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Inflammatory markers 10 weeks after myocardial infarction predict future cardiovascular events

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Abstract

Background: *The prognostic value of chronic inflammation markers in patients after myocardial infarction (MI) in the era of interventional treatment, statin and aspirin use is still unclear.*

Methods: *The study was carried out on 107 patients with a first MI who were followed up for 18 months. The end points were cardiac death, reinfarction or unstable angina pectoris. At 10 days and at 10 weeks we measured C-reactive protein (CRP), fibrinogen, soluble intercellular adhesion molecule 1 (sICAM-1), erythrocyte sedimentation rate (ESR), white blood cell count (WBC) and Chlamydia preumoniae antibodies.*

Results: *During the follow-up period there were 22 events. The patients were divided into two subgroups: those with recurrent episodes and those without coronary events. Patients with recurrent episodes had significantly higher values of CRP (7.07* vs. *3.77 mg/l, p = 0.02), ESR at 1 h (24.3* vs. *13.3 mm; p = 0.01) and sICAM-1 (287.9* vs. *260.9 ng/ml, p = 0.04) at 10 weeks following infarction. Statistical analysis showed that sICAM-1 > 270 ng/ml, CRP > 1.83 mg/l and ESR at 1 h > 14 mm measured at 10 weeks were independent risk factors for recurrent cardiovascular events. In patients with coronary events between the 10th day and 10th week there was no decrease in inflammatory indices (WBC, ESR) and a tendency towards increasing sICAM-1.*

Conclusions: *Increased inflammatory markers (CRP, ESR, sICAM-1) at 10 weeks after MI are independent risk factors for recurrent cardiovascular events. Measuring CRP, ESR and sICAM-1 at this time point is useful in long-term prognosis after MI. Changes in inflammatory indices (ESR, WBC, sICAM-1) measured at 10 days and 10 weeks following infarction show a different pattern in patients with and without recurrent cardiovascular events.* (Cardiol J 2007; 14: 50–58)

Key words: myocardial infarction, inflammation, inflammatory markers

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Editorial p. 11

Introduction

Numerous clinical and population-based studies have recently demonstrated that inflammation plays an essential role in the aetiopathogenesis of atherosclerosis and in the aetiology of acute coronary syndromes (ACS). Increased levels of C-reactive protein (CRP), interleukin-6 (IL-6), amyloid A or intercellular adhesion molecule 1 (ICAM-1) appear to reflect the inflammatory activity within the atherosclerotic plaque and predict the risk of cardiovascular events [1–4]. In patients with myocardial infarction the prognostic value of inflammatory markers is obscured by the acute phase reaction related to myocardial necrosis and in patients undergoing reperfusion by the inflammatory response after recanalisation of the infarct-related artery. Furthermore, the time for measuring inflammatory markers to optimise prognosis is not defined. Recent reports on the atherogenic properties of CRP have given rise to the question of whether nonspecific, generalised inflammatory stimulation, for instance that associated with myocardial infarction, is prognostically unfavourable irrespective of its origin [5, 6]. The pathological role of CRP could be significant only in patients with genetically inherited CRP monomerisation or vulnerability of the immune system, which reacts to mild stimuli with a higher and prolonged inflammatory response [7].

The purpose of the present study was to evaluate the prognostic value of CRP, soluble intercellular adhesion molecule 1 (sICAM-1), erythrocyte sedimentation rate (ESR), fibrinogen, and white blood cell count (WBC) measured after myocardial infarction at discharge and 10 weeks later when the necrosis-related inflammatory response is no longer present.

