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Original

1 Q2 Ischemia modified albumin levels cannot predict stress induced ischemia shown  
2 by myocardial perfusion scintigraphy<sup>☆</sup>1 Q3 Z.P. Koc<sup>a,\*</sup>, M. Erkilic<sup>b</sup>, J. Basarici<sup>c</sup>, N. Deger<sup>c</sup>, S. Ozdem<sup>d</sup>, O. Saka<sup>e</sup>3 <sup>a</sup> Nuclear Medicine Department, Firat University Medical Faculty, Elazig, Turkey4 <sup>b</sup> Nuclear Medicine Department, Akdeniz University Medical Faculty, Antalya, Turkey5 <sup>c</sup> Cardiology Department, Akdeniz University Medical Faculty, Antalya, Turkey6 <sup>d</sup> Biochemistry Department, Akdeniz University Medical Faculty, Antalya, Turkey7 <sup>e</sup> Biostatistic Department, Akdeniz University Medical Faculty, Antalya, Turkey

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## A B S T R A C T

**Purpose:** Ischemia modified albumin (IMA) is a new marker of ischemia which is used in especially emergency room. Aim of this study is showing association of IMA with stress induced ischemia on Tc-99m 2-methoxyisobutyl-nitrate (MIBI) myocardial perfusion scintigraphy (MPS).

**Methods:** 56 patients (23 F, 33 M; 56.04 ± 8.45 years old) were included in our study. Stress-rest two days protocol Tc-99m MIBI MPS single photon emission tomography (SPECT) was performed to all patients. IMA levels from the blood samples which were taken before and after the treadmill test were measured. Thirty patients additionally underwent diagnostic coronary angiography.

**Results:** The difference between IMA levels of ischemia positive and negative groups was not statistically significant. Also, there was not statistically significant difference between IMA levels of patients who have narrowing in the coronary arteries and not.

**Conclusion:** Although IMA is an important marker of ischemia, probably because of other ischemic process during stress; it cannot reflect stress induced ischemic changes on MPS.

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**Los niveles de albúmina isquémica modificada no predicen la isquemia inducida por el estrés en gammagrafía de perfusión miocárdica**

## R E S U M E N

## 9 Palabras clave:

10 Isquemia miocárdica

11 Imágenes de perfusión miocárdica

12 Isquemia albúmina modificada

13 <sup>99m</sup>Tc 2-metoxi-nitrato

14 La gammagrafía

**Propósito:** La albúmina modificada por isquemia (AMI) es un nuevo marcador de isquemia que se utiliza especialmente en la sala de urgencia. El objetivo de este estudio es mostrar la asociación de la AMI con isquemia inducida por el estrés en el <sup>99m</sup>Tc 2-metoxi-nitrato (MIBI) gammagrafía de perfusión miocárdica (MPS).

**Métodos:** 56 pacientes (23 mujeres, 33 hombres; 56, 04 ± 8,45 años) se incluyeron en nuestro estudio. Protocolo de reposo-estrés de dos días Tc99m MIBI MPS, se realiza una emisión de fotón único (SPECT) a todos los pacientes. Los niveles de AMI se midieron en todas las muestras antes y después de la prueba de esfuerzo. Además, a treinta pacientes se les realizó una coronografía diagnóstica.

**Resultados:** No se encontró una diferencia estadística significativa de los niveles de AMI en los grupos de pacientes que tienen isquemia y los que no tienen isquemia. Además, no hubo diferencia significativa estadísticamente entre los niveles de AMI de los pacientes con estrechamiento en las arterias coronarias y los que no.

**Conclusión:** A pesar de que la AMI es un marcador importante de la isquemia, probablemente a causa de otros procesos isquémicos durante el estrés, no puede reflejar el estrés inducido por cambios isquémicos en el MPS.

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## 16 Q4 Introduction

17 Ischemia modified albumin (IMA) is an ischemia marker and  
18 reflects myocardial ischemia. The blood level of this marker is

Q1 <sup>☆</sup> This paper has been presented as poster presentations in these congresses:  
2-5 May 2009, Antalya, Turkey, 21st National Nuclear Medicine Congress; 10-14  
October 2009, Barcelona Spain, Annual Congress of European Association of Nuclear  
Medicine.

