered significant. Moreover, the severity of all segments of coronary arteries and branches were evaluated on the basis of Gensini score.

Finally, the extent of "involved vessel" was determined based on Gensini score as a careful quantitative and qualitative method (see figure 1). Thus, each involved vessel apart from the kind of obstruction was considered.

To keep the results, clinical data were registered on the medical research forms.

Statistics

The association between dependent variables such as calcium score and independent factors including age and sex were obtained using the Pearson Correlation Coefficient and stepwise multiple linear regression analyses. The values were expressed as a percentage as well as means ±SD for some clinical and laboratory characteristics of the patients.

The 95% confidence interval (CS) was calculated for each odds ratio. A *P*.value of <0.05 was considered statistically significant. Differences in ratios were compared using chi-2 statistic test.

The paired *t*-test and ANOVA test were used for comparing means between two or several groups respectively. Statistical analysis was performed using SPSS-15.

Gensini score=sum of (stenosis score x functional significance score)		
		Significance score
LM: 5	p-LCx:2.5	p-RCA:1
p-LAD:2.5	d-LCx:1	m-RCA:1
m-LAD:1.5	OM:1	d-RCA:1
d-LAD:1		PD:1
1st Dx:1		PL:1
2nd Dx:0.05		
	Stenosis score	
25%:1	75%:4	99%:16
50%:2	90%:8	100%:32

LM indicated left main, LAD: left anterior descending, DX: diagonal, OM: obtuse marginal, RCA: right coronary artery, PD: posterodescending, PL: posterolateral, p:proximal, m: mid,d:distal

Figure 1. Calculation of Gensini score
(Gensisi score = sum of stenosis score x functional significance score)

Results

In the present study, we evaluated 223 patients with the gender contribution of male: 148 (71.9%) and female: 75 (28.1%).The mean age was 56.2±11.84 years.

The clinical history of the involved patients has been summarized in table 1. As shown in table1, the major cardiovascular risk factors were HLP, HTN, cigarette smoking and DM sequentially.

Table 1. The clinical and laboratory characteristics of the patients

Clinical and laboratory findings	Results
Prior history of CAD	17 (7.3%)
Mean of BMI	27.1±4.4
Mean of W/H ratio	0.98 ±0.06
Mean of systolic blood pressure (mmHg)	126 ±18
Mean of diastolic blood pressure (mm Hg)	77 ± 8
Frequency of hypertension	102(42.5%)
Mean of FBS (mg/dl)	112 ±40
Mean of HbA1c	5.7 ±1.3
Frequency of DM	62(25.8%)
Mean of total serum cholesterol (mg/dl)	160±112
Mean of serum HDL(mg/dl)	43± 11
Mean of LDL(mg/dl)	102 ±38
Frequency of hyperlipidemia	146(61.2%)
Frequency of cigarette smoking	68(28.7%)
Mean of Cr	1.08 ±0.7

The history of cardiac medications and the percentage of patients taking drugs have been shown in table 2. Almost two-thirds of patients had taken A.S.A, statins, beta blockers and ACE inhibitors.

The frequency of symptoms and percentage of patients presenting symptoms have been presented in table 3. Nearly half of the patients suffered from DOE, and typical chest pain was presented in 22.5% of patients.

Table 2. The history of taking cardiac medications

Drug history	Frequency
Statins	148(61.8%)
ASA	160(66.9%)
ARBs	24(10.1%)
Beta blockers	148(61.8%)
ACE inhibitors	142(59.6%)
Diuretics	78(32.6%)
Glibenclamide	41(16.9%)
Metformin	40(16.8%)
Nitrates	88(36.5%)

Table 3. The frequency of symptoms and percentage of patients presenting symptoms

Symptom	Frequency
Typical chest pain	53(22.5%)
Atypical chest pain	37(15.7%)
Exertional chest pain	23(15.2%)
Palpitation	28(11.8%)
DOE (dyspnea on exertion)	112(46.6%)
Asymptomatic	15(6.2%)

As shown in figure 2, we found a linear correlation between Gensini score and CACS with the coefficient correlation of 0.507 (P<0.001). Similarly, a correlation was revealed between CACS and the number of involved vessels (correlation coefficient: 0.444, P<0.001) which has been indicated in figure 3. Expectedly, we observed a reverse relationship between CACS and EF (correlation coefficient: -0.245, P<0.006) (Figure 4).

