Original paper

C-reactive protein as a predictor of major adverse cardiac events (MACE) after percutaneous coronary intervention?

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Abstract

Introduction: Interventional procedures, such as percutaneous coronary intervention (PCI) have significantly improved the prognosis in patients with acute coronary syndromes (ACS). Despite the introduction of new methods the problem of in-stent restenosis in coronary arteries is still being discussed. Therefore finding predictors of this process is crucial. Elevation of C-reactive protein (CRP) can be a useful predictor for restenosis and other major adverse cardiac events (MACE) after PCI.

Material and methods: The studied group consisted of 33 patients (23 males and 10 females; mean age 62.9±8.9) admitted to our Department with myocardial infarction (MI) in whom MACE occurred during 6 months follow-up period. The control group consisted of 33 patients (21 men and 9 women; mean age 61.8±9.8) admitted to hospital for MI, in whom no MACE occurred during 6 months follow-up period. In all patients coronarography was performed and concentrations of CRP were measured, using high sensitivity diagnostic ELISA method (hsCRP). An incorrect level was determined as higher than 6 mg/dl. Patients have been observed during 6 months follow-up. History data were taken from everyone, including information about incidences of MACE or restenosis.

Results: Both studied groups did not differ in parameters describing: sex, age and number of people. In patients with MACE, mean CRP concentration was significantly higher (median 4.8 mg/dl ±; 1.9-11.4) in comparison with the control group (median 2.2; 1.3-4.3); $p<0.05$.

Conclusion: CRP concentration can be a predictor of MACE after successful PCI.

Key words: C-reactive protein (CRP), major adverse cardiac events (MACE), percutaneous coronary intervention (PCI), restenosis, inflammation.

Introduction

Since interventional treatment in acute coronary syndromes (ACS) has been introduced to clinical practice, improvement in the clinical course of the disease, significant reduction of mortality was observed. Further development of techniques such as stent implantation has reduced the prevalence of restenosis from 30-40% to 20-30% and improved prognosis for patients with ACS [1]. Despite this advanced management, the phenomenon of restenosis after percutaneous coronary angioplasty (PCI) is still a pivotal problem in interventional cardiology. The in-stent restenosis is defined as at least 50% reduction at follow-up angiography of a lumen diameter in the previously

stented coronary artery [1]. The recurrence of stenosis can occur 2-6 months after interventional treatment with implementation of stent [1]. A large number of studies concentrate on searching factors which can predict a restenosis in the coronary arteries. In this case an intensive inflammatory response proceeding in atherosclerotic plaques, can indicate a possibility of in-stent restenosis one of major adverse cardiac events (MACE) after PCI, defined as: cardiac death, myocardial infarction, repeat revascularization (re-PCI) and coronary artery bypass graft (CABG). One of the markers of inflammatory processes is an elevated level of high sensitivity C-reactive protein (hsCRP). The aim of the study was to assess if the elevated level of hsCRP on admission to the hospital can be a predicted factor for MACE.

Material and methods

The study group included 33 patients (10 females and 23 males; mean age 62.9±8.9 years) (complete characteristics of studied groups are shown in Table I), with myocardial infarction (MI) treated with percutaneous coronary intervention (PCI), hospitalized from the beginning of year 2003 to March of 2004, in whom MACE occurred during 6 months follow-up period. The control group consisted of 30 patients (9 females 21 males, mean age 61.6±8.9) with MI after PCI without MACE as the end point.

In all patients concentrations of CRP in peripheral venous blood, using high sensitivity diagnostic ELISA method (hsCRP), were measured. An incorrect level was determined as higher than 6 mg/l. The blood samples were obtained from patients and controls during the first day of hospitalization, before PCI. Laboratory tests were performed in the Institution of Laboratory Diagnostic of the Medical University of Lodz. Coronarography (using Seldinger's or Sones' method) was made on Shimadzu angiograph with Digitex 2400 system in the Departament of Interventional Cardiology, Cardiodiabetology and Cardiac Rehabilitation, Medical University of Lodz. Patients had been observed for six months follow-up period and their history was analyzed for occurrence of MACE in that period (Table II).

Other parameters, such as: fibrinogen concentration (Fbg), glycosylated hemoglobin (HbA_{1C}), lipid disorders (expressed as: total cholesterol-TCH, high density lipoprotein cholesterol-HDL, low density lipoprotein cholesterol-LDL, triglycerides-TG), body mass index (BMI), white blood cells (WBC) and erythrocyte sedimentation rate (ESR) were also analyzed. In all patients infectious diseases were excluded by history, physical examination and laboratory tests.