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measured by serum albumin cobalt binding (ACB) test. The principle of this test is based on the fact that, in the presence of ischemia, the change in the N-terminal of albumin molecule causes a decrease in the binding capacity of albumin molecule to cobalt.<sup>1</sup> However, unfortunately this conformational change during ischemia is not specific for myocardial ischemia. As multiple factors influence with the levels of IMA, predictability of this marker is limited. However, the change in the level of IMA might accurately identifies acute coronary syndrome in patients with acute chest pain who attend to emergency services,<sup>2-5</sup> especially in those whose diagnosis are supported with ECG and troponin levels.<sup>2,6-11</sup> One of the best methods

in identifying myocardial ischemia is Tc-99m 2-methoxyisobutyl-nitrate (MIBI) myocardial perfusion scintigraphy. IMA is a good ischemic marker, however, its diagnostic efficiency is hampered because of false positive results due to the skeletal muscle ischemia during treadmill stress test. The aim of this study is to analyze if stress induced ischemia which is defined by MPS produces any difference in IMA levels before and after stress test.

## Methods

### Patients

56 patients (23 F, 33 M) with a mean age of  $56.04 \pm 8.45$  years and who were referred to the Nuclear Medicine Department from Cardiology Department of Akdeniz University Faculty of Medicine, with the suspicion of coronary artery disease were included in this prospective study. After the routine physical examination and biochemical analysis of blood (lipid profile, plasma glucose, creatinin, albumin level); 12 lead ECG test was performed in all patients. Patients who had stable angina pectoris or low risk unstable angina were included to the study. Patients who experienced myocardial infarct (MI) previously and did not have revascularization in the last six months, or had findings of active ischemia on ECG and hypoalbuminemia (plasma albumin  $<3.0$ ) were excluded. The study was confirmed by Local Ethical Committee of Akdeniz University and the informed consents of all the patients were obtained. The study was conducted according to Helsinki Declaration.

### Treadmill test

Treadmill test was performed in 56 patients. Prior to the treadmill test the patients were asked to stop their  $\beta$ -blocker medication for at least one day and to fast at least 4 h before the test. After measuring blood pressure and pulse rate, treadmill test was performed by a Full Vision, TMX425 equipment according to Bruce protocol in all the patients. The maximum heart rate was calculated according to the 220-age formula and the target pulse rate was  $>85\%$  of maximum heart rate. Maximum exercise has been reached in all the patients.

### Myocardial perfusion scintigraphy (MPS)

Stress and rest Tc-99m MIBI myocardial single photon emission tomography (SPECT) were performed in 56 patients with two-day protocol. Blood samples were obtained before and after the treadmill test and 20 mCi Tc-99m MIBI was administered via intravenous route during the near peak heart rate and then the test was continued for an additional 30–60 s. The post-exercise blood samples were obtained within the first hour after the treadmill test.

The imaging was performed after a 30–45 min waiting period from the injection of the radiopharmaceutical agent. The SPECT was performed by a Sopha DST-LXi gamma camera with low energy high resolution collimator. The images were obtained over  $360^\circ$  in step and shoot mode (40 s/step;  $128 \times 128$  matrix) in a clockwise manner with 1.33 zoom supine position and unfortunately the imaging was performed as a nongated protocol due to the technical limitations of our gamma camera. The short, vertical and horizontal long axis and bull's eye images were interpreted by two experienced nuclear medicine physician independently from each other. They evaluated myocardial activity according to the anterior, septal, lateral and inferior walls and the apical, mid and basal segments. To observe an improvement in the rest images of a segment with hypoperfusion in the stress images is considered as the ischemia of the myocardium.

### Coronary angiography

Coronary angiography and left ventriculography were performed in 30 patients. Coronary angiographies (Philips Integris H, Netherlands) of all the patients were performed according to the standard Judkins technique via femoral approach. Angiographic images were evaluated by experienced cardiologists blinded to the treadmill, IMA and scintigraphy results. Angiographically significant CAD was defined as narrowing in diameter of a major coronary artery or a small branch of it with a diameter  $>2$  mm by 50% or more in diameter.

