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Comparison of Ischemia-modified Albumin and Exercise Stress Test in Stable Angina Pectoris

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Abstract

Objectives: We aimed to compare ischemia modified albumin (IMA) and exercise stress test to determine myocardial ischemia in stable angina pectoris and investigate the diagnostic value of IMA in non-exercised patients.

Materials and Methods: One hundred and eight patients who applied to the cardiology outpatient clinic with chest pain and were diagnosed with ischemia on myocardial perfusion scintigraphy were included in the study. They were divided into groups with and without coronary artery disease (CAD) according to the results of coronary angiography and with and without ischemia according to the stress electrocardiogram (ECG) results. In addition, IMA levels of the patients were measured, and an exercise stress test was performed.

Results: The IMA was found to be 1.06±0.23 in patients with CAD and 1.12±0.18 in patients without CAD (p=0.08). Statistically, between the groups, IMA determined no significant evidence for ischemia in stable angina pectoris.

Conclusion: No significant difference was found between exercise ECG and IMA in the study of patient groups to determine myocardial ischemia in patients with stable angina pectoris. That is why it has been concluded that the measurement of IMA does not help determine myocardial ischemia in immobile patients and that it cannot be used in place of a stress ECG test.

Keywords: Ischemic modified albumin, exercise stress test, stable angina pectoris

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Introduction

Ischemic heart disease is a term that refers to the inability of enough blood and oxygen to reach the myocardium and the resulting clinical manifestations. Many pathologies that cause an imbalance between myocardial oxygen demand and supply can lead to myocardial ischemia[1]. Ischemic heart disease is the most common cause of death in developed countries. Deaths due to cardiovascular diseases are still approximately twice as high as all cancer deaths and the sum of all non-cardiovascular deaths[2]. Ischemic heart disease may present with different clinical manifestations and present with stable typical or atypical angina in approximately one-third of its cases. Acute clinical manifestations include acute coronary syndromes (unstable angina pectoris, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction) and sudden death with fatal ventricular arrhythmias. Its chronic forms are stable angina pectoris or stable clinical pictures with silent ischemia[3]. In recent years, the determination of changes in serum albumin structure in ischemia conditions has enabled the discovery of a new serum cardiac ischemia marker. The last amino-terminal in the albumin structure is the region where transition metals such as cobalt, copper and nickel are attached[4]. Hypoxia, acidosis, free radical damage and membrane disruption that occurs with ischemia reduce the binding of these transition metals to the N-terminus of albumin[5-7]. This albumin, which has changed its structure, is called "ischemia modified albumin" (IMA). Measurement of IMA level is known as albumin-cobalt binding capacity measurement and includes spectrophotometric measurement of cobalt unbound to albumin. The increase in IMA concentrations is used to evaluate coronary ischemia as a marker of myocardial ischemia[7-9].

The exercise test is a physiological stress test frequently used to reveal cardiovascular abnormalities that do not exist at rest and determine cardiac function adequacy[10]. Exercise electrocardiography is one of the most commonly used non-invasive methods for evaluating patients with suspected or proven cardiovascular disease. In addition to being non-invasive, its significant advantages are that it has few side effects and does not contain radiation.

This study aimed to compare IMA and exercise stress tests in the determination of myocardial ischemia in patients with stable angina pectoris and investigate the diagnostic value of IMA measurement in patients who are immobile or unable to perform the exercise test.

Materials and Methods

In this study, 108 (62 men/46 women) patients who applied to the cardiology outpatient clinic of our hospital with the complaint of chest pain between December 2018 - May 2019 and whose myocardial perfusion scintigraphy were interpreted as ischemia and who indicated coronary angiography were included in this study. The patients were divided into two groups according to the results of coronary angiography. Those with 50% or more stenosis in one or more of the coronary arteries were considered coronary artery disease (CAD) (+), while those with normal coronary artery were considered CAD (-). Detailed physical examinations were performed by questioning the medical histories of the patients. After 12-lead surface electrocardiograms (ECG) were taken, blood samples were taken for IMA, centrifuged and serum separated. Serum samples were stored at -70 °C. Exercise ECG testing was performed on all participants in the study group and was also used as part of the myocardial perfusion scintigraphy (MPS) application protocol. The patients did not do any physical activity before the exercise test. After blood was drawn from the patients, an exercise test was performed according to the Bruce protocol. Patients with a previous diagnosis of severe aortic stenosis, severe valvular pathologies, coronary artery bypass graft surgery history, previous myocardial infarction, heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), ventricular tachycardia, chronic renal failure (glomerular filtration rate of <60 mL/min), acute pericarditis or myocarditis, skeletal muscle disease, systemic infection, and known malignancy were excluded from the study.

