In-Hospital Prognostic Value of Inflammatory Indices in Patients with Unstable Angina

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Introduction: Inflammatory process plays an important role in the pathogenesis of acute coronary syndromes. We examined 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: CRP, 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 A consisted of 77 patients with a complicated course (2 died, 15 developed non-fatal myocardial infarction and 60 had recurrence of angina) and Group B consisted of 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 A compared to Group B. 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 to 10.9, p=0.04). MCSF levels were 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.

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Although 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 since nearly 7% of patients progress to myocardial infarction and 4% die within 6 months of their hospitalization[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[3,4,5]. Increased pro-inflammatory cytokines have also been reported in unstable angina[6,7] but little data exists regarding their prognostic value. Biasucci et al[8] reported that increasing levels of interleukin-6 (IL-6) during the first 2 days of hospitalisation 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 hospitalised with unstable angina and whether their prognostic value is independent.

Methods

Patients

We studied 141 patients (111 men and 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 a minimum of two resting angina attacks in the previous 24 hours or one episode lasting >20 but <30 minutes during an angina attack with ischaemic ST-segment changes. Electrocardiographic 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 hours later there was no evidence of myocardial infarction as detected by elevation of creatine kinase (CK). The second CK measurement was obtained to exclude an evolving non-Q myocardial infarction misclassified as unstable angina on admission. Exclusion criteria were myocardial infarction or percutaneous transluminar angioplasty 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 neoplasy or inflammatory disease. We also excluded patients who had undergone coronary artery bypass graft (CABG) and those with a left bundle-branch block or other electrocardiographic abnormalities that could invalidate ST-segment analysis.

From January 1999 to January 2001, 748 patients were admitted to our institute with a diagnosis of unstable angina; 83 were excluded because of the lack of an angina attack during the previous 24 hours, 213 had no diagnostic ST-segment shift, 32 had left bundle-branch block and 51 showed elevation of CK measured 6 hours after admission. In addition, 83 had myocardial infarction or percutaneous transluminar angioplasty within the previous 6 months, 74 had a history of CABG, 31 had symptoms or signs of heart failure and 40 had renal dysfunction, neoplasm 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. CK was measured on admission and 6 hours later and those patients with increased levels were excluded. CK was also determined every day during hospitalisation to identify complications with myocardial necrosis. Cardiac troponin I (cTnI) was also measured on admission.

All patients received heparin (the vast majority low molecular weight heparin), nitrates (intraven-

ously for at least the first 24 hours), aspirin and beta-blockers and calcium antagonists. Only a few patients received platelet glycoprotein IIb/IIIa receptor antagonists since the use of these agents was still very limited during our study. The patients were divided into 2 groups according to the in-hospital outcome: Group A consisted of 77 patients with an eventful course and Group B, consisted of 64 patients who did not experience an event.

An event was defined by the occurrence of death (2 patients), non-fatal acute myocardial infarction (15 patients) and the recurrence of angina (60 patients) while hospitalised. CK and CK-MB were used to define myocardial infarction. 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 on admission ≥0.1 ng/ml as a high risk group for cardiac events. Recurrent angina was defined as angina lasting at least 5 minutes associated with new ST-segment changes, T-wave inversions with no pathological increase of CK, or angina without electrocardiographic changes or increase of cardiac enzymes that prompted a decision for further titration of anti-ischaemic medication or early revascularization. Group A was further divided into patients who had a hard event (acute non-fatal myocardial infarction, death: 17 patients) and those with a soft event (recurrence of angina: 60 patients).

Laboratory assays

CRP was assayed by particle enhanced immuno-nephelometry (N Latex CRP mono, Date-Behring) with a range from 0.175 to 1100 mg/L. Fibrinogen was assayed with Clauss method. IL-6 was measured with high sensitivity enzyme linked immunoassay (R & D System) with a range from 0.156 to 10 pg/mL and MCSF by the quantitative sandwich immunoassay technique (R & D System) with a range from 31.2 to 2000 pg/mL, respectively. cTnI 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.

