D-dimer Level is an Early Marker of Ischaemia/reperfusion Injury After Coronary Artery Bypass Surgery

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ABSTRACT

Introduction: Myocardial Ischaemia-Reperfusion (I-R) injury produces a spectrum of clinical cardiovascular outcomes after cardiac surgery. The pathogenesis of I-R injury is complex and involves the activation and amplification of several systemic and local proinflammatory pathways. The process of restoring blood flow to the ischaemic myocardium can induce injury and paradoxically reduce the beneficial effects of myocardial reperfusion. The objective of this study was to determine the correlation between cardiac markers such as the Mb fraction of the creatine kinase (CK-MB), troponin I (cTnI) and D-dimer levels as a marker of myocardial injury secondary to I-R injury after coronary artery bypass surgery.

Patients and Methods: Herein, a prospective study was designed that included 50 consecutive coronary artery bypass grafting (CABG) patients. Pre and postoperative blood samples were taken due to study protocol and such markers as Mb fraction of the creatine kinase (CK-MB), troponin I (cTnI) and D-dimer were measured.

Results: All three markers were significantly elevated in postoperative blood samples. The D-dimer level reached its peak at the first and another peak at 12th hour postoperatively. However, the peak serum values of CK-MB and cTnI occurred at 6th and 12th hour, respectively.

Conclusion: We demonstrated that D-dimer levels as a marker of generated thrombin during reperfusion correlated with other well-known biochemical markers of myocardial damage in the postoperative period. In other words, D-dimer levels may stand as a marker of I-R-induced myocardial damage.

Key Words: Myocardial reperfusion injury; fibrin fragment D; thrombin

D-dimer Düzeyi Koroner Arter Baypas Cerrahisinden Sonra İskemi/Reperfüzyon Hasarının Bir Bulgusudur

ÖZET

Giriş: Miyokardiyal İskemi-Reperfüzyon (I-R) hasarı kalp cerrahisi sonrası birçok kardiyovasküler duruma neden olmaktadır. I-R'nin patogenezi oldukça karışık bir süreç olup, birçok sistemik ve lokal proinflamatuvar yolağın uyarılmasını ve düzenlenmesini içerir. İskemik miyokardiyuma tekrar sağlanan kan akımı paradoksal olarak reperfüzyonun faydalı etkilerini azaltabilir. Bu çalışmanın amacı miyokardiyal hasarın birer göstergesi olarak, I-R'de kreatin kinaz MB (CK-MB) ve troponin I (cTnI) ile D-dimer seviyeleri arasındaki ilişkiyi ortaya koymaktr.

Hastalar ve Yöntem: Çalışmamız prospektif olarak tasarlanmış ve 50 ardışık CABG hastası çalışmaya dahil edilmiştir. Ameliyat öncesi ve sonrası kan örnekleri çalışma protokolüne uygun olarak alınmış ve CK-MB, cTnI ve D-dimer değerleri ölçülmüştür.

Bulgular: CK-MB, cTnI ve D-dimer değerlerinin postoperatif dönemde anlamlı olarak yükseldiği tespit edildi. D-dimer seviyeleri ameliyat sonrası ilk zirve değerine 1. saatte, ikinci zirve değerine ise 12. saatte ulaştı. Ancak CK-MB ve cTnI ise zirve değerlerine sırası ile 6. ve 12. saatlerinde ulaştı.

Sonuç: Reperfüzyon sırasında oluşan trombinin bir göstergesi olan D-dimer seviyeleri, ameliyat sonrası dönemde miyokardiyal hasarın göstergesi olarak kabul edilen diğer iki belirteçe paralel olarak yükselmiştir. Başka bir deyiş ile D-dimer I-R aracılı miyokardiyal hasarın bir göstergesi olarak değerlendirilebilir.

