Original Research

The Influence of Thrombolytic Therapy on C-Reactive Protein in ST-Segment Elevation Acute Myocardial Infarction

Alexandros K. Tsakiris, Panagiotis G. Marnelos, Nearchos S. Nearchou, John E. Papadakis, Emmanouil N. Karatzis, Panagiotis D. Skoufas

1st Cardiology Department, Hellenic Red Cross Hospital - Korgialeneio-Benakeio, Athens.

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Background: Inflammation plays a crucial role in atherosclerotic processes and in acute coronary syndromes (ACS). Strong evidence of this is the elevation of C-reactive protein (CRP) serum levels during an ACS and its short- and long-term prognostic potency. The present study aimed to assess the relation between CRP serum levels and the elevation of cardiac markers in patients with ST elevation acute myocardial infarction (STEMI) as well as the effect of intravenous thrombolysis on a time series of CRP values.

Methods: Thirty-six patients with STEMI were enrolled in the study. Twenty-eight of them received intravenous thrombolysis successfully and 8 did not receive thrombolysis. We measured serum concentrations of CRP, troponin I, creatine kinase, creatine kinase isoenzyme and lactate dehydrogenase in all patients on admission, 24 and 48 hours later. CRP serum values were obtained using the turbidimetric method. Coronary angiography was performed in all patients to estimate disease severity and culprit vessel flow after treatment.

Results: Patients who were thrombolysed had lower CRP values on admission ($p<0.05$), at 24 hours ($p<0.001$) and 48 hours later ($p<0.05$), compared to those without thrombolysis. CRP values on admission had a positive correlation with markers of cardiac myocyte necrosis and a negative correlation with TIMI flow.

Conclusion: Thrombolytic therapy in patients with STEMI is associated with a less pronounced response of CRP during the first 48 hours. The close relation of CRP with cardiac enzymes and troponin I on admission adds to the proven value of this inflammatory marker and suggests directions for further research.

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Address:
Panagiotis Marnelos

2-4 M. Hatzidaki St.
15126 Marousi,
Athens, Greece
e-mail:
pmarnelos@avacom.net

The inflammatory process plays a pivotal role in the pathogenesis of atherosclerosis[1] and in plaque rupture leading to acute coronary syndromes, as many studies have demonstrated.[2-4] C-reactive protein (CRP) appears to be a sensitive and non-specific marker of inflammation, released by the liver and dependent on cytokines. Elevated plasma CRP levels detected in the first days of myocardial infarction may reflect an increased systemic inflammatory response, induced by myocardial necrosis,[2,3] and it has been reported that intravenous thrombolysis administration attenuates that inflammatory response.[2,4] Furthermore, elevated CRP on admission for an ST-segment elevation acute myocardial infarction (STEMI) has been demonstrated as a predictor of short-term[5] and long-term[6] adverse outcome.

The present study aimed to assess the effect of thrombolytic treatment on a time series of CRP values during the first 48 hours of STEMI. In addition, it attempted to determine whether this inflammatory marker is correlated with levels of cardiac enzymes and troponin within the same time interval.

Methods

Study population

The study population consisted of 36 patients with STEMI who were admitted to our emergency department and fulfilled the following criteria:[7] a) continuous anginal chest pain, present on admission, refractory to nitrates and lasting ≥30 min; b) ST-segment elevation ≥2 mm in at least 2 continuous electrocardiographic leads; and c) absence of malignancy, active infection, hepatic, renal insufficiency or chronic inflammatory disease. Patients admitted to hospital within 12 hours received thrombolytic therapy, unless a contraindication was reported, and they comprised group A (n=28, 77.8%), whereas those who were not treated with thrombolysis made up group B (n=8, 22.2%). Patients who were treated with primary percutaneous coronary intervention and those with unsuccessful thrombolytic treatment, based on clinical symptoms, electrocardiographic criteria and coronary angiography, were excluded. Thrombolysis was considered successful for those patients who presented attenuation of the clinical syndrome, return of the ST segment to the normal position, restoration of a negative T wave and an absence of ventricular ectopic beats or ventricular tachycardia on the surface electrocardiogram 60-90 minutes after the beginning of the thrombolytic procedure.[7] The success of the thrombolysis was confirmed by coronary angiography, which was performed via a femoral approach using the Seldinger technique, shortly before the patients' discharge. Angiographically, successful thrombolysis was considered to be the presence of grade 2 or 3 flow in the culprit vessel according to the TIMI criteria.[8] In addition, during hospitalisation an echocardiographic study was performed and left ventricular ejection fraction was estimated. All patients gave their informed consent before entering the study, which was carried out in conformance with the Declaration of Helsinki and medical ethics.