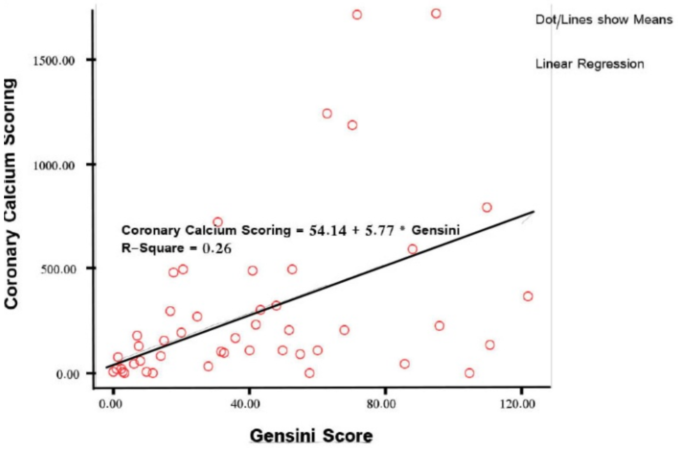

Figure 2. Correlation of CACS to Gensini score

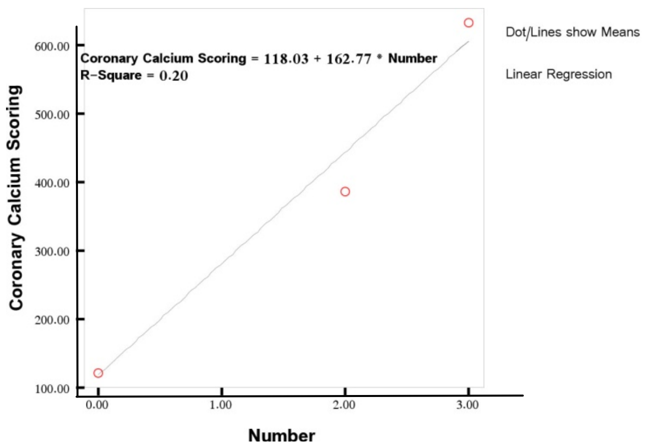

Figure 3. Correlation between CACS and the number of involved vessels

We considered each positively selected involved vessel based on Gensini score apart from its size or quality

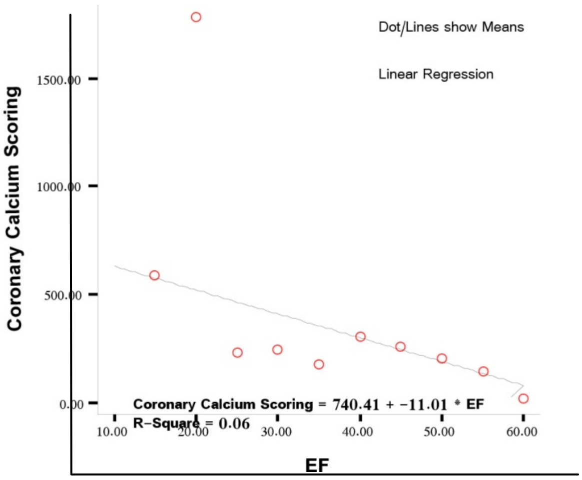

Figure 4. Relationship between CACS and EF

No calcification was detected in 67 (30.05%) patients. Eleven patients had significant coronary artery disease. Low CAC score (1-10) was found in 17 patients that 41.2% of them had obstructive CAD. A range of 10-100 CACS was revealed in 48 patients who were in conjunction with obstructive CAD in 37of them. A CACS from 100 to 400 was found in 46 patients with the significant CAD in 40 of them.

ACACS higher than 400 was observed in 46 patients. All of them except for the two with mild coronary artery disease had at least one significant involved vessel. As shown in table 6, there was no statistically significant correlation between exercise tolerance test (ETT) and CACS.

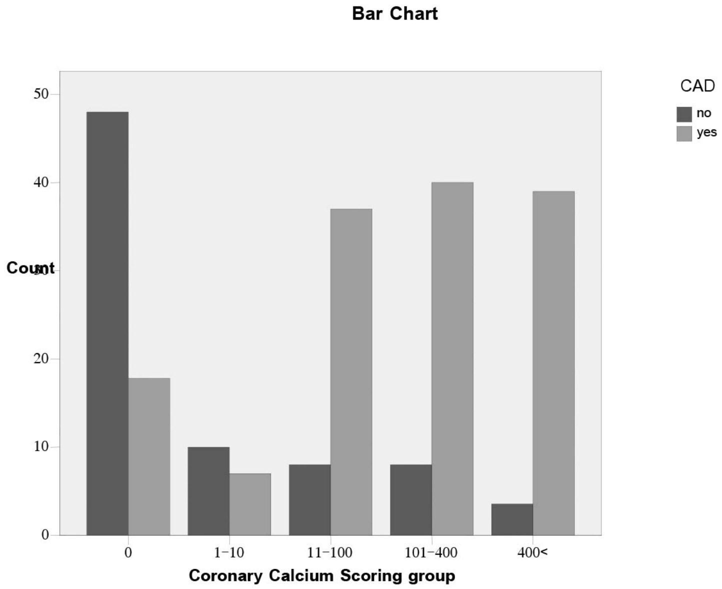

Figure 5. Distribution of CACS in patients with and without coronary artery disease