Anahtar Kelimeler: Miyokardiyal reperfüzyon hasarı; fibrin fragmanı D; trombin

INTRODUCTION

Myocardial Ischaemia-Reperfusion (I-R) injury produces a spectrum of clinical cardiovascular outcomes after cardiac surgery. Aortic cross-clamping induces myocardial ischaemia during coronary artery bypass surgery, however, restoring blood flow to the ischaemic myocardium can induce injury. This phenomenon was first mentioned in the 1960s by Jennings et al. in canine myocardium[1]. They reported cell swelling, contracture of myofibrils, disruption of the sarcolemma, and appearance of intra-mitochondrial calcium phosphate particles[2]. The pathogenesis of I-R injury is complex and involves the activation and amplification of several systemic and local proinflammatory pathways. The process of restoring blood flow to the ischaemic myocardium can induce injury and paradoxically reduce the beneficial effects of myocardial reperfusion. The injury culminates in the death of those cardiac myocytes that were viable before myocardial reperfusion. In any circumstance, this may lead to a spectrum of clinical manifestations, from myocardial stunning to permanent organ dysfunction and failure[3]. The use of cardiac markers in the diagnosis of myocardial injury is to estimate the size or severity of the injury due to their release from the myocardium during cardiac surgery. The markers of enzymatic activity include aspartate aminotransferase, creatine kinase (together with isoenzymes and isoforms), and lactate dehydrogenase and isoenzymes; the nonenzymatic markers are myoglobin and troponin T[4]. Troponin I is the most sensitive biochemical marker for the diagnosis of minimal myocardial damage and is, therefore, a good marker of the quality of myocardial protection[5]. Contribution of thrombin to myocardial I/R injury after coronary artery bypass surgery has been made evident through clinical and experimental animal studies[6,7]. Reperfusion causes a rapid increase in thrombin generation, which is associated with postoperative myocardial damage-impaired haemodynamic recovery. Thrombin has direct potentially adverse effects on the endothelium and on cardiomyocytes, independent of its procoagulant effects, which can be a possible mediator of I-R injury. Thrombin is generated due to I/R injury that converts fibrinogen to fibrin and leads to fibrinolysis. The end-point is the elevation of fibrin degradation products, especially the most popular one, D-dimer. The objective of this study was to determine the correlation between cardiac markers, such as the Mb fraction of the creatine kinase (CK-MB), cTnI and the D-dimer levels, as a marker of myocardial injury secondary to I-R injury after coronary artery bypass surgery.

PATIENTS and METHODS

Study Population

This study was prospectively performed at the Clinic of Cardiovascular Surgery at the Kartal Kosuyolu Heart Educa-tion and Research Hospital, between June 2019 and August 2019. Approval from the institutional ethical committee and written informed consent from each patient were obtained. The study population consisted of 50 consecutive patients who were scheduled for primary, elective, on-pump coronary artery bypass grafting (CABG). Exclusion criteria were as follows: concomitant valve or other cardiac surgery; neoplastic, infectious, connective tissue or inflammatory diseases; use of warfarin, unfractionated or low-molecular-weight heparin, or aspirin for < 5 days prior to the surgery; renal failure; abnormal preoperative international normalised ratio; anaemia; and thrombocytopenia. The operative risk was evaluated according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE)[8].

Surgical Technique

Management of CPB and induction of anaesthesia include weight-related doses of fentanyl, midazolam and rocuronium along with inhalational anaesthesia using sevoflurane where appropriate. The maintenance of anaesthesia was similar for all patients. Before CPB, all patients received a loading dose of heparin (3 mg/kg) to achieve an activated clotting time (ACT) of longer than 480 seconds and additional heparin was given to maintain the ACT. Extracorporeal circulation was established through cannulation of the ascending aorta and vena cava, and membrane oxygenators were also used. All the interventions were performed during CPB with mild systemic hypothermia and a temperature of 28-32°C was maintained. After cross-clamping the ascending aorta, cardioplegic arrest was achieved in all patients via an antegrade coronary infusion of 300 mL of high-potassium solution. Intermittent antegrade or continuous retrograde isothermal hyperkalaemic blood cardioplegia perfusion was administrated for myocardial protection every 20 minutes. No topical cooling of the heart was performed. Heparin was reversed by protamine (3.5 mg/kg) at the end of CPB. Surgical techniques were standardised and did not change during the study period.

