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Clinical Investigations

Prognostic Value of C-Reactive Protein, Fibrinogen, Interleukin-6, and Macrophage Colony Stimulating Factor in Severe Unstable Angina

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Summary

Background: Inflammatory process plays an important role in the pathogenesis of acute coronary syndromes.

Hypothesis: The study was undertaken to evaluate whether admission levels of C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), and macrophage colony stimulating factor (MCSF) can predict short-term prognosis in patients with unstable angina.

Methods: C-reactive protein, fibrinogen, IL-6, and MCSF were measured on admission in 141 consecutive patients, aged 59 ± 10 years, with unstable angina (Braunwald class IIIb). Patients were divided into two groups according to their in-hospital outcome: Group 1 comprised 77 patients with a complicated course (2 died, 15 developed nonfatal myocardial infarction, and 60 had recurrence of angina), and Group 2 comprised 64 patients with an uneventful course.

Results: Admission median levels of CRP (8.8 vs. 3.1 mg/l, p = 0.0002), fibrinogen (392 vs. 340 mg/dl, p = 0.008), IL-6 (8.8 vs. 4.5 pg/ml, p = 0.03), and MCSF (434 vs. 307 pg/ml, p = 0.0001) were higher in Group 1 than in Group 2. The MCSF levels were an independent risk factor for in-hospital events, with an adjusted odds ratio for eventful in-hospital outcome of 3.3 (95% confidence interval 1–10.9, p = 0.04), and correlated with levels of IL-6 (r_s = 0.52, p = 0.0001), CRP (r_s = 0.43, p = 0.0001), and fibrinogen (r_s = 0.25, p = 0.004).

Conclusions: These findings suggest that among the studied inflammatory indices only increased admission levels of MCSF are strongly and independently related with adverse short-term prognosis in patients with severe unstable angina.

Key words: C-reactive protein, fibrinogen, interleukin-6, macrophage colony stimulating factor, unstable angina

Introduction

Although the pathophysiology of unstable angina has not been fully elucidated, it is becoming increasingly clear that inflammation is a key pathogenic factor of this syndrome.[1] Despite full medical treatment, prognosis remains poor and nearly 10% progress to myocardial infarction.[2] Elevation of acute phase proteins, such as C-reactive protein (CRP) and fibrinogen, are strong predictors of short- and long-term prognosis in unstable angina.[3–5] Increased proinflammatory cytokines have also been reported in unstable angina,[6,7] but few data exist regarding the prognostic value. Biasucci *et al.*[8] reported that increasing levels of interleukin-6 (IL-6) during the first 2 days of hospitalization in unstable angina are associated with an increased risk of in-hospital coronary events. In addition, high macrophage colony stimulating factor (MCSF) levels were an independent predictor of future coronary events in patients with angina pectoris.[9] In the present study, we evaluated whether admission levels of CRP, fibrinogen, IL-6, and MCSF can predict prognosis in patients hospitalized with unstable angina and whether their prognostic value is independent.

Methods

Patients

We studied 141 patients (111 men, 30 women, aged 59 ± 10 years, range 36–75 years) who were admitted to our coronary care unit with severe unstable angina (Braunwald class IIIb). The criteria for enrollment on admission included at least two resting angina attacks in the previous 24 h or one

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episode lasting > 20 min during an angina attack with ischemic ST-segment changes. Electrocardiographic (ECG) criteria to be fulfilled were newly developed ≥ 0.1 mV ST-segment depression and/or T-wave inversion in ≥ 2 contiguous leads. On admission and 6 h later, there was no evidence of myocardial infarction (MI) as detected by elevation of creatine kinase (CK). The second CK measurement was applied to exclude an evolving non-Q wave MI misclassified as unstable angina on admission. Exclusion criteria were MI or percutaneous transluminal coronary angioplasty (PTCA) within the previous 6 months, clinical evidence of heart failure, valvular heart disease, renal dysfunction with a creatinine level > 2 mg/dl, age > 75 years, and coexistent neoplasty or inflammatory disease. We also excluded patients who had undergone coronary artery bypass graft (CABG) and those with left bundle-branch block or other ECG abnormalities that could invalidate ST-segment analysis.

