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Exercise Electrocardiography Testing in Patients with Calcific Non-obstructive Coronary Lesions at Cardiac Multislice Computed Tomography

Eslam Shawky Abdelaziz, Ashraf Al-Amir Abdelfattah, Mahmoud Gabr Ahmed Abdellateef
Cardiology Department, Faculty of Medicine, Al-Azhar University, Egypt
***Corresponding author:** Mahmoud Gabr Ahmed Abdellateef, **Email:** mahmoud.gabr.abd@gmail.com,
Mobile: (+20) 01090293399

ABSTRACT

Background: Non-obstructive coronary artery disease (NoCAD), cardiac syndrome X (CSX), conduit vessel endothelial dysfunction and microvascular angina are all terms used to describe patients that have chest pain yet no obstructive coronary artery disease on coronary angiography.

Objectives: the purpose of this study was to evaluate exercise ECG (Ex-ECG) test in patients with subclinical atherosclerosis who were diagnosed by multi-slice computed tomography (MSCT) coronary angiography to have non-obstructive lesions.

Patients and Methods: 100 patients were recruited in the current study (their age ranged from 30 – 66 years), they were classified into three groups: group (A) 30 patients with non-calcific normal coronaries by MSCT, group (B) 35 patients with non-calcific non-obstructive lesions (zero calcium score) by MSCT and group (C) 35 patients with calcific non-obstructive lesions (calcium score < 400 HU) by MSCT.

Results: There was statistically highly significant difference between the three groups as regard results of exercise ECG test (P value=0.001). Positive exercise ECG test results occurred with calcific and mixed plaques in group (C) more than soft plaque in group (B), and there is significant difference between two groups with (P-value = 0.001). Positive exercise ECG test results in group (C) occurred more frequently with higher calcium score ranged from (59 – 362) HU.

Conclusions: MSCT angiography and calcium scoring system can provide valuable results which is helpful in avoiding an extra unnecessary invasive coronary angiography in patients for whom exercise ECG test results seemed to be positive or for whom high cardiovascular mortality risk from ischemia is not present.

Keywords: Electrocardiography, Calcific Non-obstructive Coronary Lesions, Cardiac Multislice Computed Tomography.

INTRODUCTION

Non-obstructive coronary artery disease (NoCAD), cardiac syndrome X (CSX), conduit vessel endothelial dysfunction and microvascular angina are all terms used to describe patients that have chest pain yet no obstructive coronary artery disease on coronary angiography [(1)].

Among the markers of subclinical atherosclerosis that have proved predictive of future cardiac events are coronary endothelial dysfunction and coronary artery calcification (CAC)[(2)].

In particular, patients with endothelial dysfunction make up roughly two-thirds of the patients with NoCAD and display increased risk of aggregate cardiovascular events. Despite the serious nature of this entity, patients with NoCAD are often reassured without due consideration to diagnostic or treatment options [(1)].

Calcification of the coronary arteries plays a key role in the pathophysiology of atherosclerosis. Coronary calcification is an active process culminating in extracellular matrix deposition of calcium by osteoblast-like cells that has some resemblance to bone formation. Sub intimal coronary calcification is almost exclusively associated with the presence of coronary atherosclerosis and is considered the hallmark of coronary atherosclerosis. Coronary calcific lesions are considered advanced lesions and calcification following plaque rupture of a high-risk plaque is thought to be part of the healing process[(3)].

It was demonstrated that enhanced coronary artery calcification is significantly related to endothelium dysfunction in patients with suspected CAD. Endothelial dysfunction may play an important role in the process of coronary artery calcification[(4)].

Multi-detector row computed tomography (MDCT) is a promising non-invasive method of detecting coronary artery disease. A new generation of MDCT with 320-detector rows CT has become available in the clinical setting. The accuracy of MDCT for evaluating stenosis of coronary arteries in the clinical settings was reported in previous studies by comparison with angiography[(5)].

