Plasma levels of C-reactive protein after coronary stent implantation


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Aims This study was designed to investigate the role of inflammation on the occurrence of angiographic restenosis 6 months after coronary stent implantation and the influence of different kinds of antithrombotic and antiplatelet strategies on inflammation.

Methods and Results In an open randomized trial, 40 consecutive patients were treated with aspirin (100 mg day$^{-1}$) and either ticlopidine (2 × 250 mg day$^{-1}$) (n=17), or phenprocoumon (INR 2.0–3.0) and dipyridamole (3 × 160 mg day$^{-1}$) (n=23) after successful elective coronary stent implantation. Plasma levels of C-reactive protein were determined one day before stent implantation and serially thereafter twice daily up to 120 h. C-reactive protein plasma levels increased significantly ($P<0.0001$) after stent implantation. Phenprocoumon and dipyridamole or ticlopidine had no effect on C-reactive protein plasma levels ($P=0.51$) or the occurrence of angiographic restenosis ($P=0.48$). C-reactive protein plasma levels were significantly higher in patients with lesion type C compared to types A or B ($P=0.035$), respectively. C-reactive protein plasma levels were significantly higher and mean shoulder levels occurred 48 h later in patients with restenosis compared to patients without restenosis after 6 months ($P=0.038$).

Conclusions Elevated C-reactive protein plasma levels still persisting 96 h after stent implantation might reflect a prolonged inflammatory reaction to coronary stent implantation which might causally be involved in pathophysiological mechanisms leading to restenosis. (Eur Heart J 2000; 21: 1152–1158)

Key Words: Coronary artery disease, coronary stent, inflammation, C-reactive protein.

See page 1121 for the Editorial comment on this article

Introduction

The major long-term complication of percutaneous transluminal coronary revascularization (PTCR) is restenosis which usually occurs 3 to 6 months after the intervention$^{[1]}$ and can be detected angiographically in 20% to 50% of patients$^{[2]}$. Coronary stenting seems to be one of the most effective means currently available and has been shown to reduce restenosis rates by approximately 30% compared to balloon angioplasty alone$^{[3,4]}$. However, coronary stent implantation is hampered by acute and subacute stent occlusion and a remaining restenosis rate of 15 to 30%. Antiplatelet therapy has been shown to reduce subacute stent occlusion significantly compared to antithrombotic therapy$^{[5]}$ but not to reduce late restenosis$^{[6]}$. Intravascular balloon inflation of an atherosclerotic vessel injures the arterial wall. The trauma is followed by platelet activation and deposition and activation of the coagulation cascades. Both haemostatic pathways also contribute to neointimal proliferation that is assumed to play a key role in the development of restenosis$^{[7–9]}$. The influence of inflammation on the restenotic process is yet not clear. The use of antiinflammatory or antiproliferative agents e.g. ACE inhibitors$^{[10]}$, colchicine$^{[11]}$, or corticosteroids$^{[12]}$ showed a significant reduction of neointimal proliferation after balloon injury in animal models. However, in human trials these benefits were not reproducible$^{[13–15]}$.

C-reactive protein is a non-specific marker for inflammation. Elevated C-reactive protein plasma levels have been shown to predict subsequent cardiac events in patients with unstable$^{[16,17]}$ and in chronic coronary artery disease$^{[18–20]}$. Furthermore, a significant increase in C-reactive protein concentrations has been shown to
be closely related to severity of coronary artery disease[23]. The aim of this study was to investigate the prognostic value of C-reactive protein regarding the occurrence of angiographic restenosis in the follow-up angiogram which was performed at the time of clinical signs of restenosis but at the latest 6 months after stent implantation. Furthermore, we investigated the influence of antithrombotic and antiplatelet therapy regimens on C-reactive protein plasma levels within 5 days and on restenosis rates after coronary stent implantation.

Methods

Patient selection

We investigated 40 consecutive patients with clinically stable coronary artery disease undergoing elective and successful coronary balloon angioplasty with coronary stent implantation for severe stenosis (>70% narrowing of the lumen) of a major epicardial coronary artery. The patients were free of clinical symptoms at rest for the 3 months before angioplasty (CCS stages 2 and 3). A successful procedure was defined as a percent diameter stenosis of less than 30% and a lack of periprocedural complications or acute occlusion of a coronary side branch with a subsequent increase in markers of myocardial necrosis. Patients with acute myocardial infarction, a history of unstable angina within 3 months before angioplasty, significant valvular heart disease, myocarditis, cardiomyopathy, hepatic or renal disease, thyroid disease as well as patients with recent infections or acute inflammatory diseases within the last 6 months — all disease states known to influence C-reactive protein plasma levels — were excluded.

