The Relationship Between C-Reactive Protein and Diastolic Function of the Left Ventricle in Patients with Acute Myocardial Infarction

AKUT MİYOKARD İNFARKTÜSÜNDE SOL VENTRİKÜL DIYASTOLİK FONKSİYONLARI İLE C-REACTIVE PROTEİN DÜZEYLERİ ARASINDAKI İLİŞKİ

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Summary

Aims: C-reactive protein (CRP) is a sensitive, nonspecific marker of inflammation. Acute myocardial infarction triggers an acute phase response resulting in a rise of circulating CRP levels, which correlates with infarct size. We investigated the relation between CRP levels and left ventricular diastolic dysfunction in patients with acute anterior wall myocardial infarction.

Methods: We analyzed clinical, echocardiographic and biochemical data in 72 consecutive patients (aged 58 ± 12 years; 7 women) with first anterior acute myocardial infarction. Two-dimensional and Doppler echocardiographic examinations were performed within 24 hours of admission. Blood samples were obtained every day during hospitalization.

Results: Univariate correlation analysis showed a negative correlation between CRP and left ventricular ejection fraction, mitral E-wave deceleration time (r = - 0.250, p = 0.03 ; r = - 0.306 , p = 0.009, respectively). The patients were divided according to the deceleration time assessed at day 1 in 2 groups: group 1 (n=18) with deceleration time ≤ 130 ms and group 2 (n=54) with deceleration time> 130 ms. Peak serum CRP levels were significantly higher in the short deceleration time (≤130) group than in long deceleration time(>130) group (14.01 ± 6.3 mg/dl vs 9.3 ± 5.4 mg/dl, p= 0.02).

Conclusions: These results suggest that peak CRP levels correlate with left ventricular restrictive filling pattern.

Key Words: C-reactive protein,
Left ventricular diastolic dysfunction,
Acute myocardial infarction

T Klin J Cardiol 2001, 14:327-332

Özet

Amaç: C-reactive protein (CRP) inflamasyonun sensitif fakat nonspesifik bir göstergesidir. Akut miyokard infarktüsünde akut faz cevabı tetiklenir ve bunun sonucunda CRP düzeyleri artar. Artan bu CRP düzeyleri infarktüs genişliği ile korelasyon gösterir. Bu çalışmada akut miyokard infarktüslü hastalarda CRP düzeyleri sol ventrikül diyastolik fonksiyonları arasındaki ilişkiyi inceledik.

Metod: Yaş ortalamaları 58 ± 12 olan 7'si kadın 65'i erkek toplam 72 akut miyokard infarktüslü hastada ekokardiyografik inceleme yapılarak sol ventrikül sistolik ve diyastolik fonksiyonları araştırıldı. Tüm hastalardan pik CRP düzeylerinin tayini için her gün kan alındı.

Bulgular: Pik CRP düzeyleri ile sol ventrikül ejeksiyon fraksiyonu ve Mitral E dalga deselerasyon zamanı arasında negatif bir korelasyon saptandı (sırasıyla, r = - 0.250, p = 0.03; r = - 0.306, p = 0.009). İlave olarak hastalar bakılan Mitral E dalga deselerasyon zamanına göre iki gruba ayrıldı. Hastaların 18'inde deselerasyon zamanı 130 ms nin altında bulunurken (Grup 1), 54 hastada 130 ms nin üzerinde bulundu (Grup 2). Pik CRP düzeyleri 1. grupta (>130 ms) 2. gruptan (< 130 ms) yüksek bulundu (14 ± 6.3 vs 9.3 ± 5.4 mg/dl, p= 0.02).

Sonuç: Akut miyokard infarktüsü seyrinde yükselen CRP düzeyleri sol ventrikül restriktif doluş paterni ile korelasyon göstermektedir.

