The significance of admission hs-CRP in patients undergoing primary percutaneous intervention for acute myocardial infarction

Akut miyokard infarktüsü nedeniyle primer perkütan girişim uygulanan hastalarda başvuru anındaki hs-CRP düzeyinin önemi

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Objective: We evaluated the role of admission high-sensitivity C-reactive protein (hs-CRP) level in estimating myocardial reperfusion and in-hospital adverse events in patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Study design: The study included 43 consecutive patients (34 males, 9 females; mean age 59±11 years) who underwent PCI for STEMI within six hours after the onset of symptoms. Coronary angiograms were evaluated with respect to TIMI flow grade, corrected TIMI frame count, and myocardial blush grade (MBG). Electrocardiograms obtained 90 min after PCI were analyzed for ST-segment resolution. In-hospital adverse events were recorded. The hs-CRP level was measured by immunonephelometry in blood obtained immediately before PCI.

Results: The mean hs-CRP level was 1.35±1.17 mg/dl. Based on the median hs-CRP value (0.98 mg/dl), 22 patients with a low hs-CRP level had a lower frequency of hypertension (p=0.047), decreased TIMI frame counts of the left anterior descending (p=0.010) and circumflex (p=0.033) arteries, a higher rate of ST resolution (p=0.000), improved MBG (p=0.015), and shorter hospitalization (p=0.028). Adverse events occurred in six patients (14%), in five of whom (5/21) the hs-CRP level was above 0.98 mg/dl. hs-CRP was significantly correlated with corrected TIMI frame counts of the left anterior descending (r=0.388, p=0.01) and circumflex arteries (r=0.336, p=0.027), length of hospitalization (r=0.357, p=0.019), and inversely correlated with MBG (r=-0.415, p=0.006). In multivariate regression analysis, hs-CRP was found to be an independent predictor of ST resolution (p=0.008). ROC analysis showed that a higher level of hs-CRP than 0.88 mg/dl predicted poor MBG with 73% sensitivity and 31% specificity (95% CI 0.577-0.899, p=0.01).

Conclusion: In STEMI patients undergoing primary PCI, high levels of admission hs-CRP are associated with poor myocardial perfusion and longer hospitalization.

Key words: Angioplasty, transluminal, percutaneous coronary; blood flow velocity; coronary circulation; C-reactive protein; electrocardiography; myocardial infarction; myocardial reperfusion; prognosis.

Amaç: Akut ST-segment yükselmeli miyokard infarktüsü (STEMI) nedeniyle primer perkütan girişim (PKG) yapılan hastalarda, başvuru anındaki yüksek duyarlıklı C-reaktif protein (hs-CRP) düzeyinin miyokard reperfüzyonu ve hastane içi istenmeyen olaylar açısından önemi değerlendirildi.

Çalışma planı: Semptomların ilk altı saatinde akut STEMI nedeniyle PKG uygulanan ardışık 43 hastanın (34 erkek, 9 kadın; ort. yaş 59±11) koroner anjiyogramlarında, TIMI akım derecesi, düzeltilmiş TIMI kare sayısı ve miyokardın boyanma derecesi (MBD) belirlendi. İşlem sonrası 90. dakika elektrokardiyogramları ST-segment düzelmesi açısından incelendi. Hastanede yatış süresince gelişen istenmeyen kardiyovasküler olaylar kaydedildi. Perkütan girişimden hemen önce alınan kanda, immün-nefelometrik yöntemle hs-CRP düzeyi ölçüldü.

Bulgular: Ortalama hs-CRP düzeyi 1.35±1.17 mg/dl bulundu. Ortanca değerine göre (0.98 mg/dl), hs-CRP düzeyi düşük olan grupta (n=22) hipertansiyon oranı daha düşük (p=0.047), sol ön inen ve sirkumfleks arterlerin TIMI kare sayıları daha az (sırasıyla, p=0.010 ve p=0.033), ST düzelmesi daha fazla (p=0.000), MBD daha iyi (p=0.015) ve hastanede yatış süresi daha kısa (p=0.028) bulundu. Altı hastada (%14) istenmeyen kardiyovasküler olay gelişti; bunların beşinde (5/21) hs-CRP 0.98 mg/dl'nin üzerindeydi. hs-CRP düzeyi ile sol ön inen arter (r=0.388, p=0.01) ve sirkumfleks arterin (r=0.336, p=0.027) düzeltilmiş TIMI kare sayıları ve hastanede yatış süresi (r=0.357, p=0.019) arasında anlamlı pozitif; MBD arasında (r=-0.415, p=0.006) anlamlı negatif ilişki saptandı. Çoklu regresyon analizinde hs-CRP, ST düzelmesinin bağımsız göstergesi idi (p=0.008). ROC analizinde, 0.88 mg/dl'den yüksek hs-CRP'nin kötü MBD'yi tahmin etmedeki duyarlığı %73, özgüllüğü %31 bulundu (%95 güven aralığı 0.577-0.899, p=0.01).