For all parameters the arithmetical mean with a standard deviation ($\bar{x}$±SD) and median (Me), first and second quartyl (1Q-3Q) with minimal and maximum value (min-max) were accounted. Normal distribution of dates in the sample was evaluated by Shapiro-Wilk test. The statistical importance was estimated by t-Student's test for parametric distribution and Mann-Whitney U test for nonparametric distribution. Differences were recognized as statisticcally important for $p \leq 0.05$. Statistical calculations and graphical analysis were made by Stats Direct program (StatsDirect Ltd., Cheshire, UK). The studies were made basing on rules of the local Ethics Commission. All patients agreed to take part in the study.

Table I. Characteristics of the studied groups

	MACE	Control group
Number of patients	33	30
Sex (M/F)	23/10	21/9
Age	62.9±8.9	61.8±9.8
BMI	28.6±3.9	28.3±4.1
HbA_{1c}	6.5% (6.0-8.3%)	6.3% (5.8-7.1%)
TCH (mmol/l)	5.9±1.4	6.1±1.7
HDL (mmol/l)	1.4±0.5	1.4±0.3
LDL (mmol/l)	3.6±1.4	3.6±1.4
TG (mmol/l)	2.0 (1.1-2.4)	1.3 (0.7-2.2)

MACE – major adverse cardiac events, M – male, F – female, BMI – body mass index, HbA_{1c} – glycosylated hemoglobin, TCH – total cholesterol, HDL – high density lipoprotein cholesterol, LDL – low density lipoprotein cholesterol, TG – triglycerides

Table II. Characteristics of the MACE group

MACE	Number of patients	Sex (M/F)
re-PCI	25	17/8
CABG	5	3/2
Cardiac death	3	3/0

MACE – major adverse cardiac events, re-PCI – repeat percutaneous coronary intervention, CABG – coronary artery bypass graft, M – male, F – female

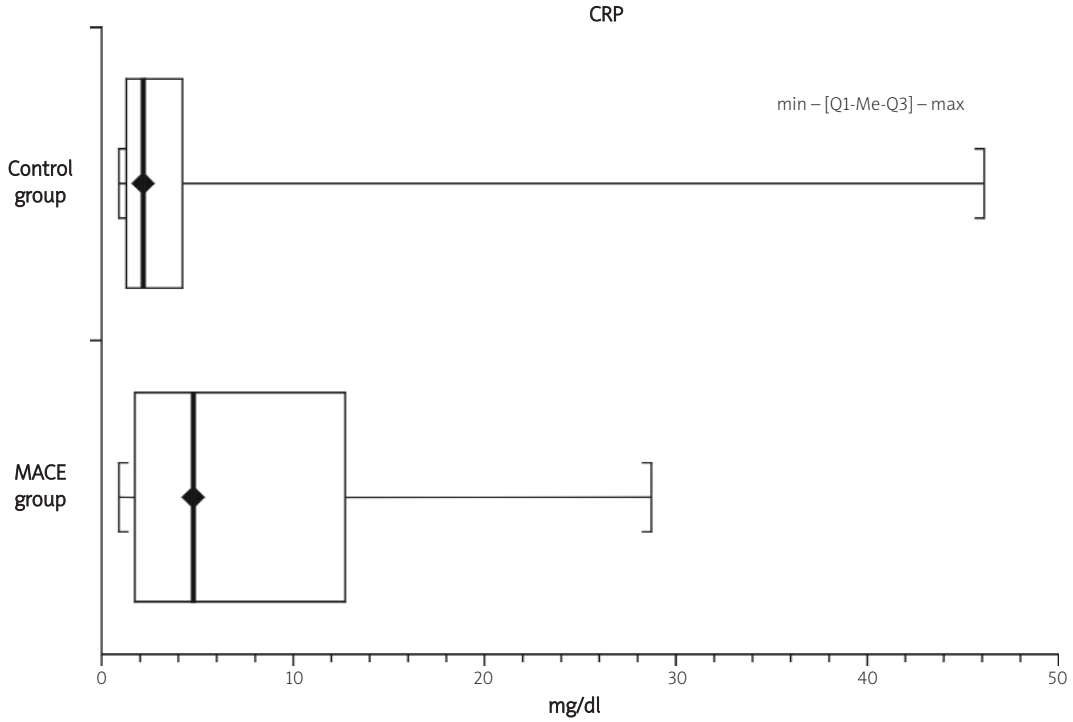
Table III. Results of CRP, WBC and SR in the studied groups

	CRP	WBC	ESR
MACE group	4.8* (1.9-11.4)	10.3±3.4	14.0 (10.0-23.5)
Control group	2.2 (1.3-4.3)	9.6±2.9	12.0 (8.0-19.0)

CRP – C-reactive protein, WBC – white blood cells, SR – sedimentation rate, MACE – major adverse cardiac events
**p<0.05*

Results

Both studied groups did not differ in parameters describing: sex, age and number of people. In patients with MACE mean CRP concentration was significantly higher in comparison with the control group (Figure 1). There were no differences in other indicators of the inflammatory state between the groups (Table III).