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 analysed 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 x^2 test. In order to evaluate the independent contribution of CRP, fibrinogen, IL-6, MCSF to the risk of in-hospital event, logistic regression analysis was used with age, sex, 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 normalise their highly skewed distribution. Logistic regression analysis was also performed after incorporating in the previous model, as an additional confounding factor, categorical data defined by cTnI levels. Using the threshold of 0.1 ng/mL, 2 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 < 0.05 was considered significant. The STATISTICA 2002 (6) statistical package was used.

Results

Baseline characteristics of the studied patients are summarised in Table 1. 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 2 groups (55.8% v 53.1%, p=0.88).

During hospitalisation 77 of 141 patients (54.6%) had an eventful in-hospital course (Group A). Of these, 2 patients died (1 suddenly and in 1 death was preceded by a myocardial infarction), 15 developed non-Q-wave myocardial infarction and 60 had a recurrence of angina of whom 33 patients did not respond to maximal medical treatment, followed by urgent coronary angiogram. Of these 33 patients, 30 underwent revascularization of whom 21 had a pre-discharge percutaneous transluminar coronary angioplasty and 9 were referred for CABG (4 had left main disease and underwent urgent CABG). In the 27 patients whose symptoms were controlled by intensification of medical treatment an appointment for coronary angiogram was given. Sixty-four of the 141 patients (45.4%) responded positively to medical treatment (Group B). They did not have a recurrence of angina during their hospitalisation and underwent a pre-discharge exercise test that determined further investigation policy.

Serum inflammatory markers

Entry levels of CRP, fibrinogen, IL-6 and MCSF were higher in Group A compared to Group B (Table 2). MCSF and CRP levels preserved the difference between Group A and subgroups of patients with soft

Table 1. Clinical characteristics and lipid profile in patients with unstable angina according to the development (Group A) or no (Group B) of an event during hospitalisation.

Variables	Group A (n=77)	Group B (n=64)	p value
Age (yrs)	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
Hypertension (%)	53.2	40.6	0.19
Diabetes mellitus (%)	32.5	20.3	0.15
Family history of CAD (%)	27.3	17.2	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

CAD=coronary artery disease, HDL=high density lipoprotein, LDL=low density lipoprotein, MI=myocardial infarction

Table 2. CRP, fibrinogen, IL-6 and MCSF levels on admission in patients with eventful (Group A) and uneventful (Group B) in-hospital course.

	Group A (n=77)	Group B (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.
CRP=C-reactive protein, IL-6=interleukin-6, MCSF=macrophage colony stimulating factor.

and hard events when compared separately (Figure 1 and 2). IL-6 lost its significance in the subgroup of patients with soft events (Figure 3) and fibrinogen in the subgroup of patients with hard events (Figure 4). Of patients with an eventful course, 49 (63.6%) had cTnI levels ≥0.1 ng/mL on admission, while of those without events 15 (23.4%) had cTnI levels ≥0.1 ng/mL (p=0.0001).

From the studied inflammatory markers, only entry levels of MCSF were an independent and the most powerful predictor of outcome with an adjusted odds ratio for events during hospitalisation of 3.3 (95% confidence interval 1 to 10.9, p=0.04) (Table 3). 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% confidence interval 0.9 to 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% confidence interval 2 to 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).
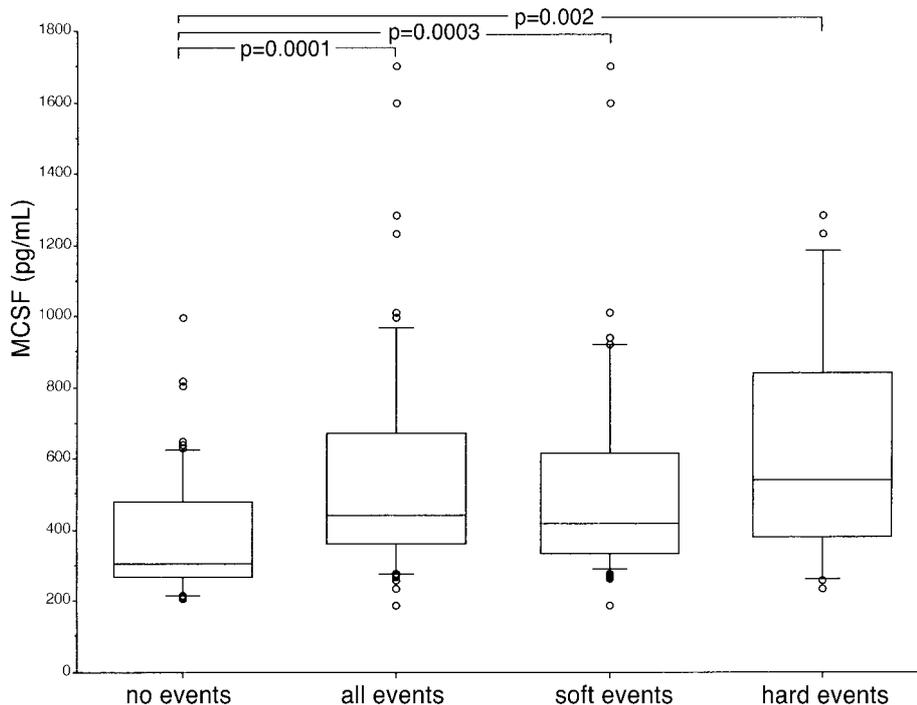