Sonuç: Primer PKG uygulanan STEMI hastalarında başvurudaki yüksek hs-CRP düzeyi kötü miyokard perfüzyonu ve hastanede yatış süresinin uzaması ile ilişkilidir.

Anahtar sözcükler: Anjiyoplasti, transluminal, perkütan koroner; kan akım hızı; koroner dolaşım; C-reaktif protein; elektrokardiyografi; miyokard infarktüsü; miyokard reperfüzyonu; prognoz.

Received: 25.07.2008 *Accepted:* 21.11.2008

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Inflammation plays a key role in the development of atherosclerosis and in the pathogenesis of acute coronary syndrome.[1] Myocardial damage, which occurs during acute myocardial infarction (AMI) induces the release of proinflammatory cytokines by means of immune, vascular and interstitial tissues. These cytokines repair the damaged tissue and provide adaptation for the new situation by acting in several biological processes such as cell enlargement and migration. However, when released excessively, they may lead to tissue damage and eventually to the development of undesirable events such as heart failure and death.[2]

C-reactive protein (CRP), one of the markers of systemic inflammatory process acts as an indicator for the development of the risk of any coronary events in healthy individuals[3] and is associated with increased short and long term cardiovascular mortality in patients with ST-segment elevation myocardial infarction (STEMI)[4] and acute coronary syndrome without ST-segment elevation.[5] Other conditions associated with high CRP level are the extent of the infarction,[6] presence of multiple complex coronary lesion detected by angiography,[7] post-AMI heart failure,[8] new onset atrial fibrillation[9] and cardiac rupture.[10]

C-reactive protein level was also assessed in patients who underwent primary percutaneous intervention (PCI). High CRP level before the procedure was considered a strong indicator of early complications in patients who underwent primary PCI due to acute STEMI.[11] Similarly, it was demonstrated that myocardial damage and 18-month mortality rate was higher in patients with high CRP levels before reperfusion, in the patient group which underwent primary PCI or thrombolytic treatment.[12]

In this study, the role of high-sensitivity C-reactive protein (hs-CRP) level at admission in estimating myocardial reperfusion markers and in-hospital adverse events in patients with acute STEMI undergoing primary PCI within six hours after the onset of symptoms was evaluated.

PATIENTS AND METHODS

Forty-three consecutive patients (34 male, 9 female; mean age 59±11 years) who underwent primary PCI due to STEMI within six hours after the onset of symptoms were included between May-November 2007. Acute STEMI diagnosis was confirmed by the ACC/AHA/ESC criteria.[13] All patients had TIMI 0-2 flow in their involved vessels before the intervention.

Patients with a coronary bypass history, saphenous vein graft lesions, those with cardiogenic shock, left main coronary artery disease, those with a history of AMI, surgical intervention or trauma within the last one month, those with chronic inflammatory, renal, endocrine disease, any active infectious disease, malignancies, and whose hs-CRP levels were >10 mg/dl were excluded from the study. The study protocol was approved by the local ethics committee of our hospital and informed consent was obtained from every patient.

A 12-lead surface electrocardiogram (ECG) at baseline visit and 90 minutes after PCI were performed for each patient. These ECG results were assessed by two investigators blinded to hs-CRP levels in terms of >70% correction of ST-segment elevation.

Primary PCI with standard techniques was applied to all patients. Routine stent procedure was performed on the involved vessel following coronary angiography and balloon angioplasty. Bare metal stent was applied (Ephesos II, Nemed, Istanbul, Turkey) to all patients. Two interventional cardiologists blinded to clinical and laboratory findings of the patients examined the following: TIMI flow rates of the involved vessel before and after the procedure, corrected TIMI frame counts of major epicardial vessels excluding the involved ones before the procedure, corrected TIMI frame counts of the involved vessel obtained with TIMI 3 flow after the procedure, and myocardial blush grade (MBG). Previous grading system was applied in defining TIMI flow rate (TIMI 0: no flow or perfusion distal to the obstruction; TIMI 1: penetration available distal to the obstruction, but no perfusion; TIMI 2: partial perfusion; TIMI 3: full perfusion)[14] Corrected TIMI frame count was defined by the Gibson et al.'s method. (The angiographic frame count for distal of standard beds of the contrast agent infused was corrected by dividing the count of left anterior descending artery by 1.7). The myocardial blush grade (MBG) was defined as follows: MBG 0: no or less myocardial blush; MBG 1: myocardial blush by contrast agent; however the blush remains until the next blush injection since the contrast agent cannot leave the microvascular structure. MBG 2: myocardial blush by contrast agent; however blush is apparent after the injection since it is washed slowly. MBG 3: normal myocardial blush and wash by contrast agent and no or less blush in the myocardium after the injection.[15]

