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Detecting probable coronary insufficiency in asymptomatic hypercholesterolemic individuals by treadmill exercise electrocardiography

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ABSTRACT

Objective: Assessment of the possible presence of silent coronary insufficiency (SMI) in hypercholesterolemic individuals who are not complaining of documented atherosclerotic disorders. *Methods:* A case – control study carried out in the outpatient's clinic, biochemical laboratory, Alexandria University Hospital. All participants undergo ETT (exercise tolerance test). The study based on selection of patients with one major risk factor (serum cholesterol ≥250 mg/dl), without any additional risk factors (like DM, hypertension etc.). The study included 70 subjects, and were divided into two groups, group A (diagnosed with hypercholesterolemia) included 50 subjects (22 males, and 28 females), in which serum cholesterol ≥ 250 mg/dL. While group B (normal control), included 20 subjects (11 males, and 9 females) with serum cholesterol ≤200 mg/dL. *Results:* Only three cases (6%) showed positive finding after performing ETT (all were in group A), however, there was no significant difference in ETT between group A and B (p-value = 0.552). *Conclusion:* The value of exercise tolerance test was limited in assessing silent myocardial ischemia

in hypercholesterolemic people, if they are free from multiple major cardiac risk factors and other conventional cardiac complaints. Due to high false positive results of the ETT in cases with a low pretest probability, it is not a reliable procedure to detect SMI in low suspicious cases.

Keywords: exercise tolerance, hypercholesterolemia, silent myocardial ischemia, major risk factor

1. INTRODUCTION

A symptomatic coronary heart disease (CHD) or silent ischemia (SMI) is recognized as a clinical syndrome with the spectrum of coronary artery disease (CAD). The association between elevated serum cholesterol and CHD was first reported in 1930s, and subsequent large epidemiological studies confirmed the strong relationship between cholesterol and CHD, which larger translated as “cholesterol hypothesis”, stating that cholesterol is associated with atherosclerosis and a reduction in serum cholesterol will reduce atherosclerotic disease (Gotto, 2011). The diagnosis of SMI depends mainly on exercise testing and ambulatory ECG monitoring. Both techniques are complementary to each other (Serhiyenko and Serhiyenko, 2018).

Cardiovascular disease (CVD) is the number one cause of death in the western world and one of the leading causes of death worldwide. The lifetime risk of atherosclerotic CVD for person at age 50 years, on average, is estimated to be 52% for men and 39% for women, with a wide variation depending on risk factor burden. Several algorithm exist to examine the risk of CVD, one of them is the Framingham risk score (estimate 10 – years risk score) (Berger *et al.*, 2010, Mohammed *et al.*, 2018). Exercise tolerance test, remains the most widely used and available technique for the investigation of known or suspected CAD. It has been estimated that 6 to 8 million treadmill tests are performed annually in the US (Rahsepar and Arbab-Zadeh, 2015).

The current work carried out to assess the possible presence of SMI in hypercholesterolemic individuals who are not complaining of documented atherosclerotic disorders.

2. PATIENTS AND METHODS

Study sample

The study included 70 subjects, and were divided into two groups, group A (diagnosed with hypercholesterolemia) included 50 subjects (22 males, and 28 females), in which serum cholesterol ≥ 250 mg/dL. While group B (normal control), included 20 subjects (11 males, and 9 females) with serum cholesterol ≤200 mg/dL.

Study setting

A case – control study carried out in the outpatient’s clinic, biochemical laboratory, Alexandria University Hospital. During the period the period between May 2017 and December 2017.All 70 participants undergo ETT (exercise tolerance test) in accordance with Bruce protocol (Bruce *et al.*, 1963), which consists of 3 – minutes stages of increasing treadmill speed and incline. The exercise must be sufficient to increase the heart rate to 85% maximum predicted heart rate (i.e. 220 – age).

The study based on selection of patients with one major risk factor (serum cholesterol ≥250 mg/dl), without any additional risk factors (like DM, hypertension etc.)

Collected data

Age, gender, BMI, blood pressure, fasting blood sugar (FBS), serum cholesterol, LDL, HDL, the duration of the procedure, Ratio of Achieved to target HR, and estimated 10 – years risk of Framingham risk score.

Chronotropic response index (CRI)

Normally the sinus rate increases progressively with exercise, Chronotropic incompetence denotes inability to increase heart rate (HR) to at least 85% to age – predicted maximum heart rate (APMHR) or an abnormal CRI, which is calculated as follow:

$$CRI = \frac{(HR_{peak} - HR_{rest})}{(APMHR - HR_{rest})}$$

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Code: 00246) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed written consent was obtained from all individual participants included in the study

Inclusion criteria

No history of cardiovascular disease, normal blood pressure, non-smoker, non-alcoholic, serum normal triglyceride, HDL, and non-diabetic. For patients in group A serum cholesterol levels ≥250 mg/dl, for group B serum cholesterol <200 mg/dl.