Anahtar Kelimeler: C-reactive protein,
Sol ventrikül diyastolik disfonksiyonu,
Akut miyokard infarktüsü

T Klin Kardiyoloji 2001, 14:327-332

Geliş Tarihi: 25.04.2001

Yazışma Adresi: Dr.Şükrü ÇELİK
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Recent studies have provided evidence that some inflammatory markers play a role in the pathogenesis of coronary heart disease (1-3). C-reactive protein (CRP) is a sensitive, nonspecific

acute phase reactant that its secretion is induced by cytokines, especially interleukin-6, which is produced by hepatocytes and activated macrophages (4,5). The levels of CRP are correlated with the presence and severity of coronary, cerebral, and peripheral atherosclerosis (6). In addition, elevated CRP levels are strongly related to occurrence of cardiovascular complications such as sudden cardiac death and acute myocardial infarction (7). Increased CRP levels are associated with a worse outcome among patients with a first acute myocardial infarction (8). Myocardial necrosis triggers a rise of circulating CRP. In conservatively treated patients with acute myocardial infarction, CRP correlates with infarct size (9).

Left ventricular systolic and diastolic dysfunction frequently coexists in patients with acute myocardial infarction even though both isolated systolic and diastolic dysfunction can be identified (10-12). Several prior studies have investigated relation of serum CRP levels to left ventricular systolic function in acute myocardial infarction (13,14). However, the relation of CRP levels to left ventricular diastolic dysfunction has not yet been elucidated in acute myocardial infarction. Accordingly, this study was designed to investigate this relation.

Materials and methods

Study Population

Between June 1999 and March 2000, we examined 108 consecutive patients with a first acute anterior wall myocardial infarction who met the following criteria: (I) chest pain lasting >30 min, (II) ST segment elevation > 2mm at least in two anterior electrocardiographic leads and /or (III) transient elevation of creatine kinase and/or MB isoenzyme. Of them, 28 patients were excluded because of the presence of concomitant systemic diseases (cancer, rheumatic diseases, chronic liver disease, renal disorders, sepsis, and other infectious diseases), 8 patients because of a poor acoustic window for echocardiographic examination. Clinical evaluation, electrocardiogram, blood pressure, and routine blood samples were performed every day during hospitalization.

Thrombolytic therapy (streptokinase or t-PA) was administered in 39 (54%) patients. The remaining patients did not receive thrombolytic therapy due to late admission after the onset of the pain or some contraindication for thrombolysis. During hospitalization, all patients received intravenous heparin (1000 IU/h) for 2 days, followed with low molecular weight heparin, and all patients received aspirin (300 mg daily).

Echocardiograms

Patients were evaluated by two-dimensional and Doppler echocardiography within 24 h after admission. All examinations were performed with HP SONOS 5500 machine, using a 2.5 MHz transducer.

Left ventricular end-diastolic and end-systolic volumes and ejection fraction were determined from apical two-and four chamber view using the Simpson's biplane formula, according to the recommendations of the American Society of Echocardiography (15). Tracing of endocardial borders in end-diastole and end-systole was performed in the technically best cardiac cycle.

In order to calculate the wall motion score index, the left ventricle was divided into 16 segments (15). Segmental wall motion was graded as follows: normal motion at rest (score=1); hypokinetic-marked reduction in endocardial motion and systolic thickening (score=2); akinetic- virtual absence of inward motion and systolic thickening (score=3); and dyskinetic- paradoxical wall motion away from the center of the left ventricle in systole (score=4). The wall motion score index was calculated by summation of individual segment scores divided by the number of interpreted segments. To determine the influence of apical asynergy, the score of the four apical segments was summed and divided by 4, thus yielding the apical wall motion score index.

