Acute-phase reactants in acute myocardial infarction: impact on 5-year prognosis

Rita Mariotti, Giuseppe Musumeci, Marco De Carlo, Ombretta Biadi, Paolo Caravelli, Ugo Limbruno, Mario Mariani

Cardio Thoracic Department, University of Pisa, Pisa, Italy

Key words:
Acute myocardial infarction; Immune system; Prognosis.

Background. **Acute-phase reactants have recently been shown to have a short-term and possibly long-term prognostic value in acute coronary syndromes. The aim of the present study was to retrospectively verify whether serum levels of inflammation markers can predict the occurrence of early and late cardiac events after myocardial infarction.**

Methods. **We reevaluated 58 consecutive patients (43 men and 15 women, mean age 66 ± 12 years) admitted to our Center during 1993 with a first myocardial infarction. Patients with non-cardiac causes of inflammation were excluded, as well as patients with a left ventricular ejection fraction < 40%. From the first blood sample obtained at admission, we evaluated C-reactive protein (CRP) and α_1-acid glycoprotein (α_1-AGP) serum levels, the erythrocyte sedimentation rate (ESR), fibrinogen levels, and the white blood cell (WBC) count. We also evaluated the highest level of serum cardiac markers. Follow-up data were collected for 55 patients in June 1999.**

Results. **Five in-hospital and 13 delayed cardiac deaths occurred. The mean follow-up of current survivors was 5.9 ± 0.4 years. Patients in whom cardiac death occurred had significantly higher CRP (7.4 ± 4.1 vs 3.0 ± 2.4 mg/dl, p < 0.001) and α_1-AGP levels (160 ± 38 vs 113 ± 24 mg/dl, p < 0.001), ESR (63 ± 30 vs 37 ± 25 mm/hour, p < 0.001), and WBC count (13 727 ± 3853 vs 10 936 ± 3358/mm^3, p = 0.004). At multivariate analysis, higher α_1-AGP (p < 0.001) and CRP serum levels (p = 0.02) were independent predictors of cardiac death. Patients in whom cardiac events occurred during follow-up showed higher CRP (5.7 ± 3.7 vs 1.6 ± 1.5 mg/dl, p < 0.001) and α_1-AGP levels (140 ± 36 vs 101 ± 23 mg/dl, p < 0.001) and ESR (50 ± 30 vs 34 ± 26 mm/hour, p = 0.06). Higher α_1-AGP (p < 0.001) and CRP serum levels (p = 0.03) were independent predictors of the occurrence of cardiac events.**

Conclusions. **The present study shows that CRP and α_1-AGP have an independent prognostic value in patients presenting with a first, uncomplicated myocardial infarction. Assays of these markers may help to better stratify patients hospitalized for acute coronary syndromes.**

(Ital Heart J 2001; 2 (4): 294-300)

Received July 3, 2000; revision received January 22, 2001; accepted January 25, 2001.

Address:

Prof.ssa Rita Mariotti

Dipartimento Cardio Toracico Ospedale Cisanello Via Paradisa, 2 56124 Pisa
E-mail: r.mariotti@dcap.med.unipi.it

Introduction

The central role of acute inflammation in the pathophysiology of acute coronary syndromes has been widely demonstrated[1-7]; more recently it has been shown that serum levels of certain markers of inflammation have a prognostic value in such syndromes[8-13]. Histological studies have demonstrated that the atherosclerotic plaque contains foci of activated macrophages, monocytes, and lymphocytes which produce several cytokines (tumor necrosis factor, interferon-γ, interleukin-1, interleukin-6) and adhesion molecules which in turn induce the production of the inflammation markers commonly assayed in serum[2,14-17]. Acute coronary syndromes result from the cyclic occurrence of acute events, such as plaque erosion and disruption, at the site of chronic inflammation on the arterial wall. Several studies have shown that patients with unstable angina have increased serum levels of various markers of inflammation, such as C-reactive protein (CRP), which correlate with the short-term prognosis[11,13,18,19]. In addition, an increase in acute-phase reactants is well documented in acute myocardial infarction (AMI), the extension of which correlates with the serum levels of CRP and α_1-acid glycoprotein (α_1-AGP)[20-22]. More recently these markers have also been shown to have a predictive value with regard to the occurrence of complications such as myocardial wall rupture and congestive heart failure[10,12].

Serum levels of inflammation markers may thus play a role in predicting the outcome of acute coronary syndromes. In particular, in the setting of AMI these markers

have been shown to have a short-term and possibly long-term prognostic value[4,12,15,16].

