C-reactive protein in unstable angina pectoris and its relation to coronary angiographic severity and diffusion scores of coronary lesions

Kararsız anjina pektoris'de C-reaktif protein ve bunun koroner lezyonların koroner anjiyografik şiddeti ve yaygınlık derecesi ile ilişkisi

Dilek Soysal, Volkan Karakuş, Hakan Haldun Yavaş, Serdar Biçeroğlu[1], Mehmet Köseoğlu**, Murat Yeşil****

From Departments of Internal Medicine 1st Division, * Nephrology, ** Biochemistry, and
***Cardiology 1st Division, Atatürk Research and Training Hospital, İzmir
[1]Department of Cardiology, Atakalp Hospital, İzmir, Turkey

Abstract

Objective: We aimed to assess the relationship between C-reactive protein (CRP) and the severity and diffusion of coronary artery lesions in patients with unstable angina pectoris (UAP) and the independent association of CRP with this clinical situation.
Methods: This cross-sectional, observational study included 50 patients. Classification by Braunwald was used for UAP. The severity and diffusion of angiographic coronary disease were graded according to Reardon's modified scoring system. Plasma CRP levels were quantified by immunoturbidimetry. Nonparametric tests were used for comparison of CRP and other risk factors, and logistic regression analysis for evaluation of independent association between CRP and unstable angina pectoris.
Results: The severity score was 46±18 points in class IIB1 UAP, 36±20 points in class IIB2 and 53±18 points in class IIIB2 (p=0.017, class IIIB2 vs IIB2). Respectively, CRP levels were 6.6 mg/L, 3.8 mg/L and 4.8 mg/L (p=0.371, class IIB1 vs IIB2 vs IIIB2). Lesions with diffusion score 4 revealed higher CRP values than lesions with diffusion score 1 (11.1 mg/L vs 3.1 mg/L, p=0.048). Adjusting age, sex and smoking, assessment of partial correlation analysis showed a positive, moderately powerful and significant association between CRP levels and the severity and diffusion scores of the coronary lesions (r=0.30; p=0.034 and r=0.31; p=0.030, respectively) in the whole study group. Multiple logistic regression analysis showed no appreciable independent association between CRP and UAP (OR: 1.63, 95%CI: 0.90-5.63, p=0.093).
Conclusion: Although, CRP was correlated with the severity and diffusion of angiographic coronary disease in patients with UAP, there was no independent association between CRP and clinical severity of UAP. *(Anadolu Kardiyol Derg 2010; 10: 421-8)*
Key words: Unstable angina, C-reactive protein, angiography, logistic regression analysis

Özet

Amaç: C-reaktif protein (CRP) düzeyleri ile kararsız anjina pektorisli (UAP) hastalarda koroner arter lezyonlarının yaygınlığı ve şiddeti arasındaki ilişkiyi ve CRP'nin kararsız anjina kliniğine bağımsız etkisini araştırmaktı.
Yöntemler: Enine-kesitli, gözlemsel bu çalışmaya yaşları 28-73 arasında 50 hasta alındı. Kararsız anjina sınıflaması Braunwald'a göre yapıldı. Hastaların anjiyografilerinde saptanan lezyonların şiddeti ve yaygınlığı Reardon'un modifiye skorlama yöntemi ile değerlendirildi. Plazma CRP düzeyleri immünotürbidimetrik yöntemle ölçüldü. Nonparametrik testler CRP ve diğer risk faktörlerinin karşılaştırılmasında, lojistik regresyon analizi CRP ve UAP arasındaki bağımsız ilişkinin araştırılmasında kullanıldı.
Bulgular: Lezyonların şiddet skoru sınıf IIB1'de 46±18 puan, sınıf IIB2'de 36±20 puan ve sınıf IIIB2'de 53±18 puandı. Sınıf IIB2 ve IIIB2 arasında anlamlı fark vardı (p=0.017). Plazma CRP değerleri ise sırasıyla, 6.6 mg/L, 3.8 mg/L ve 4.8 mg/L bulundu (p=0.371). Difüzyon skoru 4 olan hastaların CRP değerleri difüzyon skoru 1 olan hastalara göre anlamlı olarak yüksek bulundu (11.1 mg/L'ye karşı 3.1mg/L, p=0.048). Tüm çalışma grubu için uygulanan bölümsel korelasyon analizinde, yaş, cinsiyet ve sigaraya göre düzeltme yapıldıktan sonra, CRP değerleri ile koroner lezyonların şiddeti ve yaygınlığı arasında direkt, orta derecede güçlü ve anlamlı bağıntı saptandı, sırasıyla (r=0.30; p=0.034 ve r=0.31; p=0.030). C-reaktif protein ve kararsız anjina pektoris arasında olabilecek bağımsız bir ilişkiyi değerlendirmek için çoklu lojistik regresyon analizi uygulandı, fakat anlamlı bir ilişki saptanmadı (OR: 1.63, %95 GA: 0.90-5.63, p=0.093).
Sonuç: Kararsız anjina pektoris kliniğinden bağımsız olarak hastalarımızda CRP düzeyleri ile koroner arter lezyonlarının şiddeti ve yaygınlığı arasında ilişki bulunsa da, CRP ile kararsız anjina klinik şiddeti arasında bağımsız bir ilişki saptanmadı. *(Anadolu Kardiyol Derg 2010; 10: 421-8)*
Anahtar kelimeler: Kararsız anjina, C-reaktif protein, anjiyografi, lojistik regresyon analizi

