***Smyrna Tıp Dergisi*** ***Araştırma Makalesi***

# The Predictive Value of Ischemia Modified Albumin as a Reperfusion Criteria after Thrombolytic Therapy in ST-Segment Elevation Myocardial Infarction

# ST Segment Elevasyon Miyokard İnfarktüsünde Trombolitik Tedavi Sonrası Reperfüzyon Kriteri Olarak İskemi Modifiye Albuminin Öngördürücü Değeri

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**Abstract**

**Objective:** In acute ST segment elevation myocardial infarction (STEMI), thrombolytic therapy is an effective therapy for the patency of the infarct-related artery (IRA), thus protecting the heart muscle. In this study, the role of ischemia-modified albumin (IMA), a new and early marker was investigated as an indicator of reperfusion after thrombolytic therapy.

**Matherial and Methods:** The IMA, creatine kinase-MB (CKMB) mass and cardiac Troponin I (cTnI) levels were measured from blood of patients with an acute STEMI, who underwent thrombolytic therapy, at the before therapy (0. hours) and after 6, 12 and 24 hours. Relationship between these three diagnostic variables used for the diagnosis of reperfusion (troponin, CKMB mass levels and IMA levels) were investigated.

**Results:** IMA values taken from patients at the time of admission were significantly higher than in the control group. Moreover, IMA reached a peak value at a similar time as troponin and CKMB mass values.

**Coclusion:** Similar to troponin and CKMB mass values, both of which increase after reperfusion, IMA also can be used as a biochemical indication for reperfusion.

**Key Words:** Ischemia-modified albumin, ST segment elevation myocardial infarction, reperfusion

**Özet**

**Amaç:** Akut ST segment elevasyonlu miyokard infarktüsünde (STEMI) infarkt ilişkili arteri (İİA) açmak ve kalp kasını korumak için trombolitik tedavi çok önemlidir. Bu çalışmada; yeni ve erken bir iskemi belirteci olan iskemi modifiye albümin'in (İMA) trombolitik tedavi sonrası reperfüzyonu göstermedeki rolü araştırıldı.

**Gereç ve Yöntem:** Akut STEMI tanısı ile trombolitik tedavi uygulanan hastalarda, trombolitik tedavi başlangıcında (0. saat) ve sonrasında 6, 12 ve 24. saatlerde eş zamanlı olarak kanda İMA, kreatin kinaz-MB (CKMB) ve troponin I (cTnI) düzeyleri ölçüldü. Reperfüzyon tanısı amacıyla kullanılan üç tanı degişkeni (troponin, CKMB düzeyleri ile İMA düzeyleri) arasındaki ilişki incelendi.

**Bulgular:** Hasta grubunda başvuru sırasında alınan İMA değerleri kontrol grubundaki İMA değerlerine göre anlamlı oranda daha yüksek saptandı. İMA'nın troponin ve kütle CKMB ile benzer zamanlarda pik değerine ulaştığı tespit edildi.

**Sonuç:** İMA'nın reperfüzyon sonrası artış gösteren troponin ve kütle CKMB gibi reperfüzyon için biyokimyasal bir gösterge olarak kullanılabileceği düşünüldü.

**Anahtar Kelimeler:** İskemi modifiye albumin, ST segment elevasyonlu miyokard infarktüsü, reperfüzyon

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## Introduction

Myocardial infarction (MI) is one of the largest causes of death and disability in the world (1). The main purpose of the treatment of an acute ST-segment elevation myocardial infarction (STEMI) is to provide early treatment of the infarct related artery (IRA) (2). Coronary angiography provides the most accurate information regarding the perfusion status of the IRA. However, routine coronary angiography is not recommended for patients receiving thrombolytic therapy (3). Therefore, determining the perfusion status of the IRA with non-invasive methods is of great importance. Although their sensitivity and specificity are limited, the cessation of the patient's chest pain, 50% reduction of 90$^{th}$ minute ST elevation compared to admission ECG and observation of reperfusion arrhythmia have been used as non-invasive indicators of reperfusion in the clinics (2,4,5). Besides some cardiac biomarkers such as creatine kinase-MB (CKMB) mass and cardiac Troponin I (cTnI) may also be used as a reperfusion indicator (6).

Recently; ischemia modified albumin (IMA), has been frequently emphasized in many studies and has approved by United States Food and Drug Administration (FDA) to be used as a cardiac biomarker in myocardial ischemia (7). It was demonstrated that IMA levels mainly increased during myocardial ischemia triggered by the reduced blood flow and also increase during percutaneous coronary intervention (PCI) (2). Sinha et al. have proposed that an increase in the concentration of IMA can be used as an early marker of myocardial ischemia and therefore be useful in the evaluation of patients with acute coronary syndrome (ACS) (8). However, current studies that have investigated the role of IMA as a reperfusion after STEMI indicator are limited.