Left ventricular diastolic filling patterns were determined by the mitral inflow pulsed-wave Doppler examination with a 2.5 MHz transducer. In the apical 4-chamber view, the Doppler sample volume was placed in the middle of the left ventricular inflow tract (1 cm below the plane of mitral annulus between the mitral leaflet tips) where maximal flow velocity in early diastole was recorded (16). Special care was taken to align the sample volume as close to perpendicular as possible to the mitral

annular plane. From Doppler spectra of 3 to 5 consecutive cardiac cycles, average values were calculated for the following transmitral parameters: peak early (E) and late (A) transmitral filling velocities, their ratio (E/A ratio) and the deceleration time of the E velocity. The isovolumetric relaxation time, defined as the time from aortic valve closure to mitral valve opening, was assessed by simultaneously measuring the flow into the left ventricular outflow tract and mitral inflow by Doppler echocardiography (17). A deceleration time >130 ms was classified as nonrestrictive, and ≤ 130 ms was defined restrictive. This cutoff point has been shown to be consistent with restrictive hemodynamics and a powerful independent predictor of unfavorable outcome after acute myocardial infarction (18,19).

Blood sampling and assays

Venous blood samples were collected every day during hospitalization and kept at 4 ºC. Plasma or serum was separated within 2 hours. Serum was assayed for CRP by particle-enhanced immunonephelometry with the Behring Nephelometer Systems Kit (N latex CRP mono, Behring, Germany). Polystyrene particles coated with mouse monoclonal antibodies to CRP were agglutinated when mixed with samples containing CRP. Serum CRP concentrations were measured by an ultrasensitive immunonephelometry method. Plasma fibrinogen level was measured by immunonephelometry using a commercial original kit (Dade Behring, Liederbach, Germany).

Statistical analysis

Data are presented as mean ± SD. A comparison between groups was performed by means of an unpaired t test for continuous variables. Categorical variables were analyzed with contingency tables using the chi-square test and the Fisher exact test when appropriate. The Pearson's correlation analysis was performed to estimate the correlation between variables. A p value < 0.05 was considered statistically significant.

Results

Study Patients

Baseline characteristics are shown in Table 1. Seventytwo patients were included in the study. The majority of patients were male (n=65; 90%) and their mean age was 58 ± 12 years. Coronary risk factors were hypertension in 26 patients (36%), smoking in 55 (76%), hypercholesterolaemia in 28 (23%), family history in 35 (48%), and diabetes in 9 (13%). In the population studied peak concentration of CRP was 10.4 ± 6.8 mg/dl.

Table 1. Baseline characteristics of patients enrolled in the study (n=72)

Age (y)	58 ± 12
Male (%)	65 (90)
Hypertension (%)	26 (36)
Diabetes (%)	9 (13)
Smoking (%)	55 (76)
Family history (%)	35 (48)
Peak CK (U/L)	2027 ± 1337
C-reactive protein (mg/dl)	10.4 ± 6.8
Fibrinogen	437 ± 179
Thrombolysis (%)	39 (54)
Time from chest pain onset to thrombolysis	4.3 ± 1.8

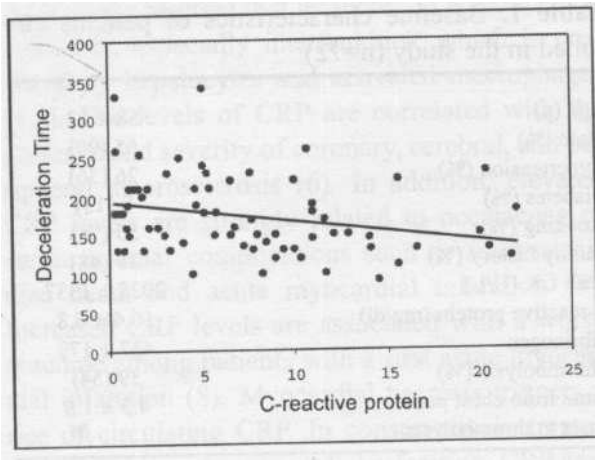
CK, creatine kinase

Table 2. Echocardiographic characteristics of the study population (n=72)