Collection of blood samples and CRP assay

Venous blood samples were obtained before the administration of any drug. The serum concentrations of CRP, troponin I, creatine kinase (CK), creatine kinase isoenzyme (CK-MB), and lactate dehydrogenase (LDH) were assessed in all patients on admission, 24 hours and 48 hours later. The analysis of plasma CRP was performed by immunoturbidimetry using the TurbiTime system (Turbicant, Dade Behring diagnostics, Marburg, GmbH) covering a range of 0.5 to 60 mg/dl. For values below the limit of detection, the lower limit value was used for statistical analysis. This method appears to have a close relation with the immunonephelometric quantitative method,[9] and the intra-assay and inter-assay coefficients of variation for CRP are 5.4 and 8.9%, respectively.

Treatment

In the group of patients who received thrombolysis (group A) the agent was either tenecteplase or reteplase. Chewable aspirin was given in a dose of 160 to 325 mg to both groups of patients on admission and was continued indefinitely. Heparin was given as a bolus of 5000 units on admission, followed by intravenous infusion titrated to a therapeutic activated partial thromboplastin time. Heparin was continued in uncomplicated cases for at least 48 hours. The remaining medication was in line with the international guidelines[7] for treatment of STEMI and was comparable for both groups.

Statistical analysis

Values were expressed as mean ± standard deviation (SD). A p-value <0.05 was regarded as the level of statistical significance. The Kolmogorov-Smirnov test was used to detect values with a normal distribution. Because of the limited number of patients (N=8) in group B, the Mann-Whitney U test (non parametric) was applied to detect differences between groups regarding quantitative data. The χ^2 or Fisher's exact test were applied as appropriate to detect differences between groups regarding qualitative data. Additionally, Spearman's coefficient of correlation (r) was estimated for CRP in relation to various parameters, especially cardiac enzymes. The statistical analysis was performed using SPSS 11.5 for Windows (SPSS Inc Chicago Illinois).

Results

Of the 36 patients who were enrolled in the study 30 (83.3%) were men. The mean age was 61.8 ± 11.91 years. The location of the infarction was the anterior wall of the left ventricle in 14 cases (38.9%), the inferior wall in 14 cases (38.9%) and other locations in 8 cases (22.2%). The mean CRP value of the total population was 0.81 ± 0.74 mg/dl on admission, 2.36 ± 2.43 mg/dl 24 hours later and 4.68 ± 4.81 mg/dl 48 hours after admission.

Table 1 shows the baseline clinical characteristics, biochemical profile and data from coronary angiography, as well as the risk stratification of each group based on TIMI risk score. Both groups presented similar risk factor profiles, as well as vessel disease severity. Patients who were given thrombolytic therapy (group A) had a lower age, lower TIMI score and were admitted to the emergency department with less prehospital delay than patients of group B. Also, CRP values were lower in group A on admission (CRP_1) as well as 24 hours (CRP_2) and 48 hours later (CRP_3), compared with group B. The latter group had higher CK, LDH and troponin-I values at admission and a trend towards higher MB levels (p=0.068) than group A. CK and MB values tended to remain higher until 48 hours later (p=0.087 and p=0.083, respectively) and LDH levels were also higher (p<0.05).

Data from coronary angiography confirmed satisfactory coronary flow (TIMI 2 or 3) in the culprit vessel of all patients of group A (this was an inclusion criterion), whereas TIMI 2 or 3 flow was detected in only half of the patients in group B (p<0.05).