Venous blood samples were taken after 12 hours of fasting for biochemical analysis. In biochemical analysis, serum lipids, total cholesterol, high-density lipoprotein (HDL), light density lipoprotein (LDL), troponin, blood urea nitrogen (BUN), uric acid, creatinine, sodium, potassium, magnesium, calcium, phosphorus, glucose and serum albumin levels viewed. Hemoglobin, white blood cell and platelet levels were measured in the complete blood count. IMA levels were measured by the colorimetric method. Spekol 1300 brand spectrophotometer was used for the measurements. Materials used cobalt 2 chloride ($CoCl_2$) solution, dithiothreitol (DTT) solution (1.5 g/dL), isotonic NaCl solution (0.9 g/dL). Working procedure 50 mL of 1 g/L cobalt chloride solution was added to 200 mL of patient serum, mixed, and incubated for 10 minutes at room temperature. Then 50 mL of 1.5 g/L DTT solution was added and mixed. It was then incubated for 2 minutes at room temperature. 1 mL of 0.9 g/L NaCl solution was added. Sample blanks were similarly prepared by adding distilled water instead of adding DTT. The absorbances of the test mixtures were read at 470 nm with the Beckman DU 530 Life Science UV/Vis Spectrophotometer. Results are reported in absorbance units (ABSUs).

According to Bruce protocol, an exercise stress test was performed with TEPA TM-PRO 2000 brand device. Routine 12-lead ECGs of all patients were taken before exercise. Heart rate, blood pressure and ECG were recorded at the end of each stage. The formula [maximum heart rate (beats/minute) = 220-age (year)] was used for target heart rate. At the end of the test, the patients were placed in the supine position. Routine hemodynamic parameters were followed for 3-5 minutes in this position. When changes were observed to terminate the test, they were followed closely until they returned to normal. Chest pain on exertion test, decrease in systolic blood pressure of 10 mmHg or more from baseline blood pressure, development of bradycardia or severe arrhythmia, downsloping of the ST segment in two or more consecutive leads or horizontally 1 mm or more 80 ms after the J junction. The presence of excessive collapse or elevation was taken as the criteria for being positive for the test. Upslopping type ST-segment depression without typical chest pain was not accepted positively.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS V23 (IBM Corp, Armonk, NY, USA) statistical analysis program. The data were presented as mean, standard deviation, median, minimum, maximum percentage, and number. The normal distribution of continuous variables was considered using the Shapiro-Wilk W-test where the sample size was <50, and the Kolmogorov-Smirnov test in the case where it was >50. For comparisons between two independent groups, the Independent Samples t-test was used dec the normal distribution condition was met, and the Mann-Whitney U test was used in case it was not met. In comparisons of 2x2 between categorical variables, the Pearson chi-square test was used if the expected value (>5), dec dec-squared yates test was used if the expected value was between (3-5), and the expected value (<3) was used Fisher's Exact test. Multiple groups were evaluated by the Anovis method. The level of statistical significance was taken as $p<0.05$.

Results

The demographic characteristics of the patients are shown in Table 1. There were 62 males and 46 females in the study group, and the mean age was 57±11 years. While 31.5% (34 patients) of the patients had a diagnosis of hypertension, 14.8% (16 patients) had diabetes. Coronary artery disease was detected in 53.7%

Table 1. Demographic characteristics of the study group

	Frequency	%
Gender		
Female	46	42.6
Male	62	57.4
Coronary artery disease	58	53.7
Hypertension	34	31.5
Diabetes mellitus	16	14.8
Effort ECG test (+)	56	51.9

ECG: Electrocardiography

(58 patients) of the patients (more than 50% of these patients had stenosis in their coronary angiographs). In comparison, the coronary arteries were normal in 46.3% (50 patients). Patients were divided into groups according to their current demographic characteristics: those with or without coronary artery disease, patients with suspected ischemia due to exercise ECG, and patients who were not considered. The results of stress electrocardiography and IMA were compared among these patients. Demographic characteristics of the biochemical parameters studied from the blood samples taken from the patients are given in Table 2.

