ORIGINAL PAPERS

Adv Clin Exp Med 2015, **24**, 6, 979–985
DOI: 10.17219/acem/46935

ISSN 1899–5276

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Prolonged CRP Increase After Percutaneous Coronary Intervention Is Associated with High Thrombin Concentrations and Low Platelet' Response to Clopidogrel in Patients with Stable Angina*

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. Inflammation is involved in all stages of development of atherosclerotic plaques. Currently, percutaneous coronary intervention (PCI) is a widely used method of treatment of coronary artery disease (CAD) when combined with optimal medical therapy (OMT). However, there is still controversy over invasive versus optimal pharmacological treatment in stable CAD (SCAD). Systemic inflammatory response triggered by PCI may limit its effectiveness in patients with SCAD.

Objectives. We aimed to evaluate plasma CRP and its relation to thrombin generation and platelet reactivity both early after the procedure and in a one-month observation following successful PCI with stent implantation, in patients with SCAD and OMT, including statins.

Material and Methods. We conducted a prospective study, in which CRP, platelet activation, thrombin generation and time course of prothrombin activation were determined at baseline, 3–5 days and 30 days after successful PCI with stent implantation, in 50 consecutive patients with SCAD, on chronic statin therapy.

Results. Early after PCI CRP increased by 176% as compared with baseline ($p < 0.001$) and one-month after angioplasty CRP was still 54% higher than before the procedure ($p = 0.002$). In multivariate model prolonged increase in CRP 1 month after PCI was independently associated with P2Y12-reactivity index (PRI) ($p = 0.04$) and maximum concentration of thrombin ($p = 0.003$), both measured 30 days after the procedure.

Conclusions. Post-procedural CRP increase, which persists at least one month in patients with SCAD, after elective PCI with stent implantation, is one of the main finding of our study. We demonstrated the relationship between prolonged post-PCI inflammatory reaction, reflected by elevated CRP, and increased thrombin generation and low platelets' response to clopidogrel, which may account for limited benefits of PCI in stable coronary patients. It may be advisable to assay post-procedural CRP in each patient with SCAD, who underwent PCI to predict those, with potentially low response to clopidogrel (**Adv Clin Exp Med 2015, 24, 6, 979–985**).

Key words: platelet reactivity, hs-CRP, percutaneous coronary intervention PCI, stable coronary artery disease, thrombin generation.

* The present study was financed by the Ministry of Science and Higher Education of Poland and the Foundation "Helping the Heart" at the Department of Coronary Disease and Heart Failure, Jagiellonian University School of Medicine.

The role of inflammation in the pathogenesis of atherosclerosis has been demonstrated in both experimental models and clinical trials [1, 2]. Inflammation is involved in all stages of development of atherosclerotic plaques-formation, vulnerability and rupture [3]. Local endothelial dysfunction promotes low-density lipoproteins (LDL) accumulation, which are then oxidized. Oxidized LDL then triggers an inflammatory reaction, which signals immune cells, such as monocytes/macrophages, neutrophils, distinct classes of T lymphocytes, dendritic cells, and potentially mast cells [1, 2]. One of the most widely used markers of systemic inflammation is C-reactive protein (CRP). It is an acute phase reactant which is produced mainly by hepatocytes in response to interleukin-6 and, to a much lesser extent, locally by coronary artery smooth muscle cells [4]. CRP has been indicated to be an independent predictor of myocardial infarction (MI), stroke and cardiovascular death both in primary prevention as well as in patients with coronary artery disease (CAD) [5–8]. The impact of CRP on long-term prognosis, in-stent restenosis and major adverse cardiovascular events (MACE) after successful percutaneous coronary intervention (PCI), has been shown in clinical trials [9, 10]. Moreover, coronary atheroma regression and MACE reduction have also been shown to correlate with statin-mediated CRP lowering in patients treated with maximally intensive statin therapy [11]. CRP has been suggested not only to be the marker of inflammation, but also to exert complex modulatory effects that participate in inflammatory processes associated with atheromatous plaque vulnerability and progression of coronary stenosis [12].

