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Original Article / Özgün Makale

The relationship between ischemia-modified albumin and myocardial infarction in on-pump coronary artery bypass grafting

On-pump koroner arter baypas greftlemede miyokard enfarktüsü ile iskemi modifiye albüminin ilişkisi

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ABSTRACT

Background: This study aims to evaluate the potential of ischemia-modified albumin (IMA) to predict the myocardial infarction in on pump coronary artery bypass grafting (ONCABG) patients.

Methods: Fifty elective isolated ONCABG patients (41 males, 9 females; mean age 66 years; range 56 to 75 years) were included in the study. Patients were divided into perioperative myocardial infarction (PMI; n=8) and non-infarction (NPMI; n=42) groups according to perioperative cardiac troponin I (cTnI) values and ECG findings. Serum IMA levels were measured preoperatively, 20 minutes after aortic cross clamping, 30 minutes, at 3, 6, 12 and 24 hours after declamping.

Results: Compared to the NPMI group, the declamping 30 minutes, 3, 6 and 12 hours IMA levels were higher in the PMI group (p=0.002, p=0.048, p=0.023, p=0.007, respectively). In both NPMI and PMI groups, the 20 minutes after aortic cross clamping IMA levels were higher compared to the preoperative IMA levels (p=0.0001, p=0.038, respectively).

Conclusion: Our study results show that IMA may be an early marker of myocardial infarction in the ONCABG patients.

Keywords: Coronary artery bypass grafting; ischemia-modified albumin; perioperative myocardial infarction.

ÖZ

Amaç: Bu çalışmada, iskemi modifiye albümin (İMA)'nin on-pump koroner arter baypas greftleme (ONCABG)'de ameliyat sırası miyokard enfarktüsünü (PME) erken dönemde öngörebilme potansiyeli değerlendirildi.

Çalışma planı: Çalışmaya elektif izole ONCABG yapılan 50 hasta (41 erkek, 9 kadın; ort. yaş 66 yıl; dağılım 56-75 yıl) dahil edildi. Hastalar, ameliyat sırası EKG bulguları ve kardiyak troponin I (cTnI) değerlerine göre, PME olanlar (n=8) ve PME olmayanlar (NPME; n=42) olarak gruplandırıldı. Serum İMA düzeyleri ameliyat öncesinde, aortik kros klemp konulduktan 20 dakika sonra, klemp kaldırıldıktan 30 dakika, 3, 6, 12 ve 24 saat sonra ölçüldü.

Bulgular: Klemp kalktıktan 30 dakika, 3, 6 ve 12 saat sonra İMA düzeyleri PME grubunda, NPME grubuna kıyasla, daha yüksekti (sırasıyla, p=0.002, p=0.048, p=0.023, p=0.007). Hem PME hem de NPME grubunda İMA düzeyleri aortik kros klemp konulduktan 20 dakika sonra, ameliyat öncesi İMA düzeylerine kıyasla yükselmişti (sırasıyla p=0.0001, p=0.038).

Sonuç: Çalışma bulgularımız, İMA'nın ONCABG yapılan hastalarda miyokard infarktüsü için erken bir belirteç olabileceğini göstermektedir.

Anahtar sözcükler: Koroner arter baypas cerrahisi; iskemi modifiye albümin; ameliyat sırası miyokardiyal infarktüs.

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Coronary artery bypass graft (CABG) surgery has been the gold standard for revascularization in various patient groups for many years.[1] Perioperative myocardial infarction (PMI) is one of the major causes of perioperative morbidity and mortality after CABG and is related to high mortality in both the early and late periods.[2-4]

The classic criteria and diagnostic methods used for myocardial infarction (MI) have serious limitations in the perioperative period,[3,5] and blood-based biomarkers are now considered to be attractive alternatives because they are easily applicable, cheap, and more rapidly reachable.[5-8] In particular, cardiac troponin I (cTnI) is known to cause myocardial damage, but it is currently accepted as the most sensitive and specific marker for diagnosing myocardial damage after CABG.[3,5,6]

Because cTnI is a necrosis marker rather than an ischemia marker,[9] new markers are needed that can define ischemia in the earlier pre-necrosis period. In addition, such markers may be useful for the early diagnosis of myocardial ischemia when it has not progressed to irreversible necrosis.