However, for the diagnosis of obstructive coronary artery disease (CAD), Ex-ECG frequently has false-positive results, which are more common in women than in men. Due to the relatively higher prevalence of false-positive Ex-ECGs, women with ST-segment depression but non-obstructive CAD are often given non-cardiac diagnoses, and further cardiologic testing or treatment is not pursued. Thus, the utility of ST-segment depression for the diagnosis of IHD in women, which can be caused by processes other than obstructive CAD[(6)].

AIM OF THE WORK

In this study we aim to evaluate exercise ECG test in patients with subclinical non-obstructive coronary atherosclerosis.

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PATIENTS AND METHODS

This study included one-hundred patients attending the outpatient clinic of the Cardiology Department, Faculty of Medicine, Al-Azhar University Hospital and Nasr City Police Hospital in the period between March 2018 and March 2019.

Patients were divided into 3 groups according to the following inclusion criteria:

- **Group (A):** included thirty patients with non-calcific normal coronaries by MSCT.
- **Group (B):** included thirty five patients with non-calcific non-obstructive lesions (zero calcium score) by MSCT.
- **Group (C):** included thirty five patients with calcific non-obstructive lesions (calcium score < 400 HU) by MSCT.

Exclusion criteria:

Patients with one or more of the following were excluded from the study:

- Clinically unstable patients or patients cannot hold breath for examination.
- Body mass index > 40 kg/m^2.
- Acute myocardial infarction.
- Unstable angina.
- Uncontrolled arrhythmia.
- Symptomatic aortic stenosis.
- Acute pulmonary embolism.
- Acute myocarditis or pericarditis.
- Acute aortic dissection.
- Patient diagnosed by MSCT as obstructive lesion.
- Patient diagnosed by MSCT as calcific non-obstructive lesion with calcium score >400 HU.
- Patient with previous PCI.
- Patient with previous CABG.
- Hypersensitivity to iodinated contrast agent.
- Renal insufficiency (serum creatinine level >1.5 mg/dl).
- Congestive heart failure.
- History of thromboembolic disorders

Ethical approval and written informed consent:

An approval of the study was obtained from Al-Azhar University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

All participants included in this study were subjected to:

Complete history taking and general examination.

Multislice computed tomography:

The examinations were carried out before starting the study by using the Toshiba Multislice Aquilion System (Toshiba Medical Systems, Tokyo, Japan) 320 multislice. Patients underwent a prospectively triggered coronary calcium scan without contrast enhancement first, followed by 320-slice MSCT coronary angiography.

Anteroposterior and lateral views were recorded then total Agatston calcium score was recorded for all patients while coronary artery calcium is identified as a dense area in the coronary artery exceeding the threshold of 130 HU. Based on the total coronary calcium score, the patients were classified as having no or minimal coronary calcification (total calcium score <10) or moderate calcification (total calcium score < 400) or extensive calcification (total calcium score >400), the last one was excluded from the study[7].

The presence of coronary plaques was visually evaluated using axial images and curved multi-planar reconstructions. If present, the plaques were classified as non-obstructive and obstructive using a 50% threshold of luminal narrowing. The patients were first classified as (I) having a normal MSCT (no plaques visible), or as (II) having coronary atherosclerosis (at least one coronary plaque detectable). In case of the presence of atherosclerosis, the patients were further classified as follows: (I) patients with non-obstructive CAD, if exclusively non-obstructive plaques are present, (II) patients with obstructive CAD, if at least one obstructive plaque was present, they were excluded from the study[8].

Exercise ECG testing:

Electronic treadmill ranges in speed between 1.6 km/h and 12.8 km/h and gradient range of 0% to 22%. Treadmills should have a front rail and at least one side rail for safety and should be fitted with an emergency stop button.

Exercise testing is performed on a treadmill according to the standard protocols (Bruce protocol). The tests are analyzed by an experienced reader and then classified as positive or negative for ischemia. The exercise test was considered positive based on the presence of 0.1 mV horizontal or downsloping ST-segment depression on the ECG at 80 ms after the J point in two contiguous leads during exercise or recovery. The exercise test was considered un-interpretable if the patient failed to attain at least 85% of the age-predicted maximum heart rate with the absence of ischemic changes, if the ECG recording artifacts were observed during testing, or if ECG changes were equivocal[8].