WMSI	1.6 ± 0.3
EF (%)	46 ± 13
LVEDV (ml)	118 ± 42
LVESV (ml)	65 ± 33
DT (ms)	173 ± 50
IVRT (ms)	86 ± 16
E peak (cm/s)	61 ± 22
A peak (cm/s)	66 ± 18
E/A ratio	1.09 ± 0,9

WMSI, wall motion score index; EF, ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; DT, deceleration time; IVRT, isovolumic relaxion time; E peak, peak velocity of E wave; A peak, peak velocity of A wave

The echocardiographic data of the study population are presented in Table 2. At echocardiographic examination, mean ejection fraction was 46 ± 13%, end-diastolic volume was 118 ± 42 ml, end-systolic volume was 65 ± 33 ml, E/A velocity ratio was 1.09 ± 0,9, E-wave deceleration time was 173 ± 50 ms, isovolumic relaxation time was 86 ± 16 ms.



C-reactive protein levels and left ventricular function

Univariate correlation analysis did not show any correlation between CRP levels and echocardiographic diastolic filling parameters, except for mitral E-wave deceleration time. There was a inverse correlation between CRP levels and mitral E-wave deceleration time (r = - 0.306, p = 0.009) (Figure 1). There was a weak inverse correlation between CRP levels and left ventricular ejection fraction (r = - 0.250, p = 0.03). There were no significant correlation between CRP levels and wall motion score index or peak creatine kinase levels (r = 0.193, p = 0.1 ; and r = - 0.043, p = 0.7, respectively) (Table 3).

C-reactive protein levels and mitral E wave deceleration time

According to left ventricular mitral E wave deceleration time, the patients were divided into two groups: group 1 (n=18) with deceleration time ≤130 and group 2 (n=54) with deceleration time >130. Serum CRP levels were significantly higher in the short deceleration time (≤ 130) group than in long deceleration time (>130) group (14.01 ± 6.3 mg/dl vs 9.3 ± 5.4 mg/dl, p= 0.02) (Table 4).

Table 3. Correlations between C-reactive protein levels and echocardiographic variables

	r	p
WMSI	0.193	0.1
EF	- 0.250	0.03
LVEDV	0.211	0.06
LVESV	0.218	0.06
DT	- 0.306	0.009
IVRT	- 0.058	0.6
E peak	- 0.065	0.5
A peak	- 0.030	0.8
E/A ratio	0.180	0.06

WMSI, wall motion score index; EF, ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; DT, deceleration time; IVRT, isovolumic relaxion time; E peak, peak velocity of E wave; A peak, peak velocity of A wave

Table 4. Baseline and echocardiographic characteristics of patients in both groups

	DT ≤ 130 (n=18)	DT > 130 (n=54)	p
Age (y)	58 ± 13	58 ± 12	0.85
Male (%)	16 (89)	49 (91)	0.82
Hypertension (%)	6 (33)	20 (39)	0.54
Diabetes (%)	2 (11)	7 (12)	0.75
Smoking (%)	13 (76)	42 (74)	0.85
Family history (%)	10 (54)	25 (46)	0.45
Peak CK (U/L)	2202 ± 1803	1968 ± 1156	0.09
C-reactive protein (mg/dl)	14.01 ± 6.3	9.3 ± 5.4	0.02
Fibrinogen	431 ± 221	439 ± 169	0.82
Thrombolysis (%)	8 (44)	31 (57)	0. 06
Prior aspirin usage (%)	7 (38)	21 (40)	0.52
WMSI	1.7 ± 0.4	1.5 ± 0.3	0.04
EF (%)	40 ± 13	48 ± 12	0.03
DT (ms)	120 ± 13	194 ± 44	0.001
IVRT (ms)	82 ± 14	87 ± 17	0.32

WMSI, wall motion score index; EF, ejection fraction; DT, deceleration time; IVRT, isovolumic relaxion time; CK, creatine kinase.