Methods

The study population consisted of 119 patients admitted with an acute first myocardial infarction to Cardiac Department No. 1 in Cracow (70 patients) and the Internal Medicine Ward of the Regional Hospital in Myslenice (49 patients). Acute myocardial infarction was diagnosed according to the World Health Organisation (WHO) criteria in force on the day on which the study began [8]. Patients were recruited into the study on the 10^{th} day after myocardial infarction. Ex-post analysis showed that about 90% of patients had acute coronary events with ST-segment elevation (STEMI). The exclusion criteria were previous myocardial infarction, cardiogenic shock, pericarditis and resuscitation. Those with a history of injury, acute or chronic infection or inflammation with autoimmune disorders, neoplasms, cardiomyopathies, severe valvular heart disease, atrial fibrillation and liver disease were also excluded. In most patients the myocardial infarction was the first manifestation of coronary artery disease and prior to it they had not received any medication for coronary artery disease. Patients were treated with streptokinase or facilliated PCI: abciximab (Reopro) and half dose tPA (Actilise) or PCI if the time to admission was under 12 h. Twelve patients who underwent elective coronary artery bypass grafting or percutaneous transluminal coronary angioplasty at follow-up were excluded from the final analysis (107 patients). Patients with an end point such as cardiac death, reinfarction or unstable angina pectoris were withdrawn from the study. Unstable angina was diagnosed on the basis of recurrence of resting angina, leading to hospitalisation, and in the absence of extracardiac causes of ischaemia. In each case acute ischaemic changes in the ECG were confirmed. During the follow-up of 18 months there were 22 events: 1 cardiac death, 5 re-infarctions and 16 episodes of unstable angina pectoris. On this basis the patients were divided into those with and those without complications. Because 7 patients had episodes before the second measurement (at 10 weeks) the group undergoing analysis and baseline measurements (at 10 days) consisted of 107 patients, including 22 with complications (all episodes), while at 10 weeks the group consisted of 100 patients, including 15 with complications (late episodes).

Laboratory tests

Biochemical measurements were done at 10 days and 10 weeks after the infarction. Blood was sampled from the antecubital vein after 12 h of fasting, centrifuged and stored at –70° C until required. CRP was measured with a high-sensitivity nephelometric assay (Dade Behring N High Sensitivity CRP, Germany). Levels of sICAM-1 were measured using an immunoenzymatic assay ELISA (R&D Systems, Inc. USA). Serum fibrinogen was measured using the modified Klauss method (Dade Behring Multifibren U). White blood cells were counted using an automatic analyser Sysmex K 4500. Sedimentation rate was measured with the Westergreen method. Chlamydia pneumoniae antibodies were assessed with Chlamydia pneumoniae IgG ELISA kit and Chlamydia pneumoniae IgA ELISA kit (DRG Instruments Gmbh).

Diagnostics of the heart

Morphological and functional indices of the left ventricle at 10 days and 10 weeks after the infarction were studied by transthoracic echocardiography

Table 1. Correlations between C-reactive protein (CRP) and other inflammatory markers (r-Pearson correlation coefficient).

CRP	Fibrinogen	ESR	WBC
r	0.58	0.40	0.37
p	< 0.0001	< 0.05	< 0.05

ESR — erythrocyte sedimentation rate, WBC — white blood cell count

with a Hewlett-Packard Sonos 2500 and 2.0/2.5 MHz transducer. Myocardial reperfusion was evaluated from coronary angiography or reduction in ST-segment elevations at 90 min by at least 70% in patients receiving fibrinolysis [9]. Diastolic dysfunction was diagnosed according to the guidelines of the European Study Group on Diastolic Heart Failure and according to Oh et al. [10, 11].

Statistical analysis

Because of the skewed distribution a non-parametric Mann Whitney U test was used. Categorical variables were analysed with contingency tables using the χ^2 test and the Fisher exact test where appropriate. Nonparametric Wilcoxon test was used for paired comparison of changes in inflammatory parameters. Pearson's correlation coefficient was used to define the relationships between the parameters. Univariate analysis and Cox proportional hazard models were used to define the effect of independent variables on the occurrence of episodes.

The presence or absence of a cardiovascular event was used as a dependent variable in regression analysis. Variables that in univariate analysis discriminated between groups with and without cardiovascular events and that are commonly recognised as risk factors for the recurrence of cardiovascular events were used as independent variables in Cox regression models. Variables that showed a strong cross-correlation were not used in the models (Table 1). In order to assess relations between independent variables and the time to cardiovascular events a Cox regression analysis was performed. The Cox regression model included variables chosen by step-wise regression. The following variables were used: age, number of coronary vessels with significant stenoses, anterior myocardial infarction, reperfusion therapy, ejection fraction < 45%, diastolic dysfunction, anti-Chlamydia pneumoniae antibodies level IgA > 15.6 EUI and IgG > 117 EIU, CRP and sICAM-1. Variables that entered the model ($p<0.05$) are summarised in Table 2. The model was adjusted to $p < 0.00001$.

Table 2. Cox regression analysis.