Exclusion criteria

Previous medical, clinical or ECG evidence suggesting underlying coronary heart disease (CHD), like DM, hypertension, and smoker.

Statistical analysis

Two samples t-test used to analyze the differences in means between two groups (if both follow normal distribution with no significant outlier), chi square test used to analyze the discrete variable. While one way ANOVA used to analyzed the different between the groups when stratified using gender (Al-Radeef *et al.*, 2019). SPSS 16.0.0 (Chicago, IL) software package used to make the statistical analysis, p value considered when appropriate to be significant if less than 0.05

3. RESULTS

The study included 70 subjects, 50 in group A and 20 in group B, there was no significant difference in their age, and BMI between both groups, while Framingham score was significantly higher in hypercholesterolemic males compared to female and male and female with normal cholesterol levels, as illustrated in table 1.

Table 1 assessment of basic demographic and clinical data

Variables	Group A		Group B		p-value
	Male	Female	Male	Female	
Number	22	28	11	9	
Age (y), mean ± SD	52.9 ± 8.5	53.9 ± 7.0	48.7 ± 7.2	49.1 ± 7.2	0.151
BMI (kg/m^2), mean ± SD	29.7 ± 4.5	29.7 ± 3.4	29.5 ± 3.9	28.6 ± 6.2	0.916
Estimated 10-years risk [#] (%)	11.1 ± 6.7^a	2.3 ± 1.2^b	4.4 ± 4.8^b	1.6 ± 0.9^b	<0.001
<6%	7	28	9	9	
6 – 10%	1	0	0	0	
11 – 20%	10	0	2	0	
>20%	4	0	0	0	

[#]Framingham point scores was used
Variables that do not share the same letter indicate significant difference
BMI: body mass index, SD: standard deviation, y: year

Serum cholesterol levels was significantly higher in group A compared to B, while the rest of the variables in table 2 show no significant difference, as illustrated in table 2 and figure 1- 3.

Table 2 comparison of various variables between group A and B

Variables	Group A	Group B	p-value
Number	50	20	-
Systolic blood pressure (mmHg)	131.0 ± 8.0	127.8 ± 9.8	0.149
Diastolic blood pressure (mmHg)	78.5 ± 4.9	78.0 ± 5.2	0.750
FBS (mg/dl)	96.6 ± 9.6	96.2 ± 10.8	0.886

Triglyceride (mg/dl)	116.9 ± 24.2	112.0 ± 27.9	0.507
HDL (mg/dl)	50.4 ± 6.8	50.5 ± 6.7	0.964
Cholesterol (mg/dl)	277.9 ± 24.8	181.8 ± 17.7	<0.001
Treadmill exercise ECG			0.552
Negative	47 (94%)	20 (100%)	
Positive	3 (6%)	0 (0%)	
Chronotropic response index			0.560
≤80	14 (28%)	4 (20%)	
>80	36 (72%)	16 (80%)	
Ratio of Achieved to target HR			0.052
≥85%	48 (96%)	16 (80%)	
<85%	2 (4%)	4 (20%)	
Duration of the procedure			0.262
≥6 minutes	41 (82%)	19 (95%)	
<6 minutes	9 (18%)	1 (5%)	
Variables presented as either: mean ± SD or number (%) FBS: fasting blood sugar, HDL: high density lipoprotein, HR: heart rate, ECG: electrocardiography			

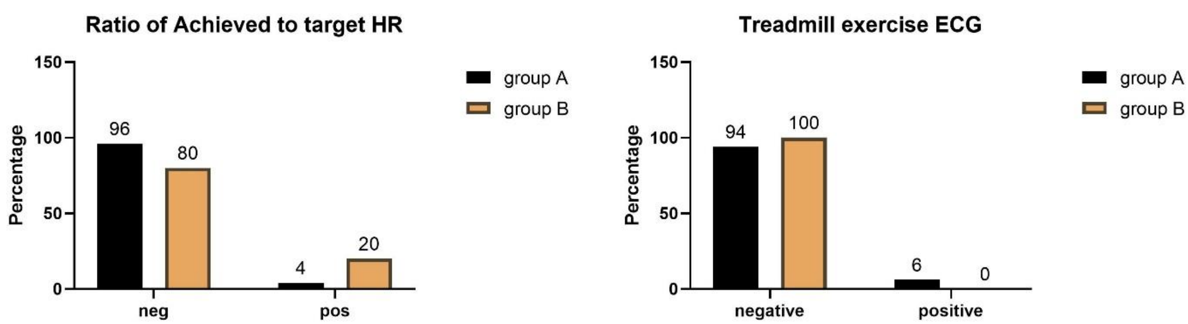

Figure 1 histogram of ratio of achieved to target hear rate (HR), and treadmill exercise ECG