### Serum IMA levels

Samples were taken just before and 1 h after a maximum exercise via intravenous route and transported by biochemical tubes with jelly. After centrifugation of the samples, they were stored at  $-70^\circ\text{C}$ . Since the minority of albumin binds to cobalt in ischemic conditions<sup>6</sup> the plasma samples were incubated with cobalt chloride. Dithiothreitol was added to this complex in order to form a colored complex with the unbound albumin. The colored complexes were analyzed by spectrophotometric method. The cut off value of IMA was accepted as 85 U/ml according to the manufacturers recommendations.

### Statistical analysis

The mean values were determined as mean  $\pm 2$  SD. The mean IMA values of the two groups were compared by Students' *t* test and Wilcoxon test was used to compare the IMA values of two groups at different time points. We used Pearson correlation analysis from parametrical tests and Spearman correlation analysis from non-parametrical test were performed to evaluate the relationship between the variables.  $P < 0.05$  accepted as statistically significant. Statistical analysis was performed at SPSS version 15.

## Results

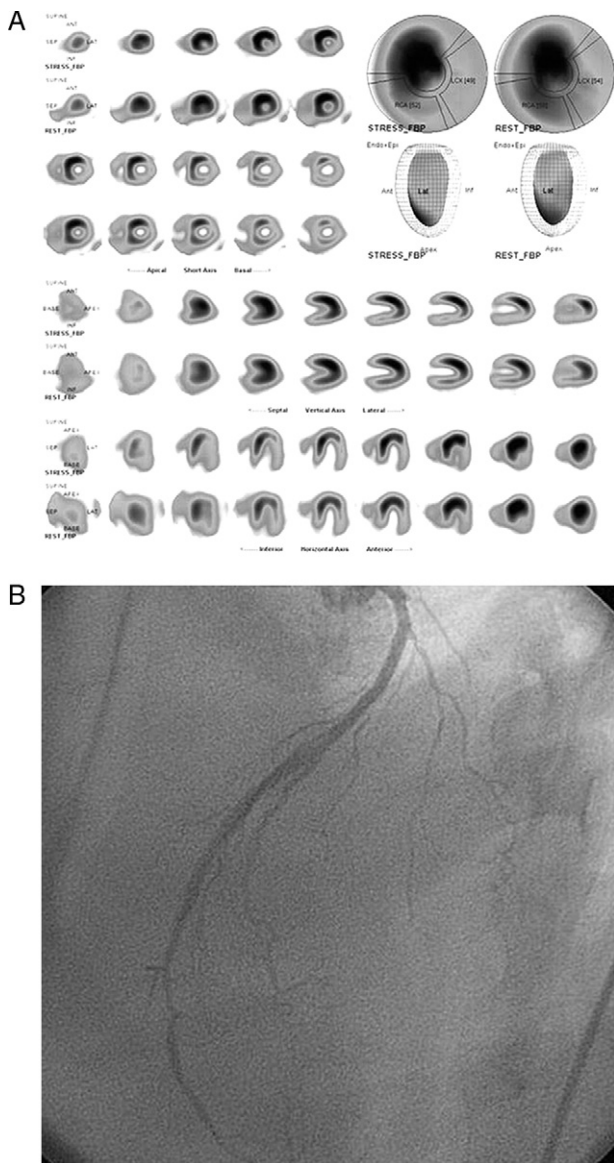
The mean IMA values of 56 patients before and after treadmill test were  $79.71 \pm 10.56$  U/ml and  $92.43 \pm 15.61$  U/ml respectively. The levels of pre and post-exercise IMA values and their elevation after exercise for ischemic patients ( $80.51 \pm 15.93$ ,  $92.22 \pm 15.58$  and  $14.91 \pm 13.73$  U/ml) and non-ischemic patients ( $79.90 \pm 9.48$ ,  $92.64 \pm 15.93$ ,  $18.12 \pm 20.79$  U/ml) were not statistically significantly different ( $P > 0.05$ ). The mean IMA values of the patients with and without CAD (luminal narrowing of any vessel  $>50\%$ ) ( $84.28 \pm 10.67$ ,  $91.41 \pm 14.57$ ,  $8.9 \pm 15.43$  and  $77.55 \pm 11.49$ ,  $87.97 \pm 15.69$ ,  $13.71 \pm 7.1$  U/ml respectively) were not also significantly different from each other ( $P > 0.05$ ).