Figure 1. Comparison of MCSF levels on admission of patients without events with those with all events, soft and hard events. Values are expressed as median and 25th and 75th percentiles by the box, largest and smallest nonoutlier values by the lines at the end of the box, and outlier values by circles.
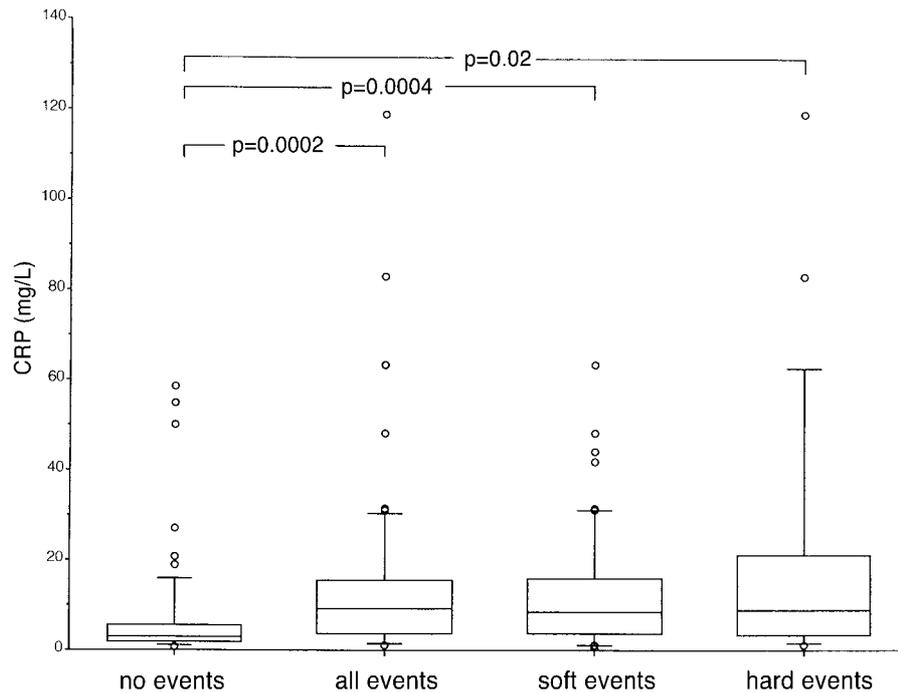
Figure 2. Comparison of CRP levels on admission of patients without events with those with all events, soft events and hard events. Values are expressed as median and 25th and 75th percentiles by the box, largest and smallest nonoutlier values by the lines at the end of the box, and outlier values by circles.

