Origin of Clinically Significant Acute Phase Reaction in Acute Coronary Syndromes: Myocardial Necrosis or Plaque Rupture?

Akut Koroner Sendromlardaki Klinik Olarak Anlamlı Akut Faz Reaksiyonun Kaynağı: Miyokardiyal Nekroz mu, Plak Rüptürü mü?

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Abstract
Purpose: This study was aimed to investigate the hypothesis that clinically significant C-reactive protein releases in acute coronary syndromes (ACS) occur secondary to myocardial necrosis in response to interleukin-6.
Materials and Methods: This prospective randomized clinical study was conducted between March 2005 and May 2005 in an emergency department of a tertiary care hospital. Patients with typical chest pain were enrolled into the study. Initial cardiac Troponin-T, interleukin-6 (IL-6) and high sensitive CRP (hsCRP) levels were measured. IL-6 and hsCRP levels were compared between patients with or without myocardial infarction.
Results: A total of 132 patients were enrolled to the study. Finally 15 (11.5%) patients were diagnosed as stable angina pectoris, 60 (46.2%) were unstable angina pectoris, 18 (13.8%) were non-ST segment elevation MI and 37 (28.5%) patients were ST segment elevation MI. hsCRP levels (81.8% vs 59.1%, p=0.047) and IL-6 (54.5% vs 30.1%, respectively; p=0.03) levels were significantly higher in patients with myocardial necrosis. A moderate correlation was also found between the levels of hsCRP and IL-6 (r=0.556).
Conclusion: High sensitivity CRP levels can increase both in plaque rupture and myocardial necrosis. ACS is associated with greater inflammation in the presence of myocardial necrosis than in cases of angina without necrosis.

Keywords: **Acute Coronary Syndrome; Acute Phase Reaction; Inflammation; Myocardial Infarction.**

Özet
Amaç: Bu çalışmada, akut koroner sendromlarda (AKS) meydana gelen klinik olarak anlamlı C-reaktif protein (CRP) artışının, myokardiyal nekroza bağlı olarak salınan İnterlökin-6'ya (IL-6) cevaben meydana geldiği hipotezini araştırmaktır.
Gereç ve Yöntem: Bu ileriye döndük randomize çalışma, bir üniversite hastanesi acil servisinde Mart 2005 ve Mayıs 2005 tarihleri arasında yapıldı. Acil servise tipik göğüs ağrısı ile başvuran hastalar çalışmaya alındı. Hastalardan başlangıç kardiyak Troponin-T, IL-6 ve yüksek duyarlıklı CRP (hsCRP) düzeyleri çalışıldı. Miyokardiyal nekrozu olan ve olmayan hastalar arsındaki IL-6 ve CRP düzeyleri karşılaştırıldı.
Bulgular: Çalışmaya 132 olgu alındı. 15 (%11,5) olguya kararlı anjina pektoris, 60 (%46,2) olguya kararsız anjina pektoris, 18 (%13,8) olguya ST segment yüksekliği olmayan miyokard infarktüsü ve 37 (%28,5) olguya da ST segment yüksekliği olan miyokard infarktüsü tanısı koyuldu. hsCRP (%81,8 vs %59,1; p=0,047) ve IL-6 (%54,5 vs %30,1; p=0,03) düzeyleri miyokardiyal nekrozu olan grupta istatistiksel olarak anlamlı biçimde yüksek bulundu. CRP ile IL-6 arasında orta düzeyde bir korelasyon belirlendi (r=0,556).
Sonuç: Yüksek duyarlılıklı CRP düzeyleri hem miyokardiyal nekrozda hem de plak rüptüründe artabilir. Akut koroner sendromlarda miyokardiyal nekroz varlığında daha fazla inflamasyon cevabı meydana gelir.

Anahtar Kelimeler: **Akut Faz Reaksiyonu; Akut Koroner Sendrom; İnflamasyon; Miyokardiyal Nekroz.**

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Introduction

Inflammation plays an important role in the pathogenesis of either atherogenesis or acute coronary syndromes (ACS) (1). Unstable angina pectoris (UAP), characterized by atherosclerotic plaque rupture and endothelial erosion with no elevations of cardiac troponin T (TnT), and acute myocardial infarction (AMI), characterized by either plaque rupture or myocardial necrosis, are associated with increased levels of C-reactive protein (CRP) and interleukin-6 (IL-6) (2, 3).

CRP is synthesized by hepatocytes as a chemical response to inflammatory states and stimulated by particularly IL-6 and to a lesser extend by IL-1 (4-7). It is not only deposited in the atherosclerotic plaque but also may play a central role in the plaque rupture resulting with ACS (8). Among many inflammatory markers that were investigated so far, CRP is the most studied and popular inflammatory marker as a predictor of cardiovascular risk (9, 10) and has been the most intensively investigated.