The aim of the present study was to retrospectively verify whether serum levels of the different markers of inflammation during AMI have an impact on the short- and long-term prognosis concerning prediction of acute complications and late events within 5 years of AMI.

Methods

Population. We retrospectively reevaluated the records of 58 consecutive patients (43 men and 15 women, mean age 66 ± 12 years) admitted to our Center with chest pain between January 1993 and December 1993 within 12 hours of the onset of symptoms, and in whom the diagnosis of a first AMI was subsequently confirmed. Patients with non-cardiac causes of ongoing acute inflammation, chronic inflammatory diseases and neoplastic diseases were excluded. Patients with an echocardiographic left ventricular ejection fraction < 40% were also excluded from the study. In fact, since the prognostic role of left ventricular dysfunction after AMI is well known, we decided to exclude this factor so as to better evaluate the possible prognostic significance of acute-phase reactants. Consequently, patients presenting with clinical signs of heart failure in Killip class III-IV were also excluded. Risk factors for coronary artery disease (age, sex, family history of coronary artery disease, arterial hypertension, diabetes, dyslipidemia, cigarette smoking), ECG monitoring records, serial chest roentgenograms, transthoracic two-dimensional color Doppler echocardiograms and coronary angiography (performed in 33 patients, 57%) were reexamined (Table I). In particular, we considered the echocardiographic left ventricular ejection fraction assessed on the fourth day following hospital admission.

Plasma protein assays. For all patients, venous blood samples were taken at the time of hospital admission, every 4 hours during the first day, and daily for the next 4 days. We evaluated the plasma levels of acute-phase reactants, in particular CRP and α_1-AGP, the erythrocyte sedimentation rate (ESR), the fibrinogen levels and the white blood cell (WBC) count in the first blood sample taken. CRP was assayed by rate nephelometry (Behring Diagnostics, Westwood, MA, USA) with a detection limit of 0.2 mg/dl. Ninety percent and 99% of normal values for CRP at our laboratory were < 0.4 and < 1.0 mg/dl respectively. The intra and interassay coefficients of variability were < 5%. We then evaluated the highest level, recorded within the first week of admission, of serum cardiac markers, in particular creatine kinase (CK), CK-MB isoenzyme, lactate dehydrogenase (LDH) and aspartate aminotransferase (AST). Finally, we reviewed drug therapy during the hospital stay, particularly that concerning the use of thrombolytic agents.

Table I. Patient characteristics.

	Group 1 (n=17)	Group 2 (n=38)	p
Sex (men/women)	14/3 (82%/18%)	28/10 (74%/26%)	NS
Age (years)	64 ± 7	69 ± 13	0.03
Age > 75 years	1 (6%)	12 (32%)	0.05
Family history of coronary artery disease	8 (47%)	25 (66%)	NS
Hypertension	5 (29%)	18 (47%)	NS
Cigarette smoking	8 (47%)	24 (63%)	NS
Dyslipidemia	7 (41%)	22 (58%)	NS
Diabetes	3 (18%)	15 (40%)	NS
Heart rate at admission (b/min)	83 ± 15	92 ± 18	NS
Systolic arterial pressure at admission (mmHg)	136 ± 29	119 ± 33	NS
Anterior wall infarction	4 (24%)	12 (32%)	NS
Thrombolysis	11 (65%)	11 (29%)	0.01
Left ventricular ejection fraction (%)	51 ± 7	47 ± 5	0.01
Creatine kinase (mg/dl)	1538 ± 1130	1478 ± 1398	NS
Creatine kinase-MB (mg/dl)	115 ± 70	125 ± 128	NS
Lactate dehydrogenase (mg/dl)	1254 ± 726	1632 ± 1449	NS
Aspartate aminotransferase (mg/dl)	222 ± 148	361 ± 637	NS
Fibrinogen (mg/dl)	417 ± 116	455 ± 163	NS
C-reactive protein (mg/dl)	1.6 ± 1.5	5.7 ± 3.7	< 0.001
C-reactive protein > 3.0 mg/dl	1 (6%)	27 (71%)	< 0.001
α_1-acid glycoprotein (mg/dl)	101 ± 23	140 ± 36	< 0.001
α_1-acid glycoprotein > 110 mg/dl	4 (24%)	31 (82%)	< 0.001
Erythrocyte sedimentation rate (mm/h)	34 ± 26	50 ± 30	0.05
Erythrocyte sedimentation rate > 35 mm/h	6 (35%)	25 (66%)	0.04
White blood cell count (no./mm^3)	10 927 ± 3106	12 262 ± 3950	NS
White blood cell count > 9200/mm^3	11 (65%)	35 (92%)	0.02

Follow-up. Follow-up data were obtained by reviewing the clinical records collected at 1, 3, 6 and 12 months after discharge and on a yearly basis thereafter. Information on the clinical status of the patients was finally collected by telephone interview between May and June 1999. Follow-up was completed for 55 patients (42 men and 13 women, 95%). Three patients were lost to follow-up.