The mean troponin values of the patients were found to be 0.006±0.012 mg/dL and were considered normal. Mean creatinine values were 0.94±0.56 mg/dL. Mean albumin values were 3.99±0.4 mg/dL, and no hypoalbuminemia was observed in the follow-up. In the study, arrhythmia (atrial fibrillation) was observed in the electrocardiography of only two patients; the ECGs of the others were normal sinus rhythm.

Table 2. Biochemical parameters of the study population (n=108)

Parameters	Mean ± SD
IMA (ABSU)	1.09±0.21
Troponine (mg/dL)	0.006±0.012
Creatinine (mg/dL)	0.94±0.56
Albumin (mg/dL)	3.99±0.40
Sodium (mmol/L)	138±3
Potassium (mmol/L)	4.12± 0.41
Magnesium (mg/dL)	1.95±00.28
Calcium (mg/dL)	9.15±0.58
Phosphorus (mg/dL)	3.38±0.75
Uric acid (mg/dL)	5.46±1.95
Blood urea nitrogen (mg/dL)	18.58±8.10
LDL - cholesterol (mg/dL)	135±62
HDL - cholesterol (mg/dL)	44±11
Triglyceride (mg/dL)	192±123
Glucose (mg/dL)	123±66
Hemoglobin (g/dL)	14.33±1.80
White blood cell (mg/dL)	8139±2186
Platelet (10^3/mL)	259±62

IMA: Ischemia modified albumin, LDL: Low-density lipoprotein, HDL: High-density Lipoprotein, ABSU: IMA levels as absorbance unit, SD: Standard deviation, n: Number

No statistically significant difference was found between those with and without coronary artery disease regarding IMA levels. IMA values were found to be 1.06±0.23 in patients with coronary artery disease and 1.12±0.18 in patients without coronary artery disease (p=0.08) (Table 3).

When the patients were divided into groups as those whose exercise ECG result was not considered ischemia (negative) and whose exercise ECG result was thought to be ischemia (positive) and were compared, no difference was observed in terms of gender in these groups. Exercise ECG was positive in 41.1% of hypertensive patients and negative in 21.2% (p=0.02). There was no significant difference between positive and negative rates on exercise ECG in diabetic patients (p=0.48). IMA levels were measured as 1.08±0.25 and 1.10±0.17 in patients with positive and negative exercise ECGs, respectively, and no statistically significant difference was observed between the two groups (p=0.08) (Table 4).

The comparisons between the exercise stress test results and the patients divided into four groups according to whether they were diagnosed with coronary artery disease in their coronary angiograms are shown in Table 5 and Table 6.

Table 3. Comparison of those with and without coronary artery disease on coronary angiography

	CAD (-) (%) (n=50)	CAD (+) (%) (n=58)	p value
Gender			
Male	48 (n=24)	65.5 (n=38)	0.06
Female	52 (n=26)	34.5 (n=20)	0.06
Hypertension	18 (n=9)	43.1 (n=25)	**0.005**
Diabetes mellitus	12 (n=6)	17.2 (n=10)	**0.44**
Effort ECG test (+)	22 (n=11)	77.6 (n=45)	**0.001**
IMA (mean ± SD)	1.12±0.18	1.06±0.23	0.08

Significant p values are shown in bold.
CAD: Coronary artery disease, ECG: Electrocardiography, SD: Standard deviation, n: Number

In the patient groups with positive exercise ECG results (80.4% of 56 patients (n=45)) and 25% (n=13) of 52 patients with negative exercise ECG results, coronary artery disease was diagnosed in these groups. However, IMA was not statistically significant (p=0.51).

Discussion

Early diagnosis and treatment of coronary artery disease is an essential condition in terms of mortality and morbidity. In studies conducted so far, it has been determined that IMA can be used to diagnose acute coronary syndromes, especially in emergency services[11-13]. However, there is no study on the use of IMA in stable CAD. In our study, IMA and exercise testing were compared in patients with and without stable CAD. The significant increase in IMA in acute coronary syndromes aroused the idea that determining the level of IMA may be beneficial in the early diagnosis of stable CAD, and this study was planned.