Interleukin-6 (IL-6) is an inflammatory marker shown to be released either from the ruptured plaque or secondary to myocardial necrosis. IL-6 synthesis is induced by interferon-gamma (11), tumor necrosis factor (11, 12), IL-1 (12) and platelet derived factor (13). It is produced by several kinds of cells such as macrophages (14), lymphocytes (15) and endothelial cells (16). The cardiac myocytes induce the production of IL-6 secondary to hypoxic stress and clinically significant IL-6 elevations occur approximately in 4 hours after myocardial injury (17). Elevated levels of circulating IL-6 is able to predict early and late cardiac events in patients with coronary artery disease (18-20), and even among healthy subjects (21).

In ACS, CRP is released by hepatocytes secondary to IL-6 aforementioned. However it is not clear whether clinically significant CRP release is secondary to plaque rupture or myocardial necrosis. Although there is much published research into the diagnostic value of among chest pain in diagnosing ACS, CRP has not come into clinical practice in emergency departments for the evaluation of chest pain patients (22, 23). Cardiac troponins are able to detect myocardial necrosis with a high sensitivity and specificity (24, 25), but there is no biochemical marker for the detection of UAP patients in the emergency setting. In this study we tested the hypothesis that clinically significant CRP releases in ACS occurs secondary to myocardial necrosis in response to IL-6. This may clarify why CRP is impracticable in detecting UAP patients in emergency setting.

Materials and Methods

This prospective randomized clinical study was conducted between March 2005 and May 2005 in an emergency department of a tertiary care hospital with an annually census of 50.000 adult patients. The study was approved by the local ethics committee.

All patients consecutively admitted to the emergency department with a typical chest pain were enrolled into the study. Typical chest pain was defined as heaviness or stabbing in the retrosternal region. Then study patients were classified as stable angina pectoris (SAP), unstable angina pectoris (UAP) and acute myocardial infarction. The exclusion criteria were defined as follows: fever (38°C) or any documented active infection, malignancy, pregnancy, history of trauma, acute or chronic renal failure, pulmonary thromboembolus and liver failure. Demographic features of patients, the onset of chest pain, the existence of cardiac risk factors and levels of cardiac enzymes were recorded to study forms.

ACS syndrome was defined as a diagnosis of acute myocardial infraction in accordance with World Health Organization criteria and the Consensus Document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction (26) or unstable angina that was classified according to the Braunwald classification (27). SAP was defined as the chest pain emerged during an effort and released by rest.

The ECG analyses was performed according to these definitions: ST segment elevation of 1 mm in 2 contiguous leads, ST segment depression of 1 mm in 2 contiguous leads, T-wave inversion 2 mm in 2 contiguous leads, Q wave 0,04 seconds and amplitude 25% of the Q:R ratio. Transient ST segment deviation (0,05 mV) or T-wave inversion (0,02 mV) with symptoms and left bundle-branch block were also categorized as an indicator of myocardial injury.

Initial blood samples were taken from all patients for the analyses of cardiac enzymes, IL-6 and high sensitive CRP levels. The samples were stored at -80°C till they were analyzed for IL-6 and hsCRP.

Cardiac troponin T was measured by electrochemiluminescense method with a Roche Elecys 2010 analyzer. Levels greater than 0.1 ng/ml for TnT was considered increased.

High sensitive CRP was assessed by a particle-enhanced immunonephelometric method in BNII nephelometry (Dade Behring). 0.3 mg/dl was considered as the cut-off value for acute coronary syndrome. The lower detection limit of this method is 0.017 mg/dl.

IL-6 is studied by ELISA method at 405 nanometers with a lower detection limit of 3 pc/ml. 6 pcg/ml was approved as the cut-off value for IL-6 as mentioned in the previous literature (28).

Study patients were observed in the emergency department at least 6 hours from the onset of chest pain for serial TnT, CKMB Mass and myoglobin measures and ECG analyses except the patients with a high initial TnT or ST segment elevation MI.

Data were analyzed with the SPSS 10.0 for Windows statistical package. The continuous data were presented as mean±SD and the categorical data were presented as frequencies and percentiles. TnT, IL-6 and hsCRP levels were dichotomized before the statistical analyses. Univariate analyses between two groups for categorical data were performed by Chi square and Mann-Whitney U tests. Pearson correlation coefficient was given for defining the linear relation between hsCRP and IL-6. A two-sided P value <0.05 was considered significant.

Results

A total of 132 patients were enrolled to the study. Despite describing typical chest pain during their admission to the ED, two patients were excluded from the study because of having diagnosed as non cardiac origin ultimately. The study subjects had a mean age of 6110.8 and 70.8% were men. There were 22 (16.9%) diabetic patients, 56 (43.1%) patients with hypertension and 48 (36.9%) with a history of coronary artery disease. The median time between onset of symptoms and admission to the emergency department was 60 minutes (range; 3-480). Patient demographic features were shown in Table I.