We performed a multivariate analysis in order to identify independent risk factors either for the occurrence of death due to cardiac causes or for cardiac events during follow-up. The cardiac events taken into consideration were the following: hospital death (death due to any cause occurring before discharge); delayed death due to cardiac causes (death due to any cardiac cause, including sudden death and death of unknown origin); recurrence of AMI (defined by standard ECG and laboratory criteria); need for myocardial revascularization at either coronary angioplasty or coronary artery bypass grafting (defined at a coronary angiography performed during follow-up because of recurrence of angina); development of congestive heart failure in New York Heart Association functional class III-IV. We then retrospectively grouped the patients according to the absence (group 1, n = 17) or presence (group 2, n = 38) of any of these events.

Statistical analysis. Data are reported as mean ± SD. Univariate analysis was performed using the χ^2 test or Fisher test, as appropriate, for discrete variables and using the two-sample Student's t-test or Mann-Whitney test, as appropriate, for continuous variables. Significance was set at $p < 0.05$ and high significance at $p < 0.001$. Cut-off points for continuous variables were identified with the use of receiver operating characteristic (ROC) curves. The actuarial freedom from cardiac death and from cardiac events was determined using the Kaplan-Meier method. The log-rank test was used to assess differences between Kaplan-Meier curves. Multivariate analysis for the identification of independent risk factors for cardiac death and for overall cardiac events during follow-up was performed by introducing parameters with $p < 0.10$ at univariate analysis in a Cox proportional hazards regression model.

Results

Early and delayed mortality. There were 5 in-hospital deaths (8.6%, 2 due to ventricular arrhythmias, 2 due to extension of the infarct area resulting in cardiogenic shock, and 1 due to papillary muscle rupture resulting in massive mitral regurgitation), 13 delayed cardiac deaths (8 due to congestive heart failure, 4 to myocardial reinfarction, and 1 sudden death), and 6 non-cardiac deaths (3 due to neoplasms, 1 to renal failure, 1 to bronchopneumonia, and 1 to a car accident) during follow-up. All 6 non-cardiac deaths occurred in group 2 patients after they had already experienced a second cardiac event. The mean follow-up of current survivors was 5.9 ± 0.4 years (range 5.0-6.4 years).

Comparing the 37 patients who did not suffer cardiac death (group A) with the 18 patients who died because of cardiac causes (group B), it was seen that the latter were older (72 ± 14 vs 65 ± 10 years, p = 0.02), but did not significantly differ with respect to the other cardiovascular risk factors examined. The percentage of patients with anterior wall infarction was similar in the two groups (27% in group A and 33% in group B, p = NS). The time interval from symptom onset to hospital admission and blood sampling was 4.8 ± 3.2 hours in group A and 5.8 ± 3.3 hours in group B (p = NS). Although not statistically significant, this difference partially explained the difference in the percentage of patients who underwent thrombolysis during AMI, being 49% in group A (18 out of 37 patients) and 22% in group B (4 out of 18 patients) (p = 0.05). In addition, contraindications to the use of thrombolytic agents were more frequent in group B patients. No correlation could be found between the time interval from symptom onset to blood sampling and the levels of the acute-phase reactants examined. The two groups of patients significantly differed with respect to the echocardiographically determined left ventricular ejection fraction assessed on the fourth day following hospital admission, being 50 ± 6% in group A and 45 ± 4% in group B (p = 0.007).

With regard to the laboratory findings at the time of AMI, compared with group B patients, those in group A had significantly lower serum levels of LDH (1166 ± 720 vs 2232 ± 1805 mg/dl, p = 0.003), AST (181 ± 137 vs 600 ± 868 mg/dl, p = 0.007), CRP (3.0 ± 2.4 vs 7.4 ± 4.1 mg/dl, p < 0.001; Fig. 1) and α_1-AGP (113 ± 24 vs 160 ± 38 mg/dl, p < 0.001; Fig. 2) and lower ESR (37 ± 25 vs 63 ± 30 mm/hour, p < 0.001) and WBC count (10 936 ± 3358 vs 13 727 ± 3853/mm^3, p = 0.004). The median and range of CRP serum levels in groups A and B were 2.1 mg/dl (range 0.3-10.9 mg/dl) and 6.2