Address for Correspondence/Yazışma Adresi: Dr. Dilek Soysal, Manolya Sok. Töbaş Sitesi, No: 44/4 Balçova, İzmir, Turkey
Phone: +90 232 278 51 59 Fax: +90 232 482 20 75 E-mail: dileksoysal@hotmail.com
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Introduction

Atherosclerosis is the main cause of coronary artery disease. Inflammation is shown to have a role in the beginning and progression of atherosclerosis and alteration of stable plaque to unstable plaque (1). The identification of unstable or so-called vulnerable plaque (VP) became an interesting target, since it is the substrate of eventual future events. The determinant factors of VP are: the size and consistence of lipid core, thickness of fibrous cap around this core, and the balance of inflammation-reparation inside this cap (2, 3). Plaque fissure is widely assumed to be the cause of unstable angina (4). The realization, that atherosclerosis is essentially an inflammatory process, has prompted the search for measurable biochemical markers of plaque inflammation, some of which are non-specific, such as serum C reactive protein (CRP) (5). The classical acute-phase protein CRP represents a highly sensitive marker of inflammation and the measurement of CRP has several advantages for detection and monitoring of the acute-phase response in general and of the relation to atheroma and its complications in particular (6). Dramatic acute phase response in acute inflammation reflects the extent of tissue injury and thus, a consistent independent association between CRP level and various cardiovascular endpoints could be established in several studies (3-8). Scoring of coronary artery disease according to the number of critically diseased vessels has traditionally been the preferred method in both angiographic and prognostic studies (9). Although, the link between elevated CRP concentrations and the presence of coronary narrowings suggests a potential pathogenetic role of the inflammatory process, the relations between levels of CRP and the presence and extent of angiographically documented coronary artery disease have seldom been investigated (10).

Therefore, in the present study, we investigated the relationship between levels of CRP and angiographic coronary artery disease as scored by means of severity and diffusion of lesions in coronary angiograms, in patients with unstable angina pectoris, and secondly the independent association of CRP with UAP.

Methods

Patient population and inclusion criteria

Of the 203 consecutive patients referred to our hospital's emergency unit with chest pain, 50 patients with unstable angina were enrolled in this prospective, observational and cross-sectional study. Unstable angina (UA) was classified by Braunwald classification (11). Patients with angina at rest within past month but not within preceding 48h were subacute class II angina, angina at rest within 48h were acute class III angina, chest pain of primarily cardiac origin were class B angina and patients without medication were in class 1 and with medication were in class 2. Sixteen patients (10 men and 6 women, aged 53±12 years) were in class IIB1, 21 patients (15 men and 6 women, aged 56±11 years) were in class IIB2 and 13 patients (10 men and 3 women, aged 55±10 years) were in class IIIB2. Thirty-six patients (72%) were taking aspirin, 34 patients (68%) were taking either beta-blocker or oral nitrate or both of them, 26 patients (52%) were taking statins and 10 patients (20%) were taking fenofibrate at admission.

Patients with a history of recent myocardial infarction or elevated serum troponin levels (0.07 ng/ml or above), dilated cardiomyopathy, hemodynamically significant valvular heart disease, pericardial effusion or massive pulmonary embolism assessed by echocardiography, grade 2 or 3 hypertension, acute or chronic inflammatory disease, renal or hepatic insufficiency, anemia, known malignant disease, oral anticoagulation within the prior four weeks were not included into the study. Informed consent was obtained from all patients. Study protocol was approved by the Ethics Committee of our hospital.