15 (11.5%) patients were diagnosed as SAP, 60 (46.2%) were UAP, 18 (13.8%) were non ST segment elevation MI (NSTEMI) and 37 (28.5%) patients were ST segment elevation MI (STEMI). A total of 55 AMI patients, 33 (60%) of them had a normal initial TnT.

In univariate analysis of demographic features between SAP, UAP and AMI patients, there was only significant difference in gender (33.3% vs 75% vs 76.4% of the groups were male respectively, p=0.03) and smoking history (100% vs 88.3% vs 37%, respectively, p=0.015).

Time to the admission from onset of symptoms were significantly different between SAP (median time:10 minutes, range: 5-60), UAP (median time:45 miutes, range: 3-360) and AMI patients (median time: 60 minutes, range: 10-480) (p=0.00). In the post hoc analysis with Mann-Whitney U test by using Bonferroni correction, all the groups were different from each other (p0.03).

The dichotomized hsCRP levels were not statistically different between SAP, UAP and AMI patients (33.3%, 65% and 61.8% respectively; p=0.076). However the rate of high hsCRP levels were tended to be higher in UAP and AMI group than in patients with SAP. But there were significant difference in hsCRP levels between SAP and ACS patients (33.3% vs 63.3%, respectively; p=0.025).

After dichotomizing IL-6 at a cut-off level of 6 pc/ml, there was no difference between SAP, UAP and AMI patients (26.7%, 28.3% and 41.8%, respectively; p=0.257). Although this difference was not statistically different, the rate of IL-6 levels in AMI patients was higher than rate in the other groups. There was not also any difference in IL-6 levels between SAP and ACS patients (26.7% vs 34.8%, p=0.532). The analysis comparing hsCRP and IL-6 levels of ACS and SAP patients was shown in Table II.

In order to investigate the origin of CRP increase in ACS patients, the ACS patients were classified as having a high troponin T during the admission or not. The reason for classifying these patients as having a high initial cardiac troponin or not was the elevation periods of hsCRP and IL-6 in inflammation. High sensitive CRP increases in the first 6-8 hours during the inflammation (8). And significant IL-6 elevations occur approximately in 4 hours after myocardial injury as aforementioned (19). hsCRP levels above 0.3 mg/dl were significantly more common in patients with high initial TnT levels (81.8% vs 59.1%, p=0.047). Furthermore, comparing the median hsCRP levels of the two groups, a statistically significant difference was found (1.45 mg/dl (min-max: 0.11-11.4) vs 0.41 mg/dl (min-max: 0.02-29.3), respectively; p=0.000). Like hsCRP levels, a significant difference was also found for IL-6 blood levels between the patients with high and normal troponin (54.5% vs 30.1%, respectively; p=0.03). Median

IL-6 levels were also higher in the group with high troponin (7.2 pc/ml (min-max: 3-1433) vs 3 pc/ml (min-max: 0.41-1221) respectively; p=0.012). The time from the symptoms onset was similar between two groups (60 min (min-max: 10-480) vs 60 min (min-max: 3-420), respectively; p=0.272). The analysis of hsCRP and IL-6 levels in TnT positive and negative patients was shown in Table III. A significant correlation was also found between hsCRP and IL-6 blood levels (r=0.556).

Table I. Baseline characteristics of SAP, USAP and AMI patients.

Variables	SAP (n=15)	UAP (n=60)	AMI (n=55)	P
Mean age±SD	59.6±12.3	61.7±9.2	60.6±12	0.699
Male, No (%)	5 (10.6)	45 (75)	42 (76.4)	0.03
Diabetes, No (%)	13 (86.7)	51 (85)	44 (80)	0.717
Hypertension, No (%)	9 (60)	31 (51.7)	34 (61.8)	0.530
History of CAD, No (%)	13 (86.7)	35 (58.3)	34 (61.8)	0.122
Family history of CAD, No (%)	15 (100)	59 (98.3)	51(92.7)	0.213
Smoking	15 (100)	53 (88.3)	40 (72.7)	0.015
Median time from the symptoms onset (range)	10 (5-60)	45 (3-360)	60 (10-480)	0.000

SD-standart deviation; CAD-coronary disease; SAP-stable angina pectoris; UAP-unstable angina pectoris; AMI-acute myocardial infarciton

Table II. hsCRP and IL-6 levels of ACS and SAP patients.