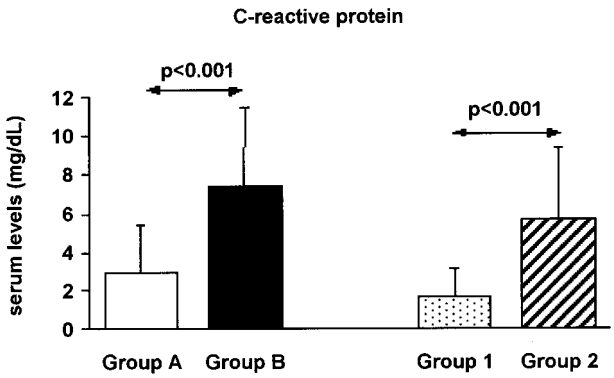

Figure 1. *Serum levels of C-reactive protein in the first blood sample obtained at admission of patients with acute myocardial infarction: comparison between patients who did not suffer either early or late cardiac death (group A) and those who did (group B) and between patients who remained event-free during follow-up (group 1) and those who suffered cardiac events (group 2).*

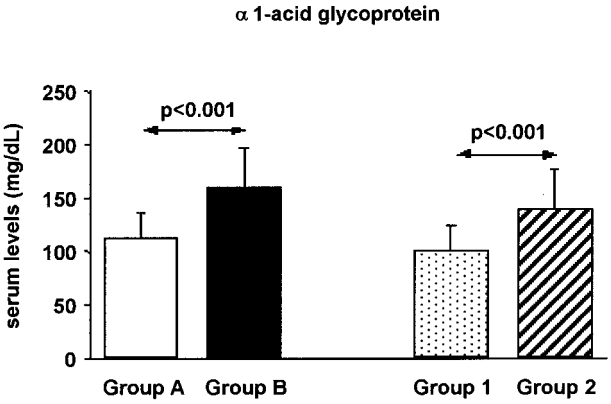

Figure 2. *Serum levels of α_1-acid glycoprotein in the first blood sample obtained at admission of patients with acute myocardial infarction: comparison between patients who did not suffer either early or late cardiac death (group A) and those who did (group B) and between patients who remained event-free during follow-up (group 1) and those who suffered cardiac events (group 2).*

mg/dl (range 2.7-15.4 mg/dl) respectively. No statistically significant differences were detected between the two groups of patients concerning CK, CK-MB and fibrinogen serum levels. Moreover, no correlation could be found between the serum levels of acute-phase reactants and those of either CK or CK-MB.

At multivariate analysis, the independent risk factors for the occurrence of cardiac death following AMI were higher α_1-AGP ($p < 0.001$) and CRP serum levels ($p = 0.02$) (Table II). Even the echocardiographic left ventricular ejection fraction at the time of AMI showed an important role, though it did not reach statistical significance ($p = 0.07$). The same analysis performed only on the 22 patients who received thrombolytic therapy at the time of AMI indicated higher CRP serum levels as the only independent risk factor for cardiac death (8.8 ± 4.5 mg/dl in patients who suffered cardiac death vs 2.4 ± 1.7 mg/dl in the remaining patients) ($p < 0.001$).

Comparing patients who died during hospital stay and discharged patients, the former had significantly higher CRP (8.2 ± 4.8 vs 4.1 ± 3.4 mg/dl, $p = 0.03$) and α_1-AGP serum levels (176 ± 41 vs 124 ± 33 mg/dl, $p = 0.007$) and WBC count (17 200 ± 4121 vs 11 416 ± 3202/mm^3, $p < 0.001$) while they did not significantly differ with respect to the risk factors for coronary artery disease. The median and range of CRP serum levels in patients who died during hospital stay and in discharged patients were 5.8 mg/dl (range 3.3-15.4 mg/dl) and 2.9 mg/dl (range 0.3-14.7 mg/dl) respectively.

Combined end-points at 5 years. Patients who remained free of events during the 5 years after AMI (group 1) were significantly younger than those who experienced early or late cardiac events (group 2) (64 ± 7 vs 69 ± 13 years, $p = 0.03$). One group 1 patient (6%) and 12 group 2 patients (32%) were older than 75 years ($p = 0.05$). The percentage of patients with anterior wall infarction was similar in the two groups (24% in group 1 and 32% in group 2) (p = NS). The time interval from symptom onset to hospital admission and blood sampling was 4.4 ± 3.2 hours in group 1 and 5.5 ± 3.2 hours in group 2 (p = NS). As already noted for groups A and B, this difference as well as the higher rate of contraindications to thrombolysis contributed to the difference in the use of thrombolytic agents during AMI, being 65% in group 1 (11 out of 17 patients) and 29% in group 2 (11 out of 38 patients) ($p = 0.01$). In group 1 patients, the echocardiographically determined left ventricular ejection fraction on the fourth day following hospital admission was 51 ± 7%, significantly better than that (47 ± 5%) observed in group 2 patients ($p = 0.01$).

