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The Role of Exercise Electrocardiographic Test in Determining the Extent of Coronary Artery Disease in Comparison to Coronary Angiography in Erbil-Iraq

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Abstract
Background and objective:
Exercise Electrocardiographic Test (EET) is one of non-invasive modalities used to assess patients with coronary artery disease (CAD). The objective of this study was to evaluate the role of this test in determining the extent of CAD in comparison with coronary angiography among a sample in Erbil-Iraq.
Patients and Methods:
The study was conducted from April 2014 to April 2015 in Erbil-Iraq. A total of 160 adult patients with anginal chest pain and normal baseline 12-lead electrocardiographic (ECG) test were evaluated. All patients underwent EET and coronary angiography. Among these patients, only 83 patients (58 males and 25 females) with positive coronary angiographic results were included in this study. Patients with positive coronary angiographic results were classified into three groups according to the number of coronary artery involved. A correlation between EET and coronary angiographic results was studied.
Results:
There were 160 patients in this study, 115 patients (71.87%) of them had positive EET. Out of 115 patients, only 83 patients (72.1%) had positive coronary angiographic test. Those patients were further classified into three groups according to the number of the coronary artery involved, Group 1; nine patients with one vessel, Group 2; 43 patients with two vessel, and Group 3; 31 patients with three vessel diseases . Typical anginal chest pain, the number of risk factors, ST/HR index, the number of leads with ST segment depression, timing, and depth of ST segment depression showed statistically significant association with the number of vessel involved.
Conclusion:
Positive EET was more in patients with two and three vessel disease. EET is of greatest diagnostic value in patients with typical anginal chest pain .
Keywords: Exercise electrocardiographic test, coronary artery disease, coronary angiography.

Introduction:

Coronary artery disease is the leading cause of mortality and morbidity worldwide and it is expected that the rate of coronary artery disease will be accelerated in the next decade.[1] Exercise is a common physiological stress used to elicit cardiovascular abnormalities not present at rest . In patients able to exercise, the standard Bruce protocol is popular and has been extensively validated, and a large diagnostic database has been published using this protocol.[2, 3] The exercise ECG test can give wide variability on sensitivity and specificity. In meta-analysis of 147 consecutively published reports involving 24074 patients who underwent both coronary angiography and exercise test, mean sensitivity was 68% with a range of 23% to 100% and mean specificity was 77% with a range of 17 % to 100%. [3]

Many investigators have correlated the results of stress testing with coronary angiographic finding in an effort to identify patient with critical forms of CAD for further diagnostic and therapeutic considerations. [4-6] Diagnostic coronary angiography is recommended whenever it is clinically important to define the presence or severity of a suspected cardiac lesion that can't be adequately evaluated by noninvasive techniques. Identification of CAD, with assessment of its extent and severity, are the most common indications for cardiac catheterization. Up to our knowledge, there was no previous study done in the same subject in Erbil city-Iraq. The objective of this study was to assess the value of EET in determining the extent of CAD by comparing the ECG response and other parameters with coronary angiographic findings.

Patients and Methods

This cross sectional study was conducted from April 2014 to April 2015. A total of 160 adult patients referred because of anginal chest pain and normal baseline ECG were evaluated in Hawler and Rizgary hospitals in Erbil city-Iraq. All patients underwent EET and coronary angiography. Only 83 patients in whom the coronary angiogram showed at least one major vessel narrowing were included in this study. Patients who cannot reach

85% of maximal predicted heart rate (MPHR) and without developing chest pain or ST-depression in any lead, patients with pre-exercise ST-segment depression of ≥ 1mm, patients with previous coronary artery bypass grafting (CABG) or had Left bundle branch block, Left ventricular hypertrophy, pre-excitation syndrome, severe valvalur heart diseases, intraventricular conduction disease, pacemaker rhythm or on digoxin were not included in this study because these situations can change the sensitivity and specificity of the test.[2,3]