Risk factors

Cigarette smoking was assessed by self-report. Cigarette-years were used to estimate the cumulative consumption of tobacco. Blood pressure was measured and defined according to the recommendations of the European Society of Hypertension (12). Diabetes was defined according to the recommendations of the American Diabetes Association (13). Obesity was defined according to the recommendations of the National Institutes of Health (14). Lipid profile was defined according to the current European recommendations (15).

Study protocol

Immediately after admission to our division, patients were monitored for the observation of recurrent ischemia and vital signs regarding the heart rate, blood pressure, arterial oxygen saturation and changes in the electrocardiography. Blood pressure data were based on the average of the first and the last two blood pressure values. The mean arterial pressure (MAP) was calculated as one third of the average systolic blood pressure plus two thirds of the average diastolic blood pressure (mmHg). Minnesota codes (16) 4.2, 5.2 and 5.3 were used in the evaluation of dynamic ST segment and T wave alterations on electrocardiograms. Echocardiography was obtained for the assessment of cardiac functions and diagnostic achievement of the other causes of chest pain for each participant.

Samples for the evaluation of C-reactive protein were obtained at admission before treatment and for the evaluation of cardiovascular risk factors after 12h fasting. Once the diagnosis was established, treatment started for relief of pain and ischemia. The initial treatment included intravenous opioids if necessary, administration of oxygen, antiplatelet therapy with a loading dose of 300 mg of aspirin, antithrombin therapy with low molecular weight heparin based on a weight-adjusted dose and anti-ischemic therapy with intravenous beta-blockers and nitrates, and was followed by oral treatment as appropriate (17).

Angiographic evaluation

Coronary angiograms were performed by the Judkins method. The diffusion and severity of the coronary lesions were graded on the basis of a modified scoring system of Reardon et al. (18). Coronary circulation was divided as follows: left main

coronary artery; proximal, middle and distal segments of the left anterior descending artery; proximal and distal segments of the right coronary artery and proximal and distal segments of the circumflex artery. Numerical values were given to these segments regarding the diffusion and severity levels of the lesions. Diffusion scores were determined as follows: normal vessel=0; isolated or diffuse lesions of second or third-order coronary branch (with normal epicardial coronary artery)=0.5; isolated lesion of principal segment=1; diffuse lesions of principal segment=2 and diffuse lesions of principal segment and its branches=2.5. The total diffusion score for each patient was then obtained from the sum of all segment scores. Severity scores were determined as follows: normal= 0; irregularity with a luminal diameter reduction< 50%=1; 50 to 75% stenosis=10; 76 to 89% stenosis=15; 90% stenosis to subtotal occlusion=20 and total occlusion=25. The total severity score was then obtained from the sum of all segment scores. All coronary angiograms were evaluated by a single observer blinded to the clinical and laboratory data.

Laboratory methods

Blood samples were obtained under standardized conditions before coronary angiograms were performed and stored at -70°C until analysis. Fasting plasma glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, uric acid and fibrinogen were determined by using standardized methods. Low-density lipoprotein (LDL) cholesterol was calculated by Friedewald formula when the triglyceride concentration was <400 mg/dl. C-reactive protein level was immunologically determined by immunoturbidimetric method (Abbott Aeroset 1600 autoanalyser, by Abbott reagents, Germany).

Statistical analysis

Means and proportions of baseline cardiovascular risk factors were used for descriptive purposes. Because CRP values were not normally distributed, data were expressed as median and range. The distribution of nonskewed data were expressed as means±standard deviations (SDs). Chi-square test was used to assess differences in the distribution of categorical variables. Nonparametric tests were used for the comparison of CRP levels and other risk factors between the two (Mann-Whitney U test) and three (Kruskal-Wallis test) classes of unstable angina pectoris. Whenever the difference between two of the three classes was tested Bonferroni's correction was applied and the significance was set at a p value <0.0167.

For correlations between CRP and continuous variables, including severity and diffusion scores of the coronary artery lesions, nonparametric Spearman's p test was used in the analysis of patients in class IIB1, IIB2 and IIIB2 and partial correlation test was used in the analysis of all participants, after adjusting age, sex and smoking. Multiple logistic regression analysis was performed to assess the association between CRP and unstable angina pectoris. Diffusion and severity scores, and markers of inflammation as fibrinogen and CRP were entered one at a time in the model as independent variables of UAP as the dependent end-point and stepwise-adjusted by backward elimination method. The result was expressed as odds ratio (OR) together with 95% confidence interval (CI). A p value <0.05 was considered significant. All calculations were carried out using SPSS, version 10.0, for Windows.