Figure 3. Comparison of IL-6 levels on admission of patients without events with those with all events, soft events and hard events. Values are expressed as median and 25th and 75th percentiles by the box, largest and smallest nonoutlier values by the lines at the end of the box, and outlier values by circles.
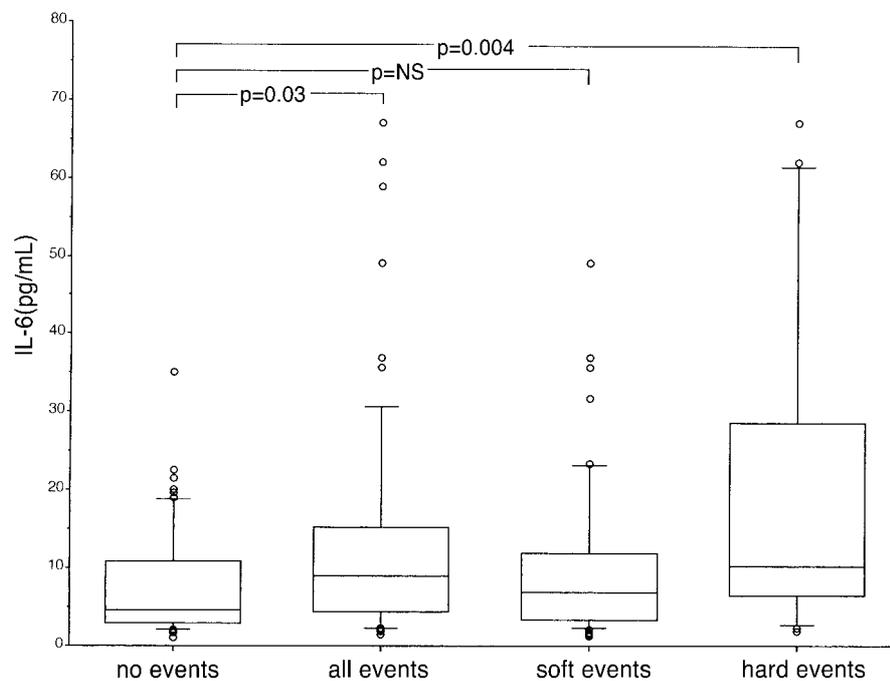
Discussion

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.

Interestingly, 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, sex, diabetes mellitus, hypertension, smoking and body mass index.
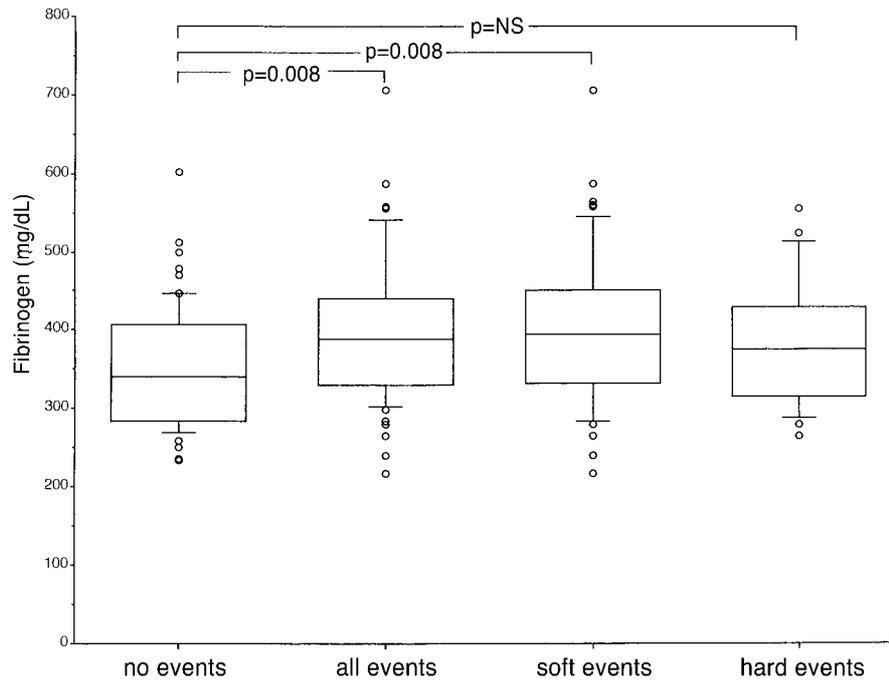
Figure 4. Comparison of fibrinogen levels on admission of patients without events with those with all events, soft events and hard events. Values are expressed as median and 25th and 75th percentiles by the box, largest and smallest nonoutlier values by the lines at the end of the box, and outlier values by circles.

