

High prevalence of coronary artery calcification in Saudi patients with normal myocardial perfusion

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BACKGROUND: Normal single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has a high negative predictive value for ischemic heart disease. Thus, the presence of subclinical coronary atherosclerosis detected by coronary artery calcification (CAC) score in patients who have undergone SPECT MPI is unknown.

OBJECTIVES: Determine the prevalence of coronary artery calcification (CAC) in patients with normal SPECT MPI and examine the association of CAC with conventional coronary artery disease (CAD) risk factors.

DESIGN: Cross-sectional analytical study using medical records from February 2010 to April 2016.

SETTINGS: Single tertiary-care center.

PATIENTS AND METHODS: We studied patients referred from the outpatient clinical services for clinically indicated noninvasive CAD diagnosis with MPI SPECT. CAC scoring was subsequently performed within 3 months after a normal MPI. We excluded patients with chest pain or decompensated heart failure or patients with a history of CAD. The study population was divided into three groups: patients with a CAC score of 0, a CAC score from 1 to 300, and a CAC score more than 300. The groups were analyzed by age and other demographic and clinical characteristics.

MAIN OUTCOME MEASURE(S): Prevalence of CAC in patients with normal MPI.

RESULTS: The prevalence of CAC was 55% (n=114) in 207 patients with a mean (SD) age of 57.1 (10.4) years. Twelve percent had severe coronary atherosclerosis (CAC score >300). All patients had a normal MPI SPECT. CAC scores were 0 for 93 patients (45%), 1 to 300 for 89 (43%), and more than 300 for 24 (12%). There was a strong association between CAC score and age ($P<.0001$), male sex ($P<.0001$), and diabetes mellitus ($P=.042$), but no association between CAC score and hypertension ($P=.153$), family history of CAD ($P=.23$), obesity ($P=.31$), hypercholesterolemia ($P=.071$), or smoking ($P=.308$).

CONCLUSIONS: The prevalence of CAC is high in this study population of patients with normal SPECT MPI. Age, male sex and diabetes were risk factors associated with CAC.

LIMITATIONS: Single center and small study population.

Myocardial perfusion imaging (MPI) with single photon emission computed tomography (SPECT) is known for its role in the diagnosis, risk stratification, and guidance of treatment decisions in the general population.^{1,2} Several studies over the past decade have reported uniformly low rates of

major adverse cardiac outcomes in patients with a normal MPI.³⁻⁵ Patients with a normal MPI have a median rate of major cardiovascular events of 0.6% per year.³⁻⁶ However, the event rate in patients with a normal perfusion SPECT study is dependent on the underlying risk in the population. The annualized event rate of 0.6%

reflects the average expected yearly occurrence of cardiac death and nonfatal myocardial infarction for intermediate-risk patients with normal perfusion findings. Patients with normal MPI who are also at higher risk (including diabetic patients, the elderly, and patients with peripheral vascular disease, or undergoing pharmacologic stress test) are expected to have event rates up to 1% to 2%.⁷ These data indicate the importance of further coronary artery disease (CAD) risk stratification and detection of subclinical coronary atherosclerosis in patients with a relatively high annual rate of MI and cardiac death. The coronary artery calcium (CAC) score is a strong indicator of CAD with prognostic application. Several studies have shown that CAC score is an independent indicator of coronary atherosclerosis and cardiovascular risk that is superior to other methods and clinical risk factors.⁸⁻¹⁰

SPECT MPI may detect obstructive CAD, but fail to discover subclinical atherosclerosis. CAC score has been reported as a surrogate for coronary atherosclerosis that correlates with outcome in large patients cohorts.¹⁰ The aim of this study was to evaluate the prevalence of CAC in patients with normal MPI and to better understand the relationship between conventional CAD risk factors and CAC.

PATIENTS AND METHODS

Study population

The study included patients referred from the outpatient clinical services of both cardiology and non-cardiology clinics between February 2010 and April 2016 for clinically indicated noninvasive CAD diagnosis with MPI SPECT who had a normal MPI. CAC score was subsequently performed within 3 months after MPI. Exclusion criteria included unstable patients (e.g; patients with chest pain, acute myocardial infarction, or patients with decompensated heart failure), a history of myocardial infarction, a history of coronary revascularization, a diagnostic Q wave on baseline ECG, known cardiomyopathy, known prior CAD, and patients with abnormal and/or nondiagnostic MPI and a nondiagnostic CAC score. Patient data was collected from medical records and the electronic database onto a standardized data collection sheet. Demographic and clinical data included age, sex, presence of diabetes, hypertension, hypercholesterolemia, a family history of CAD, and body mass index (BMI). Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, and/or taking antihypertensive therapy. Diabetes mellitus (DM) was self-reported by patients taking antidiabetic therapy. The study

was approved by the hospital ethics committee with a waiver of consent (ORA# 2161255).