Blood Samples

Serial arterial blood samples were collected at 8 time points (A-F): preoperatively (A); 1 hour after the release of the aortic clamp (B); 6 hours after the release of the aortic clamp (C); 12 hours after the release of the aortic clamp (D); 24 hours postoperatively (E); 48 hours postoperatively (F). Samples A through E were collected through a radial artery catheter and sample F was collected either through an atraumatic venepuncture or through a radial artery catheter. All samples were collected in vacuum test tubes with 3.8% sodium citrate (Venoject; Terumo Europe N.V., Leuven, Belgium). The first 5 mL of each sample was discarded. The samples were cooled on ice and centrifuged

(1500 g for 10 minutes) at +4°C. Plasma was separated and stored at -80°C.

Definition of Reperfusion

In this work, the term "reperfusion" defines the period between the release of the aortic clamp and 6 hours after release of the aortic clamp (C). It includes, therefore, the true vascular reperfusion of the ischaemic cardiac vascular bed, the period of supportive CPB after the release of the aortic clamp, and the first few hours of circulatory convalescence after CPB.

Laboratory Analysis

Serum CK-MB and cTnI levels were measured with the use of a quantitative electro-chemi-luminescence immunoassay, the results of which were determined using a calibration curve. The level of D-dimer in plasma was assessed with the use of a quantitative and automated immunoassay. A microlatex suspension was covalently coated with two complementary monoclonal antibodies that were specific for fibrin degradation. The assay was performed by mixing 50 mL of undiluted plasma with 100 mL of reaction buffer, and the test was initiated with 150 mL of latex suspension. The change in absorbance, measured at 540 nm on STA Compact analyser (Diagnostica Stago, Asnie` res, France), was automatically recorded for 140 seconds and represented a direct relationship to the D-dimer concentration in the specimen. The results were expressed in ng/mL of fibrinogen equivalent units. The normal level of D-dimer in the adult population is generally less than 500 ng/mL.

Postoperative Management and Definitions

Hospital mortality was defined as death occurring for any reason within 30 days after the operation. The definition of myocardial infarction (MI) is currently based on biochemical markers of myonecrosis but does not include the thresholds for cardiac biomarkers in the diagnosis of MI after CABG. Therefore, both cardiac biomarker levels as continuous variables and the appearance of new pathological Q-waves in the electrocardiogram were registered. Preoperative and postoperative electrocardiograms of all patients were analysed by two observers who were blinded to the CK-MB and cTnI values of the patients. New pathological Q-waves were identified according to the criteria of a recent consensus document. Respiratory failure was defined as pulmonary insufficiency requiring intubation and ventilation for a period of 72 hours or more at any time during the postoperative stay. For patients who were placed on and taken off ventilation several times, the total of these episodes was of a duration of 72 hours or more. The presence of chronic obstructive pulmonary disease was assumed in patients who required chronic (more than 3 months) bronchodilator therapy to avoid disability from obstructive airway disease, had a forced expiratory volume in 1 second less than 75 % of the predicted

value or less than 1.25 L, or had PaO_2 in their room air at less than 60 mmHg or $PaCO_2$ at more than 50 mmHg. Low cardiac output syndrome (LCOS) was defined as a cardiac index of 2.0 L/minute per m^2, requiring pharmacological support and/or counter-pulsation. Postoperative renal dysfunction was defined as an increment in the creatinine level of ≥ 1 mg/dL as compared with the preoperative value. The presence of a neurologic complication as any focal brain lesion was confirmed by clinical findings or a computed tomography study of the brain.

Statistical Analysis

All data were expressed as mean ± SD unless otherwise specified. Differences between preoperative and postoperative values within a group were determined using the Friedman and Wilcoxon sign test that did not satisfy the supposition of normality. Categorical variables were analysed by the Chi-square and Fisher's exact test. Correlations between continuous variables were performed using the Spearman rank correlation test. A two-tailed p-value of 0.05 was considered statistically significant. SPSS version 23.0 software (SPSS, Chicago, IL) was used for all statistical analyses.