Variable	β	Hazard ratio	Confidence interval	p
Number of diseased coronary arteries	1.10	0.75	0.50–1.12	0.04
Diastolic dysfunction after 10 weeks	0.98	1.40	1.04–1.89	0.01
Anterior wall infarction	–2.81	0.08	0.008–0.91	0.01
sICAM-1 > 270 ng/ml at 10 weeks	2.01	4.3	1.17–16.3	0.01
ESR >14 mm at 10 weeks	0.027	1.01	0.99–1.03	0.02
CRP > 1.83 mg/l at 10 weeks	2.14	14.39	1.94–106.7	0.04
Reperfusion therapy	0.09	0.89	0.53–1.51	0.10
Anty Chlamydia pneumoniae IgA >15.6 and IgG >117 EIU	2.25	10.4	2.43–44.9	0.003

Quantitative variables were transformed into categorical ones using the cut-off points under the receiver operated curve (ROC) and the parameters were grouped into two categories below and above the cut-off point. P-values < 0.05 were considered statistically significant.

Results

The group for analysis included 107 patients: 24 women (22.4%) and 83 men (77.6%) aged 39 – 81 years (mean age 58.3 ± 10). Sixty-two patients (57.5%) had a history of arterial hypertension, 23 (21.5%) of diabetes mellitus and 74 (69.2%) were smokers. Excess weight was evident in 51.4% (n = 55) and obesity in 22.4% (n = 24). Mean total cholesterol was 5.82 mmol/l, and 46% had LDL cholesterol > 3.5 mmol/l. The most frequent causative treatment was primary coronary angioplasty (PCI) 53.3% (n = 57) and fibrinolysis 14.9% (n = 16), whereas reperfusion was not initiated in 31.8% (n = 34) owing to late hospital admission.

Patients entered the study at 9.8 ± 3.9 days after pain onset and had a recall visit at 73.7 ± 15.5 days (10.5 weeks). Follow-up lasted 542 days ± 137 (~18 months). Tables 3 and 4 compare demographic and clinical parameters in the subgroups with and without events. Early on after the infarction (at 10 days) there were no significant differences in inflammatory markers between the groups (Fig. 1–3). At 10 weeks the patients with events had significantly higher readings for the following inflammatory

Table 3. Demographic and clinical characteristics in patients with and without cardiovascular events.

Parameter	Events – (n = 85)	Events + all (n = 22)	p	Events + late (n = 15)	p
Men	63 (74.1%)	20 (90.9%)	0.16	14 (93.3%)	0.19
Women	22 (25.9%)	2 (9.1%)	0.16	1 (6.7%)	0.19
Age (min/max)	58.4 ± 10 (39/81)	56.4± 9.8 (40/74)	0.46	52.4 ± 8.2 (40/66)	0.03
Body mass index [kg/m^2]	27.5 ± 3.9	26.8±3.6	0.41	26.9	0.54
Obesity (BMI ≥ 30 kg/m^2)	21 (24.7%)	3 (13.6%)	0.41	3 (20%)	0.94
Abdominal obesity	73 (85.9%)	18 (81.8%)	0.88	13 (87%)	0.74
Arterial hypertension	46 (54.1%)	16 (72.7%)	0.11	11 (73.3%)	0.27
Diabetes mellitus	18 (21.8%)	5 (22.7%)	0.88	3 (20%)	0.91
Family history	43 (49.4%)	10 (45.5%)	0.66	6 (9%)	0.63
Smoking	54 (63.5%)	20 (90.9%)	0.02	14 (93.3%)	0.05
Pack-years	20.1±20	19.9±10.6	0.34	24.3±9.12	0.08
LDL-cholesterol [mmol/l]	3.66±1.1	3.91±1.3	0.62	4.03±1.3	0.50
HDL-cholesterol [mmol/l]	1.26±1.0	1.1±1.1	0.05	1.16±0.3	0.24
Total cholesterol/HDL-cholesterol	4.88±1.7	5.65±1.8	0.06	5.33±1.2	0.14

