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ORIGINAL RESEARCH ARTICLE

İskemi modifiye albümin miyokart perfüzyon sintigrafisi sonuçlarının ayırıcı tanısında faydalı olabilir mi?

Can ischemia-modified albumin help in differentiating myocardial perfusion scintigraphy results?

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ÖZET

Amaç: Miyokart perfüzyon sintigrafisi (MPS) önemli koroner lezyonları tespit etmek için sıklıkla kullanılan tanı aracıdır. Ancak kuşkulu, yanlış negatif ve pozitif sonuçlar verebilir. Miyokart perfüzyon sintigrafisi sonuçlarının değerlendirilmesinde iskemi modifye albüminin (IMA) rolü ile ilgili çalışmalar çelişkili sonuçlara sahiptir. Bu yazıda, MPS sonuçlarının değerlendirilmesinde serum IMA'nın rolünü incelemeyi amaçladık.

Yöntemler: Miyokart perfüzyon sintigrafisi ile teknesyum (99mTc) sestamibi ve transtorasik ekokardiyograf uygulanan ardışık 62 hasta ileriye dönük olarak alındı. Koroner iskemisi oluşturmak için modifye Bruce protokolü ile egzersiz tredmil testi (ETT) yapıldı. Miyokart perfüzyon sintigrafisi sırasında, serum IMA için egzersiz öncesi, egzersizin en yüksek düzeyinde ve ETT sonrası altıncı saatte kan örnekleri alındı. Hastalar MPS sonuçlarına göre üç grupta sınıfandırıldı (normal, kuşkulu ve iskemi).

Bulgular: Altmış iki hasta (23 normal, 20 kuşkulu, 19 iskemili) dahil edildi. Gruplar arasında egzersiz öncesi ve en yüksek düzeyinde IMA değerleri benzerdi (p=0.706 ve 0.904). Normal ve kuşkulu grubun egzersiz sonrası IMA değerleri benzerken (p=0.733), iskemi grubununki hem normal gruptan (p<0.001) hem de kuşkulu gruptan yüksekti (p<0.001). ΔIMA (post-egzersiz ile pik-egzersiz IMA farkı) belirgin biçimde hem normal (p<0.001) hem de kuşkulu gruptan yüksekti (p<0.001).

Sonuç: Serum IMA MPS'li olgularda iskemi olması durumunda anlamlı biçimde arttığı bulunmuştur. Normal ve kuşkulu MPS'si olan kişiler test sırasında benzer değişime sahiptirler. Bu, kuşkulu sonuçların yanlış pozitif sonuçlardan ayrımında kullanılabilir.

ABSTRACT

Objective: Myocardial perfusion scintigraphy (MPS) is a diagnostic tool commonly used to detect significant coronary lesions. However equivocal, false negative or positive results can be yielded. Controversial fndings regarding the role of ischemia-modified albumin (IMA) in MPS evaluation persist. The aim of the present study was to examine the role of serum IMA in the assessment of MPS results.

Methods: Sixty-two consecutive patients who underwent MPS using technetium (99mTc) sestamibi and trans-thoracic echocardiography were prospectively enrolled. Exercise-treadmill test (ETT) with modified Bruce protocol was used to induce coronary ischemia. During MPS performance, blood samples for serum IMA were obtained: at pre-exercise, during exercise, at the peak of ETT, and 6 hours after ETT. Patients were classifed into 3 groups according to MPS results as normal, equivocal, and ischemia groups.

Results: Sixty-two patients (23 normal, 20 equivocal, 19 with ischemia) were included in the study. . Pre- and peak-exercise IMA values were similar among the groups (p=0.706 and 0.904). Post-exercise IMA values of the normal and equivocal groups were similar (p=0.733), while those of the ischemia group were significantly higher than the values of either the normal (p<0.001) or equivocal groups (p<0.001). The difference between post-exercise and peak-exercise IMA (ΔIMA) in the ischemia group was significantly higher than that of either the normal (p<0.001) or equivocal groups (p<0.001).

Conclusion: Serum IMA was found to be signifcantly increased in cases of ischemia on MPS. Subjects with normal and equivocal MPS had a similar pattern during the test. IMA may be used in the differentiation of equivocal results from false- positive results.