Following their admission to the emergency unit all patients received aspirin 300 mg, heparin 70-100 IU/kg and clopidogrel 600 mg challenge dose. The use of glycoprotein IIb/IIIa receptor antagonist was left to the surgeon's choice. Every patient was recommended to use clopidogrel 75 mg/day for at least one month.

The hs-CRP levels in peripheral venous blood samples collected immediately after electrocardiography were identified by the immunonephelometry method (IMMAGE Immunochemistry Systems; Beckman Coulter, California, USA).

The hospitalization period for every patient and all adverse cardiovascular events occurred during this period (death, recurrent myocardial infarction, recurrent symptomatic myocardial ischemia, stent thrombosis,

stroke, and hemorrhage) were recorded. The ACC/AHA/ESC criteria were used to diagnose recurrent myocardial infarction.[13] Recurrent myocardial ischemia was defined as chest pain lasting more than 10 minutes and chest pain associated with ST-segment deviation. The Academic Research Consortium definition was used to diagnose and grade stent thrombosis.[16] The TIMI Hemorrhage Classification Diagram was used to grade severe and mild hemorrhage.[17]

Statistical assessment: The SPSS 13.0 package program was used for statistical assessment. Results were defined by mean±standard deviation (SD) or percentage. The Chi square test and Fischer *exact* test were used to identify the difference between groups, while the t-test and Mann-Whitney U-test were used for independent samples. The Pearson and Spearman correlation tests were used for correlation analysis. ROC analyses were used to identify hs-CRP level for the cut point of poor MBG. A multivariate logistic regression analysis including all variables (age, sex, symptom duration, door-to-balloon time, TIMI flow rate before and after the procedure, corrected TIMI frame counts, MBG, ST-segment correction, hs-CRP level, in-hospital adverse cardiovascular events) was performed to determine independent indicators of myocardial blush grade, improvement in ST-segment elevation, and development of in-hospital adverse cardiovascular events. A p value of <0.05 was accepted as significant for all analyses.

RESULTS

Basic clinical and laboratory characteristics of the patients included in the study and results of percutaneous intervention are shown in Table 1. Following classification of patient groups according to their hs-CRP levels (0.98 mg/dl), below median hs-CRP level (n=22) and above median hs-CRP level (n=21), baseline clinical charac-

Table 1. Clinical characteristics, laboratory and percutaneous intervention data of the study groups

	Total (n=43)			hs-CRP <0.98 mg/dl (n=22)			hs-CRP ≥0.98 mg/dl (n=21)			
	Number	Percentage	Mean±SD	Number	Percentage	Mean±SD	Number	Percentage	Mean±SD	*P*
Age			59±11			58±10			61±12	0.316
Sex										0.650
Male	34	79.1		18	81.8		16	76.2		
Female	9	20.9		4	18.2		5	23.8		
Risk factors										
Diabetes mellitus	10	23.3		5	22.7		5	23.8		0.933
Hypertension	18	41.9		6	27.3		12	57.1		**0.047**
Hypercholesterolemia	15	34.9		7	31.8		8	38.1		0.666
Cigarette smoking	26	60.5		14	63.6		12	57.1		0.663
Family history	11	25.6		5	22.7		6	28.6		0.661
Medication used										
Aspirin	13	30.2		7	31.8		6	28.6		0.817
Statin	6	14.0		5	22.7		1	4.8		0.089
Angiotensin converting enzyme inhibitor	7	16.3		2	9.1		5	23.8		0.191
Angiotensin receptor blocker	4	9.3		2	9.1		2	9.5		0.961
Location of myocardial infarction										
Anterior	23	53.5		12	54.6		11	52.4		
Inferior	19	44.2		9	40.9		10	47.6		
Posterolateral	1	2.3		1	4.6		-			
Time from onset of symptoms (h)			3.3±1.7			2.9±1.6			3.7±1.7	0.093
Door-to-balloon time (min)			24.6±11.0			21.6±9.6			27.9±11.8	0.062
Involved vessel										
Left anterior descending artery	23	53.5		12	54.6		11	52.4		
Right coronary artery	17	39.5		8	36.4		9	42.9		
Circumflex artery	3	7.0		2	9.1		1	4.8		
Pre-procedure flow rate										
TIMI 0	28	65.1		12	54.6		16	76.2		
TIMI 1	6	14.0		3	13.6		3	14.3		
TIMI 2	9	20.9		7	31.8		2	9.5		
Baseline hs-CRP (mg/dl)			1.35±1.17			0.56±0.29			2.18±1.17	
Duration of hospitalization (day)			5.0±1.4			4.5±0.6			5.6±1.7	**0.028**