Exposure to ischemic tissue alters the N-terminus of albumin. This decreases its binding capacity for metals, resulting in the formation of ischemia-modified albumin (IMA).[10,11] The IMA levels, which increase within minutes after the start of ischemia, remain high for 6-12 hours and then return to normal levels within 24 hours. In this way, IMA is valuable for determining ischemia in the early period before myocardial necrosis.[12] There are currently many biomarkers for cardiac ischemia [fatty acid-binding protein (FABP), choline, and IMA], but only IMA is licensed for routine use when cardiac ischemia is present. Furthermore, IMA has been approved by the Food and Drug Administration (FDA) and has been approved for use by the European Union and thus has received Œ marking.[8,10] The aim of this study was to evaluate the potential of IMA for predicting MI in on-pump CABG (ONCABG) patients.

PATIENTS AND METHODS

Fifty elective, isolated ONCABG patients (41 males and 9 females; mean age 66 years; range 56 to 75 years) were included in this study. Those with acute coronary syndrome (ACS), high preoperative cTnI values, chronic inflammatory disease, malignancy, cirrhosis, or a plasma albumin concentration of under 20 g/L were excluded from the study as well as those who had previously undergone emergency surgery, a reoperation, combined procedures, or off-pump CABG (OPCAB). Informed consent was obtained from all of the patients, and approval for the study was given by the local ethics committee (2012-104).

The sociodemographic characteristics, the values before surgery and 48 hours after declamping, the cTnI and IMA values, the preoperative results, and the first, second, and fifth-day postoperative electrocardiogram (ECG) results of all of the patients were recorded. Forty-two patients were placed in the non-PMI group and eight in the PMI group according to their perioperative cTnI values and ECG findings. Perioperative MI was defined as a cTnI value of more than 10 times the 99th percentile of the upper reference limit (URL) during the first 48 hours following CABG based on a normal baseline cTnI value of ≤ the 99th percentile of the URL. In addition, either new pathological Q waves or a new left bundle branch block (LBBB) must also be present to have PMI.[13]

Initially, radial and pulmonary arterial catheters were introduced in the patients under local anesthesia. After standard general anesthesia, a median sternotomy was performed followed by routine aortic and right atrial cannulation. Cardiopulmonary bypass (CPB) was then carried out using membrane oxygenators and moderate systemic hypothermia. Myocardial protection was achieved via antegrade mild hypothermic (32 °C) blood cardioplegia, and this was repeated every 20 minutes or whenever needed. Heparin 3.0 mg.kg^{-1} was also administered, and the activated clotting time (ACT) was maintained at >400 seconds during the procedure. The heparin was neutralized with protamine at a ratio of 1:1.3 within 10 minutes after being weaned from CPB, and all of the patients were followed up in the intensive care unit (ICU) after surgery.

Blood samples for IMA determination were drawn preoperatively, at 20 minutes after aortic cross-clamping (ACC), at 30 minutes after declamping, and at 3, 6, 12, and 24 hours after declamping when the cross clamp was released. For standardization purposes, all of the blood samples from each subject were collected by the same venipuncture staff in vacutainer tubes without an anticoagulant. They were then centrifuged at 2000 g for 10 minutes and stored at -80 °C until the biochemical assays were performed.

The ultrasensitive cTnI levels were estimated using a chemiluminescence-based immunoassay method on the Siemens Advia Centaur® CP Immunoassay System (Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA) via the Siemens Troponin-I-Ultra assay test

(Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA) (URL= 0.04 ng/mL).

The reduced cobalt to albumin binding capacity (IMA level) was analyzed using the rapid and colorimetric method proposed by Bar-Or et al.[14] in which 200 µL of the patient's serum was placed into glass tubes and 50 µL of 0.1% cobalt chloride ($CoCl_2.6H_2O$) in H_2O (Sigma-Aldrich, St. Louis, MO, USA) was added. After gentle shaking, the solution was left for 10 minutes to ensure sufficient binding, and 50 µL of dithiothreitol (DTT) (Sigma-Aldrich, St. Louis, MO, USA) in 1.5 mg/mL H_2O was added as a colorizing agent. The reaction was quenched two minutes later by adding 1.0 mL of 0.9% sodium chloride (NaCl). Next, a colorimetric control was prepared for the pre- and postoperative serum samples, and for the colorimetric control samples, 50 µL of distilled water was substituted for the 50 µL of 1.5 mg/mL DTT. The absorbance of the specimens was analyzed at 470 nm using a Shimadzu Recording UV-1601 spectrophotometer (Shimadzu Medical Systems Oceania Pty, Ltd., Auburn, N.S.W., Australia), and we then compared the color of the DTT specimens with the color of the control samples, with the results being given as absorbance units (ABSUs).