In this study, it was aimed to investigate whether IMA has utility as a indicator of reperfusion in STEMI patients received thrombolytic therapy.

## Material and Methods

*Study subject*

This prospective study was conducted between February 2009 and September 2010 in a tertiary urban emergency department (ED) with an annual admission rate of nearly 200000. Ethical approval was obtained prior to the study from the local ethics committee. Patients were informed about the study and signed consent forms were obtained.

The study included consecutive patients, age 18 and older, who presented with chest pain that started within the first 12 hours from presentation. These patients had at least two adjacent precordial deviations or at least two contiguous extremity deviations ≥0.1 mV ST segment elevation detected by electrocardiography (ECG) and were treated with thrombolytic therapy for reperfusion.

Patients that did not consent to participate, patients with severe renal or hepatic insufficiency, peripheral vascular diseases, acute abdomen, patients with albumin levels below 3 g/dL or above 5.5 g/dL, patients who planned to undergo PCI, patients for whom thrombolytic therapy was contraindicated and patients whose IMA values could not be measured were excluded from the study. A total of 41 patients in the control group were selected from healty adults who had no active complaint, chronic disease or abnormal physical examination.

All patients received recommended treatment according to guidelines simultaneously with thrombolytic therapy. Patients were closely monitored throughout their thrombolytic therapy and every 30 minutes a 12-lead ECG at 10-mm/mV amplitude and 25mm/sec speed was obtained.

Patients were evaluated based on clinically used reperfusion indicators such as cessation of chest pain following the thrombolytic therapy, observation of reperfusion arrhythmias and a 50% reduction of ST segment elevation compared to ECG from admission. The data obtained from the participating patients were recorded into the patient follow-up forms.

*Biochemical tests*

The IMA, CK-MB mass and cTnI measurements were performed with venous blood samples obtained from the patients. The IMA, cTnI and CKMB mass levels were measured from blood of patients with an acute STEMI, who underwent thrombolytic therapy, at the before therapy (0 hours) and after 6, 12 and 24 hours. cTnI and CKMB mass measurements were done on autoanalyzer (Vitros® 3600 Johnson & Johnson) by using a chemiluminometric method. Serum albumin levels were measured with

autoanalyzer (Architect C16000 Abbott Diagnostics, USA) by using the bromocresol green method. The same blood samples were used to measure IMA.

Blood samples taken for measuring IMA were centrifuged at 3000 rpm for 10 minutes to separate the serum. Samples were stored at -80 °C until analysis. The IMA measurements were done by using albumin cobalt binding test as described by Bar-Or and colleagues. This test is based on the colorimetric measurement of formation of colored complex between dithiothreitol (DTT) and cobalt, which was added to the test sample but did not bind to albumin.

The following method was used for IMA measurement: 0.1% cobalt chloride solution, 1.5 mg/mL DTT solution, 0.9% NaCl solution, glass tubes, vortex, adjustable automatic ependorff pipettes, disposable plastic micro cuvettes and Shimadzu UV-1201V model spectrophotometer. The obtained results were given as absorbance unit (AU).

*Electrocardiography*

All patients underwent the 12-lead ECG at 10mm/mV amplitude and 25mm/sec speed in 15-minute intervals throughout the entire thrombolytic therapy procedure. We compared the basal ECG's deviation at which maximum ST segment elevation was observed with the ST segment elevation that was observed at the 90$^{th}$ minute of the thrombolytic therapy. In addition, the percent reduction of the ST segment elevation were evaluated.

*Echocardiography*

A transthoracic echocardiography (general electric vivid 3 Version 2.3) was performed within 24-48 hours after reperfusion therapy by a cardiologist.

*Statistical Analyses*

Statistical analyses were performed using SPSS 15.0 statistical software. Descriptive statistics related to the data were described in the table as mean±SD, number and percentages. The relationship between the consecutive measurements of IMA levels and three variables used for the diagnosis of reperfusion was assessed with an independent sample t test. The correlation between each of cardiac markers was assessed by Pearson's correlation test. The value of $p < 0.05$ was considered statistically significant.

## Results

During the study a total of 142 patients with STEMI were admitted to the ED. Among those patients 86 underwent PCI, while 3 patients had chronic renal failure and therefore were excluded from the study. The remaining 53 patients were included in the study.