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Myocardial perfusion scintigraphy (MPS) is a frequently used diagnostic tool of coronary artery disease (CAD) , and it has the same sensitivity, and specificity with single-photon emission tomography (SPECT). Single photon emission tomography MPS has 86 % sensitivity, and 74 % specificity in the detection of the > 50 % of stenotic lesions.[1] However in clinical conditions such as multivessel disease or left main coronary artery disease, false-negative results can be obtained because of balanced, and homogenous coronary artery ischemia.[2,3] Besides movements of the patients during the procedure, attenuation defects or inaccurate application of technical analyses may result in false- positive or equivocal outcomes leading to weakening of the specificity of the test. As a consequence, these results require application of more advanced invasive or noninvasive diagnostic tests. Because of these reasons investigation of biomarkers which can discriminate normal coronary perfusion from myocardial perfusion with equivocal or borderline modifications will be useful, and interesting.

From this perspective, ischemia-modified albumin (IMA) whose N-terminal region has a decreased binding capacity to metal ions may be a useful biomarker. Endogenous stress conditions including ischemia lead to ischemia-related hypoxia, and acidosis, formation of reactive oxygen radicals, and dysfunction of cell membrane. This condition decreases binding capacity of N-terminal region of albumin for cobalt, copper, and nickel with resultant conversion of serum albumin to IMA.[4] This conversion is realized within minutes following ischemia. The formed IMA reconverts into normal albumin within 6 and 12 hours. Controversial outcomes have been reported about the role of ischemia-modified albumin in the diagnostic evaluation of CAD by noninvasive tests.[4,5]

In this study, the role of serum IMA in the evaluation of the patients with indeterminate MPS results, and discrimination between patients with normal, and ischemic perfusion outcomes has been evaluated.

METHODS

A total of 62 successive patients aged between 18, and 65 years who were investigated for the presence of CAD were included in this prospective study. All patients underwent SPECT MPS with technetium-99m-sestamibi (99mTc MIBI) and transthoracic echocardiographic examinations.

The study was realized between January 2014, and October 2014. The patients with the following exclusion criteria were excluded from the study: patients who were previously diagnosed as CAD, cases with acute coronary syndrome, peripheral vascular disease, chronic renal failure (Cr > 1.4 mg/dL), advanced liver disease, stroke, cancer, active infection, thyroid dysfunction, symptomatic congestive heart failure, those with left ventricular ejection fraction (LVEF) ≤ 50%, congenital heart disease,and individuals with a history of coronary artery bypass surgery , and myocardial infarction based on their electrocardiographic, and echocardiographic results.

Abbreviations:

AUC. Area under curve
EST. Exercise stress test
CI: Confidence interval
IMA Ischemia-modified albumin
CAG Coronary angiography
CAD Coronary artery disease
CCTA Coronary computed tomographic angiography
LVEF Left ventricular ejection fraction
MPS Myocardial perfusion scintigraphy
SPECT Single-photon emission tomography
SRS Summed rest score
SSS Summed stress score
TSH Thyroid stimulating hormone
BMI: Body mass index

Age, gender, height, body weight, and presence of cardiovascular risk factors were questioned, and recorded. In the definition of cardiovascular risk factors the following criteria were used: family history of smoking (presence of CAD in the first degree male, and female relatives aged <55, and 65 years, respectively), smoking (active smoker or smoking history within the last 2 years), hypertension (the last three ABP measurements above 140 mm Hg or antihypertensive treatment within the last 6 months), hyperlipidemia (active user of cholesterol lowering drugs). High-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), total cholesterol, triglyceride (TG), creatinine, thyroid stimulating hormone (TSH), and fasting blood glucose levels were measured. Body mass index (BMI) was calculated, and classified based on the relevant criteria of The World Health Organization as follows: : normal (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), obese class I (VKİ 30.0-34.9 kg/m^2), obese class II (BMI 35.0-39.9 kg/m^2) or obese class III (BMI ≥ 40 kg/m^2). Undersigned enlightened consent forms were obtained from each patient, while for the study approval of the ethics committee of the institute where the investigation was performed was acquired. The study was realized in line with the principles of Helsinki Declaration.

Echocardiographic measurements were obtained before MPS procedure by a cardiologist blinded to the patients' data using a 2.5 MHz transducer (Presound alpha 7, IPF1701 Model, 2009; Hitachi Aloka Medical, Ltd. Tokyo, Japan).

