Original articles

Comparative short-term prognostic value of hemostatic and inflammatory markers in patients with non-ST elevation acute coronary syndromes

Federico Passoni, Benedetto Morelli*, Giovanni Seveso, Luisa Lazzati*, Gabriella Beria, Gianfranco Del Rosso, Maurizio D'Urbano, Francesco Cafiero, Giuseppe Mariani, Stefano De Servi

*Division of Cardiology, *Hematology Unit and Center for Blood Transfusion, Hospital of Legnano, Legnano (MI), Italy*

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Coagulation system; Inflammation; Unstable angina.

Background. **Recent data show that markers of inflammation, endothelial perturbation as well as activation of the coagulation and fibrinolytic systems are altered in unstable angina. The purpose of this study was to compare the 30-day prognostic value of the indexes of inflammation [interleukin-6 (IL-6)], endothelial activation [von Willebrand factor antigen (vWf)], fibrinolysis [plasminogen activator inhibitor-1 (PAI-1)] and coagulation (F1+2), in a consecutive series of patients with non-ST elevation acute coronary syndromes.**

Methods. **Eighty-eight patients consecutively admitted to the coronary care unit because of chest pain occurring within the previous 24 hours were included in the study. Blood was drawn on admission to the coronary care unit and 72 hours thereafter for the assessment of plasma levels of IL-6, vWf, F1+2 and PAI-1. Troponin I serum levels were measured 6 to 12 hours after admission. All patients underwent coronary arteriography.**

Results. **Patients were divided into two groups according to their 30-day outcome: 57 patients (group 1) had an uneventful outcome, whereas 31 patients had an adverse clinical event (4 died, 1 had a Q wave myocardial infarction and 26 had refractory angina). The baseline biochemical variables were similar between group 1 and group 2 patients. Seventy-two hours following admission, an increase in the serum levels of IL-6 was observed in 71% of group 2 patients and in 28% of group 1 patients (p = 0.0001). The other measured variables showed significant changes at 72 hours versus entry only in group 1 patients, and no significant difference between the two groups. The areas under the ROC curves were higher for IL-6 (0.72) than for the other variables (0.58 for F1+2, 0.52 for vWf and 0.54 for PAI-1). In a multivariate model, including clinical, angiographic, and biochemical variables, only the change in IL-6 over 72 hours was significantly associated with a worse 30-day outcome (odds ratio 8.472, 95% confidence interval 1.030-69.671).**

Conclusions. **This study shows that a mounting inflammatory process, as indicated by increasing levels of IL-6 over the first 72 hours after admission, is the most powerful predictor of the 30-day prognosis in patients with non-ST elevation acute coronary syndromes.**

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Address:

Dr. Stefano De Servi

*U.O. di Cardiologia
Ospedale Civile
Via Candiani, 2
20025 Legnano (MI)
E-mail:
emodinamica.legnano@calcol.it*

Introduction

Inflammation, endothelial cell function as well as the coagulation and fibrinolytic systems have been shown to play a major pathogenetic role in the onset and course of unstable angina[1]. All these factors may contribute to provoke abrupt changes in the atherosclerotic plaque resulting in local thrombus formation[2-4]. Recent studies suggest that high admission values of the markers of activation of the coagulation and inflammation cascades portend a poor clinical outcome[5-10]. An elevation of some of these parameters over the first few days of hospitalization seems to be an even more reliable prognostic indicator[11,12]. Increasing levels of inflammatory cytokines, such as interleukin-6 (IL-6) and IL-1Ra, were associated with an increased risk of in-hospital coronary events[11]. An early increase in the serum levels of the von Willebrand factor antigen (vWf) was also found to predict an adverse outcome in unstable coronary disease[12]. However, there are no data comparing the prognostic significance of inflammatory, hemostatic and endothelial markers, measured at entry and after 72 hours of full medical therapy in a population of patients with acute coronary syndromes and without ST-segment elevation. Accordingly, the purpose of this study was to investigate

the 30-day prognostic value of serial measurements of the markers of inflammation (IL-6), of the activation of the coagulation cascade (fragment F1+2), of endothelial perturbation (vWf), and altered fibrinolysis [plasminogen activator inhibitor-1 (PAI-1)] in 88 patients who were admitted to the coronary care unit because of unstable angina/non-Q wave myocardial infarction.