Hypercholesterolemia was characterized by a fasting serum low density lipoprotein (LDL) cholesterol level ≥ 140 mg/dL or taking lipid-lowering therapy. The subjects were considered obese if they had a BMI ≥ 30 . A family history of CAD was considered positive if the father or a first-degree male relative had CAD before 55 years of age or if the mother or a first degree female relative had CAD before 65 years of age. Age was considered a risk factor if the patient was younger than 45 years of age for males and 55 years of age for females. High-density lipoprotein (HDL) cholesterol levels lower than 40 mg/dL were considered a risk factor.

SPECT acquisition and analysis

Patients underwent rest-stress myocardial perfusion studies with either a separate-day protocol or a same-day stress-rest sequence. The choice of tracer and same-day or separate-day protocol was based on logistical requirements. The rest dose in patients who underwent a separate-day rest-stress protocol was 1100 megabecquerel (MBq) of either technetium-99 (Tc-99m) sestamibi or tetrofosmin. The stress dose in patients who underwent the same-day rest-stress protocol was 1100 MBq mCi of either (Tc-99m) sestamibi or tetrofosmin. Tc-99m sestamibi or Tc-99m tetrofosmin was injected during peak pharmacological vasodilatation with adenosine (140 μ g/kg/min), or dipyridamole. SPECT imaging was started 30 minutes after pharmacological vasodilatation. Rest SPECT MPI was initiated at approximately 60 minutes following injection. SPECT imaging was performed with a line source attenuation correction at 900 dual-detector gamma camera (Cardio MD, Philips Medical System, Milpitas, California) equipped with attenuation correction and truncation compensation. The acquisition parameters and post-processing were performed according to the most recent guidelines of the American Society of Nuclear Cardiology for nuclear cardiology procedures.¹¹ All images were reoriented in short, vertical, and horizontal views utilizing Auto SPECT (Cedars-Sinai Medical Center, Los Angeles, California) for visual interpretation by an experienced nuclear medicine physician. The reader was unaware of clinical information. Stress and rest perfusion images were scored using 17 tomographic segments, which included 6 segments each for the basal and midventricular slices, and 4 segments for the apical short-axis slices. The final segment was located on the most apical part of the left ventricle. Finally, gated short-axis images were processed with quantitative SPECT software to measure the ejec-

tion fraction. In the visual analysis the 17 segments were scored for perfusion defects on a 4-point system (0=normal; 1=mild; 2=moderate; and 3=severe) for both the stress and rest images. From this analysis, ischemia was defined as a change in segmental score between stress and rest. Segments with no change between stress and rest were classified as nonreversible. Summed stress and rest scores were calculated by summing the 17 segmental scores in each imaged set. Defect reversibility was calculated from the difference between the summed stress and rest scores, known as the summed difference score (SDS). An SDS lower than 2 was considered nonischemic, 2 to 7 was considered mild ischemia, and greater than 7 was considered moderate to severe ischemia. The reader made the final determination of an abnormal SPECT study by comparing both the perfusion and functional data. The perfusion defects represented by the perfusion scores at stress and rest were used to form the interpretation of the MPS studies. A gated SPECT result was considered normal if there was no visual perfusion defect, the summed stress score was <3, and left ventricular ejection fraction (LVEF) at rest was >50%.

Coronary artery calcium score

All patients with heart rates >70 bpm received oral β -blocker therapy, with 50 or 100 mg of metoprolol tartrate (AstraZeneca, Zoetermeer, the Netherlands) after stress testing to achieve a heart rate <70 bpm for the CAC scan. A nonenhanced CT scan (high definition CT XT; GE Healthcare) taken during breath-hold at end expiration to calculate the total CAC score was acquired with ECG triggering at 75% of the R-R interval. The scanning parameters consisted of 40 or 48 sections of 2.5-mm section thickness; gantry rotation time, 330 ms; tube voltage, 120 kV; and a tube current of 125 mA. If patients were not able to hold their breath, a free breathing CT was acquired. Post-processing was conducted at a dedicated workstation using Smartscore software (GE Healthcare). The CAC score was calculated using the standard Agatston criteria.¹² CAC score was categorized into three subgroups: patients with total coronary CAC score of 0, a CAC score of 1 to 300, and a CAC score of more than 300.