Spearman's correlation coefficient (r) of CRP with CK, MB, LDH and troponin-I was statistically significant on admission and a positive correlation was also confirmed 48 hours later with CK and troponin-I (Table 2). In addition, values of CRP showed a positive correlation with age (CRP_1: r=0.39, p=0.018; CRP_2: r=0.33, p=0.05; CRP_3: r=0.39, p=0.02) and a negative correlation with TIMI flow (CRP_1: r= -0.36,

Table 1. Clinical, biochemical and coronary angiography data of patients with (group A) or without (group B) thrombolysis treatment.

	Group A (n=28)	Group B (n=8)
Age (years) (mean ± SD)	58.86 ± 10.63	72.25 ± 0.63*
Males (n, %)	23 (82%)	7 (88%)
Hypertension	15 (53%)	6 (75%)
Hyperlipidaemia	16 (57%)	4 (50%)
Current smoking	18 (64%)	2 (25%)
Diabetes mellitus	9 (32%)	5 (63%)
Family history of CAD	2 (7%)	2 (25%)
Anterior MI or LBBB	12 (43%)	5 (63%)
Killip>1	1 (4%)	2 (25%)
TIMI risk score	1.92 ± 1.99	6.25 ± 3.33*
Multivessel disease (> 2 vessels with 50% stenosis)	10 (36%)	3 (38%)
TIMI 2-3 flow during coronary angiography	28 (100%)	4 (50%)*
CRP_1 (mg/dl)	0.62 ± 0.33	1.54 ± 1.16*
CRP_2 (mg/dl)	1.50 ± 1.38	6.05 ± 3.09†
CRP_3 (mg/dl)	3.14 ± 2.77	9.93 ± 6.40*
CK_1 (mg/dl)	812.53 ± 827.34	3214.38 ± 3760.82*
CK_2 (mg/dl)	1364.18 ± 1268.03	4652.13 ± 5895.01
CK_3 (mg/dl)	564.36 ± 774.79	3439.13 ± 5151.32
MB_1 (mg/dl)	94.21 ± 75.67	224.5 ± 198.83
MB_2 (mg/dl)	136.64 ± 118.28	218.75 ± 236.96
MB_3 (mg/dl)	43.92 ± 29.24	110.25 ± 117.57
LDH_1 (mg/dl)	557.32 ± 264.78	1092.38 ± 649.64*
LDH_2 (mg/dl)	954.53 ± 464.35	1405.75 ± 959.61
LDH_3 (mg/dl)	951.96 ± 390.88	1908.63 ± 1320.53*
$Troponin_1$ (ng/ml)	52.89 ± 95.16	107.93 ± 136.87*
$Troponin_2$ (ng/ml)	55.84 ± 70.85	150.02 ± 146.73
$Troponin_3$ (ng/ml)	24.01 ± 37.08	80.45 ± 106.71
Time to treatment (min)	163.57 ± 102.68	698.75 ± 475.05*
Ejection fraction (%)	50.45 ± 7.05	47.00 ± 4.24

*p <0.05 and †p <0.001, in comparison of patients with or without thrombolysis.
CAD – coronary artery disease; CK – creatine kinase; CRP – C-reactive protein; LBBB – left bundle branch block; LDH – lactate dehydrogenase; MB – creatine kinase isoenzyme; MI – myocardial infarction.
The indexes 1, 2 and 3 for CRP and cardiac enzymes represent measurements on admission, 24 hours and 48 hours later, respectively.

Table 2. Spearman's correlation coefficient (r) of CRP with markers of cardiac damage on admission, and 24 and 48 hours after the initiation of an ST-segment elevation myocardial infarction.

	Admission		24 hours		48 hours	
	r	p	r	p	r	p
CK	0.42	<0.05	0.08	NS	0.41	<0.05
CKMB	0.40	<0.05	0.02	NS	0.20	NS
LDH	0.48	<0.05	0.08	NS	0.32	NS
cTnI	0.37	<0.05	0.16	NS	0.45	<0.05

cTnI, troponin I. Other abbreviations as in table 1.

p=0.06; CRP_2: r= -0.51, p=0.005; CRP_3: r= -0.045, p=0.017).