From January 1999 to January 2001, 648 patients were admitted to our institute with a diagnosis of unstable angina; 63 were excluded because of the lack of an angina attack during the previous 24 h, 183 had no diagnostic ST-segment shift, 27 had left bundle-branch block, and 46 showed elevation of CK measured 6 h after admission. In addition, 68 had MI or PTCA within the previous 6 months, 64 had a history of CABG, 21 had symptoms of heart failure, and 35 had renal dysfunction, neoplasty, or inflammatory disease. The remaining 141 patients comprised the study group.

Study Design

Venous blood samples were obtained on admission for assessment of CRP, fibrinogen, IL-6, and MCSF. Creatine kinase was measured on admission and 6 h later, and those with increased levels were excluded. Creatine kinase was also determined every day during hospitalization to identify those complicated by myocardial necrosis. Cardiac troponin I (cTnI) was also measured on admission.

All patients received heparin (mostly low molecular-weight heparin), nitrates, aspirin, and beta blockers combined with calcium antagonists according to the severity of symptoms. The patients were divided into two groups according to the in-hospital outcome: Group 1 comprised 77 patients with an eventful course and Group 2 included 64 patients who did not experience an event.

An event was defined by the occurrence of death (2 patients), nonfatal acute MI (15 patients), and the recurrence of angina (60 patients) while hospitalized. Creatine kinase and CK-MB were used to define MI. The threshold for this was total CK concentration more than twice the upper normal limit and an above-normal concentration of CK-MB. In addition, we considered those with cTnI levels ≥ 0.1 ng/ml on admission as a high-risk group for cardiac events. Recurrent angina was defined as angina lasting at least 5 min associated with new ST-segment changes, T-wave inversions with no pathologic increase of CK, or angina without ECG changes or increase of cardiac enzymes that prompted a decision for further titration of anti-ischemic medication or early revascularization. Group 1 was further divided into patients who had a hard event (acute nonfatal MI, death, n = 17) and those with a soft event (recurrence of angina, n = 60).

Laboratory Assays

C-reactive protein was assayed by particle-enhanced immunonephelometry (N Latex CRP mono, Dade-Behring Marburg GmbH, Marburg, Germany) with a range of 0.175–1100 mg/l; fibrinogen was assayed with the Clauss method; IL-6 was measured with high-sensitivity enzyme-linked immunoassay (R & D Systems Europe Ltd, Abingdon, U.K.) with a range of 0.156–10 pg/ml; and MCSF by the quantitative sandwich immunoassay technique (R & D Systems) with a range of 31.2–2000 pg/ml, respectively. The intra- and interassay coefficient of variation for CRP and MCSF measurements was < 5%, for fibrinogen < 4%, and for IL-6 < 12%. Cardiac troponin 1 was measured in a one-step enzyme immunoassay based on the sandwich principle (Dimension RxL/Dade Behring). The minimal detectable concentration of this assay was 0.04 ng/ml. The intra- and interassay coefficient of variation was < 4.3% and < 9%, respectively.

Statistical Analysis

The data on CRP, fibrinogen, IL-6, and MCSF, which were not normally distributed, were expressed as medians. Differences within and between groups were analyzed by Wilcoxon signed rank test and Mann-Whitney U test. Spearman's rank correlation test was used for correlations. Discontinuous variables were tested by a contingency chi-square test. To evaluate the independent contribution of CRP, fibrinogen, IL-6, and MCSF to the risk of in-hospital event, logistic regression analysis was used, with age, gender, diabetes mellitus, hypertension, smoking, and body mass index as possible confounding factors. In this model, logarithmic transformation was made on levels of CRP, fibrinogen, IL-6, and MCSF in order to normalize their highly skewed distribution. Logistic regression analysis was also performed after incorporating categorical data defined by cTnI levels into the previous model as an additional confounding factor. Using the threshold of 0.1 ng/ml, two groups were created: high risk for events with cTnI ≥ 0.1 ng/ml and low risk for events with cTnI < 0.1 ng/ml. A p value of < 0.05 was considered significant. The Statistica 2000 (5.5) (StatSoft, Tulsa, Okla., USA) statistical package was used.

