Prognostic Significance of High Sensitivity C-Reactive Protein before and after Percutaneous Coronary Intervention in Patients with Angina Pectoris

AMR A. YOUSSEF, M.D.*; YEHIA T. KISHK, M.D.*; HEBA A. ABDEL-HAFEZ, M.D.** and TAYEB A. BAFADHL, M.D.*

The Departments of Cardiovascular* and Clinical Pathology**, Faculty of Medicine, Assiut University

Abstract

**Background:** Elevated high sensitivity C reactive protein (hs-CRP) has been identified as a strong predictor of prognosis in acute coronary syndrome. The prognostic significance of hs-CRP level in percutaneous coronary intervention (PCI) is unclear.

**Aim of the Work:** Is to assess the hs-CRP value and its prognostic significance in short and long term follow-up after PCI.

**Methods:** We prospectively studied 41 patients; 28 patients with chronic stable angina and 13 patients unstable angina, who underwent elective coronary stenting. All patients had normal troponin level before the procedure. Blood samples for hs-CRP were obtained before the procedure, 24 hours after the procedure and followed-up at 1 month and after 2 years.

**Results:** Mean hs-CRP before and post procedure in all patients who underwent PCI was 2.38 ± 2.21 µg/ml and 7.43 ± 10.6 µg/ml respectively. There was significant difference between pre procedural hs-CRP and 24 hours post procedural (p=0.007). At follow-up period (1 month), no major adverse cardiac events (MACE) have occurred. At follow-up period (2 years), MACE has occurred in 13 patients. There was a weak correlation between the level of the pre-procedural hs-CRP and occurrence of MACE (r=0.22, p=0.2) and no correlation between post procedural hs-CRP and occurrence of MACE was reported.

**Conclusion:** Mechanical disruption of atherosclerotic plaque during elective coronary stent implantation causes a systemic inflammatory response. Measuring of hs-CRP either pre-procedural or post procedural in low risk patients is not useful for predicting of either early or late cardiovascular events.

**Key Words:** Prognostic significance – C reactive protein – Coronary intervention.

Introduction

C-REACTIVE protein (CRP) is an acute phase reactant that responds as a sensitive, though non specific marker of systemic inflammation. This protein is synthesized by the liver in response to stimuli from circulating inflammatory cytokines. CRP has traditionally been used as a systemic marker of infection and tissue injury [1].

C-reactive protein has been identified as a strong predictor of prognosis in healthy individuals [2,3], in patients with stable angina [4-7] and unstable angina [8-13], and in patients after an acute myocardial infarction [14,15].

Percutaneous coronary intervention (PCI) with stent implantation is a mainstay in the management of severe coronary artery atherosclerotic disease. Indeed, PCI currently outperforms coronary artery bypass grafting, and the use of interventional procedures is projected to increase even more with the adoption of new-generation drug-eluting stents [16].

Several studies have examined the prognostic role of CRP levels after elective or emergent PCI with a positive prognostic impact. On the other hand, other interventional studies failed to show a significant correlation between CRP levels and recurrent events or re-stenosis after elective or emergent PCI [2-4,7,12,13].

Increased C-reactive protein may become an important factor in pre-procedural risk stratification. As an independent marker for the rapid progression of atherosclerosis or the presence of an increased risk of subsequent adverse clinical outcome, increased C-reactive protein may identify high-risk
patients as candidates for high dose lipid lowering therapy and treatment with Angiotensin Converting Enzyme (ACE) inhibitors [17].

**Aim of the work:**

The aim of this study is to assess the hs-CRP value and its prognostic significance in short and long term follow-up after PCI.

**Patients and Methods**

From March 2008 to March 2009, 41 patients, 28 of them with the diagnosis of chronic stable angina (CSA) and 13 with the diagnosis of unstable angina, were included in the study and underwent elective PCI of native vessels. They were admitted to the Cardiology Department at Assiut University Hospitals. The diagnosis of stable angina was established when the frequency, duration and mode of precipitation and relief of symptoms remained unchanged over a duration of 2 months or more. The definition of unstable angina is an angina pectoris (or equivalent type of ischemic discomfort) with any 1 of the 3 following features: 1) Rest angina (angina commencing when the patient is at rest), 2) New-onset (less than 2 months) severe angina, and 3) Increasing angina (increasing in intensity, duration, and/or frequency) [18]. We have excluded patients with the following criteria:

- Known inflammatory, neoplastic, or infectious disease.
- Treatment with steroids, immunosuppressive drugs, or non steroidal anti-inflammatory drugs except for low-dose aspirin.
- Angiography with or without PCI within one month.
- Myocardial infarction within previous month.
- Elevated troponin before procedure.
- Patients with left ventricular systolic dysfunction (EF <50%).
- Diabetes mellitus.