Statistical analysis

Categorical data are presented as number and percentage. A chi-square or Fisher exact test was used to compare groups. Continuous variables are presented as mean and standard deviation with the t test used to determine differences between means. A *P* value $\leq .05$ was considered statistically significant. ANOVA

was used to compare among the mean ages of the three CAC groups. The statistical software used for these tests was SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

A post-hoc power analysis was conducted using the SAS power procedure (<https://goo.gl/45GUbj>). We set the R-square at 9% and the change in R-square at 9%. The total number of covariates was three (age, gender, diabetes) and we retained two covariates as significant. The required sample size with a power at 80% was 240 subjects to have two significant covariates in the linear regression model, with CAC score as a dependent variable.

RESULTS

In the study population of 207 patients, there were 108 men (52%) and 98 women (48%) of a mean (SD) age of 57.1 (10.4) years (**Table 1**). All patients had a normal SPECT MPI. The prevalence of CAC was 55% (n=113). Twelve percent had severe subclinical coronary atherosclerosis (CAC score >300). **Figure 1** is a selected coronal image of a CAC score scan showing a total CAC score of 1500.

There was a strong association between CAC score and age ($P<.0001$) (**Figure 2**). CAC scores were also associated with male sex ($P<.0001$), diabetes mellitus ($P=.042$) and gender ($P<.0001$), but not with hypertension ($P=.153$), family history of CAD ($P=.23$), obesity ($P=.431$), hypercholesterolemia ($P=.071$), or smoking ($P=.308$) (**Table 1**).

DISCUSSION

Our study showed a high prevalence of CAC and subclinical coronary atherosclerosis in patients with normal MPI SPECT (55%). It also confirms that a normal MPI does not exclude coronary atherosclerosis; only 45% of patients with normal MPI have no coronary artery calcification. These findings are important because several recent studies have documented that the presence, particularly a severe elevation of CAC score, is a predictor of adverse outcome in patients with a normal MPI SPECT¹³ or MPI positron emission tomography (PET).¹⁴ Possible explanations of the discrepancy between normal MPI and abnormal CAC are that the presence of CAC indicates coronary atherosclerosis, but not necessarily obstructive CAD with a flow limiting lesion. Thus, a patient with a flow limiting lesion will demonstrate perfusion abnormalities on MPI, but non-obstructive CAD will have normal perfusion. In addition, the presence of CAC probably reflects concomitant endothelial and microvascular dysfunction. In rare clinical circumstances, a very high CAC score has

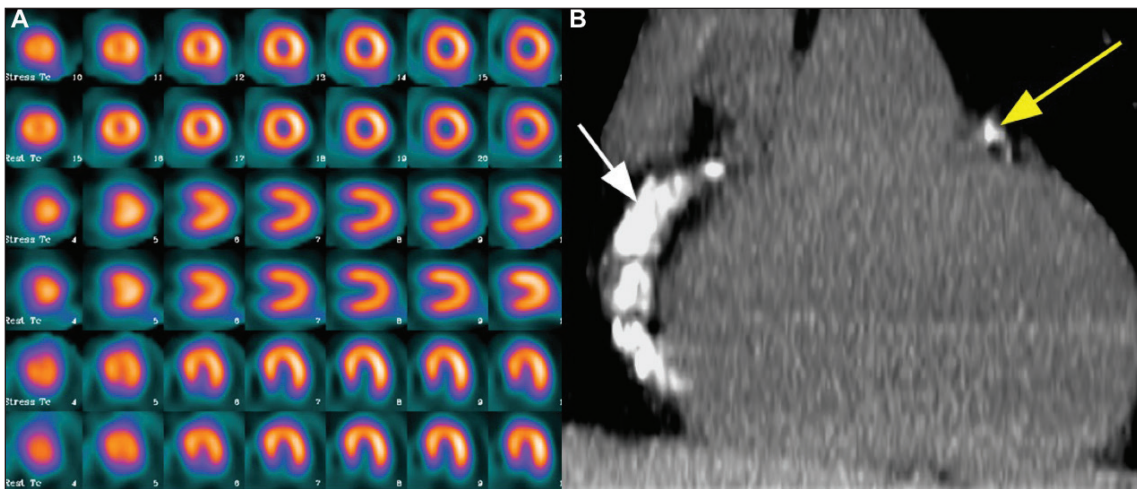


Figure 1. A 63-year-old man with hypertension and tobacco abuse presented with atypical chest pain. (a) He underwent a 1-day low-dose/high-dose adenosine Tc-99m tetrofosmin gated single photon emission computed tomography, which was normal (A). A selected coronal image of coronary artery calcium score scan of the same patient revealed a heavily calcified right coronary artery (white arrow) and left anterior descending artery (yellow arrow).