Table 4. Demographic characteristics of patients with positive and negative exercise ECG

	Effort ECG test (-) (%) (n =52)	Effort ECG test (+) (%) (n=56)	p value
Gender			
Male	46.2 (n=24)	67.9 (n=38)	
Female	53.8 (n=28)	32.1 (n=18)	**0.02**
Hypertension	21.2 (n=11)	41.1 (n=23)	0.48
Diabetes mellitus	15.4 (n=8)	14.3 (n=18)	**0.01**
IMA (mean ± SD)	1.10±0.17	1.08±0.25	0.08

Significant p values are shown in bold.
ECG: Electrocardiography, IMA: Ischemia modified albumin, SD: Standard deviation, n: Number

Table 5. Comparison of stress ECG and IMA in patients with coronary artery disease

	CAD (+), (%) (n=58)	IMA (mean ± SD)	p value
Effort ECG test (+)	80.4 (n=45)	1.06±0.123	0.51
Effort ECG test (-)	25 (n=13)	1.07±0.170	0.51

ECG: Electrocardiography, CAD: Coronary artery disease, IMA: Ischemia modified albumin, SD: Standard deviation, n: Number

Table 6. Comparison of stress ECG and IMA with patients without coronary artery disease

	CAD (-), (%) (n=50)	IMA (mean ± SD)	p value
Effort ECG test (+)	19.6 (n=11)	1.16±0.221	0.51
Effort ECG test (-)	75 (n=39)	1.10±0.174	0.51

ECG: Electrocardiography, CAD: Coronary artery disease, IMA: Ischemia modified albumin, SD: Standard deviation, n: Number

Previous studies have shown that increased IMA levels in patients evaluated in the emergency department with chest pain complaints are associated with short-term major cardiac events[14,15]. In our study, patients with stable angina were prioritized, and patients with the acute coronary syndrome were omitted. However, the idea that IMA levels after exertion can be used in the follow-up rather than the diagnosis of stable coronary heart disease was one of the main ideas of our study.

Sinha et al.[16] measured IMA and troponin T in 208 patients who presented to the emergency department with chest pain. They reported that the sensitivity for acute coronary syndrome reached 95% by evaluating IMA values of 85 U/mL and above, positive troponin T and ECG together. In the study of Mutrie et al.[15], a sensitivity of 85% was found when IMA and troponin I were evaluated together in acute coronary syndromes. Serum levels of cardiac troponin rise approximately 2-4 hours after the onset of ischemia[17]. Nevertheless, for IMA, this time is expressed in minutes[18]. Since the patients in our study were patients with stable angina pectoris, troponin values were negative. In the study of Lippi et al.[19] on healthy aerobic athletes, no change was found in troponin levels after excessive exercise. In our study, except for a few patients, the initial ECGs of all patients were average in terms of acute ischemia and arrhythmia. Ischemia occurring during the exercise test can be detected by the appearance of hemodynamic findings such as chest pain, hypotension, bradycardia, and arrhythmia during the test and only electrocardiographically determined. These ECG changes often appear as ST-segment depression or elevation. In our study, ST-segment elevation was not observed in any patients. Sensitivity and specificity of the relationship between effort test positivity and CAD. When all studies performed so far in the American

College of Cardiology (ACC) and the American Heart Association (AHA) guidelines were examined, including a group of 24,074 patients, the sensitivity was 68%, and the specificity was 77%[20]. However, nearly 30% of false-negative results have been reported in the exercise test[21].

Therefore, sometimes even severe CAD cases can have evaluation errors because the effort test is normal. Therefore, we think that determining post-exercise IMA levels and high-risk individuals in the future may play an essential role in the diagnosis, follow-up, and treatment of stable coronary heart disease. However, there are contradictory and opposing views that IMA does not increase only due to cardiac origin after exertion. Some studies show that IMA increases in the blood with ischemia that may occur in peripheral ischemia, especially in the extremity muscles. When Lippi et al.[19] compared IMA levels with professional cyclists and the sedentary control group, they found 100±13 U/mL and 94±6 U/mL, respectively ($p<0.05$)[20]. In Lippi's study, the participants were exercised first at low exercise and then at a high workload, and blood was drawn for IMA after exertion at the end of a 12-24-hour rest period. There was no information about the patients' baseline ECGs in this study, and myocardial ischemia was not included in the exclusion criteria. In our study, patients had myocardial ischemia, which was confirmed by MPS. As a result of the Lippi study, he claimed that the elevation of IMA might be due to irreversible muscle necrosis due to excessive exercise. If the increase in IMA is due to muscle necrosis, it could not be explained why it did not increase in the sedentary group subjected to the same workload. There is no cut-off value for IMA levels due to muscle ischemia in the literature. In our study, on the other hand, no exercise was difficult enough to cause muscle necrosis in patients. In addition, stable CADs without myocardial necrosis were included in the study, and no statistically significant increase was found in post-exercise IMA levels in those without CAD. Roy et al.[22], in a study conducted in a group with 23 consecutive peripheral arterial diseases, reported a significant difference in IMA levels in the treadmill effort test at baseline and peak exercise. In this patient group, myocardial ischemia was investigated by dobutamine stress echocardiography (ECHO) they applied later, and wall motion disorder was not detected in any of the patients. No significant difference was found between serum IMA levels measured at baseline and peak heart rate during dobutamine stress ECHO[22]. However, theoretically, IMA elevation may occur due to oxygen radicals that may occur during peripheral ischemia. However, we think coronary ischemia should be excluded first in future studies.