In compliance with the criteria set forth by American Society of Echocardiography, LVEF, left atrial diameter,and mitral annulus left lateral tissue Doppler Em, and Am values were measured.[6]

Myocardial perfusion scintigraphy protocol

In this study stress/rest protocol was applied. Stress test was performed between 08:00-10:00 AM, while resting state images were obtained 6 hours after stress test. For the stimulation of coronary ischemia, as a stress test all patients underwent exercise treadmill test using Bruce protocol. Physical burnout, severe angina, development of persistent ventricular tachycardia or hypotension induced with exercise were determined as endpoints of the stress test. At a timepoint closer to the peak-exercise level 99mTc-sestamibi was injected via intravenous route, and exercise test was continued for additional two minutes. Patients who could not tolerate at least 6 minutes of exercise test, and those who couldn't attain 85 % of the targeted heart rate (220-age of the patient in years) were not included in the study.

SPECT data were acquired using high-resolution low-energy collimator, and SPECT γ--camera with dual-head detectors (Philips Medical Systems Brightview Gamma Diagnost, Holland), and 'gated' technique. A total of 32 projections (35sec/projection) of Tc-99m gamma photons with an energy window centered at 140 keV with a width of 20% were acquired from 180o rotated kernels. Tomographic sections were obtained from short-axis, vertical long, and horizontal long- axis views.For semiquantitative analysis of data 4D-M SPECT software was used.. SPECT images were reconstructed with Butterworth filter (order 5; cut-off frequency 0.50), and using filtered back-projection method

Perfusion images were evaluated by an independent nuclear medicine specialist who was blinded to patients' demographic data. Myocardium was divided into 17 segments in accordance with the guidelines of American Society of Nuclear Cardiology, American Heart Association, and American Society of Cardiology [7] , and myocardial wall movements were rated between 0, and 4 points (0: Normal, 1: Mildly Hypokinetic, 2: Hypokinetic, 3: Akinetic, 4: Dyskinetic). Myocardial wall motion score over 2 was evaluated as abnormal. Based of the 17-segment-model summed stress (SSS), summed rest (SRS), and summed difference scores (SDS) were calculated.

SSS scores were classified as follows: normal, <4; 4–8 mildly impaired; 8–12 moderately impaired, and severely impaired, >13. SDS scores were classified as follows: , nonischemic; 2–4 mildly ischemic; 5–8 moderately ischemic; severely ischemic, >8..[8]

Based on MPS results of the left ventricular myocardium, the patients were divided into 3 groups. Normal group: normal gated SPECT MPS results (SSS value <4, and SDS value <2); equivocal group: patients with mild perfusion defect and/or mildly hypokinetic wall motion (SSS value 4–8 and/or 2–4); ischemia group : patients with perfusion defect in one or more than one segment and/or wall motion disorder (SSS value >8 and/or SDS value ≥ 5).[8]

All patients in whom myocardial perfusion scintigraphy detected signs of ischemia underwent conventional coronary angiography (CAG)(Philips Allura Xper FD10, Netherlands) through right femoral artery. Similarly, patients with borderline findings on MPS underwent diagnostic 64-slice coronary tomographic angiography (CBTA) (Brilliance-64; Philips, Germany, 2009) in line with the decision of the clinician or diagnostic CAG performed through right femoral artery.

Evaluation of biochemical markers

Before MPS procedure, at the peak of the exercise stress test, and at 6.hour after the post-exercise stress test 3 ml blood samples were drawn from patients. The blood samples obtained were transported to biochemical laboratory under suitable conditions, and centrifuged at a rate of 3000 rpm for 10 minutes. After centrifuging, the samples were stored in deep freeze at -80°C. When targeted number of samples were collected, serum samples of the patients were thawed under room temperature, and biochemical markers were measured using ELISA method. For relevant measurements human ischemia-modified albumin (ELABSCIENCE, Wuhan, Hubei Province CHINA) kits were used. All measurements were performed by using a microplate reader (Bio Tech Instruments, EL×800 TM, USA) in parallel with the recommendations of the relevant firms in the same laboratory. From post-exercise IMA value, peak-exercise IMA value estimated during exercise was substracted to obtain ΔIMA value.