indices: CRP (mean 7.04 ± 9.2 *vs.* 3.77 ± 4.9 mg/l, median: 5.53 *vs.* 1.78 mg/l, p = 0.02), ESR (mean 24.3 ± 18.6 *vs.* 13.3 ± 12.4 mm, median: 20 *vs.* 9 mm, p = 0.01) and sICAM-1 (mean 287.9 ± 57.7 *vs.* 260.9 ± 52.8 ng/ml, 280.0 *vs.* 255.2 ng/ml, p = 0.04) (Fig. 1–3). Fibrinogen showed only a tendency towards higher values (mean 4.23 ± ± 1.28 *vs.* 3.82 ± ± 1.08, median 4.0 *vs.* 3.6 g/l, p = 0.15). WBC did not differ significantly between groups (at 10 days: mean 7.43 ± ± 2.5 *vs.* 7.44 ± 1.6, median 6.9 *vs.* 7.0 thousand/μl, at 10 weeks mean 7.14 ± 1.8 *vs.* 6.82 ± ± 1.5, median 6.9 *vs.* 6.5 thousand/μl, p = 0.53). The patients with complications (n = 22) were more frequently smokers (p = 0.02) and received streptokinase (p = 0.01). This subgroup also had lower HDL cholesterol level (Table 3). The differences were not significant at 10 weeks following infarction. There was no correlation between inflammatory markers and cholesterol levels or infarct size. ROC analysis showed that CRP ≥ 1.83 mg/l at 10 weeks was related to a higher frequency of events. This value differentiated patients with future events with 56% sensitivity and 87% specificity. This value was also used to divide the patients into two subgroups. These subgroups did not differ significantly in fibrinolytic treatment and smoking. ROC analysis for sICAM-1 and ESR revealed that values: 270 ng/ml for sICAM-1 and 14 mm for ESR at 1 h differentiated patients with future events with a specificity of 66% and a sensitivity of 73% for ESR and 63% and 66% respectively for sICAM-1. Kaplan-Meier's analysis in groups with CRP below and above 1.83 mg/l or with ESR below 14 mm and above 14 mm showed that the events in patients with higher CRP or ESR not were only more frequent but also occurred earlier (Fig. 4, 5). Cox regression analysis showed that sICAM-1 > 270 ng/ml, CRP > 1.83 mg/l and ESR at 1 h > 14 mm measured at 10 weeks following infarction had an independent influence on cardiovascular events (Table 2). The type of reperfusion therapy affected inflammatory indices at 10 days postinfarction — those who received streptokinase had a higher WBC than the untreated 8.2 *vs.* 6.9 thousand/μl, p = 0.016) and higher sICAM-1 than those treated with facilitated PCI (293.7 *vs.* 234 ng/ml, p = 0.04) (Fig. 6). At 10 weeks postinfarction inflammatory indices, except ERS which was highest in the streptokinase subgroup, did not differ with respect to the type of treatment modality (Fig. 7). There were no differences in the use of streptokinase in the subgroups with CRP < and > 1.83 mg/l (3 and 9 subjects, respectively, p = = 0.21) and in the subgroups with sICAM-1 < and > 270 ng/ml (7 and 6 subjects respectively, p = 0.85) and ESR < and > 14 mm (5 and 8 subjects, respectively, p = 0.08).

The patients with late episodes showed a different dynamic of change in the inflammatory markers. In this group there was a smaller reduction in some inflammatory indices between the 10th day and the 10th week than in the patients with complications. CRP in patients without episodes decreased from 16.6 mg/l to 3.76 mg/l compared with 21.33 to 7.04 mg/l in patients with episodes (p for both reductions < 0.001). With respect to sICAM–1 between the 10th day and 10th week there was an

Table 4. Clinical characteristics of the subgroups with and without cardiovascular events.