RESULTS

There were 42 men and 8 women whose ages ranged from 41 years to 79 years (mean: 60.80 ± 10.27 years). All of the patients had undergone an operation with normal levels of cardiac enzymes. The demographic and clinical data are summarised in Table 1. In the intraoperative evaluation, the qualities of the vessels were good in 58%, moderate in 34%, and bad in 8% of all cases. The intraoperative characteristics of the patients are reported in Table 2. Seven patients had transient atrial fibrillation due to respiratory dysfunction. One in-hospital mortality case was observed due to LCOS. All of the patients recovered fully. The postoperative characteristics of the patients are shown in Table 3.

Laboratory Findings

The increase in CK-MB measurements at the postoperative 1st, 6th, 12th, 24th, and 48th hour were significant (p< 0.01) when compared to preoperative levels. The maximum plasma level of CK-MB was encountered at the postoperative 12th hour (Figure 1). The increase in cTnI levels at postoperative 1st, 6th, 12th, 24th, and 48th hour was significant (p< 0.01) when compared to the preoperative levels. Maximum plasma levels of cTnI were encountered at the postoperative 6th hour (Figure 2). The increase in D-dimer levels at the postoperative 1st, 6th, 12th, 24th, and 48th hour were significant (p< 0.01) when compared to the preoperative levels. The maximum plasma level of D-dimer was encountered at the postoperative 1st hour (Figure 3). The values of all markers in each hour and the relation between the

Table 1. Demographic values of patients

	n	%
Sex		
Male	42	84.0
Female	8	16.0
Diabetes mellitus	32	64.0
Dyslipidaemia	27	54.0
Smoking habbit	39	78.0
Hypertension	27	54.0
COPD	7	14.0
Peripheric arterial disease	11	22.0
Type of procedure		
Elective	36	72.0
Preferential	14	28.0
Emergency	-	-
New MI	13	26.0
LVEF		
Good	36	72.0
Moderate	12	24.0
Bad	2	4.0
Euro SCORE		
Low risk	21	42.0
Moderate risk	24	48.0
High risk	5	10.0
	Min-Max	**Mean ± SD (median)**
Age	41-79	60.80 ± 10.26
Number of critical vessels in angiography	1-3	2.48 ± 0.64 (3)

COPD: Chronic obstructive pulmonary disease, New MI: New myocardial infarction, LVEF: Left ventricular ejection fraction.

Table 2. Intraoperative values

	n	%
The usage of IMA		
Yes	49	98.0
No	1	2.0
Quality of the vessels		
Good	29	58.0
Moderate	17	34.0
Bad	4	8.0
	Min-Max	**Mean ± SD (median)**
Number of vessels	1-4	2.46 ± 0.95 (3)
ACC (min)	11-85	42.10 ± 19.65
CPB (min)	19-146	71.62 ± 31.32

IMA: Internal mammarian artery, ACC (min): Aortic cross clamping (minute), CPB: Cardiopulmonary bypass.

Table 3. Postoperative complications

	n	%
LCOS	8	16.0
Perioperative MI	0	0.0
Bleeding revision	2	4.0
Postoperative respiratory dysfunction	5	10.0
Stroke	1	2.0
Mediastinitis	1	2.0
Mortality	1	2.0
	Min-Max	Mean ± SD (median)
Length of ICU stay (d)	1-16	2.62 ± 2.87
Length of hospital stay (d)	5-27	9.04 ± 4.60

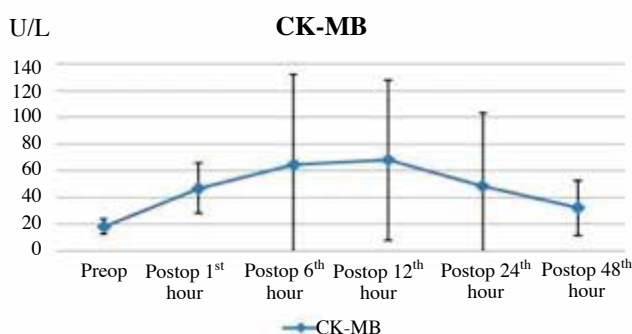LCOS: Low cardiac output syndrome, ICU: Intensive care unit, d: Day.