Methods

Study patients. Patients included in the study were consecutively admitted to the coronary care unit because of chest pain at rest associated with transient ST-segment and T wave changes occurring during the preceding 24 hours (Braunwald class III). Exclusion criteria were the presence of left bundle branch block or of a pacemaker, persistent (20 min) ST-segment elevation indicative of evolving myocardial infarction and secondary angina with a known precipitating factor (e.g., severe anemia, thyrotoxicosis, tachydysrhythmia, heart failure). Patients with known thrombotic disorders, infectious or inflammatory diseases were also excluded from the study. All enrolled patients were treated with aspirin, intravenous nitrates and heparin.

Study design. Blood was drawn upon admission to the coronary care unit and 72 hours thereafter for the assessment of plasma levels of IL-6, vWf, F1+2 and PAI-1. Troponin I was measured 6 to 12 hours after admission (mean 8.2 hours). All patients underwent coronary arteriography. Once discharged, all patients were submitted to clinical follow-up performed on an outpatients basis at 15 and 30 days. An adverse clinical outcome was defined as the occurrence, at 30 days, of one of the following events: death, acute myocardial infarction or refractory angina. Patients with events occurring between the time of admission and the 72-hour sampling were excluded from the analysis. Acute myocardial infarction was defined as the occurrence of a new episode of severe chest pain associated with persistent ST-segment elevation > 0.1 mV and with an increase in creatine kinase serum levels exceeding twice the upper normal limit. Refractory angina was defined as the recurrence of chest pain during full medical therapy.

Informed consent was obtained from all patients. The protocol was approved by the local ethical committee.

Laboratory assays. IL-6 was measured using a commercial assay kit (Quantikine human IL-6, R&D Systems, Oxon, UK). The plasma concentrations of vWf were measured with an ELISA technique (Assachrom von Willebrand factor, Roche, Basel, Switzerland) with data being expressed as a percentage of those obtained in pooled normal plasma. In our laboratory, the coefficient of variation was 10% both for the vWf and the IL-6 assays. Prothrombin fragment F1+2 was measured using an enzyme immunoassay (Enzygnost, F1+2, Behring, Mannheim, Germany), the coefficient of variation of which was 15% in our laboratory. PAI-1 serum levels were determined with a commercially available chromogenic substrate (PAI-1, Chromogenix, Molndal, Sweden). The activity was expressed in arbitrary units (AU) which were defined as the amount required to inhibit 1 IU tPA/ml plasma. In our laboratory the coefficient of variation was 10%. The reference values in 120 healthy controls aged 25 to 65 years (82 men and 38 women) and measured at our laboratory were 60 to 128% for the vWf, 0.40 to 1.1 nmol/l for F1+2, and 2 to 26 AU/ml for PAI-1. Troponin was measured using a microparticle enzyme immunoassay (Abbott Laboratories, Diagnostic Division, Chicago, IL, USA).

Statistical analysis. Data are expressed as means ± SD for continuous variables. When skewed, the median and interquartile range are used. The χ^2 test or exact Fisher test was used to compare the frequencies of categorical variables between patients with or without adverse clinical events at 30 days. The Student's t-test or Mann Whitney test were used to compare the mean or median (for skewed distribution) levels between patients with or without adverse clinical events at 30 days. The Wilcoxon sign rank test was used to compare the median levels of the various indexes at 0 and 72 hours.

The odds ratio (OR) of having adverse clinical events at 30 days, according to the change in the serum levels of the inflammatory indexes over 72 hours following admission, has been estimated together with its 95% confidence intervals (CI) by means of logistic regression analysis. For this purpose, the change has been dichotomized according to its median value. Different models have been fitted in order to compute the raw OR, the OR controlled for the basal value (after logarithmic transformation due to the skewness of data) of the indexes, and the OR controlled for both the basal value and for other potential risk factors as referred in the literature (age, sex, previous myocardial infarction, electrocardiographic changes during angina, troponin levels, coronary artery disease, and diagnosis). The model-based sensitivity, specificity and area under the ROC have been computed. These statistics were used to compare the prognostic ability of the various indexes. A p value < 0.05 has been retained for statistical significance. Stata 6.0 (Statacorp, College Station, TX, USA) has been used for computation.