Results

Baseline characteristics of the patients studied are summarized in Table I. Patients with an eventful course required more days of hospitalization. In addition, patients with an eventful outcome were older and more frequently hypertensive and diabetic than those of the uneventful group, but this difference did not reach statistically significant levels. The percentage of patients receiving aspirin prior to the day of admission was similar in the two groups (55.8 vs. 53.1%, p = 0.88).

TABLE I Clinical characteristics and lipid profile in patients with unstable angina according to whether there was development (Group 1) or not (Group 2) of an event during hospitalization

Variables	Group 1 (n =77)	Group 2 (n = 64)	p Value
Age (years)	60.3 (8.4)	57.1 (11)	0.06
Sex (male/female)	63/14	51/13	0.9
Body mass index (kg/m^2)	28.5 (4)	27.9 (3.4)	0.3
Hematocrit (%)	42.6 (4.3)	42.5 (4.4)	0.9
Creatinine (mg/dl)	1.09 (0.33)	1.02 (0.27)	0.21
Days of hospitalization	7.1 (2.8)	5.2 (0.7)	0.0001
Hypertension (%)	53.2	40.6	0.19
Diabetes mellitus (%)	32.5	20.3	0.15
Family history of CAD (%)	27.3	16	0.15
Current smokers (%)	49.3	57.8	0.4
Previous MI (%)	32.5	37.5	0.65
Lipids			
Total cholesterol (mg/dl)	223 (43)	230 (48)	0.32
Triglycerides (mg/dl)	150 (56)	164 (59)	0.16
HDL cholesterol (mg/dl)	39.7 (8.4)	37.5 (8.7)	0.13
LDL cholesterol (mg/dl)	150.8 (40)	156.4 (39)	0.32

Abbreviations: CAD = coronary artery disease, HDL = high-density lipoprotein, LDL = low-density lipoprotein, MI = myocardial infarction.

Outcome

During hospitalization, 77 of 141 patients (54.6%) had an eventful in-hospital course (Group 1). Of these, 2 died (1 suddenly and 1 preceded by an MI), 15 developed non-Q-wave MI, and 60 had a recurrence of angina, which in 33 patients did not respond to maximal medical treatment, followed by urgent coronary angiogram. Of these 33 patients, 30 underwent revascularization; 20 of these had predischarge PTCA and 10 were referred for CABG (4 had left main disease and underwent urgent CABG). Of 141 patients, 64 (45.4%) responded entirely to medical treatment (Group 2). They had no recurrence of angina during their hospitalization and underwent a predischarge exercise test that determined further investigation policy.

Serum Inflammatory Markers

Entry levels of CRP, fibrinogen, IL-6, and MCSF were higher in Group 1 than in Group 2 (Table II). Levels of separately compared MCSF and CRP preserved the difference between Group 2 and subgroups of patients with soft and hard events (Fig. 1A, B). Interleukin-6 lost its significance in the subgroup of patients with soft events (Fig. 1C), and fibrinogen in the subgroup of patients with hard events (Fig. 1D). Of patients with an eventful course, 59 (76.6%) had cTnI levels ≥ 0.1 ng/ml on admission, while of those without events 24 (37.5%) had cTnI levels ≥ 0.1 ng/ml (p = 0.0001).

From the inflammatory markers studied, only entry levels of MCSF were an independent and the most powerful predictor of outcome, with an adjusted odds ratio for events during hospitalization of 3.3 (95% confidence interval [CI] 1–10.9, p = 0.04) (Table III). Even after incorporating cTnI levels (categorical data: high risk [cTnI ≥ 0.1 ng/ml] and low risk for events [cTnI < 0.1 ng/ml]), MCSF remained an independent predictor of outcome with an adjusted odds ratio for events of 3.4 (95% CI 0.9–11.9, p = 0.04). However, in this model cTnI ≥ 0.1 ng/ml was the most powerful predictor of outcome with an adjusted odds ratio for events of 5.1 (95% CI 2–15, p = 0.008).

There was a significant positive correlation between entry levels of MCSF with IL-6 (r_s = 0.52, p = 0.0001), CRP (r_s = 0.43, p = 0.0001), and fibrinogen levels (r_s = 0.25, p = 0.004).