Endothelium plays also a major role in the reciprocal relationship between inflammation and coagulation [13]. CRP-mediated cell surface increased expression of TF, upon procoagulant activity, induces a proinflammatory response mediated by TF-FVIIa complexes directly, or through protease-activated receptors (PAR) [14]. Thrombin, whose generation is stimulated by TF, besides its clotting properties, also activates PAR receptors, which is a possible effector mechanism linked with atherosclerosis [14]. Another link between coagulation and inflammation are platelets-binding of P-selectin on activated platelets with its ligand, present on majority of leukocytes, promotes the inflammatory response [13].

PCI is currently a widely used method of treatment of CAD when combined with optimal medical therapy (OMT) [15]. However, there is still controversy over invasive vs. optimal pharmacological treatment in stable CAD (SCAD) as several studies have failed to demontrate that PCI reduces the risk of MACE over OMT in patients with SCAD [16–18]. During PCI, balloon inflation causes both plaque rupture and endothelial injury with exposure of deeper layers of artery wall. These insults are strong pro-inflammatory and procoagulant stimuli. Moreover, intervention is limited to the single plaque, whereas there may be numerous vulnerable plaques prone to destabilization by the inflammatory processes.

In previous studies PCI in patients with SCAD has been shown to cause CRP elevation [19]. We hypothesized that systemic inflammatory response triggered by PCI may limit its effectiveness in patients with SCAD. The aim of the present study was to evaluate plasma CRP and its relation to thrombin generation and platelet reactivity both early after the procedure and in a one-month observation following successful PCI with stent implantation in patients with stable angina and optimal medical treatment, including statins.

Material and Methods

The study group included 50 consecutive patients (38 male and 12 female; mean age 63 ± 9.5 years) with SCAD, on chronic statin therapy at least one month prior to the study enrolment, who underwent successful PCI with stent implantation. The authors conducted a prospective study, in which CRP was measured at baseline, 3–5 days and 30 days after PCI with stent implantation. The authors also assayed platelet activation markers (platelet aggregation, P2Y12--reactivity index/PRI/and P-selectin expression on platelets), thrombin generation, time course of prothrombin activation and oxidized low-density lipoprotein. Several atherosclerosis risk factors were assessed by medical history or laboratory analyses including: blood pressure, lipidogram, renal function, diabetes, obesity and smoking, previous CAD, stroke or PAD as well as family history of CAD.

Hypertension was defined as either the mean from at least two blood pressure measurements consistently not lower than 140 mm Hg systolic or 90 mm Hg diastolic over at least two separate days or patients currently receiving antihypertensive therapy.

In the study population, a lipid-lowering therapy or cholesterol LDL level of 1.8 mmol/L (70 mg/dL) and higher was considered diagnostic for hypercholesterolemia. Renal function impairment was assessed on the basis of a decreased glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 by the MDRD formula [20].

Diagnosis of diabetes was adopted from 2013 ESC guidelines. In brief, fasting glycemia equal to or exceeding 7.0 mmol/L (126 mg/dL) during 2 measurements or 11.0 mmol/L (200 mg/dL) in one random blood sample or patients currently receiving hypoglycemic medication was considered diagnostic.

Obesity was regarded present if the patient's body mass index (BMI) was ≥ 30 kg/m^2. Definition of metabolic syndrome was adopted from the 2009 IDF statement [21].

Patients were interviewed with regard to current or former smoking habit, CAD, stroke or PAD history and family history of CAD.

Exclusion criteria were as follows: acute coronary syndrome, history of inflammatory, autoimmune, neoplastic or infectious diseases, history of bleeding, oral anticoagulant therapy, platelet count < 100,000/μL, serum creatinine > 177 μmol/L (2 mg/dL), liver injury (alanine transaminase > 1.5 times above the upper limit of the reference range) or severe obesity (body mass index [BMI] > 35 kg/m^2).

The study was compliant with the Good Clinical Practice International Conference on Harmonization rules and was approved by the Ethics Committee of Jagiellonian University. Written informed consent was obtained from each patient.