Figure 1. Serum levels of MB isoenzyme of creatine kinase (CK-MB) after coronary artery bypass grafting.
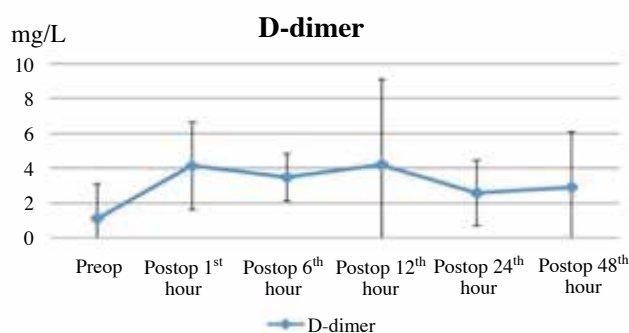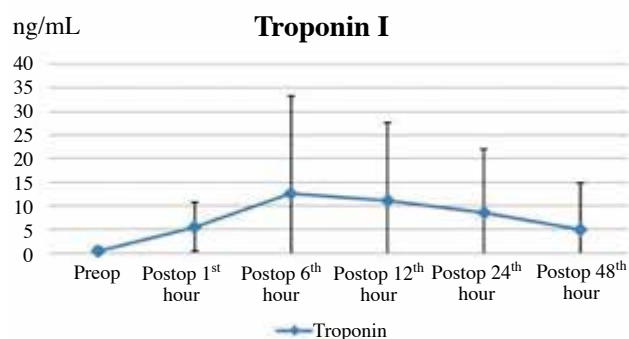

Figure 2. Serum levels of cTnI after coronary artery bypass grafting.

markers are shown in Table 4. The D-dimer level reached its peak at the 1st hour and another peak at the 12th hour postoperatively. However, the peak serum values of CK-MB and cTnI occurred at the 6th hour and 12th hour, respectively (Table 4).

Figure 3. Serum levels of D-dimer after coronary artery bypass grafting.

DISCUSSION

In current study, we demonstrated that D-dimer levels as a marker of generated thrombin during reperfusion correlated with other well-known biochemical markers of myocardial damage in the postoperative period. Secondly, D-dimer levels reached their peak levels at the 1st hour, which was earlier than CK-MB and cTnI. This suggested that D-dimer may be an early marker of I/R-induced myocardial injury after coronary artery bypass surgery.

The aim of every cardiac surgery should be to obtain a technically good result without producing myocardial damage. Perioperative myocardial damage may still produce life-threatening complications after CABG and be responsible for cardiovascular complications and mortality[9]. Surgically induced myocardial ischaemia secondary to aortic cross-clamping during CABG results from the reduction of coronary blood flow such that oxygen delivery to the myocardium is

Table 4. Association between the levels of CK-MB (MB fraction of the creatine kinase), cTnI (cardiac troponin I), and D-dimer

	CK-MB Mean ± SD	cTnI Mean ± SD	D-dimer Mean ± SD	+p
Preop	18.22 ± 5.60	0.30 ± 0.99	1.01 ± 1.99	
Postop 1st hr	46.98 ± 18.96	5.55 ± 5.19	4.13 ± 2.52	
Postop 6th hr	64.88 ± 67.45	12.65 ± 20.71	3.47 ± 1.36	**0.001**
Postop 12th hr	67.88 ± 60.12	11.07 ± 16.59	4.20 ± 4.89	
Postop 24th hr	48.20 ± 55.24	8.57 ± 13.48	2.57 ± 1.88	
Postop 48th ht	32.10 ± 20.75	4.99 ± 9.84	2.89 ± 3.19	

+: Friedman test. ** p< 0.0ts

insufficient. This provokes tissue injury that could be reversible or irreversible depending on the severity and duration of myocardial ischaemia or myocardial preservation strategies. After the aortic cross-clamp is removed, the heart is suddenly and globally reperfused with blood that is fully anticoagulated and characterised by a very high partial pressure of oxygen. And as a result, the cardiomyocytes may function normally, be stunned, or become dysfunctional from either necrosis or apoptosis due to I/R injury[10,11]. Reperfusion of ischaemic myocardium can exacerbate tissue injury, with loss or dysfunction of potentially salvageable or functional tissue[3,12]. Clinically, I/R injury after cardiac surgery can manifest as arrhythmia, myocardial stunning, low cardiac output and perioperative MI with increased mortality and prolonged hospital stay. Weman at el. demonstrated that in patients who died soon after CABG, the histologic evidence of I/R on autopsy is detected in 25-45% of patients[13].