Thirty-eight (71.7%) patients were male and the mean age was 58.4±11.6 years. When patients' medical histories were reviewed, it was determined that the most common concomitant disease was hypertension (n=31, 58.5%). A history of smoking was present in the majority of patients (n=39, 73.6%). In addition, the examination of the diagnosis distribution of patients with ECG showed that inferior MI (n=23, 43.4%) was the most common diagnosis. Patients most frequently presented to the hospital within the first two hours of symptom onset (n=25, 47.2%). When the time between the start of chest pain and beginning of patients' receiving thrombolytic therapy was examined, the earliest was at 30 minutes after chest pain onset; while the latest was 12 hours after chest pain onset.

The initial (measured upon the arrival to the hospital) mean IMA values of patients who were diagnosed with STEMI and the control group were 0.462±0.155 AU and 0.382±0.148 AU, respectively ($p<0.005$). The mean IMA values upon arrival and six hours after initiation of thrombolytic therapy were 0.462±0.155 AU and 0.677±0.179 AU, respectively ($p<0.001$).

For patients who experienced chest pain relief, and 50% resolution of ST-segment elevation with thrombolytic therapy, their IMA values upon arrival, and at 6$^{th}$ hour after the initiation of thrombolytic therapy, are shown in table 1. When cardiac markers were compared in terms of time to reach the peak value, troponin (53.01±29.82 ng/ml) was found to reach a peak value at 12 hours after initiation of thrombolytic therapy, whereas CKMB mass value (81.39±76.92 ng/ml) and IMA (0.677± 0.179 AU) reached their peak value six hours after the initiation of the thrombolytic therapy. The correlation between troponin, CKMB and IMA are shown in table 2.

***Table 1.*** *The relationship between the clinical indicators of successful reperfusion and IMA levels upon arrival to the hospital and at 6th hour after the initiation of thrombolytic therapy.*

| | | Ischemia modified albumin levels (AU) | |
|---|---|---|---|
| | | **Initial value** *(mean±SD)* | **6 hours after thrombolytic therapy** *(mean±SD)* |
| **Chest pain relief** | Positive (n=50) | 0.463±0.157 | 0.678±0.180 |
| | Negative (n=3) | 0.449±0.121 | 0.673±0.185 |
| | ***p* value** | *0.883* | *0.883* |
| **ST segment resolution** | ≥%50 (n=46) | 0.463±0.148 | 0.679±0.175 |
| | <%50 (n=7) | 0.454±0.209 | 0.665±0.219 |
| | ***p* value** | *0.885* | *0.853* |
| **Reperfusion arrhytmias** | Positive (n=17) | 0.467±0.131 | 0.677±0.157 |
| | Negative (n=36) | 0.460±0.166 | 0.677±0.190 |
| | ***p* value** | *0.883* | *0.999* |

*IMA: ischemia modified albumin*

***Table 2.*** *The correlation between troponin, CKMB mass and IMA levels of patients at the time of their presentation and after 6, 12 and 24 hours after the initiation of thrombolytic therapy*

| | IMA 0 (AU) | | IMA 6 (AU) | | IMA 12 (AU) | | IMA 24 (AU) | |
|---|---|---|---|---|---|---|---|---|
| | **r value** | **p value** | **r value** | **p value** | **r value** | **p value** | **r value** | **p value** |
| **CKMB mass 0 (ng/ml)** | **0.053** | **0.705** | 0.174 | 0.214 | 0.018 | 0.898 | 0.015 | 0.917 |
| **CKMB mass 6 (ng/ml)** | 0.115 | 0.412 | **0.057** | **0.686** | 0.104 | 0.457 | 0.003 | 0.980 |
| **CKMB mass 12 (ng/ml)** | 0.130 | 0.355 | 0.165 | 0.238 | **0.211** | **0.130** | 0.127 | 0.364 |
| **CKMB mass 24 (ng/ml)** | 0.008 | 0.957 | 0.164 | 0.240 | 0.231 | 0.096 | **0.183** | **0.191** |
| **cTnI 0 (ng/ml)** | **0.035** | **0.804** | 0.179 | 0.200 | 0.023 | 0.868 | 0.012 | 0.929 |
| **cTnI 6 (ng/ml)** | 0.150 | 0.282 | **0.107** | **0.447** | 0.015 | 0.914 | 0.086 | 0.539 |
| **cTnI 12 (ng/ml)** | 0.200 | 0.151 | 0.108 | 0.442 | **0.084** | **0.550** | 0.031 | 0.824 |
| **cTnI 24 (ng/ml)** | 0.179 | 0.200 | 0.141 | 0.315 | 0.162 | 0.247 | **0.096** | **0.496** |

*IMA:ischemia modified albumin; CKMB:creatine kinase-MB; cTnI:cardiac Troponin I.*

## Discussion

Providing coronary artery patency with the use of thrombolytic therapy for acute myocardial infarction has been shown to cause a significant reduction in mortality (9,10,11,12). In these patients, the patency of the myocardial infarction related coronary artery affects both the patients' treatment choice and prognosis (13,14).