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD) and compared by one way ANOVA test with LSD as a post-hoc test. Qualitative data were expressed as frequency and percentage and were compared by Chi-square (x^2) test. P-value <0.05 was considered significant and P<0.001 was considered highly significant.

RESULTS

Comparison between the three groups revealed statistically significant difference in mean values of age (Table 1).

Table (1): Comparison between the studied groups according to patients' age

Age	Range	Mean ± SD	P value		
Group A	30 – 58	44.87 ± 8.73	0.001*	P1	0.001*
Group B	45 – 66	52.40 ± 5.14		P2	0.001*
Group C	39 – 66	54.34 ± 6.91		P3	>0.05

P1: comparison between group 1 and 2, P2: comparison between group 1 and 3, while P3: comparison between group 2 and 3. * = statistically significant.

As regard the BMI and serum creatinine value, there was statistically **insignificant difference** between the study groups (Table 2).

Table (2): Lab examination of the studied groups (mean ±SD)

	Group A (n=30)	Group B (n=35)	Group C (n=35)	P value
BMI	27.3±2.07	27.7 ±1.86	27.69 ±2.35	>0.05
S. creatinine	0.92 ± 0.14	0.87 ± 0.17	0.89 ± 0.14	>0.05

As regard history of hypertension and history of diabetes mellitus, there was statistically **significant difference** between the study groups, on the other hand, regarding the history of smoking and history of dyslipidemia, there was statistically **insignificant difference** between the study groups (Table 3).

Table (3): Risk factors in the studied groups

Risk factor	Group A (n=30)	Group B (n=35)	Group C (n=35)	P value
Smoking	17 (56.7%)	12 (34.3%)	17 (48.6%)	>0.05
Hypertension	9 (30.0%)	21 (60.0%)	24 (68.6%)	0.005*
Diabetes	4 (13.3%)	15 (42.9%)	20 (57.1%)	0.001*
Dyslipidemia	8 (26.7%)	14 (40.0%)	18 (51.4%)	>0.05

* = statistically significant.

As regard the size and site of coronary lesions, there was statistically **insignificant difference** between the two groups B and C. While as regard type of plaques there was statistically **significant difference** between the two groups (Table 4)

Table (4): Computed tomographic findings of groups (B) and (C).

Lesions	Group B (n=35)	Group C (n=35)	P value
LAD	17 (77.1%)	32 (91.4%)	>0.05
LCX	10 (28.6%)	12 (34.3%)	>0.05
RCA	18 (51.4%)	20 (57.1%)	>0.05
Size			
Normal	0	0	
Minimum	12 (34.3%)	7 (20.0%)	>0.05
Mild	19 (54.3%)	24 (68.6%)	
Moderate	4 (11.4%)	4 (11.4%)	
Plaque			
No	0	0	
Calcific	0	32 (91.4%)	0.001*
Soft	35 (100%)	0	
Mixed	0	3 (8.6%)	

* = statistically significant.

The comparison between the three groups revealed statistically **significant difference** in mean values of calcium score (Table 5).

Table (5): Comparison between the studied groups according to calcium score

Ca score	Range	Mean ± SD	P value		
Group A	0 – 0	0.00 ± 0.00	0.001*	P1	>0.05
Group B	0 – 0	0.00 ± 0.00		P2	0.001*
Group C	5 – 362	130.43±111.85		P3	0.001*

P1: comparison between group 1 and 2, P2: comparison between group 1 and 3, while P3: comparison between group 2 and 3. * = statistically significant.

There was statistically highly **significant difference** between the three groups in exercise ECG test results. This showed more negative exercise ECG test results in groups (A and B) than group (C), and also showed more positive exercise ECG test results in group (C) than groups (A and B) (Table 6).

Table (6): Comparison between the studied groups according to results of exercise ECG.

Conclusion		Group A and B	Group C	Total	P value
Negative	N (%)	54 (83.1%)	10 (28.6%)	64 (64.0%)	0.001*
Equivocal	N (%)	7 (10.8%)	8 (22.9%)	15 (15.0%)	
Positive	N (%)	4 (6.2%)	17 (48.6%)	21 (21.0%)	
Total	N (%)	65 (100%)	35 (100%)	100 (100%)	

* = statistically significant.