Parameter	Events – (n = 85)	Events + all (n = 22)	p	Events + late (n = 15)	p
Reperfusion therapy:					
PCI	40 (47.3%)	6 (27.3%)	0.09	5 (33.3%)	0.48
facilitated PCI	9 (10.5%)	2 (9.1%)	0.85	2 (13.3%)	0.89
PCI + facilitated PCI	49 (57.8%)	8 (36.4%)	0.29	7 (46.6%)	0.66
fibrinolysis	9 (10.5%)	7 (31.8%)	0.01	3 (20%)	0.54
absent	27 (31.7%)	7 (31.8%)	0.80	5 (33.3%)	0.86
Reperfusion	50 (58.8%)	13 (59.1%)	0.83	8 (53.3%)	0.90
Time to reperfusion [h]	6.15 ± 2.9	6.9 ± 2.7	0.42	6.6 ± 2.3	0.57
Number of DCA (> 50% lesions) (% of patients with coronary angiography):					
1-vessel	31 (58.5%)	3 (27.3%)	0.45	2 (25%)	0.47
2-vessel	20 (37.7%)	3 (27.3%)	0.89	2 (25%)	0.90
3-vessel	2 (3.8%)	5 (45.4%)	0.005	4 (50%)	0.007
Medication: abciximab	20 (23.5%)	4 (18.2%)	0.80	3 (20%)	0.97
Medication on discharge:					
ASA	83 (97.6%)	22 (100%)	0.87	15 (100%)	0.69
statin	74 (87%)	16 (72.7%)	0.19	10 (66.7%)	0.10
β-blocker	83 (97.6%)	21 (95.5%)	0.86	15 (100%)	0.69
ACEI	59 (69.4%)	19 (86.4%)	0.18	12 (80%)	0.59
ticlopidyne 4 weeks	24 (28.2%)	3 (13.6%)	0.25	2 (13.3%)	0.37
cropidogrel 4 weeks	10 (11.7%)	1 (4.5%)	0.54	1 (6.6%)	0.89
Medication at 10 weeks:					
ASA	83 (97.6%)			15 (100%)	0.68
statin	75 (88.2%)			14 (93.3%)	0.89
β-blocker	83 (97.6%)			15 (100%)	0.68
ACEI	53 (62.4%)			12 (75%)	0.59
Infarct site:					
inferior	34 (40%)	11 (50%)	0.39	8 (53.3%)	0.33
anterior	23 (27.1%)	2 (9.1%)	0.15	0	0.01
lateral	11 (12.9%)	4 (18.2%)	0.77	4 (26.7%)	0.32
anterolateral	10 (11.8%)	3 (13.6%)	0.89	2 (13.3%)	0.79
posterior	7 (8.2%)	2 (9.1%)	0.88	1 (6.7%)	0.75
LVEF 10 days	51.9 ± 7.0%	52.8 ± 8.9	0.70	52.7 ± 9.4	0.89
LVEF 10 weeks	53.7 ± 6.6%			50.6 ± 8.7	0.19
LVEDV [ml] 10 days	130.5 ± 35.8	140.9 ± 38.8	0.24	143 ± 42	0.27
LVESV [ml] 10 days	64 ± 20.4	74 ± 25.4	0.19	71 ± 24	0.19
LVEDV [ml] 10 weeks	126.5 ± 32.8			146 ± 38	0.08
LVESV [ml] 10 weeks	60.1 ± 20.4			78.2 ± 26.5	0.01
WMSI 10 days	1.43 ± 0.22	1.39 ± 0.25	0.33	1.44 ± 0.22	0.73
WMSI 10 weeks	1.35 ± 0.21			1.38 ± 0.28	0.90
Infarct size:					
AUC CK	79392 ± 65571	81130 ± 56615	0.78	89253 ± 60969	0.49
infarct size 1–3	44 (51.8%)	11 (50%)	0.92	9 (60%)	0.75
number of ECG leads 4–6	31 (36.4%)	7 (31.8%)	0.87	5 (33.3%)	0.81
with ST elevations > 6	10 (11.8%)	4 (18.2%)	0.65	1 (6.7%)	0.89

PCI — percutaneous coronary intervention, DCA — diseased coronary arteries, ASA — acetylsalicylic acid, ACEI — angiotensin converting enzyme inhibitor, LVEF — left ventricular ejection fraction, LVEDV — left ventricular end-diastolic volume, LVESV — left ventricular end-systolic volume, WMSI — wall motion score index, AUC — area under curve, CK — creatine kinase

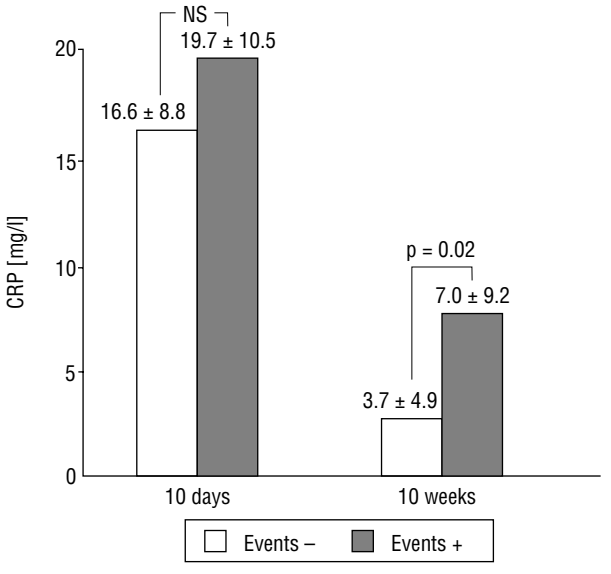

Figure 1. C-reactive protein (CRP) in patients with and without complications at 10 days and 10 weeks following infarction.