Ten patients had CAD in their angiographies; 3 of them with 100% occlusion (Fig. 1a and b) and 4 of them with 70–100% occlusion had ischemia on MPS.

The patients who had ischemia on MPS and/or who had any CAD had higher post-exercise IMA values than the cut-off level for ischemia ( $>85$ ) or had a slight elevation of IMA levels after exercise (Table 1). However this elevation was not statistically significant as we mentioned before.

## Discussion

Coronary artery disease (CAD) is the most common cause of death all over the world. The most important issue is the selection of the patients with ischemic heart disease because these patients benefit from cardiac interventions as percutaneous coronary interventions and by-pass surgery. When complete obstruction resulted



**Fig. 1.** (a) Short, vertical and horizontal axis and bulls eye MPS images of a patient that has inferolateral wall ischemia with infarct who has normal IMA levels. (b) Angiography images of same patient with 100% narrowing of circumflex artery, 80% narrowing of left anterior descending artery.

with infarction of myocardial tissue recanalization of coronary arteries with various techniques sometimes do not success. Besides its complications; social and economic results of unnecessary interventions brings the importance of selecting appropriate patients. It is important to decide who has myocardial ischemia among patients who attend emergency department with acute chest pain. The recent diagnostic marker for myocardial ischemia is IMA. This marker is considered to be useful in emergency department for diagnosis of patients who have myocardial ischemia among patients with acute chest pain.<sup>2-5</sup> All these experiences with IMA show that this new marker is directly associated with myocardial ischemia. Thus we wanted to evaluate the potential role of this marker among patients with stress-induced ischemia on MPS.

The kinetics of IMA during severe myocardial ischemia have been investigated and a high negative predictive value<sup>2,12</sup> has been found. Additionally in previous studies IMA has been observed to be a highly sensitive marker in discriminating acute coronary syndrome (ACS) patients with good negative predictive value despite a normal ECG and troponin level.<sup>9,13</sup> However, in a previous report it has been concluded that negative predictive value of IMA has to be evaluated with the other clinical and laboratory parameters.<sup>14</sup>

Comparative studies of IMA with other cardiac biomarkers as CK and TnI have brought a conclusion that its rapid elevation and high negative predictive value make IMA more advantageous.<sup>15</sup> Additionally Talwakar et al. has been indicated in their report that the TnT and IMA might be complementary markers for patients who has attended emergency with acute chest pain.<sup>16</sup> The important drawbacks of IMA in ACS diagnosis have been supposed to have relatively higher costs, low availability and restricted usage in early period from onset of symptoms.<sup>17</sup>

There exist some studies indicating the prognostic value of IMA among CAD patients and in one of them it has been shown that IMA level after cardiopulmonary resuscitation is higher in patients with poor prognosis than both those of patients with good prognosis and healthy subjects.<sup>18</sup> A report about non-ST elevation MI (NSTEMI) has shown that the cut-off level of 109 U/mL of IMA gives prognostic information about the risk of events.<sup>15</sup> Another study has similarly shown that IMA is an independent predictor of 30-day outcome and one year mortality for the patients who have referred to emergency department with acute chest pain.<sup>19</sup> The sensitivity of IMA values greater than 85 U/ml in detecting ischemia of patients with acute chest pain and combination of both IMA and cTnT values have been given as 82% and 95% respectively.<sup>14</sup> In a previous study, with larger population, the sensitivity of the combination of these markers have been given as 100% for the diagnosis of ACS with non-diagnostic ECG.<sup>20</sup>

**Table 1**

The IMA levels of patients that have ischemia on MPS and/or the patients that have any narrowing of main coronary arteries.