Discussion

Previous studies concerning CRP levels during acute myocardial infarction have demonstrated that myocardial necrosis increases CRP level (14). However, in acute myocardial infarction, the relation of CRP levels to left ventricular diastolic dysfunction has not yet been elucidated. The major findings of our study are that plasma concentrations of CRP correlates with mitral E-wave deceleration time and that CRP level is higher in patients with deceleration time ≤130 than in patients with deceleration time > 130.

C-reactive protein and infarct size

C-reactive protein is a sensitive, nonspecific, acute-phase reactant, reflecting a cytokine-mediated hepatic production induced by different kinds of inflammation and tissue damage (5). C-reactive protein increases in patients with unstable angina

and acute myocardial infarction, likely reflecting an underlying inflammatory process at the site of atherosclerotic plaques (20,21). Anzai et al (8) reported that early post-acute myocardial infarction rise of CRP associated with cardiac rupture, left ventricle aneurysm formation, and 1-year mortality. Several studies reported that post-acute myocardial infarction rise of CRP correlates with infarct size (14). However, some studies showed no correlations between CRP levels and infarct size in patients with acute myocardial infarction (13,22). In this study, we found a weak negative correlation between CRP level and left ventricular ejection fraction in patients with acute myocardial infarction.

C-reactive protein and left ventricular diastolic function

In recent years, it has been increasingly apparent that left ventricular diastolic dysfunction is commonly present in early phase of myocardial infarction and correlates to adverse outcome after acute myocardial infarction (23). Doppler echocardiography has been used to assess diastolic function in a variety of clinical settings, including acute myocardial infarction (18,24). Doppler indexes are affected by a number of other physiological factors, including heart rate, left ventricular systolic function, and ventricular preload and afterload (18). However, recent experimental data has suggested that early filling deceleration time can quantitatively assess left ventricular chamber stiffness independent of heart rate, contractility, and afterload (25). Among the various diastolic variables, shortening of the deceleration time of the early filling wave, indicative of a "restrictive" filling pattern, has been found to correlate with infarct size (26). In this study, we found a negative correlation between CRP levels and shortening of the E-wave deceleration time. Our findings suggest higher CRP levels may reflect more advanced impairment of left ventricular filling.

Limitations of the study

The most important limitation our study involves the small number of patients studied, because of selective criteria for inclusion into the study. Our patients were carefully selected to exclude other possible causes of an acute-phase response such as rheumatic diseases, chronic liver disease, renal disorders, cancer, sepsis and other infectious diseases. In his study, invasive hemodynamic measurements were not performed. However, systolic and diastolic variables have previously been correlated to simultaneous hemodynamic data.

In conclusion, peak CRP levels in patients with acute myocardial infarction correlates with restrictive filling pattern. Therefore, assay of CRP values may contribute to more complete risk stratification after a first myocardial infarction.

REFERENCES

1. Ross T. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993; 362: 801-9.
2. Libby P. Molecular basis of the acute coronary syndromes. Circulation 1995; 91: 2844-50.
3. Ridker PM. C-reactive protein and risk of future myocardial infarction and thrombotic stroke. Eur Heart J 1998; 19: 1-3.
4. Haverkate F, Thompson SG, Pyke SDM, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. Lancet 1997; 349: 462- 6.
5. Pannitteri G, Marino B, Campa PP, Martucci R, Testa U, Peschle C. Interleukins 6 and 8 as mediators of acute phase response in acute myocardial infarction. Am J Cardiol 1997; 80: 623-5.
6. Heinrich J, Schulte H, Schönfeld R, Köhler E, Assmann G. Association of variables of coagulation, fibrinolysis and acute-phase with atherosclerosis in coronary and peripheral arteries and those arteries supplying the brain. Thromb Haemostas 1995; 73: 374-8.
7. Thompson SG, Kienast J, Pyke SDM, Haverkate F, van de loo JCW. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. N Engl J Med 1995; 332: 635-41.
8. Anzai T, Yoshikawa T, Shiraki H, et al. C-reactive protein as a predictor of infarct expansion and cardiac rupture after a first q wave acute myocardial infarction. Circulation 1997; 96: 778-84.
9. Pietilä KO, Harmoinen AP, Hermens WT, Simoons ML, van de Werf F, Verstraete M. Serum C-reactive protein and infarct size in myocardial infarct patients with a closed versus an open infarct-related coronary artery after thrombolytic therapy. Eur Heart J 1993; 14: 915-9.
10. Gianuzzi P, Imparato A, Temporelli PL, et al. Doppler derived mitral deceleration time of early filling as a strong predictor of pulmonary capillary wedge pressure in postinfarction patients with left ventricular systolic dysfunction. J Am Coll Cardiol 1994; 23: 1630-7.
11. Williamson BD, Lim MJ, Buda AJ. Transient left ventricular filling abnormalities (diastolic stunning) after acute myocardial infarction. Am J Cardiol 1990; 66: 897-903.