Statistical analysis

Descriptive statistical analysis was applied to all the studied variables. Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range, as appropriate. The group means for the continuous variables were compared using either Student's t-test or the Mann-Whitney U test. Furthermore, we utilized either a paired samples t test or the Wilcoxon signed-rank test for dependent continuous variable analyses. Categorical variables were expressed as percentages and were compared using a chi-square test. A two-tailed value of $p<0.05$ was considered to be statistically significant.

RESULTS

As previously mentioned, PMI was observed in eight (16%) patients while 42 (84%) did not have this condition (non-PMI group). The two groups were similar in age, gender, and body surface area (BSA) (Table 1), but the hospital stays of the PMI group were longer than for the non-PMI group (p=0.014) (Table 2). In addition, a hospital death occurred in the non-PMI group.

The IMA levels preoperatively and at 20 minutes after ACC were also similar in the PMI and non-PMI groups (p=0.071 and p=0.393, respectively). However, the IMA levels of the PMI group at 30 minutes and at three, six, and 12 hours after declamping were higher (p=0.002, p=0.048, p=0.023, and p=0.007, respectively), but at 24 hours after declamping, the IMA levels were similar in the two groups (p=0.221) (Table 3).

With regard to PMI development, the IMA had a cut-off value of 0.904 with 75% sensitivity and 72.2% specificity 30 minutes after declamping, whereas three hours after declamping, it had a cut-off value of 0.834 with 75% sensitivity and 50% specificity. Moreover, in both groups, the IMA levels 30 minutes after ACC were higher when compared to the preoperative IMA levels (p=0.038 and p=0.0001, respectively).

DISCUSSION

In spite of improvements on the part of surgeons and the development of new operative techniques and devices, PMI after CABG is still a serious and frequent complication,[3-5] and the effective management of patients after heart surgery is dependent on quickly evaluating the perioperative myocardial damage.[7] Therefore, it is important to determine the PMI in the early period.

Ischemia-modified albumin is one of the most reliable markers for myocardial ischemia, and several studies have shown that this condition is closely related to IMA.[8,10,12] In addition, IMA is recognized as a biomarker of temporary myocardial ischemia induced by coronary vasospasm.[15] Moreover, during primary percutaneous coronary intervention (PCI), IMA has been identified as an independent predictor of incomplete ST-segment resolution.[16] Sinha et al.[17] also noted increased IMA levels in patients who experienced chest pain and ischemic ECG changes during PCI. In our study, the IMA levels at 20 minutes after ACC increased significantly in the two groups when the preoperative IMA levels were compared, which supports the fact that the IMA levels are significantly elevated when myocardial ischemia occurs during ONCABG.

Other studies have found that IMA, which increases almost immediately after ischemia, was superior to other necrosis markers for diagnosing ACS at admission.[8,9,18,19] Moreover, in a study composed of 538 patients, the IMA showed 100% sensitivity in the final diagnosis of acute myocardial infarction (AMI).[18] Furthermore, for patients who were admitted to the emergency room within three hours after the onset of chest pain, IMA was shown to be superior to 12-lead ECG, cardio troponin T (cTnT), and cTnI for diagnosing ACS.[9,19]