La Due published the first account of the use of a biochemical marker in the study of myocardial injury in 1954[1]. The cardiac markers were used to find the extent and severity of myocardial injury. None of them is completely sensitive and specific for myocardial injury, particularly in the hours following the onset of symptoms. The similarity of the canine heart to the human heart has resulted in the canine heart being used as an experimental model for induced MI, in which cTnT and cTnI have been found to be sensitive and specific for cardiac injury as compared with lactate dehydrogenase and creatine kinase isoenzymes[14].

Thrombin has direct potentially adverse effects on the endothelium and on cardiomyocytes, which can be a possible mediator of ischaemia-reperfusion injury[15,16]. Thrombin generation due to I/R injury converts fibrinogen to fibrin, which leads to perioperative fibrinolysis and causes the elevation of fibrin degradation products, especially the most popular one, i.e., D-dimer[17]. Several experimental models of I/R suggest that thrombin plays a role as a mediator of myocardial I/R

injury[18,19]. A study by Jormalainen et al. in a porcine model of CPB showed that thrombin inhibition with hirudin, when added to standard heparin anticoagulation, improved immediate myocardial recovery and hemodynamics after I/R[7]. Erlich used a rabbit coronary ligation model to investigate the role of TF in acute myocardial I/R injury and denoted that direct thrombin inhibition with hirudin reduced the size of MI injury[6]. Since D-dimer is a measure of fibrinolysis and shows fibrin formation, D-dimer levels may measure thrombin level, which mainly acts on the fibrin-dependent pathway. In other words, the contribution of thrombin to I/R-induced myocardial damage after D-dimer levels may measure coronary artery bypass surgery. Although the association between the thrombin burst during reperfusion and myocardial damage has been demonstrated, the causal mechanisms for this phenomenon are not clear. It has been postulated that the most possible mechanism could be myocardial thrombotic microangiopathy.

In the current study, full heparinisation did not prevent profound thrombin generation, which was evident by a rise in D-dimer levels after the release of the aortic clamp. This occurred despite high ACT levels (> 600). In our cases, high ACT levels as a measurement of heparinisation helped us to ensure that any potential association between thrombin generation and myocardial damage could not be attributed to insufficient anticoagulation during CPB.

The early appearance of a marker released into the bloodstream soon after an injury may facilitate early diagnosis[20]. In our study, the maximal serum value of CK-MB occurred at the 12th hour, and serum levels of troponin I were maximum at the 6th hour after the operation in patients. Maximal serum values of D-dimer occurred in the 1st hour. Also, there was statistically significant relationship between CK-MB, cTnI and D-dimer levels after the removal of the cross-clamp. The interesting finding was that the D-dimer rise reached its peak at the 1st hour, which suggests that apart from being a marker of myocardial damage, D-dimer may be an

early marker of I/R-induced myocardial injury after coronary artery bypass surgery.

This study has certain limitations. It does not reveal the mechanisms by which thrombin could mediate myocardial damage. It is possible that the burst in thrombin generation occurred in vascular beds rather than in the myocardium. In order to show thrombin levels instead of D-dimer, which indirectly shows fibrin formation, analysing the prothrombin fragments' measurements could be more sensitive and indicative.

CONFLICT of INTEREST

The authors declare that there was no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: HE, KÇ, CK

Analysis/Interpretation: HE, CK, GK

Data Acquisition: HE

Writting: HE, ES, ÖY

Critical Revision: CK, GK

Final Approval: All of authors.

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