Table 4. CACS in coronary artery disease. Distribution of CACS in patients with and without coronary artery disease

CACS	Negative CAD	Positive CAD	Total
0	56 (83.6%)	11 (16.4%)	67(100%)
1-10	10(58.8%)	7(41.2%)	17(100%)
11-100	8(17.8%)	37(82.2%)	45(100%)
101-400	8(16.7%)	40(83.3%)	48(100%)
400<	2(4.4%)	44(95.6%)	46(100%)
Total	84 (37.7%)	139 (62.3%)	223(100%)

Table 5. Sensitivity, specificity, PPV and NPV for diagnosing of coronary artery disease

CACS	Sensitivity %	Specificity %	PPV%	NPV%
1	86.6%	40.7%	78.8%	71.6%
10	81.7%	71.6%	83.4%	69%
100	55.6%	81.5%	83.2%	51.2%
400	29.9%	97.3%	95.6%	41.8%

PPV= positive predictive value; NPV= negative predictive value

Table 6. Correlation between the result of ETT and CACS

CACS	Negative ETT	Positive ETT	Total
0	14(46.7%)	16(53.3%)	30(100%)
1-10	2(50%)	2(50%)	4(100%)
11-100	2(33.3%)	4(66.7%)	6(100%)
101-400	4(66.7%)	2(33.3%)	6(100%)
400<	3(42.9%)	4(57.1%)	7(100%)
Total	25(47.2%)	28(52.8%)	53(100%)

Discussion

Although we found a considerable association between CACS and the severity of coronary artery disease, but the absence of coronary artery calcification (zero score) cannot completely exclude the presence of significant coronary artery disease.On the other hand, the high CACS (more than 400) is usually related to obstructive coronary artery disease.

In our study, the prevalence of coronary artery disease was high, considering all patients scheduled to undergo CAG based on clinics or the findings of non-invasive tests. The sensitivity of CACS among the subjects with the negative score was relatively high (86%) while the specificity of the test was lower (40%) in our study. Therefore in the absence of a further diagnostic test, some subjects might be missed and not sent for coronary artery angiography.

There was an inverse relationship between specificity and sensitivity of positive calcium score and the elevated number of CACS in subjects in the present study. It means that along with the increasing number of scores in CACS, the specificity of the test enhanced gradually (40.7% for 1 CACS, 71.6% for 10 CACS, 81.5 % for 100 CACS, 97.3 % for>400 CACS respectively), while the sensitivity of the test dropped constantly (86.6% for 1 CACS, 81.7 % for 10 CACS, 55.6 % for 100 CACS, 29.9 % for >400 CACS respectively). In comparison, all patients with CACS >400 except for the two, had at least one significant symptoms of CAD.

The study performed by Nieman and the colleagues revealed that CACS was a reliable test to exclude the stable CAD obstruction in symptomatic patients (3/170, 2%) (9).

In contrast, Henerman and et al reported that roughly 40% of the patients with negative CACS showed obstructive CAD beside suspected acute coronary syndrome. It demonstrated that, a zero CACS did not rule out significant CAD (10). This discrepancy seems to result from studying on various groups of involved patients which were relatively low risk in the first study and high risk in the second one.

Interestingly, due to the results indicating that 16.4% of subjects with zero score had obstructive CAD, our findings were different from the previous studies in this field (8-12).

Importantly, we indicated a substantial correlation between high CACS and suffering from CAD in 95% of patients. Thus, CACS may be a suitable complementary method in subjects' candidate to perform other noninvasive tests. It would be reasonable to firstly perform CACS and then planned the subjects to angiography or other diagnostic tests. CACS is an appropriate tool for the risk assessment of asymptomatic individuals either intermediate or low risk with a family history of premature coronary heart disease.(2) High CACS in these subjects can be an important indicative for following the coronary artery disease in them. The planning of screening in patients with low-intermediate CACS (10-400) could be more challenging.

In conclusion, there are some debates about the choosing and performing a suitable functional test to work up the patients without high CACS. It seems that all methods will be helpful if they are selected correctly considering patient's history and physical examination. In addition, more investigation on designing of non-invasive diagnostic tests other than CACS seems to be worthwhile.

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