When comparing the laboratory findings at the time of AMI in group 1 and group 2 patients, the former showed lower CRP (1.6 ± 1.5 vs 5.7 ± 3.7 mg/dl, $p < 0.001$; Fig. 1) and α_1-AGP serum levels (101 ± 23 vs 140 ± 36 mg/dl, $p < 0.001$; Fig. 2) and lower ESR (34 ± 26 vs 50 ± 30 mm/hour, $p = 0.06$) but not WBC count (10 927 ± 3106 vs 12 262 ± 3950/mm^3, $p = 0.11$) (Table I). The median and range of CRP serum levels in groups 1 and 2 were 2.1 mg/dl (range 0.3-5.8 mg/dl) and 5.3 mg/dl (range 0.3-15.4 mg/dl) respectively. As for cardiac death, CK, CK-MB, and fibrinogen serum levels did not significantly differ between group 1 and group 2 patients.

We then identified the cut-off points which allowed the best differentiation between group 1 and group 2 pa-

Table II. Independent predictors of cardiac death and of cardiac events at multivariate analysis.

Characteristic	Cardiac death		Cardiac events	
	Univariate	Multivariate	Univariate	Multivariate
Age	0.02	NS	0.03	NS
Thrombolysis	0.05	NS	0.01	NS
Left ventricular ejection fraction	0.007	0.07	0.01	NS
Lactate dehydrogenase	< 0.001	NS	> 0.20	NS
Aspartate aminotransferase	0.007	NS	> 0.20	NS
C-reactive protein	< 0.001	0.02	< 0.001	0.03
α_1-acid glycoprotein	< 0.001	< 0.001	< 0.001	< 0.001
Erythrocyte sedimentation rate	< 0.001	NS	0.06	NS
White blood cell count	0.004	NS	0.11	NS

tients. With regard to age, the cut-off value was 75 years; for CRP serum levels it was 3.0 mg/dl; for α_1-AGP serum levels it was 110 mg/dl; the ESR and WBC count thresholds were 35 mm/hour and 9200/mm^3 respectively (Table III). The sensitivity, specificity, positive predictive value and negative predictive value for these cut-off points in distinguishing between patients with different prognosis are also reported in table III. Among laboratory findings, the single best criterion for classifying patients according to the occurrence of cardiac events following AMI was the CRP serum level, the area under the ROC curve being 0.868.

At multivariate analysis, the independent risk factors for the occurrence of cardiac events following AMI were higher α_1-AGP ($p < 0.001$) and CRP serum levels ($p = 0.03$) (Table II). When the subgroup of the 22 patients who received thrombolytic therapy during AMI was considered, Cox analysis indicated higher CRP serum levels as the only independent risk factor for cardiac events in the first 5 years after AMI. In fact, CRP serum levels were 5.8 ± 3.5 mg/dl in patients who suffered cardiac events vs 1.4 ± 1.0 mg/dl in the remaining patients ($p < 0.001$).

The overall survival at 5 years was 58 ± 7%. The 5-year actuarial freedom from cardiac death in the whole population was 68 ± 7%, being 93 ± 5% for patients with CRP serum levels ≤ 3 mg/dl and 38 ± 11% for patients with CRP serum levels > 3 mg/dl ($p < 0.001$; Fig. 3), and being 94 ± 5% for patients with α_1-AGP serum levels ≤ 110 mg/dl and 49 ± 9% for patients with α_1-AGP serum levels > 110 mg/dl ($p = 0.002$).

The 5-year actuarial freedom from cardiac events in the whole population was 36 ± 6%, being 67 ± 9% for patients with CRP levels ≤ 3 mg/dl and 7 ± 5% for patients with CRP levels > 3 mg/dl ($p < 0.001$; Fig. 4), and being 70 ± 10% for patients with α_1-AGP serum levels ≤ 110 mg/dl and 17 ± 6% for patients with α_1-AGP serum levels > 110 mg/dl ($p < 0.001$).