Discussion

Our study indicates that patients with severe unstable angina and worsening in-hospital outcome have higher levels of acute phase proteins and cytokines than those who do not experience an event. It is interesting that MCSF was the only independent and most powerful predictor for in-hospital outcome after adjustment to other inflammatory indices and confounding factors such as age, gender, diabetes mellitus, hypertension, smoking, and body mass index.

We did not aim to compare the prognostic value of inflammatory indices with the established prognostic value of cTnI, which is a highly specific and sensitive marker of myocardial necrosis with proven utility for risk assessment in unstable angina.[10] Morrow *et al.*,[11] using the same cTnI assay, showed that patients with unstable angina and cTnI ≥ 0.1 ng/ml had an adverse short-term prognosis. The relatively low cTnI threshold that they proposed is related to the high analytic sensitivity of the cTnI assay that they used. Our study confirmed that cTnI ≥ 0.1 ng/ml on admission is a strong and independent predictor for in-hospital complications in patients with severe unstable angina.

The rate of hard events (deaths and nonfatal MI) in our study was relatively high; this is mainly due to our inclusion criteria.

TABLE II C-reactive protein, fibrinogen, interleukin-6, and macrophage colony stimulating factor levels on admission in patients with eventful (Group 1) and uneventful (Group 2) in-hospital course

	Group 1 (n = 77)	Group 2 (n = 64)	p Value
CRP (mg/l)	8.8 (3.4–15.9)	3.1 (1.5–5.7)	0.0002
Fibrinogen (mg/dl)	392 (325–444)	340 (282–408)	0.008
IL-6 (pg/ml)	8.8 (3.3–14.4)	4.5 (2.7–10.8)	0.03
MCSF (pg/ml)	434 (338–652)	307 (261–479)	0.0001

Values are expressed as median and 25th and 75th percentile.
Abbreviations: CRP = C-reactive protein, IL-6 = interleukin-6, MCSF = macrophage colony stimulating factor.