Laboratory Investigations

Fasting blood samples were obtained between 8.00 and 10.00 am, after at least 10 h of fasting, from an antecubital vein with minimal stasis. Routine blood tests (complete blood count, glucose, lipid profile, serum creatinine) were assayed by automated laboratory techniques. Blood samples were centrifuged within 30 min of collection and the supernatant was stored at –80°C. High-sensitivity C-reactive protein was measured by latex nephelometry. Platelet reactivity was measured by light transmittance aggregometry upon stimulation with 5 and 20 mmol/L of ADP and 0.5 mmol/L of arachidonic acid; PRI was calculated according to standard protocols and a standardized assay with quantitative flow cytometry; P-selectin expression on the platelets was determined by flow cytometry. The CAT was used to analyze thrombogram. For the analysis we used the maximum concentration of thrombin generated (Cmax). Prothrombin fragment 1.2(F1.2) was determined by immunoenzymatic assays. The time course of prothrombin activation was analyzed and quantified by quantitative Western blotting. All laboratory investigations were performed by the investigator blinded to the sample origin.

Statistical Analysis

STATISTICA 8.0 software package (Statsoft Inc.) was used for statistical analyses. Continuous variables were expressed as mean ± SD or median (IQR) and categorical variables as numbers (percentage). First, the Shapiro-Wilk statistic was used to check continuous variables for normal distribution. When the variables were not normally distributed, non-parametric test were used. CRP levels of three time points were compared with the use of the Friedman test. The Wilcoxon test was used to examine the differences between baseline and 3–5 days as well as between baseline and 1 month CRP level. To test the association between two variables, the Pearson rank correlation coefficient was calculated. Forward stepwise logistic regression analysis was performed including demographic and clinical parameters. A probability value < 0.05 was considered statistically significant.

Results

We analyzed 50 consecutive patients (38 male and 12 female; mean age 63 ± 9.5 years) with SCAD on chronic statin therapy who were undergoing PCI. Baseline demographics, clinical characteristics, procedural characteristics, and laboratory results of study population are shown in Table 1.

CRP in 3 time points were found to be statistically significant ($p < 0.01$). Its baseline concentration was 2.21 (0.1–8.22) mg/L. Early after PCI, CRP increased by 176% as compared with baseline (6.12 (0.1–28.77) mg/L; $p < 0.001$). One-month after PCI, CRP level did not return to baseline values (3.41 (0.1–22.32) mg/L) and was still 54% higher than before the procedure ($p = 0.002$) (Fig. 1).