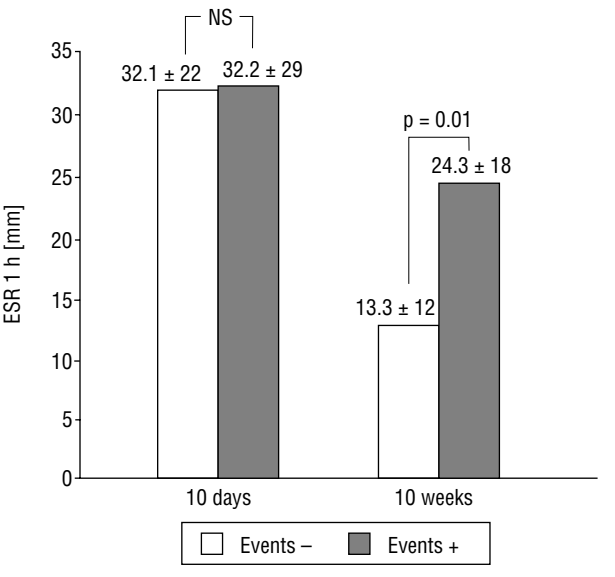

Figure 3. Erythrocyte sedimentation rate (ESR) at 1 h in patients with and without complications at 10 days and 10 weeks following infarction.

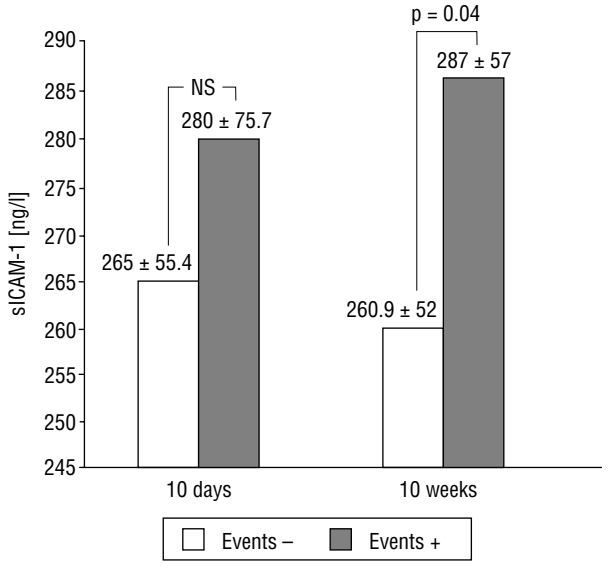

Figure 2. Soluble intercellular adhesion molecule 1 (sICAM-1) in patients with and without complications at 10 days and 10 weeks following infarction.

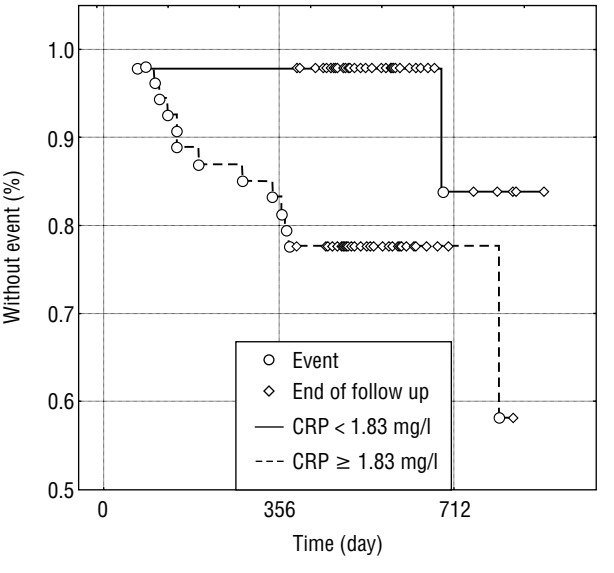

Figure 4. Kaplan-Meier curve for events in groups with C-reactive protein < 1.83 mg/l and ≥ 1.83 mg/l; long--rang test p = 0.006

increasing tendency (medians: 282.1 and 287.9 ng/ml) in patients with episodes as compared with a decreasing tendency (p = 0.18) in patients without episodes (medians: 265.5 and 260.9 ng/ml). WBC in patients with episodes remained unchanged between the 10th day and the 10th week (from 7.49 ± 3.0 to 7.15 ± 1.8 thousand/μl, p = 0.42), whereas in patients without complications it decreased (from 7.44 ± 1.67 to 6.82 ± 1.58 thousand/μl, p = 0.004). Similar results were obtained for ESR: in patients with episodes ESR did not decrease (from 38.9 to 24.3 mm, p = 0.06), whereas in patients without complications a reduction was evident (from 32.1 to 13.3 mm, p < 0.0001).