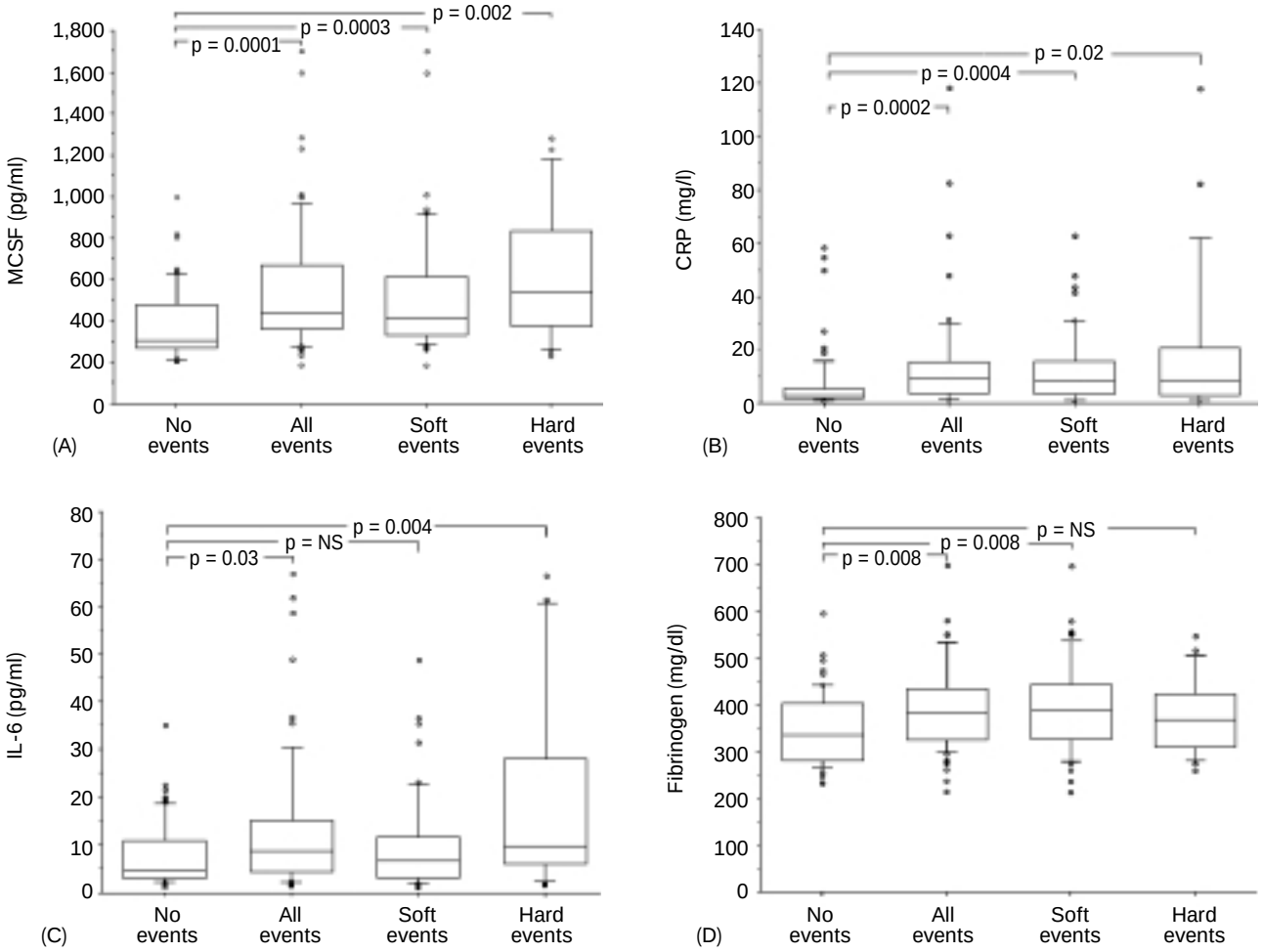

FIG. 1 Comparison of levels of admission of the following in patients without events and those with all events, soft events, and hard events (A) macrophage colony stimulating factor (MCSF), (B) C-reactive protein (CRP), (C) interleukin-6 (IL-6), and (D) fibrinogen. Values are expressed as median and 25th and 75th percentiles by the box, largest and smallest nonoutlier values by the lines at the ends of the box, and outlier values by circles. NS = not significant.

TABLE III Odds ratio for cardiac event during hospitalization

	Odds ratio	95% CI	p Value
MCSF	3.3	1–10.9	0.04
IL-6	0.9	0.49–1.7	0.75
CRP	1.5	0.9–2.4	0.08
Fibrinogen	1.45	0.15–13.6	0.74
Age	1.01	0.96–1.07	0.5
Sex	1.35	0.4–4.5	0.62
Diabetes mellitus	1.29	0.45–3.63	0.63
Hypertension	1.09	0.44–2.7	0.84
Cigarette smoking	0.61	0.24–1.5	0.29
Body mass index	1.06	0.94–1.2	0.32

Abbreviation: CI = confidence interval. Other abbreviations as in Table II.

All our patients had ECG changes (ST-segment depression or T-wave inversion) during a resting angina attack within 24 h prior to admission, characteristics that identify those more likely to have an unfavorable prognosis.[12, 13] It has been proposed that the prognostic implications of ST-T changes are probably related to a larger magnitude of ischemia.

Previous Studies

Elevated levels of MCSF have been described in patients with stable angina compared with normal subjects.[14] It has also been reported that MCSF is higher in patients with unstable rather than stable angina.[7,9] In addition, a transient increase in MCSF has been found in patients with uncomplicated MI.[15] Recently, Saitoh *et al*.[9] demonstrated that high MCSF levels predict cardiac events during a mean follow-up period of 14 months in patients with stable and unstable angina. They also proposed that MCSF levels ≥ 950 pg/ml were an independent risk factor for an unfavorable outcome.