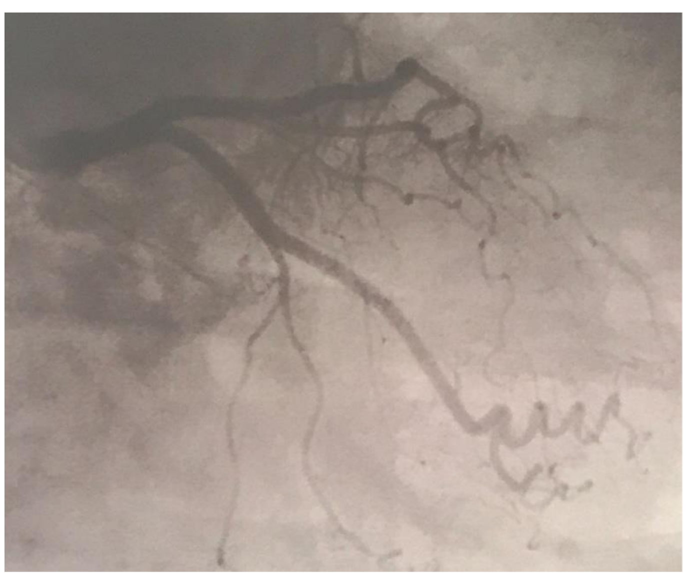

Figure 2 coronary angiography, RAO view of case 2 showing LMC, LAD, LCX

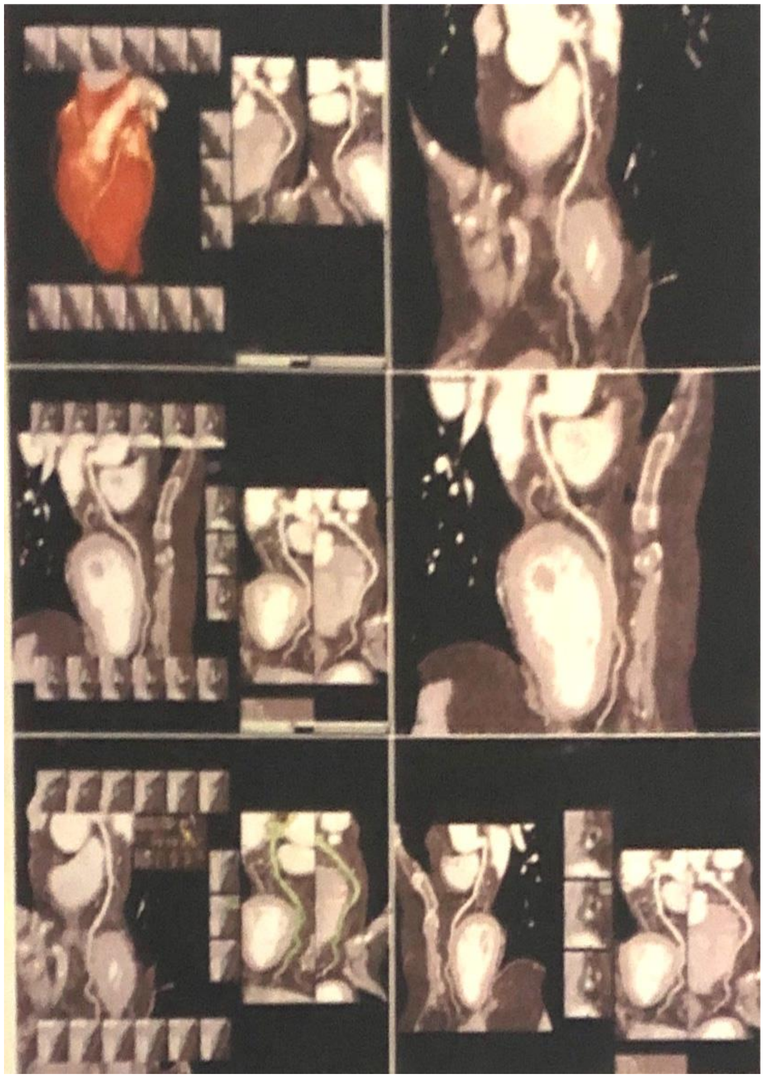

Figure 3 Cardiac CT angiogram of case 3 (LAD)

4. DISCUSSION

Among the main objectives of clinical cardiology is the detection of coronary atherosclerosis, in consideration of its potential role in the pathogenesis of ischemic heart disease (Burgess, 2003). SMI is the most common form of ischemia occurring in all subsets of CAD patients, the detection of SMI is of great importance because SMI has a higher incidence rate of unfavorable clinical outcomes such as silent myocardial infraction (MI), arrhythmia, or sudden death (Kolte and Panza, 2016).