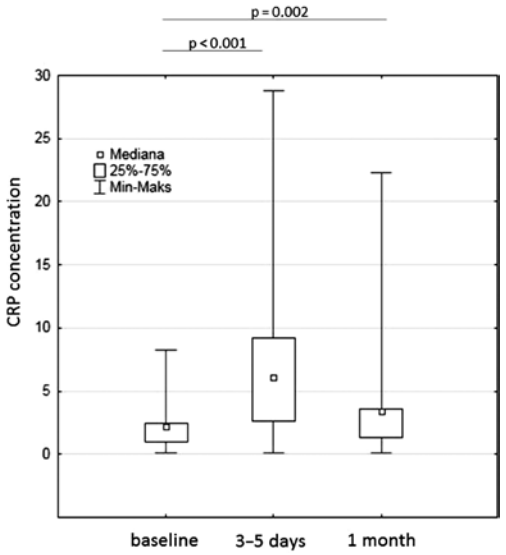

Fig. 1. CRP in 3 time points

Table 1. Baseline characteristic of study population

Age (years ± SD)	63.1 ± 9.5
Female gender; n(%)	12 (24)
History of CAD; years (min–max)	7.5 (1–30)
Fasting glucose; mmol/L (min–max)	5.4 (4.1–13.1)
BMI kg/m^2 (min–max)	29 (21–39)
MVD; n (%)	38 (77.6)
Previous MI; n (%)	20 (40)
Previous CABG; n (%)	5 (10)
Previous stroke; n (%)	14 (28)
Previous PCI; n (%)	9 (18)
Hypertension; n (%)	48 (96)
DM; n (%)	16 (32)
Insulin; n (%)	5 (10)
Hyperlipidemia; n (%)	50 (100)
Smokers; n (%)	24 (48)
Current smoking; n (%)	10 (20)
Family history of CAD; n (%)	30 (60)
CKD (GFR < 60); n (%)	10 (20)
Metabolic syndrome; n (%)	36 (72)
Beta-blocker; n (%)	43 (86)
ACE-I; n (%)	44 (88)
AT1; n (%)	7 (14)
Statins; n (%)	50 (100)
Nitrates; n (%)	20 (40)
Ca-blockers; n (%)	26 (52)

CAD – coronary artery disease; BMI – body mass index; MVD – multivessel disease; MI – myocardial infarction; CABG – coronary artery by-pass grafting; PCI – percutaneous coronary intervention; DM – diabetes mellitus; CKD – chronic kidney disease; ACE-I – angiotensin converting enzyme inhibitors; AT1 – angiotensin 1 receptor antagonists; Ca-blockers – calcium channel antagonists.

Univariate linear regression showed that both CRP 3–5 days after PCI, as well as early post-procedural CRP increases were associated with factor XIII measured 3–5 days after PCI (p = 0.012 and p = 0.026, respectively). Early post-procedural CRP level was associated with expression of P-selectin on the platelets at the same time (0 = 0.017). We have also observed the association between the rate of prothrombin activation and platelets reactivity upon stimulation with 20 mmol/L of ADP 3–5 days after PCI (p = 0.025) and between the rate of prothrombin activation and PRI one month after the procedure (p = 0.016). In the univariate model CRP in a 1 month follow-up was associated with stent size (p = 0.032).

In multivariate model (Forward Stepwise Regression) prolonged increase in CRP 1 month after PCI was independently associated with PRI (p = 0.04) and maximum concentration of thrombin (p = 0.003), both measured 30 days after the procedure (Table 2).

Discussion

We have shown that PCI with stent implantation causes an early increase in hs-CRP in stable coronary patients on optimal pharmacological treatment, including chronic statin therapy, antiplatelet drugs and beta-blockers. To the best of our knowledge, our study is the first to demonstrate prolonged inflammatory reaction to at least 1 month after PCI. Moreover, we have found that prolonged post-angioplasty CRP increase is associated with higher thrombin generation and lower platelets' response to clopidogrel, which are also novel findings.

Our observation of early CRP increase after PCI is in accordance with other clinical trials [19, 22]. Our study followed post-procedural CRP in the long-term, which only few other studies assessed [23]. We have observed the relationship between post-angioplasty CRP increase in 1 month follow-up and higher PRI measured 30 days after PCI. This suggests that post-procedural systemic inflammatory reaction diminished platelets' response to clopidogrel. This mechanism may potentially limit PCI benefits in stable coronary patients. In previous studies, higher CRP has been shown to predict the risk of in-stent thrombosis after treatment with DES [24], which might be related to the lower platelets' response to clopidogrel observed in our study. Moreover, Bernlochner et al. have demonstrated that elevated CRP and white blood count were associated with high platelet reactivity in patients under chronic clopidogrel treatment [25]. Of note, high on-treatment platelet reactivity is an important predictor of poor clinical outcomes in patients undergoing coronary stenting [26]. Nevertheless, high platelet reactivity on dual antiplatelet therapy with aspirin and clopidogrel is quite frequent, especially in patients with cytochrome P450 2C19 loss-of-function polymorphism [15].