Macrophage Colony Stimulating Factor and Cardiac Events

Atherosclerosis is a chronic inflammatory disease[16] and macrophages are the predominant inflammatory cells in atherosclerotic plaques. Unstable angina is associated with an exaggerated inflammatory reaction and is characterized by a significantly larger amount of macrophage-rich plaques compared with stable angina.[17] The MCSF is a hematopoietic growth factor released by the injured endothelium and has the ability to stimulate proliferation, differentiation, and maturation of monocytes and macrophages.[18] In addition, MCSF can stimulate the production of further MCSF from local endothelium and macrophages.[19] Macrophage involvement in cardiac events include various mechanisms such as thrombus organization, smooth muscle cell migration and proliferation, and secretion of proteolytic enzymes.[20] The increased levels of MCSF in unstable angina may represent a potential inducer of macrophages. The precise signal of MSCF production in acute coronary syndromes is unknown. In vitro studies showed that minimally modified low-density lipoprotein (LDL) induces the expression of MCSF,[21] and therefore oxidized LDL could be a candidate as an inducer of MCSF production.

It has also been reported that MCSF levels are related to the degree of ischemia detected by Holter monitoring and exercise testing in patients with stable angina.[14] It has been postulated that MCSF may initiate and prolong ischemic episodes by promoting the formation of microthrombi,[22] increasing coronary tone,[23] and impairing vasodilatation.[24] Therefore, the higher levels of MCSF in our study may not only reflect the extent of ischemia but may also play an active role in triggering or worsening ischemia.

C-Reactive Protein, Interleukin-6, Fibrinogen, and Cardiac Events

In our study, admission levels of CRP, fibrinogen, and IL-6 were higher in patients with a complicated in-hospital course. However, after adjustment to other risk factors, the statistical significance of these factors was eliminated. Of the variety of circulating markers, CRP has been best studied with the most consistent relationship to future risk, both in healthy subjects and in patients with stable or unstable angina.[25,26] There is growing evidence that CRP may constitute an independent cardiovascular risk factor and not only an epiphenomenon.[27] Fibrinogen like CRP is an acute phase reactant, as it is in addition a pivotal component of the coagulation system.[28] The double nature of fibrinogen, as an inflammatory index and a thrombotic risk factor,[29] enhances its possibility to be more directly involved in the clinical expression of unstable angina. Interleukin-6 is a pleiotropic cytokine[30] that controls CRP and fibrinogen hepatic production.[31] It can be produced by many vascular cells including endothelial cells, smooth muscle cells, lymphocytes, and macrophages.[32] It has been reported to predict short-term prognosis in unstable angina.[6]

The exact interaction among MCSF, IL-6, CRP, and fibrinogen is unknown. It is tempting to hypothesize that MCSF is one of the initial triggers in this series of events. Macrophage colony stimulating factor is released by the injured endothelium and induces activation of macrophages that further release IL-6, as it is the principal regulator of CRP and fibrinogen production. The interaction among MCSF, IL-6, CRP, and fibrinogen is enforced by the positive association found in our study of MCSF with IL-6, CRP, and fibrinogen. A correlation between MCSF and CRP has also been reported in stable angina.[14]

Study Limitations

The following limitations should be noted. First, there was no documentation of coronary artery disease with coronary angiogram in all patients who had an uneventful in-hospital outcome. Therefore, a few patients could, in fact, have had noncardiac chest pain. However, our inclusion criterion of ischemic ST changes during angina attacks minimizes the number of patients who possibly had a noncardiac chest pain. Second, in order to exclude patients with an evolving MI on admission, we applied a CK determination 6 h after admission; however, there is a possibility that a few patients with normal CK at 6 h already had an evolving MI. Even if this should be the case, the value of our findings is not affected since MCSF levels are higher in patients with both hard and soft events. Third, our data were derived from a selected cohort at high-risk for in-hospital complications, which represents approximately 20% of our entire population with unstable angina. Therefore, our findings cannot be applied to every patient admitted with the diagnosis of unstable angina. Finally, the study was not designed to determine whether the increase of MCSF in patients with unstable angina is the cause or the consequence of plaque instability.

Conclusions

The results of our study suggest that among the inflammatory markers studied only increased admission levels of MCSF could predict independently a worse short- term prognosis in patients with severe unstable angina. These findings confirm the primary role of the inflammatory component in the pathogenesis of acute coronary syndromes and suggest a possible key role of MCSF. However, further studies are required to establish the exact mechanism by which MCSF contributes to plaque instability and acute coronary events.

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