Table 1. Demographic data of the groups

	Non-PMI (n=42)			PMI (n=8)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			64.1±10.3			65.9±8.6	0.658
Number of males	34	81		7	87.5		0.659
Body surface area (m^2)			1.8±0.1			1.8±1.0	0.262
Urea (mg/dL)			38.1±12.2			38.3±12.9	0.982
Creatinine (mg/dL)			0.9±0.3			1.1±0.2	0.204
Alanine aminotransferase (U/L)			24.1±12.9			24.4±11.5	0.962
Aspartate aminotransferase (U/L)			28.4±11.5			25.1±6.8	0.444
Angiotensin-converting enzyme inhibitors	16	38.1		4	50.0		0.697
Calcium antagonists	1	2.4		1	12.5		0.297
Beta blockers	11	26.2		2	25.0		0.944
Nitrates	7	16.7		0	0		0.213
Diuretics	4	9.5		0	0		1.000
Hypertension	28	66.7		8	100.0		0.054
Diabetes mellitus	13	31.0		2	25.0		0.736
Chronic obstructive pulmonary disease	5	11.9		2	25.0		0.328
Peripheral arterial disease	3	7.1		0	0		1.000
Cerebrovascular disease	2	4.8		0	0		1.000
Smokers	9	21.4		4	50.0		0.091
Alcohol users	1	2.4		0	0		1.000
Canadian Cardiovascular Society classification							
Class 2	28	66.7		4	50.0		0.368
Class 3	14	33.3		4	50.0		0.368
Left ventricular ejection fraction			54.5±9.5			51.3±10.9	0.387
Left main coronary artery disease	3	7.1		0	0		1.000

PMI: Perioperative myocardial infarction; SD: Standard deviation.

Perioperative myocardial ischemia may occur at varying degrees after cardiac surgery and can be identified early via IMA.[10] Dong et al.[11] found that the IMA levels at the third postoperative hour in OPCAB patients were higher in cases that involved PMI. In our study, there were similar IMA levels at 20 minutes after ACC and preoperatively in both the PMI and non-PMI groups. However, at 30 minutes and at three, six, and 12 hours after declamping, the IMA levels of the PMI group were significantly higher. In the end, all of our findings suggest that IMA may be used as an early marker for the diagnosis of PMI in ONCABG patients.

Irreversible damage to the myocardial tissue due to either mechanical or ischemic injury can lead to the destruction of the cell membrane and the contractile apparatus. In turn, this leads to the release of classic cardiac markers into extracellular space.[3,7]

Table 2. Perioperative variables of the groups

	Non-PMI (n=42)			PMI (n=8)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Number of grafts			2.95±0.94			2.88±0.64	0.824
Left internal mammary artery use	34	85.7		8	100.0		0.254
Cardiopulmonary bypass time (minutes)			97.57±28.53			113.75±42.00	0.181
Aortic cross-clamp time (minutes)			46.38±20.25			63.13±23.82	0.093
Intensive care unit stay (hours)			26.12±15.17			51.13±30.64	0.055
Hospital stay (days)			5.76±1.21			7.00±1.51	0.014
Hospital deaths	1	2.4		0	0		1.000

PMI: Perioperative myocardial infarction; SD: Standard deviation.

Table 3. Cardiac troponin I and ischemia-modified albumin levels of the groups

	Non-PMI (n=42)			PMI (n=8)			
	Median	IQR	Mean±SD	Median	IQR	Mean±SD	*p*
Cardiac troponin I values (ng/mL)							
Preoperative	0.0175	0.03		0.0180	0.02		0.557
48 hours after declamping	1.083	1.47		6.78	9.36		0.003
Ischemia-modified albumin values							
Preoperative			0.696±0.14			0.797±0.14	0.071
20 minutes after aortic cross-clamp			0.918±0.10			0.951±0.06	0.393
30 minutes after declamping			0.833±0.11			0.970±0.09	0.002
3 hours after declamping			0.823±0.11			0.907±0.11	0.048
6 hours after declamping			0.794±0.11			0.904±0.15	0.023
12 hours after declamping			0.789±0.11			0.910±0.10	0.007
24 hours after declamping			0.757±0.10			0.818±0.17	0.221

PMI: Perioperative myocardial infarction; IQR: Interquartile range; SD: Standard deviation.

The *in vivo* production of IMA, on the other hand, can be interpreted as an effective endogenous response to the ischemia,[20] and during PCI, it has been shown that it can be an early marker of myocardial ischemia as well as an indicator of both the size and duration of the ischemia.[21] During PCI, the increased IMA levels parallel those of transmyocardial lactate, which is the gold standard for ischemia.[22] However, IMA is currently the most reliable biomarker for the early detection of ischemia before the onset of irreversible cardiac injury.[10]

Our results showed that elevated IMA levels can be used to detect myocardial ischemia and early myocardial necrosis in ONCABG patients. In addition, IMA can be utilized to predict myocardial necrosis in ONCABG patients, especially when it is ischemic in origin. However, the predictive value of IMA as an early marker for PMI in ONCABG patients needs to be confirmed via large-scale prospective studies.