In the present study only 3 (6%) patients had positive ETT findings (all in group A) and none in group B, which is comparable to the prevalence of abnormal exercise electrographic result in middle aged asymptomatic men which ranges from 5 – 12% (Chaitman, 2011). By carrying out sophisticated investigations to confirm the ECG findings of ETT, 2 out of the 3 cases had been found to be incorrect, while the 3rdcase was partially correct (these modalities were Multi detector computed tomography MDCT 128, and Percutaneous transluminal coronary angioplasty PTCA).

The third case was female with a partial positive ETT and showed a stenosis of 40% in the proximal LAD, which considered mild significance (<50% stenosis). This patient experienced anginal pain at the end of the test. Her ETT credibility was debatable, but her non-ECG data (which was in the intermediate and high risk prognostic range) may help in explaining her actual status when we did the MDCT 128.

The ST segment depression in the 1st case was 1 mm slow up sloping in V6 at maximum exercise. The test evaluation of the 2nd case was <1 mm ST depression in leads II, III, and aVF, with new ST depression in aVL, and V_3 – V_6.In the 3rd case horizontal 1 mm ST depression in the inferior leads at peak exercise and resolved after 1 minute of recovery. From these findings the probability of false positive results in the 3rd case would be expected. Myers and Froelicher found that ST changes isolated to the inferior leads were frequently lase positive (Myers and Froelicher, 1993).

The Framingham score was 10% (male), 2% (female), and 2% (female) for the 1st, 2nd, and 3rd cases, respectively. The duration of test was 10, 5.4, and 6.2 minutes, respectively. Finally, the non-ECG data suggest; low risk, between low to intermediate risk, and between intermediate to high risk prognosis, respectively. Thus for the 1st case intermediate Framingham score, low non-ECG data refutes the ECG results of the ETT, this was confirmed by MDCT 128. For the 2nd case with low Framingham score, low to intermediate non-ECG data, disproves the ECG results which were confirmed by PCTA. The 3rd case with partial true positive results was confirmed by MDCT 128, her angina was in favor of the true positive ECG data.

Michael et al., found that there is an inverse relationship between the duration of exercise and both the severity and incidence of coronary arterial stenosis, and that the accuracy of the exercise tests was also inversely related to the duration of exercise (Sketch *et al.*, 1978). The coronaries of the 1st and 2ndcases were normal, which concludes that a single risk factor, the morbid elevation of serum cholesterol, did not significantly affect the patency of the coronaries.

From the above results, two important issues were challenged; 1st lack pf multiplicity of coronary risk factors, leading to a low probability of SMI presence, and 2ndthe low credibility of ETT results in the set of low pretest probability. The presence of multiple risk factors for CHD had a multiplicative rather than additive effect on the risk of silent ischemia in addition; there is a synergism between the effects of risk factors with each other. This is consistent with results reported by Gordon et al in which they found that the relative risk for hypertension was 2.6 folds, for elevated cholesterol levels was 3.3 folds, and the combination of these two risk factors resulted in 6.5 folds increased relative risk (Gordon *et al.*, 1979), as suggested by other studies (Stamler, 1979, Petersson *et al.*, 1984).

Gibbons et al. showed that the effect of risk factors on 25,927 asymptomatic men (mean age 43 years), a positive exercise test was associated with an age – adjusted relative risk (RR) of CAD death in 21 in those with no risk factor, 27 in those with single risk factor, 54 in those with two risk factors, and 80 in those with ≥3 risk factors (Gibbons *et al.*, 2000). In detecting SMI, Megnien and Simon stated that in symptom – free subjects, ETT has a doubtful utility for detecting latent CHD because of frequent false positive (Megnien and Simon, 2009).

5. CONCLUSION

The value of exercise tolerance test was limited in assessing silent myocardial ischemia in hypercholesterolemic people, if they are free from multiple major cardiac risk factors and other conventional cardiac complaints. Due to high false positive results of the ETT in cases with a low pretest probability, it is not a reliable procedure to detect SMI in low suspicious cases.

Author contribution

Raed Dheyaa Jaafar: Conception and design of the work, the acquisition, analysis, and interpretation of data for the work, drafting the work, revising it critically for important intellectual content, and final version of the research.

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Conflicts of Interest: The authors declare no conflict of interest.

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