Coronary angioplasty and stent implantation

Coronary angiography was performed with Judkins catheters via the right femoral artery using a digital angiographic system (Hicor, Siemens, Erlangen, Germany). PTCA was performed by use of conventional rapid-exchange balloon catheters (Express Supra, Scimed, Vienna, Austria, and Speedy Plus, Schneider, Basel, Switzerland). Angiography, PTCA, and stent implantation (Palmaz-Schatz 15 mm, Johnson and Johnson; AVE 8 mm and 16 mm, Medtronic) were performed by experienced investigators only (D.G., P.P., K.H.). The type of angiographic lesion was determined according to ACC/AHA criteria[23]. Catheter-related parameters were determined as follows: maximal balloon size, and maximal pressure during balloon inflation. Control angiography was performed 6 months after angioplasty or earlier, in cases of recurrence of angina.

Quantitative coronary angiographic assessment and definition of restenosis

An end-diastolic frame of the vessel segment was quantitatively analysed with the computer-based coronary angiography analysis system (CMS version 2.3D, Medis Inc., The Netherlands) which is described extensively elsewhere[23,24]. In short, the boundaries of a selected coronary vessel segment were detected automatically from optically magnified and digitized portions of the cine frame. In this system vessel diameter is calculated in absolute values (mm) by comparing the catheter diameter with the known catheter size in millimetres. The reference vessel diameter is based on the computer estimation of the original arterial dimensions at the stenosis site (interpolated reference). The percent diameter stenosis was computed by comparing the minimal diameter at the stenosis with the corresponding reference diameter:

\[ \text{% diameter stenosis} = \left(1 - \frac{\text{minimal diameter}}{\text{reference diameter}}\right) \times 100. \]

Angiographic restenosis was evaluated by quantitative coronary angiography and defined as a percent diameter stenosis of more than 50% at the time of follow-up angiography.

Antiplatelet and anticoagulant therapy

All patients received aspirin (100 mg . day \(^{-1}\) p.o.) and a slow-release preparation of isosorbide dinitrate (ISDN; 2 \(\times\) 20 mg . day \(^{-1}\)) throughout the study. Immediately before PTCR, patients were treated with a bolus of unfractioned heparin (10 000 U), thereafter a continuous heparin infusion was adjusted to achieve a partial thromboplastin time of 60 to 80 s for 24 h. After that, heparin was discontinued. Starting on the day of angioplasty one group of patients received ticlopidine (2 \(\times\) 250 mg . day \(^{-1}\)) over 4 weeks while the other group of patients received phenprocoumon (INR 2–3) plus dipyridamole (3 \(\times\) 160 mg . day \(^{-1}\)) over 3 months.

Blood sampling and measurements of C-reactive protein

Venous blood was drawn one day before PTCR (baseline blood sample taken from the resting patient after a 14 h overnight fast) and serially thereafter on 5 consecutive days every 12 h directly into plastic tubes containing EDTA (5 \(\times\) 10\(^{-2}\) M final concentration) for determination of C-reactive protein plasma levels. Tubes were centrifuged immediately at 3000 \(\times\) g for 10 min at 4 \(^{\circ}\)C and plasma was stored at \(-70\) \(^{\circ}\)C until use. Plasma levels of C-reactive protein were determined by use of the NycoCard \(^{\text{C}}\)-C-reactive protein Serum/Plasma test (Nycomed Heilmittelwerke, Vienna, Austria).
The restenosis rate was not significantly different between patients receiving phenprocoumon plus dipyridamole and those who received ticlopidine. Procedure-related data are listed in Table 2. No restenosis was found in 11/40 patients (28%).

Table 1 Demographic data

<table>
<thead>
<tr>
<th></th>
<th>No restenosis (n=29)</th>
<th>Restenosis (n=11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y/m)</td>
<td>60±9</td>
<td>64±7</td>
<td>0.14</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>20/9</td>
<td>10/1</td>
<td>0.23</td>
</tr>
<tr>
<td>Smoking (y/n)</td>
<td>12/17</td>
<td>4/7</td>
<td>0.77</td>
</tr>
<tr>
<td>Hypertension (y/n)</td>
<td>20/9</td>
<td>7/4</td>
<td>0.75</td>
</tr>
<tr>
<td>Diabetes (y/n)</td>
<td>6/23</td>
<td>4/7</td>
<td>0.51</td>
</tr>
<tr>
<td>Prior MI</td>
<td>16/13</td>
<td>6/5</td>
<td>0.97</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.75±1.25</td>
<td>24.82</td>
<td>0.89</td>
</tr>
<tr>
<td>Fibrinogen (mg. 100 ml⁻¹)</td>
<td>262.9±37.4</td>
<td>265.6±41.9</td>
<td>0.84</td>
</tr>
<tr>
<td>Cholesterol (mg. 100 ml⁻¹)</td>
<td>191.10</td>
<td>6/5</td>
<td>0.52</td>
</tr>
<tr>
<td>lipids (y/n)</td>
<td>217.3±33.7</td>
<td>211.3±32.8</td>
<td>0.62</td>
</tr>
<tr>
<td>triglycerides (mg. 100 ml⁻¹)</td>
<td>140.8±29.0</td>
<td>132.2±23.3</td>
<td>0.38</td>
</tr>
</tbody>
</table>