Results

Fifty patients (mean age: 55.0±11.0 year, 70% were males) were included in the study. Table 1 presents the demographical, clinical and baseline laboratory characteristics of the patients. Patients were classified according to their clinical status of unstable angina and data obtained from demographic, clinic and laboratory measurements were compared with each other on the basis of this classification. Except for the difference in mean values of triglycerides between patients in class IIB2 and IIIB2, there were no significant differences in the analysis of demographic, clinic and laboratory measurements between patients in UAP classes. Although, the median value of plasma CRP was higher in females than in males (5.1mg/L vs. 4.5mg/L), the difference was not statistically significant (p=0.624).

Angiographic scores and distribution of CRP

Table 2 presents the severity scores of coronary artery lesions and median values of CRP in cases with UAP. Patients with acute UAP (class IIIB2) had significantly higher severity scores than patients with subacute UAP (class IIB2) with medication (p=0.017). More severe lesions were observed in acute unstable angina compared with less severe lesions in subacute unstable angina (p=0.035 for trend), however, similar trend for CRP levels was not observed (p>0.05). C-reactive protein though not statistically significant was somewhat higher among patients in class IIB1 subacute angina and who were not receiving medication at hospitalization than among patients in class IIB2 subacute angina and IIIB2 acute angina and who were already receiving medication at hospitalization (p=0.371).

For the purpose of analysis and clinical interpretation of the data, patients were subdivided into four groups according to the sum of diffusion scores. Of the 16 patients (32%) in group 1 (four patients in class IIB1, 11 patients in class IIB2 and one patient in class IIIB2) had a score of 1 point, 12 patients (24%) in group 2 (four patients for each UAP class) had a score of 2 points, 12 patients (24%) in group 3 (four patients in class IIB1,three patients in class IIB2 and five patients in class IIIB2) had a score of 3 points and 10 patients (20%) in group 4 (four patients in class IIB1 and three patients in classes IIB2 and IIIB2 for each) had a score of 4 points. Median values of CRP, related to these scores, were assessed in each group (Table 3), and found to be higher in group 4 with 4 points than in groups with 3, 2 and 1 point of diffusion scores (p=0.139 for trend). A statistical significant difference was observed in CRP values between groups with 1 point and 4 points (p=0.048). Of the 16 patients in class IIB1, patients with different diffusion scores were equally distributed as 4 patients (25%) for each group. The distribution of patients in class IIB2 was as follows: 11 patients (52%) received 1 point, 4 patients (19%)-2 points, 3 patients (14%)-3 points and 3 patients (14%)-4 points, and

Table 1. Baseline characteristics of the patients according to their clinical presentation

Characteristics	Class IIB1 (n=16)	Class IIB2 (n=21)	Class IIIB2 (n=13)	p_1	p_2	p_3	χ^2	p
Age, years	53±12 (28-71)	56±11 (40-73)	55±10 (28-66)	0.461	0.759	0.645	0.604	0.739
Gender, male n (%)	10 (62.5)	15 (71.4)	10 (76.9)				0.746	0.689
Smoking, (P/year)	25.5±24.1 (0-80)	25.2±17.9 (0-60)	14.7±16.8 (0-50)	0.743	0.223	0.078	3.055	0.217
MAP, mm/Hg	105.0±8.9 (86-116)	110.0±10.5 (83-123)	102.0±13.6 (83-120)	0.080	0.756	0.086	4.336	0.114
DM, n (%)	4 (25)	3 (14.2)	4 (30.8)				1.395	0.498
BMI, kg/m^2	26.0±2.6 (22-32)	2.08±4.1 (23-36)	27.9±3.9 (23-34)	0.099	0.278	0.816	2.752	0.253
LDL-C, mg/dl	161.1±36.4 (117-272)	154.5±29.8 (100-198)	159.5±26.0 (115-203)	0.927	0.693	0.683	0.210	0.900
HDL-C, mg/dl	37.9±7.1 (29-51)	36.0±9.3 (15-58)	38.5±6.9 (28-52)	0.498	0.709	0.294	1.178	0.555
Triglycerides, mg/dl	225.6±90.1 (89-385)	187.1±54.2 (86-325)	278.8±147.7 (122-571)	0.187	0.380	0.050	4.348	0.114
Uric acid, mg/dl	5.3±0.8 (3.5-6.2)	5.0±1.2 (3.0-7.2)	4.8±1.2 (3.0-7.0)	0.601	0.292	0.546	1.109	0.574
Fibrinogen, mg/dl	318.4±199.0 (166-1037)	281.2±101.5 (125-596)	294.5±102.3 (178-501)	0.256	0.483	0.790	1.297	0.523
CRP, mg/L	6.6 (3.12-12.5)	3.8 (3.12-5.17)	4.8 (3.12-10.6)	0.204	0.929	0.278	1.984	0.371