The exercise ECG results were more positive with presence of (calcific and mixed) plaques in group (C) than with presence of soft plaque in group (B), and there was significant difference between the two groups (Table 7).

Table (7): Correlation between exercise ECG test results and type of plaque in groups B and C

Ex-ECG	Group B	Group C			P value
	Soft	Calcific	Mixed	Total	
Negative	25 (71.4%)	9 (28.1%)	1 (33.3%)	10 (28.6%)	0.001*
Equivocal	6 (17.1%)	8 (25.0%)	0	8 (22.9%)	>0.05
Positive	4 (11.4%)	15 (46.9%)	2 (66.7%)	17 (48.6%)	0.001*
Total	35 (100%)	32 (100%)	3 (100%)	35 (100%)	
P-value	0.001*				

* = statistically significant.

Positive exercise ECG test results occurred more frequently in patients with higher calcium scoring in group C (Table 8).

Table (8): The correlation between the exercise ECG findings and the calcium score

Calcium score	Negative	Equivocal	Positive
Range	5 – 75	22 – 222	59 – 362
Mean ± SD	37.0 ± 21.92	74.75 ± 62.83	211.59 ± 102.86
p. value	0.001*		

* = statistically significant.

There was no relation between the exercise ECG results and the size or site of coronary lesions in both groups B and C (Tables 9 and 10).

Table (9): The correlation between the exercise ECG findings and the size and site of coronary lesion by MSCT in group (B)

Variables		Exercise ECG			P value
		Negative	Equivocal	Positive	
Size	Minimal	10 (40%)	2 (33.3%)	0	>0.05
	Mild	14 (56%)	3 (50%)	2 (50%)	
	Moderate	1 (4%)	1 (16.7%)	2 (50%)	
LAD	Yes	19 (76%)	5 (83.3%)	3 (75%)	>0.05
	No	6 (24%)	1 (16.7%)	1 (25%)	
LCX	Yes	6 (24%)	3 (50%)	1 (25%)	>0.05
	No	19 (76%)	3 (50%)	3 (75%)	
RCA	Yes	14 (56%)	3 (50%)	1 (25%)	>0.05
	No	11 (44%)	3 (50%)	3 (75%)	

Table (10): The correlation between the exercise ECG findings and the size and site of coronary lesion by MSCT in group (C).

Variables		Exercise ECG			P value
		Negative	Equivocal	Positive	
Size	Minimal	5 (50%)	1 (12.5%)	1 (5.9%)	>0.05
	Mild	4 (40%)	6 (75%)	14 (82.4%)	
	Moderate	1 (10%)	1 (12.5%)	2 (11.8%)	
LAD	Yes	10 (100%)	6 (75%)	16 (94.1%)	>0.05
	No	0	2 (25%)	1 (5.9%)	
LCX	Yes	4 (40%)	4 (50%)	4 (23.5%)	>0.05
	No	6 (60%)	4 (50%)	13 (76.5%)	
RCA	Yes	5 (50%)	5 (62.5%)	5 (29.4%)	>0.05
	No	5 (50%)	3 (37.5%)	12 (70.6%)	

DISCUSSION

In the current study, comparison between the three groups revealed statistically significant difference in mean values of age, while the difference in gender was insignificant.

This is in agreement with study done by **Chaudhry *et al.*** [11], which revealed that in men and women, obstructive-CAD groups is significantly different from the healthy cohort group ($p < 0.001$) and not statistically different compared to the non-obstructive (NO)-CAD and symptomatic normal coronary groups ($P = 0.88$ and 0.65 respectively) with 60% of men with NO-CAD had microvascular dysfunction, while not statistically different compared to the NO-CAD and symptomatic normal coronary groups ($P = 0.55$ and 0.057 respectively) with 66% of women with NO-CAD had microvascular dysfunction.