No restenosis=6 months after stent implantation percent diameter stenosis<50%; restenosis=6 months after stent implantation percent diameter stenosis>50%; lipids=total cholesterol >4 mmol. dl⁻¹; hypertension=blood pressure at rest ≥150 mmHg systolic and/or ≥90 mmHg diastolic at rest or under hypertension therapy; MI=myocardial infarction.

Statistical analysis

Data are presented as mean (standard deviation, SD) if not stated otherwise. Analysis of variance (ANOVA) was performed to find differences between patients who showed signs of restenosis in the follow-up angiogram and patients who kept free of restenosis. The comparison of C-reactive protein levels during 120 h after stent implantation was compared by ANOVA for repeated measures (Huynh–Feldt). For non-parametric comparisons, the chi-square test was chosen. Analyses were performed by using a statistical computer program (SPSS vs 8.0). Differences were considered statistically significant when the P-values were less than 0.05.

Results

Percutaneous transluminal coronary revascularization (PTCR) was performed by stent implantation in 40 patients. In this open randomized study 23 patients received phenprocoumon and dipyridamole 3 months after the procedure and 17 patients received ticlopidine for 4 weeks after PTCR. Patient-related data are summarized in Table 1. There were no significant differences in demographic data between patients receiving phenprocoumon and dipyridamole and patients receiving ticlopidine. Procedure-related data are listed in Table 2. Initial success was evaluated by quantitative coronary angiography. All patients underwent follow-up angiography (mean 6.2–3.9 months after PTCR) to evaluate angiographic long-term outcome after stent implantation. Restenosis was found in 11/40 patients (28%). The restenosis rate was not significantly different between patients receiving ticlopidine and patients receiving phenprocoumon and dipyridamole (6/17, 35%; 5/23, 22%), respectively (P=0.48).

In all patients C-reactive protein plasma levels were normal before stent implantation. After stent implantation C-reactive protein plasma levels were elevated throughout the 5 day period after the procedure (P<0.0001; Fig. 1). C-reactive protein plasma levels within the first 120 h after stent implantation were not significantly different between patients receiving phenprocoumon plus dipyridamole and those who received ticlopidine (Fig. 2; P=0.51). However, in patients with subsequent angiographic restenosis C-reactive protein plasma levels increased up to 96 h after stent implantation, whereas patients without, peaked after 48 h and decreased subsequently (Fig. 3). Furthermore, patients with angiographic restenosis also had significantly higher C-reactive protein peak levels (Fig. 3, P=0.038).

Lesions were categorized according to the AHA/ACC guidelines. Patients with complex lesions (type C) before angioplasty had significantly higher post-procedural C-reactive protein plasma levels than those with lesion type A or B (Fig. 4; P=0.035). The lesion type itself, however, had no influence on the occurrence of restenosis on the angiogram 6 months after stent implantation (P=0.60).

Discussion

C-reactive protein, an acute phase protein which activates the complement system and facilitates neutrophile adhesion, has been shown to be an independent risk factor in atherosclerotic disease. C-reactive protein also seems to reflect an inflammatory reaction of the arterial wall and might therefore indicate an ongoing and inflammation mediated atherosclerotic process. This hypothesis is confirmed by several clinical studies: Kuller et al.[25] have shown a four times higher risk for myocardial infarction in patients with increased C-reactive protein plasma levels. Accordingly, Ridker et al.[26] could demonstrate, that patients with C-reactive protein plasma levels in the upper quartile of the C-reactive protein range are the most likely to suffer...
later from acute coronary syndromes. Furthermore, these authors were able to show that a reduction in C-reactive protein plasma levels significantly decreases the risk of myocardial infarction: individuals, treated with aspirin, were in lower C-reactive protein ranges and exhibited the lowest incidence of complications from coronary artery disease. Although C-reactive protein is influenced by age, smoking, body mass index, serum fibrinogen, total cholesterol, as well as triglycerides it is an independent predictor of atherosclerotic events and might function as a marker of the activity of the underlying disease[18–21,25–27]. To exclude other inflammatory influences on C-reactive protein plasma levels, we only studied patients with clinically stable coronary artery disease and normal C-reactive protein plasma levels before elective PTCR. Our study shows for the first time that the C-reactive protein plasma level after coronary stent implantation can serve as a predictor for late angiographic restenosis.