We did not aim to compare the prognostic value of inflammatory indices with the established prognostic value of cTnI. cTnI 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 $\geq 0,1$ ng/mL had an adverse short-term prognosis. The relatively low cTnI threshold that they proposed is related to the high analytic sensitivity of cTnI assay that they used. Our study confirmed that cTnI $\geq 0,1$ ng/mL on admission is a strong and independent predictor for in-hospital complications in patients with severe unstable angina.

Table 3. Odds ratio for cardiac event during hospitalisation.

	odds ratio	95% CI	p value
MCSF	3.3	1.00-10.9	0.04
IL-6	0.9	0.49-1.70	0.75
CRP	1.5	0.90-2.40	0.08
Fibrinogen	1.45	0.15-13.60	0.74
Age	1.01	0.96-1.07	0.5
Sex	1.35	0.40-4.50	0.62
Diabetes mellitus	1.29	0.45-3.63	0.63
Hypertension	1.09	0.44-2.70	0.84
Cigarette smoking	0.61	0.24-1.50	0.29
Body mass index	1.06	0.94-1.20	0.32

CI=confidence interval, CRP=C-reactive protein, IL-6=interleukin-6, MCSF=macrophage colony stimulating factor.

The rate of hard events (deaths and non-fatal myocardial infarctions) in our study was relatively high. This is mainly due to our inclusion criteria. All our patients had electrocardiographic changes (ST segment depression or T wave inversion) during a resting angina attack within 24 hours prior 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 ischaemia.

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 myocardial infarction[15]. 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.

MCSF and cardiac events

Atherosclerosis is a chronic inflammatory disease[16,17] and macrophages are the predominant inflammatory cells in atherosclerotic plaques. Unstable angina is associated with an exaggerated inflammatory reaction and is characterised by a significantly larger amount of macrophage-rich plaques compared to stable angina[18]. 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[19]. In addition, MCSF can stimulate the production of further MCSF from local endothelium and macrophages[20]. Macrophage involvement in cardiac events include various mechanisms such as thrombus organisation, smooth muscle cell migration and proliferation and secretion of proteolytic enzymes[21]. 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 LDL induces the expression of MCSF[22] and therefore oxidised LDL could be a candidate as an inducer of MCSF production.

It has been reported that MCSF levels are related to the degree of ischaemia detected by Holter monitoring (48 hours) and exercise testing in patients with stable angina[14]. It has been postulated that MCSF may initiate and prolong ischaemic episodes by promoting the formation of microthrombi[23], increasing coronary tone[24] and impairing vasodilatation[25]. Therefore, the higher levels of MCSF in our study may not only reflect the extent of ischaemia but may also play an active role in triggering or worsening the ischaemia. This is reinforced by recent studies which reported that MCSF can induce apoptosis of vascular smooth muscle cells[26] and can stimulate the expression of membrane type 3-matrix matalloproteinase[27], mechanisms which both destabilize the atherosclerotic plaque.

CRP, IL-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[28,29]. There is growing evidence that CRP may constitute an independent cardiovascular risk factor and not only an epiphenomenon[30,31]. Fibrinogen like CRP is an acute phase reactant, being in addition a pivotal component of the coagulation system[32]. The double nature of fibrinogen, as an inflammatory index and a thrombotic risk factor[33], enhances its possibility to be more directly involved in the clinical expression of unstable angina. IL-6 is a pleiotropic cytokine[34] which controls CRP and fibrinogen hepatic production[35]. It can be produced by many vascular cells including endothelial cells, smooth muscle cells, lymphocytes and macrophages[36]. IL-6 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. MCSF is released by the injured endothelium and induces activation of macrophages that further release IL-6, being 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].

Conclusions

The results of our study suggest that among the studied inflammatory markers only increased admission levels of MCSF could independently predict 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. Finally, our data do not recommend the prognostic stratification of coronary patients by the introduction of MCSF instead of CRP or cTnI which remain the best-established prognostic markers that are widely used in daily clinical practice.

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