12.Chenzbraun A, Keren A, Stern S. Doppler echocardiographic patterns of left ventricular filling in patients early after acute myocardial infarction. Am J Cardiol 1992; 79: 711-4.

13.Tommasi S, Carluccio E, Bentivoglio M, et al. C-reactive protein as a marker for cardiac ischemic events in the year after a first, uncomplicated myocardial infarction. Am J Cardiol 1999; 83: 1595-9.

14.Lagrant WK, Viser CA, Hermens WT, et al. C-reactive protein as a cardiovascular risk factor. Circulation 1999; 100: 96-102.

15.Schiller NB, Shah PM, Crawford M et al. Recommendation for quantification of the left ventricle by two dimensional echocardiography. J Am Soc Echocardiogr 1989; 2: 358-68.

16.Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity pattern to left ventricular diastolic function: new insight from a combined hemodynamic and Doppler echocardiographic study. J Am Coll Cardiol 1988; 12: 426-40.

17.Nishimura RA, Housmans PR, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: Background and current applications of Doppler of Doppler echocardiography. Part I. Physiologic and pathophysiologic features. Mayo Clin Proc 1989; 64: 71-81.

18.Oh JK, Ding ZP, Gersh BJ, Bailey KR, Tajik J. Restrictive left ventricular diastolic filling identifies patients with heart failure after acute myocardial infarction. J Am Soc Echocardiogr 1992; 5: 497-503.

19.Nijland F, Kamp O, Karreman AJP, van Eenige MJ, Visser CE. Prognostic implications of restrictive left ventricular filling in acute myocardial infarction: a serial Doppler echocardiographic study. J Am Coll Cardiol 1997; 30: 1618-24.

20.Liuzzo G, Biasucci L, Gallimore J, et al. The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. N Engl J Med 1994; 331: 417-24.

21. De Beer FC, Hind CRK, Fox KM, Allan RM, Maseri A, Pepys MB. Measurement of serum C-reactive protein concentration in myocardial ischemia and infarction. Br Heart J 1982; 47: 239-43.

22.Pietilä K, Harmoinen A, Teppo A-M. Acute phase reaction, infarct size and in-hospital morbidity in myocardial infarction patients treated with streptokinase or recombinant tissue type plasminogen activator. Ann Med 1991; 23: 529-35.

23.Poulsen SH, Jensen SE, Egstrup K. Longitudinal changes and prognostic implications of left ventricular diastolic function in first acute myocardial infarction. Am Heart J 1999; 137: 910-8.

24.Nishimura RA, Tajik J. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is clinican's Rosetta Stone. J Am Coll Cardiol 1997; 30: 8-18.

25.Little WC, Ohno M, Kitzman DW, Thomas JD, Cheng C-P. Determination of left ventricular chamber stiffness from the time for deceleration of early left ventricular filling. Circulation 1995; 92: 1933-36.

26.Popovic AD, Neskovic AN, Marinkovic J, Lee J-C, Tan M, Thomas JD. Serial assessment of left ventricular chamber stiffness after acute myocardial infarction. Am J Cardiol 1996; 77: 361-4.