been shown to unmask obstructive CAD in patient with normal MPI SPECT studies.¹⁵ The presence of CAC is a highly sensitive and moderately specific test to predict significant coronary artery stenosis, but the presence of abnormal calcium may place patients into a high-risk group in terms of future cardiovascular events.¹⁶

Relationship between CAC and conventional cardiovascular risk factors

Our results document that there is a strong association between the presence of CAC and age, male sex, and diabetes. However, there was no association between CAC and other CAD risk factors such as hypertension, smoking, hypocholesteremia, obesity, or a family history of CAD. Our results are in accordance with international published data. The results from a multiethnic study of atherosclerosis (MESA), showed that there was significant difference in extent of CAC by race with differences across the age and sex. In MESA, McClelland and co-workers studied 6110 patients and found that men have a higher calcium level than women, and the amount of calcium and prevalence increased steadily with age.¹⁷ In another analysis of MESA, Lakaski et al. investigated 3601 women aged 45 to 84 years, excluding diabetic women older than 79 years of age. The presence of CAC was predictive of future cardiac events in women considered at low risk based on the Framingham risk score (FRS). Advanced CAC identified a subset of low-risk women at high risk based on current risk stratification strategies.¹⁸ Certainly, there is a strong difference in patterns of age and cardiovascular structure and function in

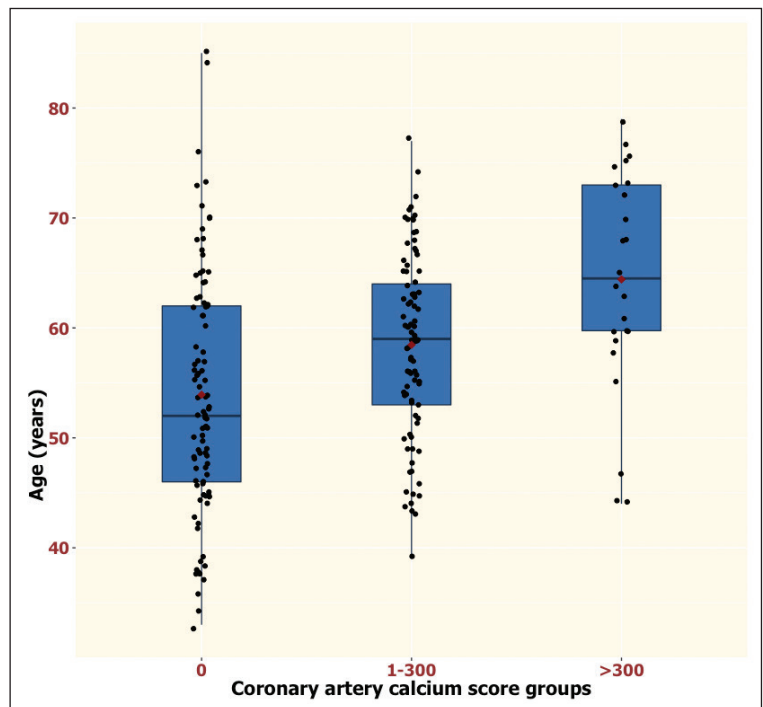


Figure 2. Coronary artery calcium score groups by age (median, interquartile range, mean [red dot]).

men and women. Both hormonal and nonhormonal factors underlie sex differences in cardiovascular aging and the development of age- and sex-related disease. There are also differences between men and women in other cardiovascular imaging markers; for example, carotid

intima-media thickening is more consistently associated with conventional risk factors in men than women.¹⁹ The presence of CAC in women improves risk stratification of CVD in low-risk women and older women but not older men.²⁰ Finally, men are more likely to have severe plaque and plaques with more high-risk features.²¹ Several studies have reported the extent of CAC in type 1 diabetic patients; one study reported that CAC correlated with most CVD risk factors. CAC had an 84% sensitivity for clinical CAD in men and 71% sensitivity in women, and 100% sensitivity for MI or obstructive CAD. A CAC score cut point of 400 was the most efficient coronary calcium correlate of CAD.²² Furthermore, type 2 asymptomatic diabetic patients had a significant increase in CAC compared with a matched nondiabetic control group.²³ In general, our data suggesting that age, male sex, and diabetes are the most predictive factors for the presence and extent of CAC in patients with normal MPI SPECT. Differences among different tools used in the assess-

ment of subclinical atherosclerotic disease are not new. It is not uncommon in patients with inflammatory arthritis, mainly rheumatoid arthritis (RA). In patients with RA without a history of cardiovascular events, diabetes or chronic kidney disease show a correlation between CAC score and the presence of carotid plaques.²⁴ However, a substantial number of RA patients without cardiovascular disease, who apparently did not have atherosclerosis according to CAC score results, had severe carotid ultrasonography abnormalities, mainly carotid plaques in another study.²⁵ These data highlight the importance of using more than one tool to exclude subclinical atherosclerotic disease in patients with conditions associated with high cardiovascular risk."