EET was performed according to the Bruce protocol, [2, 3] using the graded multistage treadmill. The protocol has six stages, each lasting 3 minutes. The test was performed on (GE CASE V6.01 ©2005) advanced system which was a dedicated stress test unit and had automatic speed acceleration starting from 1.7 to 5.5 Mile per hour (MPH). A resting baseline 12-lead ECGs, both sitting and standing were performed before exercise, at end of each stage and at 1-minute intervals for a period of 10 minutes after exercise or until the changes disappeared. During exercises, all 12- leads were monitored continuously and 12-lead ECG was recorded at end of each stage. Cuff blood pressure measurements were made before and at the end of each stage. Patients were encouraged to exercise to the maximum of their physical capacity unless typical anginal chest pain , significant ST segment depression or elevation in non Q-wave lead, arrhythmias like sustained (>30 sec) ventricular tachycardia , systolic blood pressure exceeded 220 mmhg or diastolic exceeded 120mmhg , more than 10 mmhg drop in systolic blood pressure or drop in heart rate of more than 20 beats/minute from baseline or non-cardiac symptoms (like ataxia, dizziness or near-syncope) , signs of poor perfusion (cyanosis or pallor) or subject's desire to stop led to premature termination of their exercise.[2-6] Characterization of chest discomfort during exercise can be a useful diagnostic finding.[3] Chest pain was categorized into two groups, typical and atypical chest pain. Typical anginal chest pain was defined as (1) substernal chest discomfort with characteristic quality and duration (2) provoked by exertion or emotional stress and (3) relieved with rest or nitroglycerin. Atypical anginal chest pain-which is a chest discomfort with two of the above typical angina characteristics .In some patients, chest discomfort may be the only signal that obstructive CAD is present.[3] A positive exercise ECG test was defined as horizontal (planner) or down sloping ST segment depression or elevation (in non-Q wave lead) of>1mm in three adjacent complexes, for at least 80 millisecond after J-point (ST 80) in any of the 12 ECG leads except aVR . In general, the ST 60 measurement should be used at heart rates higher than 130 beats /minute.[7]

The test was considered negative only if the patient achieved at least 85% of their MPHR without ST segment depression or elevation. The heart rate should reach or exceeds 85% of maximum predicted heart rate calculated according to the formulae, MPHR=220-age (in years). The test was declared non-conclusive if the exercise was submaximal. [3] The recovery was continued for 10 minutes or delayed until normalization of ECG changes.

All patients underwent coronary angiography according to conventional Judkins' techniques using a percutaneous transfemoral approach. Only lesions of the main arteries and their major secondary branches were considered. Significant obstructions of one, two, or three major coronary arteries and / or their major branches have been labeled one, two, and three vessel disease. The major coronary arteries are right coronary artery (RCA), left circumflex branch (LCX), left anterior descending artery (LAD) and left main stem coronary artery (LMS). A major coronary artery was considered diseased if there was ≥ 70% stenosis of luminal diameter, except for the left main coronary artery, which was considered diseased if there was a stenosis ≥ 50%. [8] Angiographic data in this study were reviewed carefully.

The data were collected by interviewing the patients using a questionnaire designed by the researchers. The questionnaire included information about socio-demographic data, hypertension, risk factors like hyperlipidemia, IHD, obesity, family history, others), and history of smoking and alcoholism.

Ethical considerations: The study protocol was approved by the ethics committee of the College of Medicine of Hawler Medical University. This study was conducted by using an informed verbal consent from the patients prior to participation in the study. The purpose of the study was carefully explained to each patient.

The statistical analysis used in this study was percentage test and $\chi 2$ (chi-square) tests. Chi-square test was used to find out associations (relations) between dependent and independent variables. When Chi-square is inappropriate, Fisher Exact or linear by linear association were used. P-value less than 0.05 were regarded as statistically significant.

Results

Among 160 patients (85males and 75 females) with anginal chest pain were studied by multistage stress testing, 115 patients (71.87%) had positive EET while 37 patients (23.13%) had negative test. Out of 115 patients , only 83 patients (72.17%) showed positive coronary arteriogram results with at least one major vessel narrowing , while 32 patients showed normal coronary angiograms results . Accordingly, only 83 patients (58 males and 25 females) were included in this study, while 32 patients with normal coronary angiography were excluded.

The mean age (SD) of the included patients was 53.18±9.4 years. Other basic characteristics and descriptive statistics of some continuous variables of the included patients were shown in Table 1.

There was no statistically significant difference in gender and age between males and females regarding vessel involvement (Table 2, 3). The sensitivity of the positive EET in detecting CAD was 72.17%.

The patients were classified into three groups according to the number of the coronary artery involved; **Group**1;Nine (10.8%) patients with one (single) vessel disease; **Group**2;Fourty three (51.8%) patients with two vessel disease, and **Group** 3;Thirty one (37.4%) patients with three (triple) vessel disease.

In group 1, there were 6 patients had LAD diseased and 3 patients had RCA diseased, while LCX artery alone was not involved in any case. In group 2, 30 patients had LAD+RCA, 9 patients had RCA+LCX, 2 patients had LAD+LCX, one patient had LMS+RCA and one patient had LMS+LCX.