Results

Out of 101 patients included in the study, 13 were excluded because they developed new Q waves on the electrocardiogram with an increase in the total creatine kinase serum levels exceeding 5 times the upper normal limit. Only 9 of the remaining 88 patients were secondary referrals to our center. Patients were divided in-

to two groups according to their 30-day outcome: group 1 comprised 57 patients with an uneventful outcome, group 2 comprised 31 patients with an adverse clinical event: 4 patients died, 1 had a Q wave myocardial infarction and 26 had refractory angina. A revascularization procedure was successfully performed in 36 patients of group 1 (26 had coronary angioplasty, 10 bypass surgery) and in 24 patients of group 2 (10 had coronary angioplasty and 14 bypass surgery).

The clinical and angiographic variables in the two groups are shown in table I. Group 2 patients were older, prevalently non-smokers and more frequently had a prior myocardial infarction and multivessel coronary artery disease.

On admission, IL-6 values were higher in group 1 than in group 2 ($p = 0.005$). However, this parameter changed from the admission value of 5.07 pg/ml (0.00 to 19.8) to the 72-hour value of 3.22 pg/ml (0.00 to 52) in group 1 and from 1.27 (0.00 to 16.4) to 6.28 pg/ml (0.00 to 48) in group 2 patients. An increase over the median admission values was observed in 16 patients (28%) of group 1 and in 22 patients (71%) of group 2 ($p = 0.0001$) (Fig. 1).

F1+2 median values were not different between the two groups both at entry and at 72 hours, changing from 0.94 (0.15 to 3.37) to 1.39 nmol/l (0.34 to 6.21) in group 1 and from 1.23 (0.35 to 2.59) to 1.40 nmol/l (0.35 to 2.51) in group 2. An increase over the median admission levels was seen in 27 patients (47%) of group 1 and in 11 (35%) of group 2 ($p = 0.21$) (Fig. 1).

The activity of the vWf varied from 115 (32 to 200) to 122% (44 to 149) in group 1 and from 118 (62 to 143) to 121% (98 to 145) in group 2, an increase over the median admission values having occurred in 21 (37%) group 1 patients and in 10 (32%) group 2 patients ($p = 0.92$) (Fig. 1).

No difference was observed between the admission values of PAI-1 between the two groups. This parameter decreased from 20 (0.00 to 65) to 14 AU (0.00 to 44) in group 1 and from 20 (5 to 50) to 19 AU (6 to 45) in group 2. A decrease over the median admission values was found in 23 (40%) group 1 patients and in 13 (42%) group 2 patients ($p = 0.47$) (Fig. 1).

In a multivariate model including clinical, electrocardiographic and angiographic variables, age (OR 1.13, 95% CI 1.02-1.27), female sex (OR 5.89, 95% CI 1.04-33.4), prior myocardial infarction (OR 9.02, 95% CI 1.42-57.2), and multivessel coronary disease (OR 13.13, 95% CI 1.06-16.30) were significantly related to the 30-day outcome. When the values of the various indexes at entry or their changes over 72 hours were included in the model, only the change in the serum levels of IL-6 over 72 hours was significantly associated with a worse 30-day outcome, whereas age, sex, prior myocardial infarction and multivessel disease only had borderline significance (Table II).

The areas under the ROC, computed for the changes of the various indexes over 72 hours following admis-

Table I. Clinical and angiographic characteristics of the two study groups at follow-up.

	Group 1 (n=57)	Group 2 (n=31)	p
Age (years)	62.8 ± 10.2	69.6 ± 8.7	0.0016
Sex (M/F)	46/11	21/10	0.20
Hypertension	17 (30%)	11 (35%)	0.636
Diabetes	5 (9%)	4 (13%)	0.7
Smokers	17 (30%)	1 (3%)	0.003
Prior PTCA	6 (16%)	4 (13%)	0.7
Prior CABG	8 (14%)	3 (10%)	0.7
Prior MI	6 (10%)	11 (35%)	0.009
Non-Q wave MI	13 (23%)	2 (6%)	0.07
Troponin I > 1 ng/ml	29 (51%)	181 (56%)	0.6
ST/T changes	36/16	19/9	0.9
No. diseased vessels (0/1/2/3)	3/30/15/9	4/9/5/13	0.01
LVEF < 50%	7 (12%)	6 (19%)	0.19

CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; ST/T changes = ST-segment depression and or T wave changes during pain.