Prior studies in Saudi Arabia and Middle Eastern population

Unfortunately, studies in the Middle East are very limited and are mostly retrospective and from single centers.

Table 1. Association between coronary artery calcium scores and demographic and clinical characteristics of patients (n=207).

	Coronary artery calcium score categories				P value
	Zero	1-300	>300		
Number of patients	93 (45)	89 (43)	24 (12)		
Age (years), mean (standard deviation)	54 (11)	58 (8)	64 (10)		.0001
Gender	Male	36 (33)	58 (54)	14 (13)	.0001
	Female	57 (58)	31 (32)	10 (10)	
Diabetes	Yes	47 (50)	61 (68)	16 (64)	.042
	No	46 (50)	28 (32)	8 (36)	
Hypertension	Yes	65 (70)	50 (56)	10 (40)	.153
	No	28 (30)	39 (44)	14 (60)	
Smoking	Yes	11 (12)	13 (15)	6 (24)	.308
	No	82 (88)	76 (85)	18 (76)	
Hypercholesterolemia	Yes	50 (54)	62 (70)	16 (68)	.071
	No	43 (46)	27 (30)	8 (32)	
Family history	Yes	9 (10)	3 (3)	2 (8)	.23
	No	84 (90)	86 (97)	22 (92)	
Obesity	Yes	50 (54)	49 (55)	17 (71)	.431
	No	43 (46)	40 (45)	7 (29)	

Values are n (%) except for age. Statistical analysis by chi-square tests for dichotomous variables and by one-way ANOVA for age vs CAC score category (F=12.374).

Fathala and coworkers, in a retrospective study of 101 Saudi women, aged a mean (SD) of 56 (11) years, without a history of CAD, reported that moderate to severe CAC scores were associated with ischemic MPI in more than 50% of asymptomatic women with two or more CAD risk factors; a calcium score of 0 was rarely associated with an abnormal MPI.²⁶ In another retrospective study by the same author, 157 patients with known cancer who underwent positron emission tomography/computed tomography (PET/CT) for cancer management and MPI SPECT for preoperative cardiac risk stratification without known CAD, the author concluded that visual detection of CAC in the CT component of PET/CT is a strong predictor of MPI results. The presence of CAC was associated with a high likelihood of abnormal MPS and an absence of CAC was rarely associated with abnormal MPI.²⁷ In a comparative study between a middle eastern and an American veterans population, investigators found a discordance between the two populations: the middle eastern population had low CAC scores with high FRS, while the US veterans had high CAC scores with low FRS. The authors suggested that there may be etiologic factors not accounted for by the FRS in the middle eastern population that contributed to this difference. They recommended further large regional prospective studies to better understand the baseline characteristics of CAD risk factors in middle eastern populations.²⁸ An earlier study in the Middle East by Dakik et al on the prevalence of CAC in 1154 asymptomatic men and women in Lebanon found that the mean CAC score as well as the percentiles increased consistently with age, except for those more than 74 years old. The CAC scores were higher in men than women in each age group, findings that suggest that the CAC score distribution in the Middle East is

similar to published international data.²⁹ However, investigators in Saudi Arabia, who retrospectively studied 918 women with no history of CAD, unexpectedly found that CAC scores in the study population were significantly higher than published international percentiles. The authors recommended a large prospective study to better establish local CAC score percentiles. Applying international CAC score percentiles may underestimate the severity of subclinical coronary atherosclerosis and may not be an optimum strategy for CAD risk stratification.³⁰

Study limitations

There are several limitations to our study. It was retrospective and thus nonrandomized and only studied the population in a single tertiary care center. The relatively small size of the study population may have an impact in the correlation between CAC score and CAD risk factors. There was a long-term follow up to investigate the long-term prognosis based on combined CAC score and normal MPI, but the local data is very limited and the study may stimulate further investigation and workup locally.

In summary, 55% of patients with normal SPECT MPI had CAC, and 12% of these patients had severe subclinical coronary atherosclerosis. Age, sex and presence of diabetes were risk factors associated with CAC. Further prospective large multicenter studies are needed to investigate the presence of subclinical coronary atherosclerosis, CAC scores, and normal or abnormal MPI for better risk stratification and for CAD risk factor modification.

Conflict of interest

The authors report no conflict of interest.

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