Discussion

Recent studies demonstrated that inflammation plays a major role in the pathophysiology of acute coronary syndromes[1-7]. In fact, activated vascular cells, such as endothelial cells, smooth muscle cells, macrophages and T lymphocytes, produce interleukins, endothelin, adhesion molecules, growth factors and also have a procoagulant activity. Thus, they exert an influence on local thrombogenicity and vascular reactivity. The elevation in the circulating levels of acute-phase reactants observed in patients with unstable angina or with AMI

Table III. Cut-off values for variables associated with the 5-year prognosis at univariate analysis.

	Cut-off	Sensitivity	Specificity	PPV	NPV
Age (years)	75	0.3421	0.9412	0.9286	0.3902
C-reactive protein (mg/dl)	3.0	0.7105	0.9412	0.9643	0.5926
α_1-acid glycoprotein (mg/dl)	110	0.8158	0.7647	0.8857	0.6500
Erythrocyte sedimentation rate (mm/h)	35	0.6579	0.6471	0.8065	0.4583
White blood cell count (no./mm^3)	9200	0.8158	0.3529	0.7381	0.4615

NPV = negative predictive value; PPV = positive predictive value.

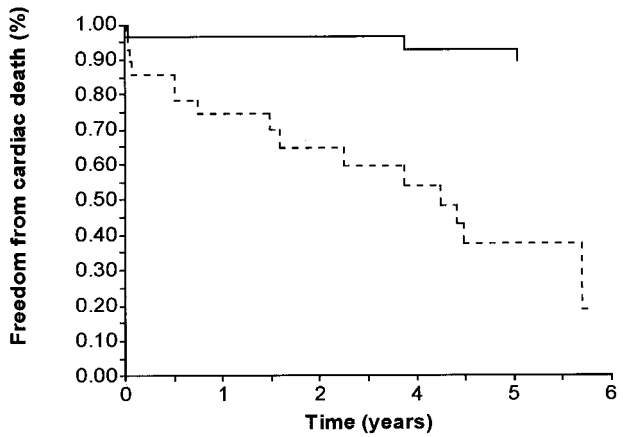

Figure 3. *Serum levels of C-reactive protein in the first blood sample obtained at admission during myocardial infarction: actuarial freedom from cardiac death in patients with C-reactive protein serum levels ≤ 3 mg/dl* (continuous line) *and > 3 mg/dl* (dashed line). *Comparison between the two groups was performed using the log-rank test.*

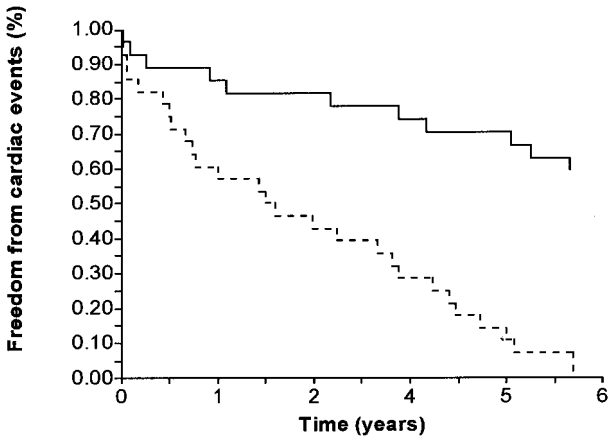

Figure 4. *Serum levels of C-reactive protein in the first blood sample obtained at admission during myocardial infarction: actuarial freedom from cardiac events in patients with C-reactive protein serum levels ≤ 3 mg/dl* (continuous line) *and > 3 mg/dl* (dashed line). *Comparison between the two groups was performed using the log-rank test.*

has been considered to be due to an underlying inflammatory process at the site of atherosclerotic plaques in the coronary arteries[17,18,23]. In patients with unstable angina, the acute-phase response may be induced by several autoantigens expressed in the atherosclerotic plaque, such as oxidized LDL and heat shock proteins, while in the setting of AMI the most potent proinflammatory stimulus is certainly represented by myocardial cell necrosis[18].

CRP is a sensitive, nonspecific, acute-phase inflammatory marker, but its role in acute coronary syndromes may go beyond that of merely being an epiphenomenon, as recently postulated by Lagrand et al.[24]. In fact, different studies have indicated that high plasma CRP levels predict the risk of myocardial infarction in apparently healthy subjects[25], predict the occurrence of coronary events in patients with both stable[3] and unstable angina[3,11,18] even after correction for other cardiovascular risk factors, and predict both in-hospital mortality[22,26] and the long-term outcome[19,27] after AMI. Moreover, CRP can be localized in inflamed tissues, particularly in atherosclerotic plaques and infarcted myocardium[28]. In addition, Torzewski et al.[29] demonstrated a chemotactic action of CRP for freshly isolated human blood monocytes, mediated by a specific CRP receptor. Lagrand et al.[24] postulate that CRP binds to lysophospholipids in ischemic (but not in normal) myocardium; ligand-bound CRP activates the classic pathway of complement, thus enhancing inflammation and contributing to myocardial tissue damage and dysfunction. Griselli et al.[30] demonstrated that injection of human CRP into rats after ligation of the coronary arteries reproducibly increased the infarct size via complement activation. In fact, complement activation determines attraction and degranulation of neutrophils, induces clot formation via tissue factor expression, produces cell lysis and favors arrhythmia and vasoconstriction.