A combination of ST segment resolution, along with cardiac markers, is a strong early indicator of successful coronary reperfusion (15). There are no studies in the literature that compare IMA levels with clinical indicators of reperfusion after thrombolytic therapy such as cessation of chest pain, 50% reduction of ST-segment elevation at 90th minute compared to ECG from admission and presence of reperfusion arrhythmias. Similarly, there is no study investigating the possible utility of IMA as a new biomarker of successful reperfusion.

In this study, a significant relationship was not detected between the clinical indicators of successful reperfusion with IMA levels of patients measured upon arrival to the hospital, and measured six hours after the initiation of the thrombolytic therapy (table 1). Similarly, there was no significant correlation between troponin, CKMB mass and IMA levels measured upon arrival and at 6th, 12th and 24th hour after the initiation of thrombolytic therapy (table 2). In a meta-analysis that investigated the role of IMA in exclusion of ACS in the ED, investigators determined that in patients admitted with chest pain, non-diagnostic ECG along, with negative troponin and negative IMA values the negative predictive value was high (17).

Debashis R et al. investigated the diagnostic value of IMA in patients admitted to the ED with chest pain, normal ECG findings and negative troponin values and determined that IMA levels were higher in patients with ischemic chest pain (18). In this study, the serum IMA levels of patients with a STEMI measured upon the admission to the hospital were higher than serum IMA levels of individuals in the control group; this suggests that IMA levels can be used as an early period marker of ACS. Studies in the literature are also consistent with this notion.

Several studies have reported that in patients who underwent elective percutaneous transluminal coronary angioplasty (PTCA), IMA levels measured after the procedure were significantly higher than IMA values measured prior to the procedure (19,20,21,22). This elevation has been shown to have a significant correlation with coronary collateral circulation, the balloon inflation time, number and pressure, chest pain generated during the procedure, and ECG changes.

Kircher et al. have shown that early peaking of CKMB, troponin and myoglobin values after thrombolytic therapy could be used as an indicator of successful reperfusion (6). In our study, we determined that IMA and CKMB mass reached their peak value 6 hours after initiation of thrombolytic therapy, while troponin reached its peak value 12 hours after the initiation of the therapy. These results suggest that similar to CKMB mass and troponin, IMA can be used as a indicator of reperfusion after thrombolytic therapy and that compared to troponin, IMA can indicate reperfusion at an earlier period.

Although the clinical reperfusion features analyzed at 90 minutes after the thrombolytic therapy, we have preferred to check IMA levels at $6^{th}$ and $12^{th}$ hours together with other cardiac biomarkers such as, CKMB mass and troponin.

## Limitations

In the study, serum IMA levels were measured before the thrombolytic therapy (0. hours) and 6, 12 and 24 hours after the thrombolytic therapy. Therefore, the earliest time point after the initiation of thrombolytic therapy was six hours. Earlier measurements of IMA levels with more frequent time points would elucidate whether or not IMA values peak at an earlier time point.

## Conclusion

Any relationship between the IMA levels and cessation of chest pain was not detected, 50% reduction in the elevation of ST segment at $90^{th}$ minute compared to ECG from admission and formation of reperfusion arrhythmias. However, the IMA levels of reperfused patients showed a similar increase with troponin and CK-MB mass.

## Conflict of interest

There are no conflicts of interests.