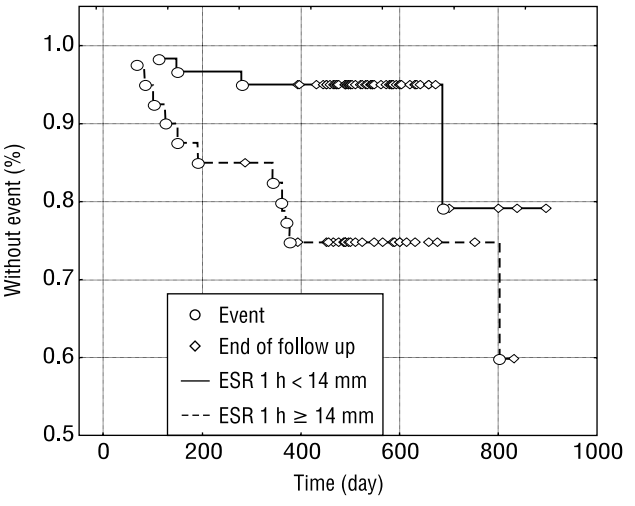

Figure 5. Kaplan-Meier curve for events in groups at 10 weeks with erythrocyte sedimentation rate (ESR) at 1 h < 14 mm and ≥ 14 mm (log rang test p = 0.009).

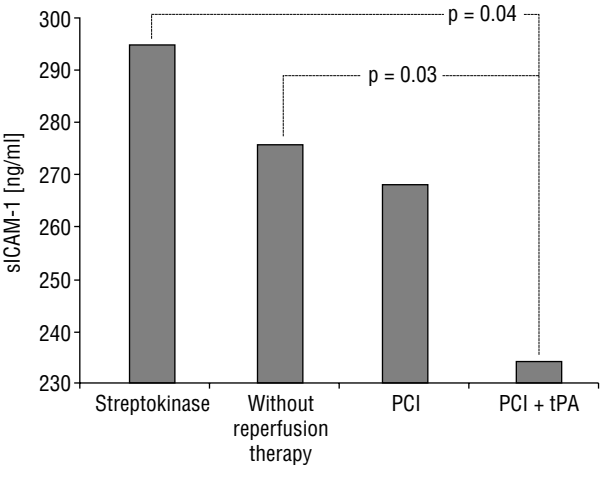

Figure 6. Levels of soluble intercellular adhesion molecule 1 (sICAM-1) at 10 days in group with different kind of reperfusion treatment.

Discussion

Evidence shows that inflammation is not limited only to a single plaque but involves the whole vascular system [12, 13]. Apart from the infarct size, the inflammatory response after acute coronary episodes may be modified by therapy (thrombolysis, statins and aspirin), which may blunt the relationship between the level of inflammatory markers and cardiovascular risk. Although according to the guidelines of the American Heart Association [14] the measuring of inflammatory markers is not recommended in secondary prevention, their prognostic value in patients after myocardial infarction has been demonstrated [15–17]. In the present study there was a significant difference in CRP levels at 10 weeks after myocardial infarction between patients with secondary cardiovascular events (7.04 mg/l) and patients without such complications (3.77 mg/l) at long-term follow-up. Multifactorial analysis also revealed that higher ESR, CRP, sICAM-1 at 10 weeks after myocardial infarction were independent risk factors for cardiovascular events.

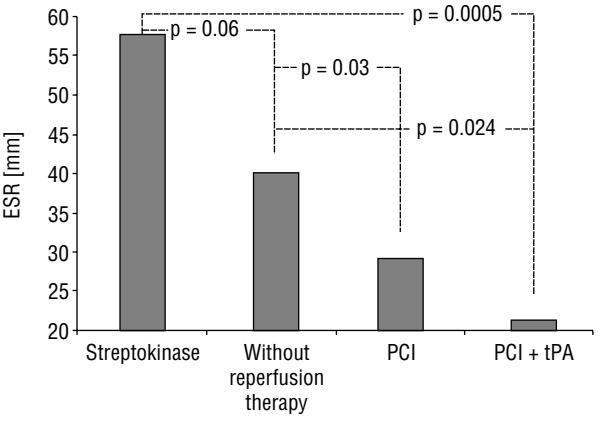

Figure 7. Levels of erythrocyte sedimentation rate (ESR) (2 h) at 10 weeks in group with different kind of reperfusion treatment.

Slightly different results were obtained in the THROMBO trial [16], in which measurements were made at 8 weeks following infarction. Of 957 patients CRP was significantly higher in patients with events, constituting 7%. Univariate analysis showed a higher risk in patients with CRP in the highest quartile, but multifactorial analysis revealed that inflammatory markers such as CRP and serum amyloid A (SAA) were not independent risk factors for cardiovascular events. It is noteworthy that 20% of patients had a history of previous myocardial infarction and cannot be compared directly with the present homogenous group, and that the group of patients with complications during a follow-up of 2 years constituted only 7% of the whole population, decreasing the statistical power.