Variables	ACS (n=115)	SAP (n=15)	P
High hsCRP, No (%)	73 (63.5)	5 (33.3)	0.025
Median hsCRP, (range)	0.5 (0.02-29.3)	0.23 (0.04-5.3)	0.115
High IL-6, No (%)	4 (26.7)	38 (34.8)	0.532
Median IL-6 (Range)	3 (0.41-1433)	3.3 (3-24)	0.981

hsCRP, high sensitive C-reactive protein; IL-6, interleukin 6; ACS, acute coronary syndrome; SAP, stable angina pectoris.

Table III. The comparison of hsCRP and IL-6 levels of ACS patients according to their initial TnT.

Variables*	Patients with a high initial TnT* (n=22)	Patients with a normal initial TnT (n=93)	P
hsCRP, No (%)	18 (81.8)	55 (59.1)	0.047
Median hsCRP levels, (Range)	1.45 (0.11-11.4)	0.41 (0.02-29.3)	0.000
IL-6, No (%)	12 (54.5)	28 (30.1)	0.030
Median IL-6 levels, (Range)	7.2 (3-1433)	3 (0.41-1221)	0.012

hsCRP, high sensitive C-reactive protein; IL-6, interleukin 6; TnT, troponin T.

Discussion

It is evident that IL-6 and CRP can predict the future cardiac events either in ACS or normal healthy patients. However, this is not true for the diagnosis of acute coronary syndromes. Neither marker has an additive role to troponin in diagnosing AMI.

The findings of this study demonstrate that an acute phase reaction (APR) occurred both in plaque rupture and myocardial injury. But myocardial injury may particularly be the major cause of clinically significant APR in ACS according to the results of this study. Although hsCRP levels were statistically significant among the SAP, UAP and AMI patients, there was an obvious elevation in UAP and AMI patients rather than SAP patients. The non significant p values were associated with the sample size. A study with a larger sample size should cause smaller p values connoting statistically significant difference. However, this trend was not seen for IL-6 in UAP patients. Only in AMI patients, IL-6 levels tended to be higher. This finding demonstrates that IL-6 elevations seen in ACS might develop due to the myocardial necrosis rather than plaque rupture. Although this finding is correlated with the literature showed the elevations of IL-6 in AMI (29), it is in discordance with the study by Biasucci et al. showed the IL-6 elevations in UAP patients (2). This dissociation may be due to the differences in their half lives, 4 hours for IL-6 (30) and 19 hours for CRP (31). The levels of hsCRP were found to be significantly higher in the ACS group rather than SAP patients, but this was not true for IL-6. Anyway IL-6 was tended to be higher in the ACS group (34.8% vs 26.7%).

One of the evident shown by this study is that the clinically significant inflammatory response seen in ACS occurs due to the myocardial necrosis. The median hsCRP and IL-6 levels in troponin positive patients were found 1.45 mg/dl and 7.2 pg/ml, respectively. However, it was 0.41 mg/dl and 3 mg/dl for the patients with a normal troponin. Hoffmeister et al also showed the relationship between the minor myocardial damage and inflammatory APR in ACS patients (32). A challenging point here is the normal median IL-6 levels of ACS patients without a myocardial necrosis unlike the hsCRP. This finding may indicate that clinically significant levels of circulating levels of IL-6 is induced by the myocardial necrosis contrary to the previous studies showed the existence of IL-6 in atherosclerotic plaques (33) and elevations of circulating IL-6 in UAP patients (2). An interesting finding is the higher rates of hsCRP according to IL-6 both in troponin

positive (81.8% vs 54.5, respectively) and negative patients (59.1% vs 30.1%, respectively). It may be explicable by the other cytokines like IL-1 inducing the synthesis of CRP from the hepatocytes (7).

The moderate correlation rate between IL-6 and hsCRP shows that IL-6 may be the major inducer of CRP synthesis from the hepatocytes (r=0.556). However, despite this correlation, the remaining correlation may indicate the existence of aforementioned cytokines inducing CRP synthesis.

There are also some limitations in this study. The UAP patients were diagnosed by a clinical definition like most of the previous studies in the literature. Strict inclusion and exclusion criteria as described before were used to prevent a possible heterogeneity in UAP group. Furthermore serial IL-6 analyses could be achieved to show probable increases among the patients with a normal IL-6. But the median times of the symptoms onset for troponin positive and negative patients were the same and it could not be disregarded that hsCRP begin to elevate in the circulation after IL-6. And the sample size of this study is not also big enough to detect the small differences between groups. It may be the reason of some statistically non significant p values although there was an obvious difference. Even though some patients might be missed due to the overcrowding of ED, it was not a disadvantage for randomization. Because these patients were missed without bias.

Inflammation plays and important role in ACS. High sensitivity CRP levels may increase both in plaque rupture and myocardial necrosis. ACS is associated with greater inflammation in the presence of myocardial necrosis than in cases of angina without necrosis. This suggests some of the inflammatory stimulus stems from myocardial necrosis.

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