Statistical analysis

The number of patients to be included in the study was determined based on the study performed by Koc et al. which measured serum IMA levels, and investigated stress-induced ischemia.[9]

Power Analysis and Sample Size (PASS 6.0, Jerry Hintze, Kaysville, USA) program was used to gain 80% test power at a level of 5% alpha, and requirement of at least 18 patients in each group was determined to achieve adequate statistical power. Study data were analyzed using SPSS package program (version. 18.0; SPSS Inc., Chicago, IL, USA). Normal distribution of continuous variables was evaluated using Kolmogorov-Smirnov test. Serum creatinine, pre-exercise, peak- exercise,and post-exercise serum IMA values, MET, body weight , SSS, SRS, and SDS values had non-normal distribution, while other data had normal distribution. Among continuous variables, creatinine, serum IMA values, MET, body weights, SSS, SRS, and SDS values were expressed as their median values (25–75% [IQR]), while other continuous variables were indicated as mean ± standard deviation. Categorical variables were shown as percentages. Intergroup differences between categorical variables were evaluated with *chi*-square or Fisher's exact test. Median values of continuous variables (serum creatinine, and IMA values, MET, body weight, SSS, SRS, and SDS values) were compared using Mann-Whitney U-test ve Kruskal-Wallis tests, while means of variables with normal distribution were compared using Student's test, and ANOVA. In the evaluation of repeated measurements priorly Friedman test with Bonferroni correction was utilized. If statistically significant difference was seen, then using Wilcoxon-signed test with Bonferroni correction the conditions which caused the intergroup differences were detected. Correlation analysis between variables with normal distribution, was performed using Pearson correlation analysis, while the correlation between variables with non-normal distribution was evaluated with Spearman correlation test. Diagnostic decisiveness properties of post-exercise IMA, and ΔIMA values were examined using ROC curve analysis. $P < 0.05$ was accepted as the level of statistical significance.

RESULTS

Sixty-two patients (male, n=40, and female, n=22) were included in the study. As detected using MPS, patients had normal (n=23), equivocal (n=20), and ischemic (n=19) perfusion results. Demographic data of the patients are shown in Table 1. Treadmill test results were comparable between groups (Table 1). All groups had statistically comparable LVEF, LA diameter , and Em/Am ratios. Similarly, serum FBG, TSH, creatinine, and fasting lipid profile values were comparable in all groups (Table 2).

SSS, SRS, and SDS values of the patients are shown in Table 2. SSS values of the ischemia group were higher than those of the equivocal ($p<0.001$ $z=-5.374$), and normal groups ($p<0.001$ $z=-5.595$). Similarly, SDS values of the ischemia group were higher than those of the groups with equivocal ($p<0.001$ $z=-5.413$), and normal ($p<0.001$ $z=-5.701$) perfusion results. SSS, and SDS values of the group with equivocal perfusion test results were significantly higher than those of the group with normal perfusion values (z scores were -5.687 , and -5.819, respectively; p value for both groups was <0.001).

Pre-exercise median IMA values were comparable in all groups ($p=0.706$). Post-exercise median IMA values of patients who had normal perfusion results on myocardial perfusion scintigraphy were similar to those with post-exercise median IMA values of the patients with equivocal perfusion results (Table 3). However post-exercise median IMA values of the patients with ischemic perfusion findings were predominantly higher than those detected both in groups with normal ($p<0.001$ $z=-4.728$) or equivocal ($p<0.001$ $z=-4.596$) perfusion test results Mean ΔIMA values of the groups with normal, and equivocal perfusion test results were comparable ($p=0.644$), while mean ΔIMA value of the ischemia group was higher than that of both normal ($p<0.001$), and equivocal ($p<0.001$) perfusion groups

At peak-exercise period median serum pre-exercise IMA values dropped statistically significantly from 5.7 (IQR 5.05–6.26) ng/ ml down to 3.3 (IQR 3.01–3.60) ng/ml ($p<0.001$). In subgroup analyses, as detected on MPS in the ischemia group, median pre-exercise serum IMA levels also decreased statistically significantly from 5.6 (IQR 5.35–6.24) ng/ml down to 3.2 (IQR 3.13–3.60) ng/ml ($p<0.001$). In the group with normal perfusion values on MPS, median pre-exercise serum IMA values statistically significantly dropped from 5.9 (IQR 4.85– 6.33) ng/ml down to 3.3 (IQR 3.01–3.60) ng/ml ($p<0.001$). The group with equivocal perfusion results on myocardial perfusion scintigraphy, median pre-exercise serum IMA levels dropped from 5.7 (IQR 5.14–6.41) ng/ml down to 3.3 (IQR 2.95–3.82) ng/ml ($p<0.001$).