Data are expressed as mean±SD (range), median (range) values and number (percentage)
Chi - square test for comparison of categorical variables
Kruskal Wallis test with Bonferroni correction (significance is set at p<0.0167) for comparison of continuous variables between 3 groups
Mann Whitney U test for pairwise comparison of continuous variables: p_1- comparison of variables between IIB1 and IIB2; p_2 - comparison of variables between IIB1 and IIIB2, p_3 - comparison of variables between IIB2 and IIIB2
BMI - body mass index, CRP - C-reactive protein, DM - diabetes mellitus, HDL - C- high density lipoprotein cholesterol, LDL - C- low density lipoprotein cholesterol, MAP - mean arterial pressure

Table 2. Severity scores of coronary artery lesions and related CRP levels in patients with UAP with regards to Braunwald's classification

Classification of UAP	Class IIB1	Class IIB2	Class IIIB2	p_1	p_2	p_3	χ^2	p
Patients, n (%)	16 (32)	21 (42)	13 (26)					
Severity scores, points	46±18 (25-90)	36.2±20 (10-80)	52.7±18.4 (26-80)	0.089	0.280	0.017	6.698	0.035
CRP, mg/L	6.6 (3.12-12.5)	3.8 (3.12-5.17)	4.8 (3.12-10.6)	0.204	0.929	0.278	1.984	0.371

Data are expressed as mean±SD (range) and median (range) values
Kruskal Wallis test with Bonferroni correction (significance is set at p<0.0167) for comparison of 3 groups
Mann Whitney U test for pairwise comparison of continuous variables: p_1 - comparison of variables between IIB1 and IIB2; p_2 - comparison of variables between IIB1 and IIIB2, p_3 - comparison of variables between IIB2 and IIIB2
CRP- C-reactive protein, UAP-unstable angina pectoris

in class IIIB2: 1 patient (7%) received 1 point, 4 patients (31%)-2 points, 5 patients (38%)-3 points and 3 patients (23%)-4 points.

Correlation analysis

Although, CRP was found to be moderately and directly correlated with the severity scores of coronary lesions in patients with acute UAP (class IIIB2), (r_S=0.42), and with the diffusion scores of coronary lesions in patients with acute (class IIIB2), (r_S=0.35) and subacute UAP (class IIB1), (r_S=0.33), they were not statistically significant (p=0.158, p=0.241 and p=0.214, respectively). Considering the fact that the result might be influenced by the inadequate statistical power due to the small sample size in each UAP classes, further analysis for correlations between CRP and angiographic coronary artery disease and between CRP and cardiovascular risk factors was performed by partial correlation analysis after adjustments were made for age, sex and smoking.

The analysis included all the 50 patients from different classes of UAP at once. The coefficients of partial correlation analysis are presented in Table 4. There were no significant correlations between CRP and cardiovascular risk factors, however, moderately powerful, direct and significant correlations were assessed between CRP and severity and diffusion scores of coronary artery lesions (r=0.30; p=0.034 and r=0.31; p=0.030, respectively). Another direct and moderately powerful correlation was assessed between LDL-cholesterol and triglycerides (r=0.40; p=0.005).

Finally, the independent association between CRP and unstable angina was evaluated by multiple logistic regression analysis in the whole study population. Diffusion and severity scores of coronary lesions and markers of inflammation as fibrinogen and CRP were entered one at a time in the model as independent variables of UAP as the dependent end-point. There was a 1.63-fold increase in the risk of having UAP by the increase in CRP, although the OR for unstable angina as regards CRP was not significant (OR:1.63, 95% CI: 0.90-5.63, p=0.093).