Conclusion

While this study involved a relatively small sample size, we believe that our findings indicate the very real possibility that IMA may be an effective marker for the early identification of PMI in ONCABG patients, and it is our hope that these results will encourage further research on this topic. In addition, more trials are needed to evaluate the diagnostic role that IMA plays in PMI.

Declaration of conflicting interests

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REFERENCES

1. Lafci G, Cagli K, Özcan F. Coronary artery bypass graft surgery: an update. Turk Gogus Kalp Dama 2014;22:211-5.
2. Koksal C, Kudsioglu T, Yapici N, Altuntas Y, Tuncel Z, Aykac Z. A comparison of preconditioning effects of propofol and desflurane on myocardial protection in cardiac surgery. Turk Gogus Kalp Dama 2013;21:371-7.
3. Peivandi AA, Dahm M, Opfermann UT, Peetz D, Doerr F, Loos A, et al. Comparison of cardiac troponin I versus T and creatine kinase MB after coronary artery bypass grafting in patients with and without perioperative myocardial infarction. Herz 2004;29:658-64.
4. Onorati F, De Feo M, Mastroroberto P, Cristodoro L, Pezzo F, Renzulli A, et al. Determinants and prognosis of myocardial damage after coronary artery bypass grafting. Ann Thorac Surg 2005;79:837-45.
5. Noora J, Ricci C, Hastings D, Hill S, Cybulsky I. Determination of troponin I release after CABG surgery. J Card Surg 2005;20:129-35.
6. Tzimas PG, Milionis HJ, Arnaoutoglou HM, Kalantzi KJ, Pappas K, Karfis E, et al. Cardiac troponin I versus creatine kinase-MB in the detection of postoperative cardiac events after coronary artery bypass grafting surgery. J Cardiovasc Surg (Torino) 2008;49:95-101.
7. Petzold T, Feindt P, Sunderdiek U, Boeken U, Fischer Y, Gams E. Heart-type fatty acid binding protein (hFABP) in the diagnosis of myocardial damage in coronary artery bypass grafting. Eur J Cardiothorac Surg 2001;19:859-64.
8. Gaze DC. Ischemia modified albumin: a novel biomarker for the detection of cardiac ischemia. Drug Metab Pharmacokinet 2009;24:333-41.
9. Shen XL, Lin CJ, Han LL, Lin L, Pan L, Pu XD. Assessment of ischemia-modified albumin levels for emergency room

diagnosis of acute coronary syndrome. Int J Cardiol 2011;149:296-8.
10. Sbarouni E, Georgiadou P, Voudris V. Ischemia modified albumin changes - review and clinical implications. Clin Chem Lab Med 2011;49:177-84.
11. Dong SY, Wang XJ, Xiao F, Wang J, Li YF, Li Y. Detection of perioperative myocardial infarction with ischemia-modified albumin. Asian Cardiovasc Thorac Ann 2012;20:252-6.
12. Pantazopoulos I, Papadimitriou L, Dontas I, Demestiha T, Iakovidou N, Xanthos T. Ischaemia modified albumin in the diagnosis of acute coronary syndromes. Resuscitation 2009;80:306-10.
13. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. Circulation 2012;126:2020-35.
14. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med 2000;19:311-5.
15. Cho DK, Choi JO, Kim SH, Choi J, Rhee I, Ki CS, et al. Ischemia-modified albumin is a highly sensitive serum marker of transient myocardial ischemia induced by coronary vasospasm. Coron Artery Dis 2007;18:83-7.
16. Dominguez-Rodriguez A, 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;203:576-80.
17. 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;107:2403-5.
18. Collinson PO, Gaze DC, Bainbridge K, Morris F, Morris B, Price A, et al. Utility of admission cardiac troponin and "Ischemia Modified Albumin" measurements for rapid evaluation and rule out of suspected acute myocardial infarction in the emergency department. Emerg Med J 2006;23:256-61.
19. 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;21:29-34.
20. Lippi G, Montagnana M, Guidi GC. Albumin cobalt binding and ischemia modified albumin generation: an endogenous response to ischemia? Int J Cardiol 2006;108:410-1.
21. 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;92:322-4.
22. 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;92:1852-3.