Table 1. Demographic, and clinical data of the patients

	Normal group (n=23)			Equivocal group (n=20)			Ischemia group n (n=19)			*p*
	n	%	Mean ± SD	n	%	Mean ± SD	n	%	Mean ± SD	
Age (year)			52±12			48±10			54±10	0.161
Gender										
Female	17	74		12	60		11	58		0.489
Male	6	26		8	40		8	42		
Height (cm)			162±4			161±4			164±3	0.100
Weight (kg)			71±3			71±4			72±6	0.511
Body mass index (kg/m^2)			27.1±1.65			27.5 ±1.61			27.0±2.21	0.445
Diabetes mellitus	7	30		4	20		3	16		0.499
Hypertension	8	35		2	10		6	32		0.142
Smoking	4	17		6	30		5	26		0.608
Family history of CAD	5	22		3	15		4	21		0.834
Hyperlipidemia	1	4		0	0		3	15		0.117
Systolic blood pressure (mmHg)			120±11			121±10			127±11	0.169
Diastolic blood pressure (mmHg)			76±4			77±3			75±4	0.279
Duration of exercise (sec)			600±140			651±124			616±155	0.553
Blood pressure at maximum exercise (mmHg/min)			25805±4413			25502±5101			27147±4775	0.467
Maximum workload (MET)			10.8±2.11			11.2±2.02			11.0±2.22	0.847

SS: Standard deviation ; CAD Coronary artery disease

In groups with normal, and equivocal perfusion test results, median post-exercise IMA values statistically significantly came closer to pre-exercise levels (for both comparisons :p<0.001). On MPS, post-exercise IMA values statistically significantly continued to rise, and exceeded pre-exercise levels. (p<0.001).

Median pre-exercise IMA values were similar both in women, and men (women, 5.7 [5.03–6.24] ng/ ml; men, 5.7 [5.12–6.46] ng/ml, p=0.718). Besides a significant correlation did not exist between age, and pre-exercise IMA values (r=0.087; p=0.502).

ROC curve analysis was performed to determine predictive value of post-exercise IMA value in the detection of ischemia using MPS.When threshold value for post-exercise IMA was accepted as 5.50 ng/ml, sensitivity, and specificity of the test were 89.5, and 83.6 %, respectively (Area Under Curve [AUC]: 0.928 [95% Confidence interval (CI) 0.804–1.000] p<0.001). For this post-exercise IMA value, postive-, and negative-predictive values were 89.5, and 82.6 %, respectively. This test had a diagnostic accuracy of 85.7 % in the prediction of MPS result

Similarly, ROC curve analysis was also performed for ΔIMA value. In this analysis, when threshold value was accepted as 1.61 ng/ml to assert the presence of ischemia detected with MPS, ΔIMA measurement had 89.5 % sensitivity, and 73.9 % specificity (AUC:0.924 [95 % CI, 0.843–1.000] p<0.001). For this ΔIMA value, positive-,and negative predictive values were 89.5, and 73.9 %, respectively. This test had a diagnostic accuracy of 81.0 %in the prediction of MPS result.

Summed stress score significantly correlated with both post-exercise IMA (r=0.652 p<0.001) and ΔIMA (r=0.631 p<0.001) values, while it did not correlate with pre-exercise (p=0.993), and peak exercise (p=0.890) IMA values. Similarly, SDS value demonstrated significant correlation with post-exercise IMA (r=0.601 p<0.001), and ΔIMA (r=0.602 p<0.001) values, while it did not correlate with pre-exercise (p=0.352), and peak exercise (p=0.734)IMA values.

Table 2. Echocardiographic, laboratory, and myocardial perfusion scintigraphy data of the patients

	Normal group (n=23)	Equivocal group (n=20)	Ischemia group (n=19)	*p*
Left ventricular ejection fraction (%)	62±3	64±3	62±2	0.061
Left atrial diameter mm)	37±3	37±2	39±2	0.070
Mitral annulus lateral TDI Em/Am	1.5±0.78	1.7±0.60	1.3±0.66	0.364
Fasting blood sugar (mg/dl)	110±29	108±34	112±35	0.425
Creatinine (mg/dl)	0.8±0.19	0.9±0.12	0.9±0.13	0.334
Total cholesterol (mg/dl)	193±24	189±24	194±26	0.515
Trygliceride (mg/dl)	155±60	161±57	164±56	0.724
High-density lipoprotein (mg/dl)	47±8	43±10	42±6	0.161
Low-density lipoprotein (mg/dl)	116±22	115±17	121±20	0.416
Tiroid stimulating hormone (IU/L)	1.8±0.74 2	1.9±1.28	1.5±0.75 14	0.621
Summed stress score	(1.0-2.0)	5 (4.0-6.0)	(13.0-16.0)	<0.001
Summed rest score	1 (0.0–2.0)	2 (1.0–2.8)	2 (2.0–3.0)	<0.005
Summed difference score	1 (0.0–1.0)	3 (3.0–4.0)	12 (12.0–15.0)	<0.001