Table 3. Diffusion scores of coronary artery lesions and related CRP levels in patients with UAP, regardless of Braunwald's classification

Diffusion scores, points	1	2	3	4	χ^2	p
Patients, n (%)	16 (32)	12 (24)	12 (24)	10 (20)	8.410	0.210
CRP,† mg/L	3.1 (3.12-10.6)	3.9 (3.12-6.18)	5.1 (3.12-7.17)	11.1 (3.95-12.5)	5.495	0.139 0.048*

Data are expressed as number (percentage) and median (range) values
Chi-square test for comparison of categorical variables
Kruskal Wallis test with Bonferroni correction (significance is set at p<0.0167) for comparison of 3 groups
*- Mann Whitney U test for pairwise comparison of variables between patients with one and four points of diffusion scores
CRP - C-reactive protein

Table 4. Coefficients of partial correlation analysis for cardiovascular risk factors, and severity and diffusion scores related to CRP in the overall study population

Variables	r	p
Mean arterial pressure, mmHg	-0.018	0.902
Body mass index, kg/m^2	0.17	0.226
LDL-cholesterol, mg/dl	0.10	0.482
HDL-cholesterol, mg/dl	0.14	0.315
Triglycerides, mg/dl	0.035	0.812
Uric acid, mg/dl	-0.02	0.892
Fibrinogen, mg/dl	0.12	0.386
Severity score, points	0.30	0.034*
Diffusion score, points	0.31	0.030*

Spearman correlation analysis with adjustments for age, sex and smoking
*p<0.05
CRP - C-reactive protein, HDL - high density lipoprotein, LDL - low density lipoprotein

Discussion

Recently, in a variety of cardiovascular conditions, the prognostic role of CRP has been emphasized (5-7, 9, 10, 19-28), or vice versa (29, 30). Besides studies confirming the existing relation between CRP levels and the presence of coronary artery disease documented by coronary angiography (31, 32), some studies found no correlation between the extent of coronary artery disease and CRP levels (10, 29, 33-35). In respect to these studies, our first aim was to investigate the relationship between CRP and angiographic coronary artery disease in patients with unstable angina pectoris. Secondly, we evaluated the independent association between CRP and UAP. Coronary artery lesions in angiograms were evaluated by means of scoring the severity and diffusion of lesions by Reardon's modified method. Angiographies depicted coronary anatomy from a planar two-dimensional silhouette of the lumen and could not detect early signs of atherosclerosis or disease activity (34). By this method, it was not possible to evaluate the quality of atherosclerotic plaque. Intravascular ultrasound (IVUS) of coronary arteries was likely to provide more accurate information regarding atherosclerotic burden (31, 34), but, we did not have the possibility of performing the study by IVUS. The main finding of our study was that, regardless of the UAP classes the patients were involved, CRP levels were moderately correlated with the severity and extension of angiographic coronary artery disease, and that CRP was not associated independently with the risk of having UAP.

C-reactive protein induces synthesis of tissue factor in monocytes and endothelial cells and tissue factor activates the extrinsic coagulation cascade, providing a link between inflammation and thrombosis (6, 10, 21, 28, 29). Inflammation contributes to endothelial dysfunction while endothelial dysfunction promotes inflammation (21). It has already been shown that patients with unstable angina and increased levels of CRP (>3.0 mg/L) experienced more ischemic episodes, required more frequent revascularization and more often developed an acute MI than those with lower CRP levels (6). A crucial point in understanding the clinical and pathophysiological meaning of C- reactive protein elevation in acute coronary syndromes is whether CRP release is predominantly a response to even small amounts of myocardial necrosis, for which troponin is a sensitive and specific marker, or is an independent indicator of the inflammatory process occurring in that clinical condition (3). Our findings might confirm the role of an inflammatory component in unstable angina by showing that CRP levels were elevated in 76% of our patients (patients with 3.12 mg/L of CRP levels were not included for the reason that the lower range of the laboratory kit was 3.12 mg/L), with values above the accepted range of 3.0 mg/L recommended by Centers for Disease Control and Prevention (36).