ST segment depression was the main ECG response seen during the exercise test. Among 9 patients with one vessel disease, 6 patients had ST segment depression from V4 to V6 leads [LAD disease] , and 3 patients had ST segment depression in leads II,III and aVF [RCA disease] . Among 43 patients with two vessel diseases, all of them had ST segment depression in leads II, III, aVF, and there was an associated involvement of leads V4 to V6 in 36 (83%) of the cases.

Among 31patients with three vessel diseases, all of them had ST segment depression in leads II, III, aVF, and V5-V6 chest leads. 96% of ST segment depressions were in both lateral chest leads (V4-V6) and inferior limb leads (II III and aVF).

Anginal chest pain was the main reason for referral for exercise test. Typical chest pain was present in 51 cases (61%) and atypical chest pain was present in the remaining 32 cases (39%).It shows statistically significant difference in the three groups, with typical anginal chest pain present more in patients with three vessel disease than others, as shown in Table 4.

Regarding risk factors, 76 patients (91.5%) had risk factors in whom 23 patients (27.7%) had at least one risk factor and 53 patients (63.8%) had two or more risk factors. Single risk factors were smoking, hyperlipidemia, obesity, hypertension and diabetes mellitus affecting nine, seven, four, two, and one patients respectively. Patients with two and three vessel disease had significantly higher risk factors, as shown in Table 5,6.

There were also significant statistical associations between some variables of the test and the three groups of patients with vessel involvement. One of these is the ST/HR index, which represents the average change of ST segment depression with heart rate throughout the course of the exercise test. An index of 1.6 μV/bpm is defined as abnormal. In this study, the ST/HR index was highly positive in patients with three vessel disease comparing other groups with a P value of 0.014, as shown in Table 7.

Timing of ST segment depression and maximum depth showed also statistically significant association with vessel involvement. Early onset of ST depression in the exercise test and an increment in the depth of ST depression were related with more number of vessel involvement with a p value of 0.01 for timing and 0.02 for the depth, as shown in Table 7.

The number of leads with ST segment depression has also showed a significant statistical association with the vessel involvement. Patients with three vessel involvement had more number of leads with ST segment depression than other groups, with a p value of < 0.001, as shown in Table 7.

Discussion

The mean age of the patients was (53.13±9.4) years. This showed that our patients were at least 7 years younger to what is seen in first stage CAD patients. This is in parallel to other studies,[9] but against others. [10] The result of this study revealed that occurrence of CAD in our population is starting in younger age group.

In this study, the sensitivity of the positive EET in detecting CAD was 72.17%. This is compatible with other studies, as we mentioned previously. [3, 11]

In patients with one vessel disease , LCX artery alone was not involved in any case. This is compatible with other studies. Anoop Chauhan et al, in a study done in 1997, suggested that the exercise ECG was a poor predictor of circumflex coronary artery ischemia. [12]

ST segment depression was the main ECG response seen during the exercise test. This is compatible with other studies.[4, 5] There was a high controversy between researchers about the significance of ST segment depression seen during exercise test in localizing and detecting the extent of coronary artery stenosis. In this study, among nine patients with one vessel disease, six patients had ST segment depression from V4 to V6 leads [LAD disease] , and three patients had ST segment depression in leads II,III and aVF [RCA disease].This is compatible with other studies. Myrvin Ellesttad in his study of 5,336 patients who were followed for 6 years, mentioned that ST depression seen in the inferior leads and V4 to V6 leads , reflecting involvement of LAD [60% sensitivity], while ST depression in the inferior leads alone reflecting involvement of RCA [30%-70% sensitivity] [13] .These results were also compatible with a study done by Fox et al [14, 15] . But other studies like that done in 2004 by Skjaggestadt et al and in 2005 by Weinsaft et al, found no correlation between the site of ST depression and the location of the coronary artery stenosis on angiography .[5, 6]

In patients with two and three vessel disease, ST segment depression was mostly seen in both inferior

(II, III and aVF) and V4 to V6 leads. In this study , 96% of ST segment depressions were seen in both lateral chest leads (V4-V6) and inferior limb leads (II III and aVF).This study revealed that ST segment depression in these leads strongly favors occlusion of more than one vessel disease. This is consistent with findings of previous studies. [5, 13, 16,17]

In this study, among 83 patients with abnormal coronary angiography , 51 patients had typical chest pain. Typical chest pain showed statistically significant association with the number of the vessel involvement; typical anginal chest pain was present more in patients with three vessel disease than others. Characterization of chest discomfort during exercise can be a useful diagnostic finding. In some patients, chest discomfort may be the only signal of obstructive CAD .[2, 3]

Regarding risk factors, patients with two and three vessel disease had significantly higher risk factors. The age and gender of the patient and the co-existing risk factors like hypertension, abnormal BMI, diabetes and current smoking are strongly related to higher chances of positivity of the test to detect CAD [18, 19]