**Coronary angiography and PCI:**

In all patients, 300mg of clopidogrel were loaded before the procedure. An intravenous bolus of unfractionated heparin was given during the procedure according to activated clotting time (ACT) level. PCI was performed from the femoral artery approach with standard techniques. We used bare metal stents in all patients. The intervention was considered successful when the stenosis was dilated less than 20% residual narrowing. All the patients involved in the study had undergone successful procedures. After the procedure, the patients received 75mg clopidogrel for at least 3 months and aspirin indefinitely. Statin, ACE Inhibitors, and Beta Blocker (BB) were prescribed according to the physician’s discretion.

**Laboratory assays:**

The venous blood samples were obtained before the procedure, and 24 hours after the procedure for hs-CRP and troponin I determination. The blood samples were placed into plain tubes without additives. The samples were centrifuged within 2 hours, and stored at −200 until the cytokinase assay were performed.

- CRP concentration was determined in serum by high sensitive method using Enzyme linked immunosorbent assay (ELISA), a solid phase reaction was done for quantitative measurement. [Accu Bind Elisa Microwells (Monobind, USA)] [19].
- Troponin I was measured in serum by ELISA, a solid phase reaction was done for quantitative measurement. [Accu Bind Elisa MicrowellsR (Monobind, USA)] [20].

**End point and follow-up:**

The end point was defined as the occurrence of major adverse cardiac events (MACE) including cardiac death, non fatal myocardial infarction, unstable angina, and any coronary repeated revascularization either surgery or PCI at 1 month and after follow-up for two years. Follow-up was obtained through telephone contact with patients and also with personal interview.

**Statistical analysis:**

Quantitative variables were represented by mean ± standard deviation (SD). Qualitative variables were represented by frequencies (numbers and percentages). Paired and unpaired Student “t” test was used. Correlation coefficient (r) was used. p-value is considered significant when it is <0.05. All analysis was performed with SPSS version 10.0.

**Results**

The clinical characteristics of the population of the study are presented in Table (1). Mean ± SD of age was 53.7, SD±8.85. Table (2) shows mean hs-CRP before procedure, 24 hours post procedure, and at 1 month after procedure in patients who underwent PCI (stable and unstable angina). The mean ± SD of hs-CRP before the procedure in unstable angina patients was higher than that in stable angina patients with a mean difference of 2.07 which is statistically significant (p=0.023). As shown in Table (2), in all patients who under-
went PCI, there was a statistically significant difference between the pre-procedural hs-CRP and the 24 hours post procedure ($p=0.007$) and there was a highly statistically significant difference between the pre-procedural hs-CRP and the 1 month post procedural value ($p=0.000$). In stable angina; there was a statistically a significant difference between pre and post procedural hs-CRP ($p=0.008$) and significant difference between pre-procedural hs-CRP and 1 month post procedure ($p=0.001$). In unstable angina; hs-CRP was elevated 24 hours post procedure but this elevation was statistically not significant ($p\text{-value}=0.225$).

There was also a significant difference between pre-procedural hs-CRP and 1 month post procedure ($p=0.025$). Procedural complications are presented in Table (3). During the follow up period (1 month); no MACE has occurred. However, 24 patients (58.5%) complained of chest pain. There were no significant correlation between either pre-procedural or 24 hours after procedure hs-CRP and the occurrence of chest pain ($r=0.13, 0.2$ respectively). At long term follow-up: 7 cases were missed. One case (2.4%) died from cardiovascular cause. Twelve cases (29.3%) complained from chest pain and admitted to CCU. Seven cases (17.1%) underwent revascularization, 5 patients of them undertook PCI and 2 patients underwent CABG. There was a weak correlation between the level of the pre-procedural hs-CRP and occurrence of MACE ($r=0.22, p=0.2$) and no correlation between post procedural hs-CRP and occurrence of MACE. There was significant relation between patients who complained of chest pain at 1 month of follow-up and occurrence of MACE ($p=0.054$). There was no significant difference in the level of pre-procedural hs-CRP or level of 24 hours post procedural hs-CRP between patients who develop MACE versus those who did not [mean pre-procedural hs-CRP in patients with MACE was 3.58 and who did not 2.33 with a mean difference of 1.25 which was statistically not significant, $p=0.24$ and mean post procedural hs-CRP in patients who developed MACE was 9.32 and who did not was 5.41 with a mean difference of 3.90 which was also statistically not significant $p=0.36$] (Table 4).