CRP – C-reactive protein
p=0.0217

Figure 1. Concentrations of CRP in both groups

Discussion

CRP is strongly associated with an inflammatory process and it can also be helpful in the assessment of the cardiovascular risk (CVR) [2]. Values of hsCRP: lower than 1 mg/l, between 1 and 3 mg/l and higher than 3 mg/l indicate a small, intermediate and high CVR, respectively [2, 3]. Levels higher than 10 mg/l are found in bacterial or septic states and rather exclude the cardiac reason for elevated CRP [4]. In patients after PCI with stent implantation increased CRP concentration indicates the presence of inflammation [5]. According to Japanese investigations, CRP is released particularly from vulnerable atherosclerotic plaques and from coronary arteries injured during stenting. It markedly proves that there is an inflammatory process connected with plaque instability [6]. The intensification of inflammation is quite similar in patients treated with bare metal stents (BMS) and drug-eluting stents (DES). A decreased prevalence of restenosis in the case of DES implantation is not associated with attenuation of the inflammatory response [7].

This acute phase reactant has been found to be connected with a prognosis of ACS and stable angina. It is also a valuable predictor of restenosis risk and major adverse cardiac events (MACE), such as: cardiac death, repeat myocardial infarction and repeat revascularization, defined as TLR, Target Lesion Revascularization (re-PCI or CABG) [8], which was documented in our investigations. CRP is an independent predictor from other risk factors describing a high risk of TLR and MACE [8]. The role of pre- and postinterventional CRP analysis in restenosis prediction is still being discussed. The literature shows divergent results of investigations. Scientists from Turkey have proved that post-procedural CRP levels higher than 3 mg/l measured in the third month after stent implantation can predict angiographic in-stent restenosis [9]. The elevated CRP concentration (≥24 mg/l) on the second day after stent implantation was found to be statistical higher in patients with restenosis [10]. Nevertheless in another study this correlation was not observed. Pre- and post-procedural CRP concentrations were similar in restenotic and non-restenotic patients [11]. Elevated CRP levels strongly correlated with the progression of new atheromatous stenoses [11]. However, in this and other assessments a significant increase of CRP has been documented in MACE prediction. It was related to the recurrence of stenocardial symptoms [12] and a number of complex angiographic stenoses, indicating coronary artery disease activity [13]. This conclusion was not confirmed in British studies, whereas the neutrophil count has been found connected with these stenoses complexity [14]. Other descriptions have shown the role of incorrect CRP in recurrent angina complaints, but not in the MACE assessment (in

this paper elevated concentrations of fibrinogen and lipoprotein (a) were correlated with MACE prediction) [15].

There is a suggestion of combined: CRP and tumour necrosis factor alpha (TNF alpha) determination in clinical restenosis and risk of MACE. These both analyzed parameters can indicate increased probability of TLR and MACE [16]. Biochemical investigations can also be improved by matrix metalloproteinases (MMP) determinations. Especially a higher MMP-9 level is related to restenosis development [17]. However, scientists from the Netherlands have shown that there is no statistically important connexion between the concentration of CRP and a higher prevalence of restenosis and TLR. On the other hand, patients with an incorrect CRP level presented a trend of higher risk of nonfatal myocardial infarction during one year observation [18]. In this paper it has also been documented that treatment with statins, as anti-inflammatory therapy, was an independent factor decreasing a TLR necessity. Patients, who did not receive statins had higher levels of CRP probably leading to restenosis [19]. The problem of using statins is connected with a low density lipoprotein cholesterol (LDL). It has been proved that an elevated CRP is a better and stronger predictor of CVR than LDL, which was confirmed in our analysis. Patients with the high CRP concentration and low LDL have worse prognosis than patients with the correct CRP and increased LDL level [20].

A complementary biochemical diagnosis with preprocedural interleukin-6 (IL-6) measurements did not define both CRP and IL-6 as predictors of late coronary angiographic in-stent restenosis [21]. During other investigations it has been documented that preprocedural concentrations of IL-8 and CRP are only independent predictors of MACE. In the same paper, there was a conclusion about postprocedural high IL-8 level and stent length as independent predictors of restenosis phenomenon [22].

As it shows, results of investigations are very divergent, so the role of CRP measurements has to be still discussed as a probable predictor of MACE, including the TLR risk.

Conclusion

CRP concentration can be a predictor of major adverse cardiac events after earlier successful PCI.

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