Table 2. Characteristics of percutaneous intervention in patient groups

	hs-CRP <0.98 mg/dl (n=22)	hs-CRP ≥0.98 mg/dl (n=21)	*p*
TIMI flow rate			
Before the procedure	0.77±0.92	0.33±0.65	0.081
After the procedure	2.77±0.43	2.57±0.67	0.248
TIMI frame count			
Left anterior descending artery	26.81±22.74	38.42±23.78	**0.010**
Circumflex artery	20.9±11.95	32.0±22.4	**0.033**
Right coronary artery	16.09±7.62	20.47±11.47	0.146
Correction of ST segment elevation (n, %)	19 (86%)	3 (14%)	**0.000**
Myocardial blush grade	0.54±0.50	0.19±0.40	**0.015**

teristics, PCI findings and in-hospital clinical results were compared. No difference was found in terms of age, sex, diabetes mellitus, hypercholesterolemia, family history, cigarette smoking, aspirin, statin, angiotensin converting enzyme inhibitor and angiotensin receptor blocker use. The frequency of hypertension (p=0.047) and duration of hospitalization (p=0.028) were significantly lower in the group with low hs-CRP level (Table 1).

Characteristics of percutaneous intervention are shown in Table 2. The results demonstrated that corrected TIMI frame counts of the left anterior descending artery and circumflex artery were lower (p=0.010 and p=0.033, respectively), ST-segment correction was higher (p=0.000), and the MBG was better (p=0.015) in patients with lower hs-CRP levels.

In-hospital adverse cardiovascular events developed in six patients (14%). One of the patients had acute and subacute thrombosis; one had recurrent symptomatic myocardial ischemia, two had mild and one had severe hemorrhage related to the intervention site. One of the patients with mild hemorrhage was given a glycoprotein IIb/IIIa receptor antagonist.

Patients with in-hospital adverse cardiovascular events had similar door-to-balloon time (28.3±12.1 min and 24.0±10.9 min; p=0.341) and TIMI MBG (0.17±0.40 0.40±0.49; p=0.267) and higher hs-CRP levels (2.17±1.08 mg/dl and 1.22±1.14 mg/dl; p=0.035) compared to patients without adverse events. On the other hand, only one of the 22 patients with hs-CRP level <0.98 mg/dl had adverse cardiovascular event and five of the 21 patients with higher hs-CRP levels had adverse cardiovascular events. However the difference did not reach a level of significance (p=0.068).

A significant positive relation was found between the hs-CRP level and corrected TIMI frame counts of the left anterior descending artery (r=0.388; p=0.01) and circumflex artery (r=0.336, p=0.027) and duration of hospitalization (r=0.357; p=0.019), whereas a significant negative relation was found between hs-CRP level and MBG (r=-0.415; p=0.006), in the correlation analysis. In addition to myocardial blush grade (MBG) and hs-CRP level, a significant negative relation was found between corrected TIMI frame counts of the left anterior descending artery (r=-0.447; p=0.003) and circumflex artery (r=-0.348; p=0.032), whereas a significant positive relation was found between post-procedure TIMI flow rate of the involved vessel (r=0.448; p=0.003). Furthermore, a significant positive relation was demonstrated between duration of hospitalization, age (r=0.429; p=0.004), hs-CRP level (r=0.357; p=0.019) and door-to-balloon time (r=0.329; p=0.031), while there was a significant negative relation regarding MBG (r=-0.310; p=0.043).

ROC analysis showed that a higher level of hs-CRP more than 0.88 mg/dl predicted a poor MBG with 73% sensitivity and 31% specificity (95% CI 0.577-0.899, p=0.01).

Multivariate regression analysis also showed that correction of ST-segment was an independent predictor of MBG (p=0.01), hs-CRP level was an independent predictor of correction of ST-segment elevation (p=0.008) and age was an independent predictor of develepment of adverse cardiovascular events (p=0.012).