<table>
<thead>
<tr>
<th>Risk factor or drug</th>
<th>All patients</th>
<th>Patients with CSA (n = 28)</th>
<th>Patients with UA (n = 13)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>53.7±8.85</td>
<td>54±8.93</td>
<td>53±8.89</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>36 (87.8%)</td>
<td>23 (82.1%)</td>
<td>13 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (31.7%)</td>
<td>8 (28.6%)</td>
<td>5 (38.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>+ve family history</td>
<td>17 (41.7%)</td>
<td>8 (28.6%)</td>
<td>9 (69.2%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>21 (51.2%)</td>
<td>13 (46.7%)</td>
<td>8 (61.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoker</td>
<td>3 (7.3%)</td>
<td>3 (10.7%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Overweight</td>
<td>9 (22%)</td>
<td>5 (17.9%)</td>
<td>4 (30.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>30 (73.2%)</td>
<td>19 (67.7%)</td>
<td>11 (84.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Statin</td>
<td>19 (46.3%)</td>
<td>12 (42.9%)</td>
<td>7 (53.8%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

CSA: Chronic stable angina.  
NS: Non significant.  
PCI: Percutaneous coronary intervention.  
UA: Unstable angina.  
p-value*: Comparison between CSA and UA patients.  
+ve: Positive.

<table>
<thead>
<tr>
<th>hs-CRP µ/ml</th>
<th>Patients underwent PCI</th>
<th>Patients with CSA</th>
<th>Patients with UA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=41</td>
<td>N=28</td>
<td>N=13</td>
</tr>
<tr>
<td>Pre</td>
<td>2.83±2.21</td>
<td>2.22±2.21</td>
<td>4.253±3.297</td>
</tr>
<tr>
<td>24 hr post</td>
<td>7.43±10.6</td>
<td>6.48±10.6</td>
<td>9.467±14.632</td>
</tr>
<tr>
<td>p-value</td>
<td>0.007</td>
<td>0.008</td>
<td>0.225</td>
</tr>
</tbody>
</table>

CSA: Chronic stable angina.  
PCi: Percutaneous coronary intervention.  
UA: Unstable angina.  
Pre: Preprocedural.  
Post: Post procedural.
Table (3): The prevalence of procedural complications.

<table>
<thead>
<tr>
<th>Complication</th>
<th>All Patients</th>
<th>Patients with CSA with UA</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side branch occlusion</td>
<td>1 (2.4%)</td>
<td>0</td>
<td>(7.7%)</td>
</tr>
<tr>
<td>Thrombus formation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Coronary dissection</td>
<td>2 (4.9%)</td>
<td>1 (3.6%)</td>
<td>(7.7%)</td>
</tr>
<tr>
<td>Embolization</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (7.3%)</td>
<td>2 (7.1%)</td>
<td>(7.7%)</td>
</tr>
<tr>
<td>Plaque shift</td>
<td>3 (7.3%)</td>
<td>1 (3.1%)</td>
<td>2 (15.4%)</td>
</tr>
</tbody>
</table>

CSA: Chronic stable angina.
UA: Unstable angina.
NS: Non significant.

Data regarding the value of pre-procedural hs-CRP level and further cardiovascular events are confusing. Several studies have examined the prognostic role of CRP levels after elective or emergent PCI with a positive prognostic impact. Buffon et al., [27] demonstrated that pre-procedural CRP is a powerful predictor of both early and late outcome during follow-up in 52 patients with diagnosis of stable angina and 59 patients with the diagnosis of unstable angina underwent single vessel PCI. Fournier et al., [28] examined hs-CRP level after 1 month of bare metal stent implantation. The 12-month event free survival rate was greater when hs-CRP level was > 2.5mg/L. They concluded that measuring hs-CRP level at 30 days after stenting may be useful for predicting late cardiovascular events. Kyeong H. et al., [29] studied 381 patients with acute coronary syndrome who underwent elective PCI and were followed-up for 1 year, and they concluded that post procedural hs-CRP elevation >3mg/L was associated with higher incidence of MACE. The patients enrolled in that study had higher incidence of myocardial infarction, complex lesions (ACC/AHA type B2/C lesion) in addition to multi vessel stenting. These criteria of patients were excluded from our study. Chew et al., [30] studied 272 patients who underwent PCI and were presented with NYHA class III-IV, with prior PCI, CABG, or included patients with complex lesions and saphenous vein graft intervention. They concluded that the elevated baseline CRP is independently predictive of early (30 days) adverse outcome after PCI. On the other hand, other interventional studies failed to show a significant correlation between hs-CRP and recurrent events or re-stenosis after elective or emergent PCI. Zairis MN [31] at the GENERATION study found no association between increased pre-procedural hs-CRP and instant re-stenosis. Rittersma et al., [32] also could not find any association or trend between CRP concentration and angiographic re-stenosis in 345 patients who underwent non urgent PCI, and who underwent clinical angiographic follow-up at 6-10 months. The patients enrolled in this study were at low risk as 9% were diabetic and 3% underwent CABG. In our study, we exclude diabetic patients and patients who underwent CABG.

The limitation of this study was the relatively small sample size. We recommend a further study with wide inclusion criteria of patients and larger numbers of patients.

**Conclusion:**

Mechanical disruption of atherosclerotic plaque during elective coronary stent implantation causes
a systemic inflammatory response. Measuring of hs-CRP either pre-procedural or post procedural in low risk patients is not useful for predicting either early or late cardiovascular events.

References