## References

1. Thygesen K, Alpert JS, White HD. Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Eur Heart J 2007;28(20):2525-38.
2. Rodriguez AD, Kaski JC, Abreu-Gonzalez P, Samimi-Fard S. Role of ischemia modified albumin to ST-segment resolution after mechanical reperfusion in patients with ST-segment elevation myocardial infarction. Atherosclerosis 2009;203(2):576-80.
3. Rogers WJ, Baim DS, Gore JM, Brown BG, Roberts R, Williams DO, et al. Comparison of immediate invasive, delayed invasive, and conservative strategies after tissue-type plasminogen activator. Results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II-A trial. Circulation 1990;81(5):1457-76.
4. Ghaemmaghami CA, Burt DR. Acute reperfusion therapy in acute myocardial infarction. Emerg Med Clin North Am 2005;23(4):1043-63.
5. Klootwijk P, Langer A, Meij S, Green C, Veldkamp RF, Ross AM, et al. Non-invasive prediction of reperfusion and coronary artery patency by continuous ST segment monitoring in the GUSTO-I trial. Eur Heart J 1996;17(5):689-98.
6. Kircher BJ, Topol EJ, O'Neill WW, Pitt B. Prediction of infarct coronary artery recanalization after intravenous thrombolytic therapy. Am J Cardiol 1987;59(6):513-5.
7. Morrow DA, Cannon CP, Jesse RL, Newby LK, Ravkilde J, Storrow AB, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical characteristics and utilization of biochemical markers in acute

coronary syndromes. Clin Chem 2007;53(4):552-74.
8. Sinha MK, Roy D, Gaze DC, Collinson PO, Kaski JC. Role of "Ischemia modified albumin", a new biochemical marker of myocardial ischaemia, in the early diagnosis of acute coronary syndromes. Emerg Med J 2004;21(1):29-34.
9. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival. Should the paradigm be expanded ? Circulation 1989;79(2):441-4.
10. Granger CB, Califf RM, Topol EJ. Thrombolytic therapy for acute myocardial infarction: A Review. Drugs 1992;44(3):293-325.
11. GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329(22):1615-22.
12. Popović AD, Nesković AN, Babić R, Obradović V, Bozinović L, Marinković J, et al. Independent impact of thrombolytic therapy and vessel patency on left ventricular dilation after myocardial infarction. Serial echocardiographic follow-up. Circulation 1994;90(2):800-7.
13. Galvani M, Ottani F, Ferrini D, Sorbello F, Rusticali F. Patency of the infarct-related artery and left ventricular function as the major determinants of survival after Q-wave acute myocardial infarction. Am J Cardiol 1993;71(1):1-7.
14. Vogt A, von Essen R, Tebbe U, Feuerer W, Appel KF, Neuhaus KL. Impact of early perfusion status of the infarct-related artery on short-term mortality after thrombolysis for acute myocardial infarction: retrospective analysis of four German multicenter studies. J Am Coll Cardiol 1993;21(6):1391-5.
15. Braunwald E. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 5th ed. USA, Elsevier Inc, 2005;1242-3.
16. Anwaruddin S, Januzzi JL Jr, Baggish AL, Lewandrowski EL, Lewandrowski KB. Ischemia-modified albumin improves the usefulness of standard cardiac biomarkers for the diagnosis of myocardial ischemia in the emergency department setting. Am J Clin Pathol 2005;123(1):140-5.
17. Peacock F, Morris DL, Anwaruddin S, Christenson RH, Collinson PO, Goodacre SW, et al. Meta-analysis of ischemia-modified albumin to rule out acute coronary syndromes in the emergency department. Am Heart J 2006;152(2):253-62.
18. Roy D, Quiles J, Aldama G, Sinha M, Avanzas P, Arroyo-Espliguero R, et al. Ischemia modified albumin for the assessment of patients presenting to the emergency department with acute chest pain but normal or non-diagnostic 12-lead electrocardiograms and negative cardiac troponin T. Int J Cardiol 2004;97(2):297-301.
19. Sinha MK, Vazquez JM, Calvino R, Gaze DC, Collinson PO, Kaski JC. Effects of balloon occlusion during percutaneous coronary intervention on circulating ischemia modified albumin and transmyocardial lactate extraction. Heart 2006;92(12):1852-3.
20. Quiles J, Roy D, Gaze D, Garrido IP, Avanzas P, Sinha M, et al. Relation of ischemia-modified albumin (IMA) levels following elective angioplasty for stable angina pectoris to duration of balloon-induced myocardial ischemia. Am J Cardiol 2003;92(3):322-4.
21. Sinha MK, Gaze DC, Tippins JR, Collinson PO, Kaski JC. Ischemia modified albumin is a sensitive marker of myocardial ischemia after percutaneous coronary intervention. Circulation 2003;107(19):2403-5.
22. Garrido IP, Roy D, Calviño R, Vazquez-Rodriguez JM, Aldama G, Cosin-Sales J, et al. Comparison of ischemia-modified albumin levels in patients undergoing percutaneous coronary intervention for unstable angina pectoris with versus without coronary collaterals. Am J Cardiol 2004;93(1):88-90.

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