By further evaluation, we observed that our patients in class IIB2 and IIIB2 who were receiving medication had lower median values of CRP than patients in class IIB1 who were not receiving medication at admission. If we considered the fact that 72% of our patients were taking aspirin, 52% were taking statins and 20% were taking fenofibrates at admission, this result might be attributed to the concomitant medication that was supposed to intervene with inflammation, because drugs such as aspirin,

statins and fibrates are known to reduce the serum levels of CRP (6, 21, 22, 24, 27, 37, 38). Studies revealed that aspirin reduces the incidence and frequency of ischemic episodes as well as systemic concentrations of hemostatic and inflammatory markers thus reducing the CRP levels (22, 37), and studies indicating the statin therapy emphasized that the reduced progression of atherosclerosis is significantly related to greater reductions in CRP levels regardless of the baseline LDL cholesterol level. These observations were found to be independent of lipid lowering and suggested to be additional non-lipid, anti-atherothrombotic and anti-inflammatory effects (6, 21, 24, 27, 38) in particular. Also, patients with hypertriglyceridemia or combined hyperlipidemia benefit from fenofibrate therapy in lowering CRP levels (21).

In the study, most of our patients had high concentrations of LDL cholesterol and triglycerides with low concentrations of HDL cholesterol, and almost 70% of the patients were heavy smokers, and 72% were either overweight or obese. Despite the fact that cardiovascular risk factors are associated with the thrombotic process, as well as the inflammatory reactions (6), we found no consistent correlations between plasma levels of CRP and cardiovascular risk factors in the study. Among these factors, there was a direct correlation between LDL cholesterol and triglycerides merely. In a small sample size study, Li et al. (39) reported no correlation between plasma levels of CRP and serum total cholesterol as well as HDL cholesterol in patients with UAP and stable angina. The same study showed no correlation between plasma levels of CRP and severity of coronary stenosis in patients with UAP. However, results from the two large community based studies showed strong associations between CRP, age, BMI, smoking and diabetes (20), and between CRP, obesity and smoking (25) in samples of initially healthy individuals without a history of coronary heart disease.

Scoring of coronary artery disease according to the number of critically diseased vessels has traditionally been the preferred method in both angiographic and prognostic studies. In the present study, we used the modified method of Reardon in scoring the severity and diffusion of coronary artery lesions. Elevated levels of CRP were evaluated in patients with higher diffusion scores than in patients with lower diffusion scores and a level of significance was assessed between patients with the lowest and highest scores. Although, the most severe lesions were observed in class IIIB2 patients, the highest median value of CRP was assessed in class IIB1 patients. In class IIB1 patients, in addition to their high, but not the highest, severity scores, the means of fibrinogen, LDL cholesterol, uric acid and cigarette consumption were higher than the means of these risk factors in class IIB2 and IIIB2 patients. It was noteworthy that patients in class IIB1 were not receiving any cardiac medication before hospitalization. The lowest severity score and median value of CRP belonged to patients in class IIB2 who had subacute form of unstable angina and some had already been receiving cardiac medication before hospitalization. In a study by Arroyo-Espliguero (9), angiographic coronary disease severity was graded using a vessel score and extent of disease with an extension score in patients followed up for a year and patients who suffered cardiac adverse events including Braunwald's class IIIB unstable angina had higher vessel score, extension score and CRP levels compared to patients without events.

In the present study, another finding was that, CRP was directly and moderately correlated with the severity and diffusion scores in patients with acute angina (class IIIB2), and with the diffusion score in patients with subacute angina (class IIB1). However, the correlations were not statistically significant and the result was attributed to the small sample size in each angina class. We applied a further analysis to the whole sample size for correlations between CRP, severity and diffusion scores and cardiac risk factors, considering that the patients were clinically different but that they had the same physiopathology of the disease. After adjustments were made for age, sex and smoking, we observed direct, moderate and statistically significant correlations between plasma CRP levels and angiographic coronary disease. These findings suggested that the link between CRP levels and coronary artery disease is present as far as acute events are concerned, for the fact inflammation might be an important triggering mechanism of acute coronary events related to plaque rupture rather than a promoter of chronic atherosclerosis (10). Zebrack et al. (31) showed a low but significant correlation between CRP levels and the severity/ extent of coronary artery disease. Their suggestion, because CRP is weakly correlated with angiographic plaque burden, it appears that CRP is stimulated not only by the extent of atherosclerosis but, by other factors, also emphasized by Veselka et al. (33) in their study, in which CRP level was not related to the extent or the presence of coronary atherosclerosis assessed by coronary angiography. It was also assumed that (19), the increase in CRP was not secondary to the extent and severity of myocardial ischemia, but might be an independent marker of the inflammatory component involved in the pathogenesis of acute coronary syndromes on the basis of clinical evidence that high concentrations of CRP in patients with UAP was associated with a worse prognosis independently of the extent and severity of myocardial ischemia. Katritsis et al. (32) assessed the association of CRP concentrations with UAP and high-risk angiographic features of coronary lesions. Increased levels of CRP were strongly associated with UAP and with specific high-risk features of the culprit coronary lesions. Gökçe et al. (35) assessed that serum CRP levels were higher in UAP class III patients than in UAP class II and UAP class I patients, and in patients with type C lesions than in patients with type A and B lesions. However, they found no correlations between CRP levels and the extent of coronary artery disease. They stated, inflammatory components might be detectable in UAP and were correlated with the clinical severity and lesion morphology, but were not correlated with the extent of coronary artery disease. Similarly, evaluation of CRP, fibrinogen and antithrombin-III as risk factors in angiographically documented coronary artery disease patients revealed no difference in the values of these factors among patients with single, double and triple vessel disease, although the level of CRP was higher in patients with unstable angina than in patients with stable coronary artery disease (40).