DISCUSSION

C-reactive protein is a sensitive, but nonspecific acute phase reactant which is synthesized in liver in association with the cytokine release (particularly IL-6) induced by inflammation or tissue damage. Both inflammation at the atherosclerotic plaque site[18] and tissue necrosis at the infarction site[19] increases CRP level in acute coronary syndromes. In this study, in patients undergoing primary PCI for acute STEMI, the baseline visit hs-CRP level was found to be associated with markers suggesting poor myocardial perfusion according to the angiography and electrocardiography results and duration of hospitalization.

The major goal of reperfusion approaches performed in acute STEMI is to provide reperfusion of the myocardium in the infarction site beyond the involved epicardial vessel. Effective myocardial perfusion cannot be ensured due to microvascular damage[20] and reperfusion damage[21] even in patients with restored TIMI 3 flow in the involved vessel. The two most commonly used parameters in clinical evaluation of myocardial perfusion are electrocardiographic ST-segment correction and TIMI MBG.

Correction of the ST-segment is a parameter which gives information about the patency of the involved vessel and of the prognosis of myocardial infarction, and which can easily be obtained.[22] Studies have shown that patients with uncorrected ST-segment following angiographically effective primary PCI are at a risk for left ventricular dysfunction and mortality.[23] The hs-CRP level was found an independent predictor for ST-segment correction in our study. This data suggests that patients with high baseline visit hs-CRP levels are at risk for myocardial perfusion and eventually may have poor clinical prognosis following PCI.

TIMI MBG, another marker is based on qualitative assessment of the entry and exit of contrast agent to the myocardium. MBG which shows myocardial perfusion independent of epicardial blood flow gives prognostic data as well as epicardial flow.[15,24] Despite all supportive aggressive treatments, the rate of achieving TIMI MBG 3 following PCI was about 50%.[24,25] Similar to the literature, TIMI MBG was found to be poorer in patients with higher hs-CRP levels compared to those with lower levels and a negative significant relationship was found between hs-CRP level and TIMI MBG in our study. Multivariate analysis demonstrated that correction of ST-segment was the only variable associated with MBG. These findings suggest that hs-CRP level is associated with electro-cardiographically and angiographically poor myocardial perfusion and there is a complementary relation among different myocardial perfusion indicators. Although a strong relation was reported between TIMI MBG and short and long term clinical adverse events in the literature, no relation was found between TIMI MBG and clinical adverse events in our study. This may also be due to the small sample size and clinical adverse events including both ischemic and hemorrhagic events.

Another result in our study is the positive relation between hs-CRP level and corrected TIMI frame counts of the left anterior descending artery and circumflex artery. TIMI frame count is a simple parameter which helps in estimating the amount of blood flow in the involved artery. It is the angiographical frame count until the contrast agent arrives at the distal of the involved vessel. It also is an independent predictor of in-hospital mortality in patients with STEMI besides showing the risk levels of patients with TIMI 3 flow.[26] The positive relation between hs-CRP and TIMI frame count has shown that, a blood marker that can be measured before PCI could indicate the angiographical efficacy of the intervention and hence prognosis of the disease.

Although clinical adverse events developed more frequently in patients with higher hs-CRP levels, this difference did not reach significance, and only age was found to be an independent predictor of clinical adverse events. The relation between hs-CRP and post-PCI ischemic events have been shown in some studies. Yip et al.[27] found that baseline hs-CRP level was associated with a 30-day major cardiac event risk in patients with STEMI who underwent primary PCI within 6 hours following the onset of the symptoms. Similarly, it was reported that CRP level was associated with ischemic events following the intervention in patients who underwent balloon angioplasty or bare metal stenting[28,29] or drug-coated stenting.[30] The association between hs-CRP level and hemorrhagic events is unclear. C-reactive protein has a proatherogenic effect on both endothelial and vascular smooth muscle cells and lead to endothelial dysfunction in the aorta via lectin-like oxidized low-density lipoprotein (oxLDL) receptor-1 (LOX-1).[31] Whether endothelial dysfunction may or may not increase hemorrhagic events by inducing local hemostatis is an open area for research. On the other hand, the positive relation between hs-CRP level and the duration of hospitalization may be explained by more frequent clinical adverse events in patients with high hs-CRP level and thereby longer hospitalization periods.

Consequently, baseline visit hs-CRP levels of patients with STEMI will help us to predict the angiographical success of the intervention and projection of this success to clinical end points and thus will contribute to the risk evaluation of the patient. Further large-scale studies are required to determine “high risk patients” with high baseline visit hs-CRP levels and modify the follow-up strategies.

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