In this study, the ST/HR index was highly positive in patients with three vessel disease comparing other groups with a p value of 0.014. A lot of studies show that this index improves the sensitivity of the test, particularly the prediction of multivessel CAD [3,5,7,20] and it becomes increasingly popular for assessment of occult CAD and its severity .[20,21]

Patients with three vessel involvement had more number of leads with ST segment depression than other groups, with a p value of < 0.001. Many studies concentrate on correlation between the number of coronary arteries disease in angiography and the number of leads showing ST segment depression in exercise ECG test. Most of these studies noticed positive correlation between this parameter and multivessel disease. [2 ,3] Other studies said that patients exhibit ST segment depression in 5 leads or more are more likely to be associated with multivessel disease.[4,5,7] Early onset of ischemic ST segment depression is associated with an adverse prognosis and multivessel disease. [2,3,7] Myrvin Ellesttad, in his study mentioned that 3 mm or greater ST depression predicted a greater number of coronary events if the changes occurred within the first 3 minutes of exercise. [13] This is also compatible with other studies.[22,23]

Conclusions

1.In patients with one vessel disease, exercise ECG is a poor predictor of circumflex coronary artery disease.
2.ST segment depression seen during exercise ECG has a role in localizing and detecting the extent of coronary artery disease.
3.This study revealed that ST segment depression in both lateral chest and inferior limb leads strongly favors occlusion of more than one vessel disease.
4.Typical chest pain , high risk factors, high ST/HR index , increased number of the leads with ST depression, earlier ST segment depression and increased depth of ST depression, were associated with two or three vessel involvement.

Recommendations

1-Patients who had typical anginal chest pain and high risk factors, regardless of the age and sex, should undergo coronary angiography even if the EET is negative or in-conclusive.
2- To obtain a satisfactory EET result, patients should be properly selected.

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Table 1: Basic characteristics and descriptive Statistics of some continuous variables of total sample.

Variables	Mean	Std. Deviation
Age(years)	53.18	9.40
Weight(kg)	77.95	11.99
Height(cm)	165.40	8.15
BMI	28.56	4.449
THR	166.78	9.36
Maximum HR achieved	136.52	16.002
Predicted %	81.30	8.83
Exercise time(minutes)	6.25	2.46
METs	8.68	2.08
SBP(mmHg)	175.98	28.50
DBP(mmHg)	88.63	10.39

Table 2: Sex variable by vessels involvement

sex	Vessels involvement			Total	P-value
	One vessel disease	Two vessel disease	Three vessel disease		
Male	7	31	21	58	0.824
Female	2	12	10	25	
Total	9	43	31	83	

Table 3: Age variable by vessels involvement

Variables	Vessels involvement			P-value
	One vessel disease	Two vessel disease	Three vessel disease	
	Mean	Mean	Mean	
Age (mean), years	50	52	56	0.074

Table 4: Anginal pain category by vessel involvement

Anginal pain	Vessels involvement			Total	P-value
	One vessel disease	Two vessel disease	Three vessel disease		
atypical	7	17	8	32	0.018*
typical	2	26	23	51	
Total	9	43	31	83	

*Statistically significant

Table 5: Risk factor categories by coronary angiography results

Risk Factor Categories	Abnormal coronary angiography			Total
	One vessel disease	Two vessel disease	Three vessel disease	
No risk factor	1	6	0	7
More than one risk factor	4	28	21	53
One risk factor	4	9	10	23
Total	9	43	31	83

Table 6: Risk factor categories by vessels involvement

Risk factor category	Vessels involvement			Total	P-value
	One vessel disease	Two vessel disease	Three vessel disease		
No risk factor	1	6	0	7	0.015*
Risk factor	8	37	31	76	
Total	9	43	31	83	

***Statistically significant**

Table 7.Comparison between the means of some variables according to vessel involevemnt.

Variables	Vessels involvement			P-value
	One vessel disease	Two vessel disease	Three vessel disease	
	Mean	Mean	Mean	
Age(years , mean)	50	52	56	0.074
Weight(kg)	80	78	77	0.788
Height(cm)	166	166	164	0.567
BMI(kg/m²)	29.12	28.38	28.68	0.891
THR	170	168	165	0.218
Max. HR achieved	140	138	133	0.291
Predicted %	82.2	81.8	80.4	0.763
ST_HR index	5.68	5.55	8.08	0.014*
No. of leads with ST depression	4	6	7	<0.001*
Timing of ST Depression (Minutes)	4.87	3.60	2.96	0.01*
Maximum depth (mm)	2.0	2.2	2.5	0.02*