TDI: Tissue Doppler İmaging

Table 3. ischemia-modified albumin measurements

	Normal group (n=23)	Equivocal group (n=20)	Ischemia group (n=19)	*p*
Pre-exercise IMA (ng/ml)	5.9 (4.85–6.33)	5.7 (5.14–6.41)	5.6 (5.35–6.24)	0.904
Peak exercise IMA (ng/ml)	3.3 (3.01–3.60)	3.3 (2.95–3.82)	3.2 (3.13–3.60)	0.706
Post-exercise IMA (ng/ml)	4.4 (4.11–5.14)	4.4 (4.05–5.01)	7.9 (6.19–8.79)	<0.001
ΔIMA (ng/ml)	1.2 (0.53–2.13)	1.0 (0.52–1.55)	4.1 (2.92–5.43)	<0.001

IMA: Ischemia-modified albumin; ΔIMA: Difference between post-exercise, and peak-exercise IMA.

Diagnostic CAGs performed on patients (n=19) whose perfusion scintigraphies detected myocardial ischemia, revealed the presence of occlusive CAD in 17, and non-occlusive CAD in 2 patients (these 2 patients had ΔIMA values of 1.16 ng/ml, and 4.11 ng/ ml, and IMA values of 4.13, and .71 ng/ml, respectively). CAGs or coronary computed tomography angiograms of the patients (n=20) with equivocal myocardial perfusion scintigraphy results were evaluated, and detected angiographically normal coronary arteries in 11 patients, while coronary calcium scores of 4 patients were equal to zero. Three patients had non-occlusive, and two patients occlusive lesions (the latter 2 patients had ΔIMA values of 3.11 ng/ml, and 3.43 ng/ ml, and post-exercise IMA values of 6.00, and 6.32 ng/ml, respectively.

Based on coronary angiography, and CCTA results, diagnostic sensitivity, and specificity of MPS for CAD were 89.5, and 90%, respectively.

On the other hand if we accept post-exercise threshold value of IMA as 5.27 ng/ml, then post-exercise IMA test had diagnostic sensitivity, and specificity as 94.7, and 90%, respectively (AUC:0.968 [95%CI, 0.00–1.00], p<0.001).

DISCUSSION

In this study, we aimed to determine if IMA measurements are important in the differentiation of MPS results, and if so we also intended to specify the time period where MPS results convey importance in this differentiation process. To this end 62 successive patients who underwent treadmill exercise tests were included in the study. Based on MPS results, the patients were divided into normal, equivocal, and ischemia groups. In this study serum IMA levels dropped significantly in all groups with exercise, however after peak exercise IMA values returned to pre-exercise levels in normal, and equivocal perfusion groups, while they continued to rise in the ischemia group

Currently, myocardial perfusion scintigraphy is frequently used in the guidance of diagnosis, and treatment of CAD. However because of patient-related factors, and technical reasons, false-positive, and false-negative results are encountered. Many biochemical parametres were tried to increase sensitivity, and specificity of myocardial perfusion scintigraphy in addition to findings of perfusion. We also previously demonstrated that analysis of copeptin in addition to perfusion scintigraphy performed with exercise stress test might be valuable in the evaluation of MPS results.[10] In this test we investigated the role of IMA values which increased after coronary ischemia, and stresful conditions in the evaluation of myocardial perfusion.

Variations in serum IMA values in association with exercise stress test (EST) have been investigated in various studies. Sbarouni et al. demonstrated that peak-exercise IMA values decreased predominantly when compared with pre-exercise levels.[11] They indicated that this decrease was associated with increase in lactate levels with exercise, and also relative decrease in IMA values secondary to higher serum albumin levels developed due to exercise- induced hemoconcentration. Also in our study, predominant decrease in peak-exercise IMA values was detected in all groups