Data concerning the role of other acute-phase reactants such as α_1-AGP in the setting of AMI are less consistent and more controversial. Casl et al.[31] suggest that α_1-AGP and α_1-antichymotrypsin serum levels are not associated with cardiovascular disease, while Kazmierczak et al.[10] reported that higher circulating levels of CRP and α_1-AGP were associated with acute heart failure following AMI even after correction for the extent of myocardial necrosis as assessed by serum cardiac markers.

Our results confirm that acute-phase reactants, particularly CRP but also α_1-AGP, have an important prognostic value in patients presenting with a first AMI. Both markers clearly distinguished, at the time of hospital admission, patients destined to further coronary events after AMI from those who were not. Considerations regarding the association between elevated serum levels of CRP or of α_1-AGP and coronary events were made possible by the exclusion from the study of patients with acute or chronic inflammatory diseases and with neoplastic diseases which could elicit a confounding acute-phase response. In addition, we excluded from the study patients who showed clinical signs of congestive heart failure in Killip class III-IV or left ventricular dysfunction at echocardiography, thus eliminating a potent prognostic predictor and focusing on the role of inflammation markers in the prediction of outcome after AMI. The exclusion of patients with larger infarcts, who showed signs of ventricular dysfunction at hospital admission, may also explain why peak CK levels were not significantly higher in patients who died before discharge compared with hospital survivors.

Higher CRP and α_1-AGP serum levels at the time of AMI appeared to be independent predictors of both death due to cardiac causes and of cardiac events in the first 5 years after AMI. Interestingly, high CRP serum levels maintained a predictive value on prognosis even when considering only the more homogeneous group of those patients who underwent thrombolysis during AMI. The identification of significant cut-off values for both protein serum levels facilitates the task of prognostic stratification in these patients. In agreement with Lagrand et al.[24], it can be hypothesized that a higher CRP response after AMI may lead to more intense CRP-mediated myocardial tissue damage. The fact that high CRP levels may directly cause myocardial cell injury possibly accounts for the prominent prognostic role of this serum protein, which goes beyond that of merely being a generic marker of inflammation. On the other hand, subjective differences in the acute-phase response elicited by similar inflammatory stimuli could be due to genetic factors, with high responders being at higher risk for cardiovascular events. The hypothesis of different individual acute-phase responsiveness has recently been supported by the observation by Liuzzo et al.[18] that patients with preinfarction unstable angina have a markedly greater acute-phase response than patients with totally unheralded AMI.

An important limitation of our study is represented by the presence of many potentially confounding factors which can influence the short- and long-term prognosis after a first, uncomplicated AMI. Further prospective studies involving a larger but more homogeneous population of patients are required for a better understanding of the prognostic value of acute-phase reactants at the time of hospital admission for an acute coronary syndrome.

In conclusion, the present study confirms that acute-phase reactants, particularly CRP but also α_1-AGP, have an independent prognostic value in patients presenting with a first AMI. Both inflammatory markers, measured at the time of hospital admission, were significant predictors of the occurrence of further cardiac events in the medium-term after a first myocardial infarction. Assays of these acute-phase proteins may help to better stratify patients hospitalized for acute coronary syndromes and thus play a relevant role in the management and follow-up of such patients.