We have also found that prolonged post-procedural CRP increase was associated with thrombin generation, which may reflect inflammation-dependent coagulation response to endothelium injury [27] and may also account for

Table 2. Multiple Regression Model with CRP increase 1 month after PCI as the dependent variable

	b*	Std. err. of b*	b	Std. err. of b	p
Thrombin_2	0.717	0.209	0.072	0.020	0.003
PRI_2	0.466	0.210	0.126	0.056	0.039
Age	0.296	0.192	0.171	0.110	0.141
Creatinine	–0.278	0.187	–0.071	0.048	0.156
FXIII%_2	–0.190	0.180	–0.060	0.057	0.304

PCI – percutaneous coronary intervention; b* – standardized regression coefficients; Std. err. of b* – standardized error of b*; b – raw regression coefficients; Std. err. of b – standardized error of b; thrombin_2 – maximum concentration of thrombin generated 1 month after percutaneous coronary intervention (PCI); PRI_2 – P2Y12 reactivity index 1 month after PCI; FXIII%_2 – factor XIII 1 month after PCI.

limited PCI benefits in stable angina. In SCAD, the atherosclerotic plaque is covered with a non-thrombogenic endothelialized fibrous cap. Disruption of this cap during PCI enables circulating blood to contact procoagulant elements within the plaque [29] with subsequent coagulation and activation of platelets. Increased thrombin generation after balloon-mediated plaque injury has been shown in both patients with ineffective anticoagulation [28] and those adequately heparinized [29]. Association between high CRP and thrombin generation in CAD has previously been reported in patients with advanced SCAD [30], unstable angina [31] and 5 years after acute myocardial infarction, especially in those with new coronary ischemic events [32]. However, we have not found other studies to demonstrate the correlation between prolonged post-angioplasty CRP increase and higher thrombin generation in patients with SCAD.

The extent of thrombin generation has been shown to be related with the extent of vascular injury [29]. In patients with higher thrombin generation after PCI, increased platelet activation has been observed [28]. This may be due to high thrombin concentrations- a potent platelet activator, or balloon-mediated plaque injury. In our study we did not observe a correlation between thrombin generation and platelet activation. However, we found an association between the rate of prothrombin activation and platelets reactivity 3–5 days after PCI and between the rate of prothrombin activation and PRI one month after the procedure. In our study patients received dual antiplatelet therapy with aspirin and clopidogrel, thus one may expect stronger platelet inhibition. Moreover, they were on chronic statin therapy, known to affect thrombin generation, platelet activity and CRP [33]. Nevertheless, it is possible that lower platelets' response to clopidogrel observed in our study was related to higher thrombin generation.

Increased thrombin generation may have great clinical implications in the long term. Besides activating platelets, thrombin acts as a growth factor on vascular smooth muscle. Therefore, thrombin participates in intimal hyperplasia, and potentially restenosis, due to increased smooth muscle proliferation [29]. The impact of thrombin on both the early stages of plaque formation and in the advanced stages of atherosclerotic plaque progression, and subsequent destabilization, has been shown [27].

We hypothesize that a systemic inflammatory reaction triggered by coronary angioplasty may destabilize non-target plaques and as a consequence, cause the progression of atherosclerosis. This may be another factor that limits the benefits of PCI in stable coronary patients. It has previously been shown that increased CRP predicted progression of non-target lesions in patients, who underwent PCI with stent implantation for culprit lesions in SCAD [10]. Rapid progression of stenosis is a strong predictor of cardiovascular risk, regardless of being clinically silent or associated with acute coronary events [34].

Our study has several limitations. First, the study population was limited. Also we did not assess clinical end-points in long-term observation, thus we were not able to assess the effect of persistent post-PCI inflammatory reaction on clinical outcome. Control angiography for determining potential progression of atherosclerotic lesions in long-term follow-up was not performed, thus we did not assess the impact of long-term post-procedural CRP increase on clinically silent atherosclerotic plaque progression.

In conclusion, a post-procedural CRP increase, which persists at least one month in patients with stable CAD, who underwent elective coronary angioplasty with stent implantation, is one of the main findings of our study. Moreover, we have demonstrated the relationship between prolonged post-PCI inflammatory reaction,

reflected by elevated CRP and increased thrombin generation and low platelets' response to clopidogrel, which may account for limited benefits of PCI in stable coronary patients. According to our findings, it may be advisable to assay post-procedural CRP in each patient with SCAD, who underwent coronary angioplasty to predict those, with potentially low-response to clopidogrel.

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Conflict of interest: None declared

Received: 5.03.2015
Revised: 21.05.2015
Accepted: 3.08.2015