In the current study comparison between the three groups revealed statistically insignificant difference in mean values of BMI. This indicated that increase in BMI increases the risk of CAD which not coincides with **Alkhawam *et al.*** [12] who concluded that having a BMI ≥30 appears to be a risk factor for early development of CAD. Severity of CAD in obese patients is depicted on non-modifiable and modifiable risk factors such as the male gender and smoking or greater than one risk factor, respectively.

In the current study, comparison between the three groups revealed statistically insignificant difference in mean values of serum creatinine. This indicated that increase of serum creatinine does not affect non-obstructive coronary lesion in this study. This is discordant to the study of **Jędrychowska *et al.*** [14] who stated that increase of serum creatinine is considered one of the predictors for coronary artery disease.

In the current study there was statistically insignificant difference between three groups in history of smoking. So, we found no association between smoking and coronary artery disease. This is discordant with many previous studies which may be contributed to the small sample number in our study and we did not study the smoking dose per day and different component of cigarettes. A Polish study by **Iwanicka *et al.*** [15] indicated the presence of a strong synergistic effect between the TT genotype and cigarette smoking. Cigarette smoke contains a number of oxidizing compounds and is an important source of free radicals which contribute to both the development of atherosclerosis and an increase in the incidence of cardiovascular events among smokers.

In the current study there was statistically highly significant difference between three groups in history of hypertension. These results are in agreement with **Weber *et al.*** [16] who stated that high blood pressure is a major modifiable risk factor for all clinical manifestations of CAD.

In the current study also there was statistically significant difference between three groups in history of diabetes. So, this study indicated that diabetes mellitus is considered a risk factor for calcific non-obstructive lesions. This was in agreement with **Feuchtner *et al.*** [17] who stated that diabetes is a risk factor with non-obstructive lesion and differs in that these lesions are not calcific and added that a high prevalence of ischemia in non-obstructive lesions with high-risk plaque features (40% and 25%), but not in calcified. But they found a correlation of increasing

plaque density for calcified lesions and diabetes mellitus.

In the current study there was statistically insignificant difference between three groups in history of dyslipidemia. This is discordant with many studies because our sample included only non-obstructive coronary lesions only. However, **Segev *et al.*** [18] found a significant increase in dyslipidemia in non-obstructive patients compared to normal ($P < 0.01$).

In the current study as regard multi-detector computed tomography (MDCT) data, there was statistically insignificant difference between two groups (B and C) in the LAD, LCX, and RCA lesions. However, the difference was statistically significant between both group B and C and group A (controls). This was in accordance with **Homsi *et al.*** [19] who found a statistically significant difference in diagnosis of coronary lesions between patients and controls,

especially in partial or total occlusion of LAD, LCX, and RCA.

The accuracy of MDCT to detect or exclude significant coronary artery stenosis was high in many published studies with sensitivity of 76–99%, specificity of 87–99%, positive predictive value of 56–89%, and a negative predictive value of 95–100%[20, 21]. This agrees with the previous results of our study.

In the current study there was statistically insignificant difference between two groups (B and C) in size of lesions. **Lu *et al.*** [22] found the same results and added that the size and shape of the plaques are affected by their calcification. They found the predictors present over 80% of AUC (area under the curve) and higher odds ratio. The Kappa statistics was 0.68 for the combinations of shape and stiffness into logistic regression.

In the current study there was statistically significant difference between the two groups B and C in type of plaque. This is in agreement with currently in patients presenting with acute chest pain having non-obstructive coronary lesions, one can assume that some are vulnerable plaques that may lead to future acute coronary events. It should be noted that the accuracy of cardiac MDCT to morphologically detect non-obstructive vulnerable plaques is limited[18]. Added that the likelihood of plaque rupture is based on plaque composition rather than plaque volume. Most ruptures occur in plaques containing a soft, lipid-rich core covered by a thin, inflamed fibrous cap. A thin fibrous cap is on the order of 70 mm, which is 10 times beyond the present in-plane resolution of MDCT (750 mm)[23].

In the current study, comparison between the three groups (A, B and C) revealed statistically significant difference in mean values of calcium score.