Evaluation of the independent association between CRP and clinical presentation (UAP) showed a 1.63-fold increase in the risk of having UAP with the increasing values of CRP, but it was not statistically significant. Mulvihill et al. (41) evaluated the predictive value of CRP in the prognosis of patients with UAP. Raised concentrations of CRP were found to be predictive of an increased risk of major adverse cardiovascular events in these patients six months after presentation with UAP with CRP levels above 3mg/L. These findings suggest that the intensity of the vascular inflammatory process at the time of presentation is a determinant of clinical outcome in unstable coronary artery disease. On the contrary, as Schnabel et al. (7) emphasized CRP may be a weaker predictor than other biomarkers in acute coronary syndrome, because patients with acute coronary syndrome and within the upper quartile values of CRP revealed a trend towards increased risk of future cardiovascular events compared with patients within the lower quartile values of CRP. In the study of C-reactive protein and coronary heart disease in Western Turkey (42), a 4.2-fold increased risk of coronary heart disease with regards to CRP levels between the highest and lowest quartiles was assessed. This association between CRP and coronary heart disease is attributed to be independent of, or in addition to, the effects of conventional risk factors, suggesting that the contribution of chronic low-grade inflammation to the atherothrombotic process is present even in the setting of low cholesterol levels.

Published reports on CRP in cardiovascular risk prediction revealed that, as CRP is an independent indicator of the long-term event rate in patients with known coronary artery disease, repeated measurements of CRP levels may help to identify patients at higher risk of further cardiac events (43).

Study limitations

The study included a relatively small number of patients due to the strict enrollment criteria, which could have led to a partial lack of power of the study. One of the difficulties in this study was the discrimination of unstable angina and non-ST elevated myocardial infarction (MI). In patients with chest pain at rest but without ST-segment elevation on the electrocardiogram, the diagnosis of unstable angina and non-ST elevated MI was made by testing for elevated levels of serum cardiac markers. Since the cardiac troponin I is highly specific for myocardial tissue, is not detectable in the blood of healthy persons and shows a greater proportional increase above the upper limit of the reference interval in patients with MI (44), patients were enrolled on their cardiac troponin I levels rather than creatine kinase and its MB isoenzyme at admission. Patients with cardiac troponin I levels higher than the hospital's analytical range of 0.06 ng/ml were considered non-ST elevated MI and excluded from the study. Another limitation was the assay used for the analysis of CRP levels. The assay we used for the determination of CRP levels was not high sensitivity, with an analytical range of 3.12 mg/L and above. As in a previous study of Negri et al. (18), in the present study, coronary angiograms were assessed and scored according to the method proposed by Reardon, and we did not discriminate eccentric or complex coronary lesions on angiograms. An IVUS study would be better for this type of discrimination, but we did not have the possibility of using IVUS. Lastly, we did not have patients of suspected unstable angina pectoris with normal coronary arteries or patients with stable angina pectoris or healthy controls for further comparisons and evaluations.

Conclusion

In this study, elevated levels of CRP were associated with vessel burden in clinically and angiographically defined unstable angina pectoris. We can only speculate that the high levels of CRP observed in our patients at baseline might represent an acute exacerbation of chronic inflammatory process regarding the clinical situation. Although, serum levels of CRP did not show an independent association with unstable angina in our data, repeated measurements of CRP levels in coronary artery disease patients could help to discriminate those at high risk of further events.

Conflict of interest: None declared.

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