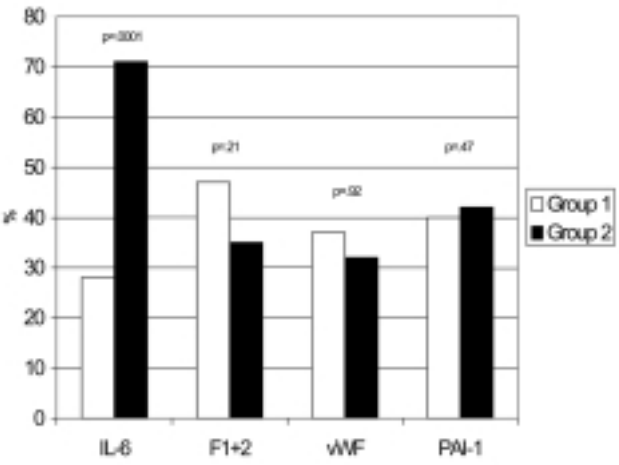

Figure 1. *Percentage of both group 1 and group 2 patients showing an increase in interleukin-6 (IL-6), activation of coagulation (F1+2), and von Willebrand factor antigen (vWf) or a decrease in plasminogen activator inhibitor-1 (PAI-1) over the median admission values of the measured markers.*

Table II. Results of multivariate analysis.

Variables	OR	95% CI	p
Delta IL-6	8.472	1.030-69.671	0.047
Age	1.109	0.997-1.235	0.056
Female sex	9.108	0.929-89.307	0.058
Previous MI	6.810	0.869-53.368	0.068
Troponin I < 0.1 ng/ml	0.207	0.032-1.321	0.096
Multivessel disease	6.973	0.807-60.232	0.077

CI = confidence interval; IL-6 = interleukin-6; MI = myocardial infarction; OR = odds ratio.

sion, were 0.72 for IL-6, 0.58 for F1+2, 0.52 for the vWf, and 0.54 for PAI-1. When the analysis was restricted to 41 patients without troponin I elevation (< 1 ng/ml), the areas under the ROC were still higher for IL-6 (0.72) than for the other measured variables (0.60 for F1+2, 0.55 for the vWf, 0.70 for PAI-1).

Discussion

Inflammatory and hemostatic factors in non-ST elevation acute coronary syndromes. This study shows that increasing levels of IL-6 are the most powerful predictor of the 30-day prognosis in patients with non-ST segment elevation acute coronary syndromes compared to the other indexes evaluated. Inflammation has been recognized to play a pathogenetic role in atherogenesis and may precipitate thrombogenesis in unstable angina or other acute coronary syndromes[1-4]. An increase in circulating activated lymphocytes[13], as well as in neutrophil and monocyte adhesion molecules[14,15] has been observed in unstable angina patients. Moreover, elevated plasma levels of C-reactive protein and of IL-6 have been demonstrated in such patients[16,17], particularly in those with recurrent clinical instability during follow-up[18]. In addition, increasing levels of IL-1Ra and of IL-6 during the first 2 days of hospitalization permit the identification of a subgroup of unstable angina patients with a complicated hospital course[11].

Hemostatic factors have also been associated with acute manifestations of ischemic heart disease. A significant elevation in the serum levels of F1+2 has been reported in patients with acute myocardial infarction and unstable angina[16,19], indicating the activation of the end stages of the coagulation process. However, sudden bursts of thrombin formation were found to be poorly related to episodes of myocardial ischemia in unstable angina patients, suggesting that the mechanisms responsible for instability are complex and that they do not only involve the coagulation process[20].

A reduced activity of the fibrinolytic system may also play a significant role in the pathogenesis of unstable angina, in view of the fact that in contrast with a normal tissue-type plasminogen activator activity, increased levels of PAI-1 were found in patients with this clinical condition by Zalewski et al.[21]. Such PAI-1 elevation was shown to be related to recurrent coronary events[22,23] and was still observed months and years after myocardial infarction[24].

Higher vWf levels have been linked with a greater risk of acute events among patients with ischemic heart disease[25-27]. An increase in the serum levels of the vWf over the first 48 hours of hospitalization in patients with unstable angina and non-Q wave myocardial infarction was also found to be a significant and independent predictor of an adverse clinical outcome at 14 and 30 days[12].