In the Japanese OACIS study [17] in a population of 1307 patients at 25 days following infarction the investigators found that CRP levels did not correlate with the infarct size and that CRP was an independent prognosticator of death after myocardial infarction at long-term follow-up. The present findings are compatible with the results of the CARE study [18]. In this study CRP was measured between 3 and 21 months following infarction in a population of 4159 patients. A subgroup

of 391 patients with re-infarction or cardiac death was compared with 391 matched controls without cardiovascular events. The patients were randomised to receive pravastatin or placebo. CRP levels were higher in patients with cardiovascular events than in the controls, 5.6 *vs.* 4.8 mg/l ($p = 0.03$), and multifactorial analysis revealed that CRP was an independent risk factor for cardiovascular events.

The present study shows that the 10th week following infarction is a good time point to measure inflammatory indices. We should also bear in mind that over three quarters of the patients received statins (simvastatin in 90% of cases), which can reduce CRP levels within several weeks [19]. In spite of this, both subgroups showed higher chronic CRP levels. This is in line with previous findings that patients with ischaemic heart disease had CRP levels twice as high as healthy controls [18, 20]. Jenkins et al. [21] also suggest that beta blockers may decrease CRP levels. These drugs could blunt the effect of CRP on the study end points and consequently blunt the relationships in multifactorial analysis. The present finding could also have been modified by postinfarction changes in lifestyle, such as cessation of smoking and increased physical activity, which reduce CRP and fibrinogen levels but not ICAM-1. In the present study the fact that patients with cardiovascular events identified 10 days following infarction more frequently received fibrinolysis could be the confounding factor in the assessment of chronic inflammation. Streptokinase resulted in higher levels of sICAM-1 at 10 days and ESR at 10 weeks, although without effects on CRP at 10 weeks. In patients with cardiovascular events identified at 10 weeks following infarction and in patients with CRP > 1.83 mg/l there were no differences in the use of streptokinase, a situation similar to that of patients with sICAM-1 > 270 ng/ml. These data indicate that in the present study the type of reperfusion did not affect the levels of inflammatory markers in the two subgroups. A comparison of factors that could influence end points in the subgroups showed that cardiovascular complications were more frequent in patients with multivessel disease; infarct size and infarct location did not influence the occurrence of cardiovascular events. The difference in frequency of anterior myocardial infarction was caused by early events (before the 10th week after myocardial infarction) in two patients with anterior myocardial infarction. The group was therefore homogenous, and the difference in coronary events was caused by plaque instability (unstable angina and acute myocardial infarction were responsible for 95% of all end points) and not by electrical instability, which is influenced by the infarct area, ejection fraction and left ventricular end-diastolic volume. Plaque instability is also responsible for the absence of a strong correlation between these prognostic factors and the recurrence of cardiovascular events in the study subgroup. Another factor may be the duration of follow-up (which was too short for the development of congestive heart failure) and the small numbers of patients in the subgroups, a limitation of our study. Because our study was directed at assessing the clinical prognostic utility of inflammatory markers, our group, with different types of reperfusion therapy and with patients that did not receive reperfusion therapy at all, corresponded to a real-life population of myocardial infarction patients, but this of course is another limitation of the study in case of small patient number in the subgroups.

The pattern of changes in inflammatory markers was significantly different between the groups during follow-up. In patients without cardiovascular events between the 10th day and the 10th week following infarction white blood cell count was markedly lower but this was not the case in patients with cardiovascular events. Similarly, ESR did not decrease in patients with cardiovascular events and only a tendency for sICAM-1 was observed. These data suggest that patients with secondary cardiovascular events constitute a group of subjects with prolonged inflammatory reaction related to the presence of unstable atherosclerotic plaques or that inflammatory activation and enhanced expression of adhesive molecules on the endothelium result from hyperactivity of the immune system in response to mild stimuli.

Conclusions

1. Increased inflammatory indices (CRP, ESR, sICAM-1) at 10 weeks after infarction are independent predictors of secondary cardiovascular events. Measurements of CRP, ESR or sICAM-1 are useful in long-term prognosis after myocardial infarction.
2. Inflammatory indices (ESR, WBC) measured at 10 days and 10 weeks following infarction show a different pattern of changes in patients with and without cardiovascular events

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