Actually, non-obstructive plaque volume, non-obstructive calcified and non-obstructive non-calcified NCP volumes were better predictors of future cardiac events than clinical variables. However, most of these patients are in the intermediate risk group, in whom prognosis and management are less well defined. Accordingly, these patients need additional testing with one or more of the established noninvasive modalities, which include exercise electrocardiography, stress SPECT imaging, or stress echocardiography. All these techniques aim at detecting ischemia, and proved to be predictive of future cardiac events when abnormalities were found and were associated with a low risk for events when the test results were normal[24].

There was a great interest in calcium score as a risk stratification tool, mainly in asymptomatic patients[25]. The technique is attractive, as it provides a fast measurement of presence and severity of CAD, with a minimal radiation dose and no use of contrast medium. However, especially in symptomatic patients, a zero calcium score does not rule out CAD[26].

In the current study, there was statistically highly significant difference between the three groups in conclusion of exercise ECG test. These results were similar to **Zeljkovic *et al.*** [27] as they found a statistically highly significant difference ($P < 0.01$) as regard exercise-ECG test yielded a total accuracy of (45.1%) with a sensitivity of (68.1%) and specificity (36.6%).

Lin *et al.* [28] noted a high yield of visualized plaque on MDCT- identified non-obstructive CAD compared with exercise-ECG alone in same populations, with false-positive and false-negative results noted. The association of functional ischemia was stronger with mixed plaque than calcified plaque alone.

In the current study, there was no relation between the exercise ECG findings and the size of lesion. Also there was no relation between the exercise ECG findings and the site of coronary lesion in both groups.

The current study revealed the correlation between the exercise ECG findings and type of plaque by MSCT in group (B) and group (C). Exercise ECG was more negative with soft plaque in group (B) than calcific and mixed plaques in group (C), and there was statically significant difference between the two groups. Exercise ECG was more positive with calcific and mixed plaques in group (C) than soft plaque in group (B), and there was statically significant difference between the two groups.

In agreement with the present study, **Kim *et al.*** [29] who performed both CCTA and exercise-ECG at the same day for 296 patients and they found that exercise-ECG was more sensitive in small and soft plaque patients than in calcified plaques, but this depended on exercise duration. Several reports demonstrated that plaque characteristic (soft, fibrous, calcified, or mixed type), location, extent, and distribution on CTCA were associated with poor cardiovascular outcome [30]. **Kim *et al.*** [29] concluded that computed coronary tomography angiography (CCTA) was better than exercise electrocardiography (ex-ECG) for prediction of cardiovascular long-term outcome.

The present study found that the equivocal and positive exercise ECG tests occurred in patients with higher calcium scoring in group C. Coincides with our results **Cho *et al.*** [31] verified that calcification, which might be a surrogate for arterial stiffness, could predict exercise SBP response and cardiovascular outcomes in the elderly who are prone to calcification, irrespective of coronary atherosclerosis. Coronary artery calcification generally occurs in the intimal layer of an atherosclerotic plaque[32].

In our population 6% of patients presenting with zero calcium score had a significant lesion on CCTA, which is comparable to previous reports. Other reports indicated that patients with a zero calcium score have a

low prevalence of inducible ischemia on PET/CT, but prevalence was still about 1%[33].

Several considerations that might explain the shortcoming of calcium scoring in the patient group; for instance, calcium score does not take into account presence of non-calcified plaques, while these seem to be more vulnerable to rupture, consequently posing greater risk on a cardiovascular event[34].

Importantly, the presence of obstructive CAD could be excluded by MSCT in the majority of patients with an uninterpretable exercise test result. Accordingly, MSCT could also possibly provide valuable information in patients with an uninterpretable exercise test as previously suggested[35].

CONCLUSION

The presence of subclinical atherosclerosis in the form coronary artery calcification (CAC) leads to endothelial dysfunction which contributes to false positive exercise ECG results. So, MSCT angiography and calcium scoring system can provide valuable results, which are helpful in avoiding an extra unnecessary invasive coronary angiography in patients for whom exercise ECG test results seemed to be positive or for whom high cardiovascular mortality risk from ischemia is not present.

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