References

1. Berk BC, Weintraub WS, Alexander RW. Elevation of C-reactive protein in "active" coronary artery disease. Am J Cardiol 1990; 65: 168-72.
2. Mazzone A, De Servi S, Ricevuti G, et al. Increased expression of neutrophil and monocyte adhesion molecules in unstable coronary artery disease. Circulation 1993; 88: 358-63.
3. Haverkate F, Thompson SG, Pyke SD, et al. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Lancet 1997; 349: 462-6.
4. Neri Serneri GG, Prisco D, Martini F, et al. Acute T-cell activation is detectable in unstable angina. Circulation 1997; 95: 1806-12.
5. Oltrona L, Ardissino D, Merlini PA, et al. C-reactive protein elevation and early outcome in patients with unstable angina pectoris. Am J Cardiol 1997; 80: 1002-6.
6. Hartmann F, Kampmann M, Frey N, et al. Biochemical markers in the diagnosis of coronary artery disease. Eur Heart J 1998; 19 (Suppl N): N2-N7.
7. Zanini R, Curello S, Bonandi L, et al. Etiopathogenesis of acute myocardial infarction: role of early leukocytosis. Cardiologia 1998; 43: 925-31.
8. Kamijikkoku S, Murohara T, Tayama S, et al. Acute myocardial infarction and increased soluble intercellular adhesion molecule-1: a marker of vascular inflammation and a risk of early restenosis? Am Heart J 1998; 136: 231-6.
9. Becker RC, Cannon CP, Bovill EG, et al. Prognostic value of plasma fibrinogen concentration in patients with unstable angina and non-Q-wave myocardial infarction (TIMI IIIB trial). Am J Cardiol 1996; 78: 142-7.
10. Kazmierczak M, Sobieska M, Wiktorowicz K, et al. Changes of acute phase proteins glycosylation profile as a possible prognostic marker in myocardial infarction. Int J Cardiol 1995; 49: 201-7.
11. Liuzzo G, Biasucci LM, Gallimore JR, 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.
12. Ueda S, Ikeda U, Yamamoto K, et al. C-reactive protein as a predictor of cardiac rupture after acute myocardial infarction. Am Heart J 1996; 131: 857-60.
13. Morrow DA, Rifai N, Antman EM, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in Myocardial Infarction. J Am Coll Cardiol 1998; 31: 1460-5.
14. Neri Serneri GG, Abbate R, Gori AM, et al. Transient intermittent lymphocyte activation is responsible for the instability of angina. Circulation 1992; 86: 790-7.
15. Libby P, Hansson GK. Involvement of the immune system in human atherogenesis: current knowledge and unanswered questions. Lab Invest 1991; 64: 5-15.
16. Takeshita S, Isshiki T, Ochiai M, et al. Systemic inflammatory responses in acute coronary syndrome: increased activity observed in polymorphonuclear leukocytes but not T lymphocytes. Atherosclerosis 1997; 135: 187-92.
17. van der Wal AC, Piek JJ, de Boer OJ, et al. Recent activation of the plaque immune response in coronary lesions underlying acute coronary syndromes. Heart 1998; 80: 14-8.
18. Liuzzo G, Biasucci LM, Gallimore JR, et al. Enhanced inflammatory response in patients with preinfarction unstable angina. J Am Coll Cardiol 1999; 34: 1696-703.
19. Toss H, Lindahl B, Siegbahn A, et al. Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. Circulation 1997; 96: 4204-10.
20. de Beer FC, Hind CR, Fox KM, et al. Measurement of serum C-reactive protein concentration in myocardial ischaemia and infarction. Br Heart J 1982; 47: 239-43.
21. Chapelle JP, Albert A, Smeets JP, et al. The prognostic significance of serum alpha 1-acid glycoprotein changes in acute myocardial infarction. Clin Chim Acta 1981; 115: 199-209.
22. Pietila K, Harmoinen A, Hermens W, et al. 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.
23. Liuzzo G, Buffon A, Biasucci LM, et al. Enhanced inflammatory response to coronary angioplasty in patients with severe unstable angina. Circulation 1998; 98: 2370-6.
24. Lagrand WK, Visser CA, Hermens WT, et al. C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? Circulation 1999; 100: 96-102.
25. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336: 973-9.
26. 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.
27. Pietila KO, Harmoinen AP, Jokiniitty J, et al. Serum C-reactive protein concentration in acute myocardial infarction and its relationship to mortality during 24 months of follow-up in patients under thrombolytic treatment. Eur Heart J 1996; 17: 1345-9.
28. Lagrand WK, Niessen HW, Wolbink GJ, et al. C-reactive protein colocalizes with complement in human hearts during acute myocardial infarction. Circulation 1997; 95: 97-103.
29. Torzewski M, Rist C, Mortensen RF, et al. C-reactive protein in the arterial intima: role of C-reactive protein receptor-dependent monocyte recruitment in the atherogenesis. Arterioscler Thromb Vasc Biol 2000; 20: 2094-9.
30. Griselli M, Herbert J, Hutchinson WL, et al. C-reactive protein and complement are important mediators of tissue damage in acute myocardial infarction. J Exp Med 1999; 190: 1733-40.
31. Casl MT, Surina B, Glojnaric-Spasic I, et al. Serum amyloid A protein in patients with acute myocardial infarction. Ann Clin Biochem 1995; 32: 196-200.