In the literature contradictory results have been published regarding the correlation between post-exercise EST results, and IMA values [11,12] In some studies lack of any correlation between EST results, and IMA values was indicated , however some authors reported that in proportion with the impact of coronary ischemia serum IMA levels increased more than those without coronary ischemia..[11,12] These diverse results related to exercise stress test, and IMA might be that in EST, workload has not been standardized yet, and diagnosis of ischemia was made based only on electrocardiography. In addition, post-EST serum IMA measurements obtained within different time periods were compared. For instance, Koc et al. used treadmill test, and used MPS for the detection of ischemia, though without any statistical significance, found that EST was associated with increased serum IMA values. However in this study, as mentioned above, serum IMA value was determined at first hour after EST, and data related to EST workload were not presented. [9]

Indeed even if decrease in IMA values related to exercise is seen, in patients whose coronary ischemia is induced as an outcome of EST increase in IMA values is an anticipated finding. Indeed, in some studies in the medical literature, the authors indicated that serum IMA levels increased in acute coronary syndrome, and myocardial infarction, and this finding could be used to rule out the presence of coronary ischemia..[13,14] Whereas, Zhong et al. reported that serum IMA levels are higher in patients with stable CAD, and increases in direct proportion with the extent of CAD.[15] In our study, In patients in whom ischemia was detected in our study during MPS procedure, IMA values at post-exercise 6. hour were higher than those without ischemia. Besides a significant correlation was detected between SSS, and SDS values which demonstrated extent of ischemia, and post-exercise IMA, and ΔIMA values.

Myocardial perfusion scintigraphy is not a gold standard test in the determination of CAD. Therefore, it is important to determine whether increase in IMA levels in patients with post-exercise ischemia detected as a result of MPS is an outcome of occlusive coronary artery disease. To this end, we performed coronary angiographic examinations as gold standard diagnostic test for CAD on patients with ischemia detected during MPS procedures. Seventeen patients had occlusive, and 2 patients non-occlusive CAD. These findings were consistent with specificity, and sensitivity of MPS.[1] Post-exercise IMA values of the patients with non-occlusive CAD were lower than the median IMA value of the ischemia group. Though statistical significance of this outcome can not be demonstrated because of scarce number of patients, the present study can lead the way for larger-scale randomized studies.

The second important finding was related to the patients with equivocal MPS results due to patient-related or technical factors which could not be decidedly associated with either ischemic or normal outcomes. In this patient group variations in pre-exercise, peak-exercise, and post-exercise serum IMA values were comparable to those with normal MPS results. Since these two patient groups without additional stress factor had similar workloads, both of them had expectedly similar IMA values. Doubtlessly, in patients with equivocal MPS results moving away from the diagnosis of CAD is important to reach such a conclusion.

To this end, follow-up evaluation of this patient population using CAG or CCTA detected 11 patients with angiographically normal coronary arteries 4 with calcium score of zero. While 3 patients had non-occlusive, and 2 cases occlusive lesions. Post-exercise IMA, and ΔIMA values of patients with occlusive CAD were higher than those of median, and mean values of the equivocal group. Though its statistical significance is not obvious, based on this outcome one can say that serum IMA values increase in cases with severe occlusion, and in this group variations in IMA values are relatively associated with only exercise.

This finding is important in that it allows more reliable identification of patients with equivocal MPS. To that end ROC analyses were performed to determine threshold values of post-exercise IMA, and ΔIMA which predict the presence of ischemia. In this analysis, it has been foreseen that post-exercise IMA and ΔIMA values of 5.50 , and 1.61 ng/ ml can reveal whether ischemia exists with significant sensitivity , and specificity. Especially in patients with equivocal MPS results, these threshold values can be used to classify patients more reliably. In the literature, although changing patient's position on X-ray table or use of new İmaging softwares have been tried, use of serum IMA measurement in this patient group has not been studied yet.[16,17]

Even though CAG is a gold standard diagnostic tool for CAD, for the diagnosis, and treatment of CAD ischemia detected in MPS in patients with anatomically normal coronary arteries should be conclusively correlated with microvascular dysfunction [18,19] If one think that post-exercise IMA, and ΔIMA values increase in parallel with ischemia, use of serum IMA values may be useful in this patient group of patients with normal ischemic MPS, and CAG results. In this analysis we performed, we demonstrated that post-exercise IMA, and ΔIMA values correlate with TSS, and SDS.

In conclusion, post-exercise serum IMA, and ΔIMA values may be useful in the determination of the presence of ischemia using MPS Besides, exercise –induced variations in serum IMA levels in patients with equivocal MPS results are similar to the patients without ischemia which may be helpful in the evaluation of the patients with equivocal MPS results.