Discussion

In the present study of patients with STEMI we noticed a close correlation of CRP serum levels with the cardiac enzymes and troponin I on admission. This relation was also evident with CK and troponin I 48 hours later. Furthermore, thrombolysis was associated with a lower inflammatory response during the first two days compared with non-reperfusion therapy.

CRP is an acute phase protein that is generated in the liver after the stimulation of circulating cytokines, especially interleukin-6, by inflammable tissues. Inflammation characterises all the phases of coronary vessel atherosclerosis, from endothelial dysfunction[10] and the formation of plaques until the acute rupture, which leads to the occlusion of the vessel and the onset of myocardial infarction.[1] Consequently, during the acute phase of STEMI the inflammatory cascade is activated in the jeopardised myocardium, resulting in the release of cytokines.[11]

Our study groups presented with similar risk factors for atherosclerosis and with comparable coronary artery disease severity. However, the age of the patients in group B was higher and a more delayed hospital admission (12 vs. 2 hours) was reported. These two factors led to a more conservative strategy without thrombolysis administration. TIMI risk score was higher in patients without thrombolysis, since this score takes into account age and time to treatment.[8,12]

Several lines of evidence demonstrate that the variation of myocardial enzymes and troponin I values in the acute phase of a myocardial infarction are an indirect marker for the extent of myocardial necrosis.[7,12,13] CRP plasma levels on admission for STEMI could mirror the presence of pre-existing inflammation and represent the extent of the myocardium in jeopardy for ischaemia and necrosis. As reperfusion therapy was not administered to patients of group B, they presented with more extensive myocardial necrosis. The fact that the CRP response was more pronounced in those not thrombolysed indicates a higher grade of inflammatory response, which also seems to be in line with markers of necrosis.

In the present study there was a close correlation between CRP values and the values of myocardial enzymes and troponin I on admission for STEMI. The variation in CRP was correlated with the variation in myocardial enzymes and troponin I, a fact also noticed in previous studies.[12,14] It seems that myocardial necrosis and inflammatory response are processes that evolve contemporaneously during the acute phase of STEMI.

The pathogenetic mechanism through which thrombolysis attenuates the inflammatory response, as represented by CRP values, during the acute phase of STEMI, is not fully understood. Moreover, whether inflammation is a cause or a consequence of atherosclerosis and atherothrombotic events remains elusive.[15] The hypothesis of a direct "anti-inflammatory" action of thrombolysis could possibly represent one scenario. Nevertheless, the restoration of the patency of the artery responsible for the infarction and the reperfusion of the jeopardised myocardium, which minimises the release of the inflammatory mediators, might be a more probable pathogenetic mechanism for the lower inflammatory response of thrombolysed patients. Support for this concept comes from the negative correlation of CRP with TIMI flow grade in the culprit artery, detected in our study and also evident in previous studies,[6] indicating that more satisfactory patency is associated with less inflammatory response. Furthermore, the attenuated release of cytokines and inflammatory factors by reperfusion could reduce endothelial injury and endothelial dysfunction, which is evident in the acute phase of an acute coronary syndrome,[16,17] enhancing the antithrombotic, antioxidant and anti-inflammatory properties of vascular endothelium.

At this point we must mention that the available method for assessing CRP at our hospital was immunoturbimetry and not the currently recommended high sensitivity CRP. This could be a limitation, although immunoturbimetry appears to be closely related to the immunonephelometric method.[7,9]

In addition, the small number of patients in group B must be considered. The reason is that this group

consisted mainly of patients with a delayed hospital admission and a higher age, without thrombolysis administration, and was not the result of randomised patient allocation. The small total population also limits the power of the statistical analysis and, although multivariate analysis appears plausible, application of more complicated multivariate analysis in small populations is inconvenient. Therefore, our results and the proposed mechanisms need further confirmation by a larger patient series.

CRP serum levels were closely correlated with cardiac enzymes and troponin I in patients admitted for STEMI. Patients who were successfully thrombolysed after infarction presented serial CRP serum values for the first 48 hours after infarction that were significantly lower than those in non-thrombolysed patients. Although the patient population of our study was relatively small, it suggests that there is value in CRP assessment during the acute phase of STEMI. This concept deserves more research in order to verify these early findings.

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