Prognostic value of inflammatory and hemostatic factors. Although all the above-mentioned variables have been shown to predict the short-term outcome in selected patients with unstable angina, data about the prognostic value of inflammatory, hemostatic and endothelial markers, simultaneously determined in a clinically defined population of patients with non-ST elevation acute coronary syndromes, are scarce. The serum levels of C-reactive protein, fibrinogen and the erythrocyte sedimentation rate, measured on admission in 211 patients with angina at rest[5] were associated with the in-hospital outcome, whereas no association was observed between the markers of coagulation activation or endothelial cell function on the one hand and the in-hospital course on the other. Montalescot et al.[12] studied 68 patients with unstable angina or with a non-Q wave myocardial infarction in whom the serum levels of C-reactive protein, fibrinogen, vWf, endothelin-1 and troponin I were measured on admission and 48 hours later. At multivariate analysis, a rise in the serum levels of the vWf was the only variable related to the 1-month prognosis, whereas all the other parameters failed to predict outcome. Biasucci et al.[11] studied 43 patients with Braunwald III unstable angina, treated with full medical therapy and without increased serum levels of creatine kinase and troponin T. In each patient, the plasma levels of IL-1Ra and of IL-6 were measured at entry and 48 hours after admission. A fall in these two parameters after admission correlated with an uneventful clinical course, whereas an increase was associated with a complicated hospital course. The role of hemostatic and endothelial markers was however not analyzed in this study.

In the present investigation, we compared the 30-day prognostic value of serial measurements of the markers of inflammation (IL-6) and of the markers of the activation of coagulation (F1+2), endothelial perturbation (vWf), and altered fibrinolysis (PAI-1) in 88 patients who were admitted to the coronary care unit because of unstable angina/non-Q wave myocardial infarction. Our data indicate that not only was IL-6 superior to the other indexes, as indicated by the model-based areas under the ROC, but that it was also the most powerful indicator of the 30-day outcome even when clinical and angiographic variables, such as age, prior myocardial infarction and multivessel coronary disease, were included in the model. These results lend further support to the hypothesis that the inflammatory activity, reflecting the severity of the underlying process at the level of the culprit plaque, determines the clinical presentation and outcome of patients with unstable coronary syndromes[5].

Contrary to the data presented by Biasucci et al.[11], in our patients only the rise in the serum levels of IL-6 over the first 72 hours of hospitalization, and not its admission value, was related to the subsequent clinical outcome. This discrepancy is likely to be secondary to the different criteria employed in patient selection: in our study only few patients were secondary referrals to

our center, whereas such patients represented more than half of the total study population in Biasucci's work. Most patients referred for further investigation to tertiary centers have enhanced disease activity and are likely to have a complicated clinical course. Thus, it is not surprising that in that study, baseline serum levels of IL-6 were already elevated in patients who then had an unfavorable outcome.

Study limitations. In contrast to previous observations[5,11], we included all patients with non-ST elevation acute coronary syndromes, not excluding those with a final diagnosis of a non-Q wave myocardial infarction and those with unstable angina and increased serum levels of troponin I. It could be objected that an increase in inflammation indexes might have been triggered by myocardial injury or necrosis. However, we decided to include even such patients because our intent was to compare the prognostic value of the various indexes in a population of patients which could be representative of the entire spectrum of non-ST elevation acute coronary syndromes. Moreover, the areas under the ROC showed that IL-6 was superior to all other indexes even when the analysis was restricted to patients without increased troponin I serum levels.

In the present investigation, only one parameter was measured for each of the systems studied. However, there are no data showing that other variables have a greater predictive value or are more representative of the various pathogenetic processes than the selected ones. IL-6 was measured instead of C-reactive protein (to which it is strictly related[8]) because of its shorter half-life allowing for the assessment of rapid changes in inflammatory activity.

Troponin I serum levels were not measured serially, but only once, 6 to 12 hours after admission. Although we acknowledge that sequential measurements of this parameter could have improved its prognostic value, it has been shown that a single determination of this parameter at a time similar to that used in the present investigation seems appropriate to assess the risk and may have important therapeutic implications[28].

In summary, this study shows that, compared to the other indexes evaluated, a mounting inflammatory process, as revealed by increasing levels of IL-6 over the first 72 hours after admission, is the most powerful predictor of the 30-day prognosis in patients with non-ST elevation acute coronary syndromes.

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