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REFERENCES

1. Pakkal M, Raj V, McCann GP. Non-invasive İmaging in coronary artery disease including anatomical and functional evaluation of ischaemia and viability assessment. Br J Radiol 2011;84 Spec No 3:S280–95. **Crossref**
2. Melikian N, De Bondt P, Tonino P, De Winter O, Wyffels E, Bartunek J, et al. Fractional fow reserve and myocardial perfusion İmaging in patients with angiographic multivessel coronary artery disease. JACC Cardiovasc Interv 2010;3:307–14.
3. Berman DS, Kang X, Slomka PJ, Gerlach J, de Yang L, Hayes SW, et al. Underestımation of extent of ischemia by gated SPECT myocardial perfusion İmaging in patients with left main coronary artery disease. J Nucl Cardiol 2007;14:521–8.
4. Sbarouni E, Georgiadou P, Panagiotakos D, Kyrzopoulos S, Tsiapras D, Voudris V, et al. Ischemia modified albumin in relation to pharmacologic stress testing in coronary artery disease. Clin Chim Acta 2008;396:58–61. **Crossref**
5. Sbarouni E, Georgiadou P, Theodorakis GN, Kremastinos DT. Ischemia-modified albumin in relation to exercise stress testing. J Am Coll Cardiol 2006;48:2482–4. **Crossref**
6. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantifcation: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantifcation Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63. **Crossref**
7. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic İmaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539–42.
8. Ozdemir S, Barutcu A, Gazi E, Tan YZ, Turkon H. The Relationship Between Some Complete Blood Count Parameters and Myocardial Perfusion: A Scintigraphic Approach. World J Nucl Med 2015;14:197–201. **Crossref**
9. Koc ZP, Erkilic M, Basarıcı I, Deger N, Ozdem S, Saka O. Ischemia modified albumin levels cannot predict stress induced ischemia shown by myocardial perfusion scintigraphy. Rev Esp Med Nucl Imagen Mol 2012;31:202–6. **Crossref**
10. Ede H, Karaçavuş S, Göçmen AY, Yaylak B, Akkaya S, Açıkgöz B, et al. Serum copeptin level can be a helpful bio-

marker in evaluation of myocardial perfusion scintigraphy results. Cardiol J 2016;23:71–7. **Crossref**
11. Sbarouni E, Georgiadou P, Theodorakis GN, Kremastinos DT. Ischemia-modified albumin in relation to exercise stress testing. J Am Coll Cardiol 2006;48:2482–4. **Crossref**
12. Lee DH, Jeon HK, Park HJ, Shin WS, Lee SW, Youn HJ, et al. Change in ischemia-modified albumin and its clinical signifcance during exercise stress testing. Circ J 2010;74:484–9.
13. Bhakthavatsala Reddy C, Cyriac C, Desle HB. Role of "Ischemia Modified Albumin" (IMA) in acute coronary syndromes. Indian Heart J 2014;66:656–62. **Crossref**
14. Gurumurthy P, Borra SK, Yeruva RK, Victor D, Babu S, Cherian KM. Estımation of Ischemia Modified Albumin (IMA) Levels in Patients with Acute Coronary Syndrome. Indian J Clin Biochem 2014;29:367–71. **Crossref**
15. Zhong Y, Wang N, Xu H, Hou X, Xu P, Zhou Z. Ischemia-modified albumin in stable coronary atherosclerotic heart dis-ease: clinical diagnosis and risk stratifcation. Coron Artery Dis 2012;23:538–41. **Crossref**
16. Qutub MA, Dowsley T, Ali I, Wells RG, Chen L, Ruddy TD, et al.. Incremental diagnostic beneft of resolution recovery software in patients with equivocal myocardial perfusion single-photon emission computed tomography (SPECT). J Nucl Cardiol 2013;20:545–52. **Crossref**
17. Ben-Haim S, Almukhailed O, Neill J, Slomka P, Allie R, Shiti D, et al. Clinical value of supine and upright myocardial perfusion İmaging in obese patients using the D-SPECT camera. J Nucl Cardiol 2014;21:478–85. **Crossref**
18. Lim MJ, White CJ. Coronary angiography is the gold standard for patients with signifcant left ventricular dysfunction. Prog Cardiovasc Dis 2013;55:504–8. **Crossref**
19. Kuruvilla S, Kramer CM. Coronary microvascular dysfunction in women: an overview of diagnostic strategies. Expert Rev Cardiovasc Ther 2013;11:1515–25. **Crossref**

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