	MPS	Angiography	IMA-pre <sup>a</sup>	IMA-post <sup>b</sup>
1	Inferolateral ischemia	LAD (80%), Cx (100%)	75	112
2	Anterior ischemia	LAD (30%)	98	103
3	Normal	Cx (30%)	89	115
4	Inferoseptal ischemia	RCA (70%)	93	95
5	Anteroseptal ischemia	LAD (80%), Cx (70%)	78	103
6	Anteroseptal ischemia	Normal	99	122
7	Anterior ischemia	LAD (70%)	69	105
8	Inferoseptal ischemia	LAD (70%), Cx (70%), RCA (100%)	66	83
9	Inferoseptal ischemia	LAD (50%), Cx (70%), RCA (70%)	74	109
10	Inferior ischemia	LAD (80%), Cx (90%)	84	110
11	Normal	LAD (30%)	106	131
12	Inferior ischemia	LAD (40%), Cx (70%), RCA (50%)	76	81
13	Inferior ischemia	Cx (30%), RCA (70%)	72	98
14	Normal	LAD (70%)	95	112
15	Septal ischemia	LAD (30%)	67	98

<sup>a</sup> Pre-exercise IMA value.

<sup>b</sup> Post-exercise IMA value.

In a comparative study about ACS patients who have attended to emergency room it has been concluded that IMA is more sensitive and more specific than C-reactive protein (CRP).<sup>4</sup>

Contrary to all of the above reports we observed there was neither correlation nor significant association between IMA values and ischemia on MPS or luminal narrowing on angiography in our study. This might probably be associated with the influence of exercise on the IMA results. A study about marathon runners in which IMA levels have been found to mildly decrease supports this idea<sup>21,22</sup> and the researchers has thought that it might be a possible consequence of a decrease in blood albumin level, peripheral tissue ischemia or increase of blood lactate level during exercise.<sup>22</sup> Roy et al. has also shown an important decrease in blood IMA levels immediately after exercise in patients with peripheral vascular disease and intermittent claudication.<sup>23</sup>

Although the manufacturer gives a range of albumin level that influence with IMA levels, a previous study has shown that there exist a clear negative relationship between plasma albumin and IMA levels.<sup>24</sup>

Many studies have concluded that IMA has not been an ancillary marker in showing exercise induced myocardial ischemia<sup>25-27</sup> and in one of them which has investigated IMA levels at many time points and same alterations have been found both in ischemia positive and negative group with simultaneous alterations of plasma albumin levels for all time points.<sup>24</sup> However contrary to these findings, Kurz et al. has reported that stable CAD patients have higher IMA values after exercise.<sup>28</sup>

The sensitivity and specificity of treadmill test range between 60 and 70%<sup>29</sup> and combination with an ischemia marker might be helpful but it is not possible to perform due to the reasons mentioned above. As a consequent, to employ IMA as an additive parameter to MPS is not possible. In a study in which TI-201 myocardial perfusion scintigraphy is performed; the authors have concluded that IMA is not advantageous in exercise induced ischemia but might be more advantageous in pharmacological stress.<sup>27</sup> In this study we had a larger study population with ischemic findings on MPS and with IMA results thus as a consequence, we did not identify a significant relationship between ischemia on MPS and IMA.

The variability in healthy population<sup>30</sup> and differences between races<sup>31</sup> are the other handicaps about IMA. Special cut-off values have to be determined for all age and ethnic groups.

Effect of plasma albumin concentrations is another limitation for IMA value and so, we have corrected the values according to manufacturer's advises for high albumin concentrations. The effect of albumin on IMA levels may not be associated with only high albumin concentrations but also for all albumin levels.<sup>24</sup> In that case the effect of albumin levels on IMA levels cannot be excluded.

We observed a higher post-exercise IMA level and/or a slight elevation in IMA level after exercise for ischemia positive patients. However, no statistically significance was found and this was an expected finding since possible influences with further ischemic processes elsewhere in the body on IMA levels (peripheral tissue ischemia, gastrointestinal system ischemia) might cause inconclusive IMA results. Additionally, our patients who underwent angiography were smaller in number than the population we had planned and also patients with normal MPS were out of follow up.

## Conclusion

We came to a conclusion that a significant relationship between ischemia on MPS and IMA did not exist. However future studies are warranted including pharmacological stress protocols of MPS and IMA.

## Conflict of interest

The authors have no conflict of interests to declare.

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