In a study by Apple et al.[23] on 14 marathon runners, they found a biphasic response to baseline in IMA levels. Initial IMA levels decreased significantly in the measurement immediately after exertion and returned to normal levels in the first hour. Therefore, they argued that the reliability of IMA in the diagnosis of post-exercise myocardial ischemia is low[23]. However, during strenuous exercise, hemoconcentration and excessive lactate production occur during exertion. The excess lactate formed may cause low IMA levels by cross-reacting during the albumin binding test. An exercise stress test cannot be considered a demanding exercise test like marathon running. Excessive proteinuria occurs during strenuous exercise such as a marathon. Therefore, the result in Apple et al.'s[23] study may be due to excessive exercise-induced urinary proteinuria. In our study, serum lactate levels were not evaluated. The number of patients in our study was relatively high compared to Apple et al.'s[23] study. However, no disease group that could cause proteinuria was included in our study.

In conclusion, our study observed that measuring IMA levels in stable coronary artery patients and in immobile patients who could not perform an exercise ECG did not make a statistically significant contribution to the diagnosis of myocardial ischemia. Several previous studies investigated the relationship between IMA and myocardial ischemia in diagnosing asymptomatic coronary heart disease using MPS and pharmacological stress echocardiography methods. However, it is difficult

to say that scintigraphy and stress echocardiography show one hundred percent coronary artery disease. Furthermore, no study has been found in the literature comparing IMA levels with exercise ECG in patients with stable angina. Our study is a first in this regard.

Study Limitations

One of the limitations of our study is that patients whose MPS results were interpreted in favor of ischemia present with average coronary artery results, and the study was affected in this direction because of false-positive results of scintigraphy. Another aspect was that our study group was limited to only stable coronary artery patients. Therefore, our findings cannot be applied to all patients with acute coronary syndrome.

Conclusion

Ischemic heart disease is a severe health problem worldwide, as in our country. Diagnostic tests used today are primarily used to diagnose and determine the extent of ischemia and necrosis area. The high levels of troponin and Creatine kinase-MB, which are among the available biomarkers, are very useful in diagnosing and determining the width of the necrosis area. In patients with acute coronary syndrome without necrosis and stable angina pectoris, these tests are insufficient for diagnosis. They are not sufficient to determine the prevalence of CAD. IMA levels increase in the early stages of ischemia in patients with acute coronary syndrome presenting with NSTEMI/USAP clinic and may indicate ischemia. As a result of our study, it was observed that IMA, whose sensitivity and specificity are significant in the diagnosis of CAD, is not a significant biomarker in predicting myocardial ischemia in patients with stable angina. Compared with the exercise ECG, IMA was not significant in demonstrating myocardial ischemia in patients. It has been determined that IMA is not a significant biochemical marker in demonstrating myocardial ischemia in immobile or unable to exercise patients with stable angina pectoris.

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Ethics

Ethics Committee Approval: Atatürk University Faculty of Medicine approved compliance with the study with the Declaration of Helsinki and the ethical rules of the Medicine Ethics Committee (decision number: 06/27, date: 04.10.2018).

Informed Consent: Signed consent form was received from patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Özmen M, Karakelleoğlu Ş, Design: Özmen M, Karakelleoğlu Ş, Analysis and/or Interpretation: Özmen M, Karakelleoğlu Ş, Ardahanlı İ, Literature Search Özmen M, Karakelleoğlu Ş, Ardahanlı İ, Writing: Özmen M, Ardahanlı İ.

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