The development of an atherosclerotic plaque is different from the development of restenosis with respect to the initial pathophysiological mechanisms, participating cells, time to develop, and final outcome: development of atherosclerosis is caused by molecular and biological alterations in the arterial wall, such as oxidation of low density lipoprotein and lipoprotein(a); lipid accumulation; production of inflammatory and matrix degenerating substances; plaque fissuring followed by thrombus formation and consecutive fibromuscular organization of the thrombus. Most likely, a combination of these

Table 2 Percutaneous transluminal coronary revascularization (PTCR) related data

<table>
<thead>
<tr>
<th></th>
<th>No restenosis (n=29)</th>
<th>Restenosis (n=11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target vessel (LAD/LCx/RCA)</td>
<td>12/5/12</td>
<td>14/6</td>
<td>0.13</td>
</tr>
<tr>
<td>ACC/AHA lesion type (A/B/C)</td>
<td>6/18/5</td>
<td>4/5/2</td>
<td>0.56</td>
</tr>
<tr>
<td>Before PTCR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>3.10 (0.79)</td>
<td>3.03 (0.54)</td>
<td>0.78</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>1.22 (0.48)</td>
<td>1.39 (0.55)</td>
<td>0.35</td>
</tr>
<tr>
<td>%DS</td>
<td>60.51 (13.50)</td>
<td>53.72 (17.18)</td>
<td>0.20</td>
</tr>
<tr>
<td>Catheter related parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon size (mm)</td>
<td>3.45 (0.41)</td>
<td>3.41 (0.54)</td>
<td>0.81</td>
</tr>
<tr>
<td>Maximal balloon pressure (atm)</td>
<td>4.62 (2.64)</td>
<td>4.64 (2.01)</td>
<td>0.99</td>
</tr>
<tr>
<td>After PTCR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>3.36 (0.71)</td>
<td>3.50 (0.60)</td>
<td>0.59</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>2.63 (0.62)</td>
<td>2.80 (0.68)</td>
<td>0.47</td>
</tr>
<tr>
<td>%DS</td>
<td>21.36 (11.95)</td>
<td>20.35 (9.51)</td>
<td>0.80</td>
</tr>
<tr>
<td>Acute gain (mm)</td>
<td>1.41 (0.69)</td>
<td>1.41 (0.72)</td>
<td>0.99</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>3.28 (0.77)</td>
<td>2.92 (1.25)</td>
<td>0.27</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>2.47 (0.81)</td>
<td>1.28 (0.89)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>%DS</td>
<td>25.63 (12.96)</td>
<td>57.75 (17.69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Late lumen loss (mm)</td>
<td>−0.27 (1.06)</td>
<td>−1.51 (0.91)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

No restenosis=6 months after stent implantation percent diameter stenosis <50%; restenosis=6 months after stent implantation percent diameter stenosis ≥50%; LAD= left anterior descendent artery; LCx= left circumflex artery; RCA= right coronary artery; MLD= minimal lumen diameter; DS%= percent diameter stenosis.

Figure 1 C-reactive protein mean plasma levels (SEM) before stent implantation and during the following 120 h (P<0.0001).

Figure 2 C-reactive protein mean plasma levels (SEM) in patients receiving phenprocoumon plus dipyridamole (○) and patients receiving ticlopidine (●) (P=0.51).
changes within the arterial wall lead to increased wall thickening and often to narrowing of the vessel lumen[20].

In contrast, the initial trigger of restenosis is a mechanical injury of the atherosclerotic plaque by balloon inflation which leads to neointimal proliferation by smooth muscle cells, and as a consequence, in 30% to 50% of cases to angiographically detected restenosis. Local inflammatory mechanisms seem to contribute to the process of restenosis as leukocytes have been found in restenotic lesions[29-31], probably reflecting the inflammatory response to the initial injury by balloon dilatation and/or stent implantation. In contrast to the atherosclerotic process, which takes years to decades to develop restenosis develops over only 3 to 6 months after angioplasty[1]. Furthermore, the restenotic process is only rarely followed by total occlusion of the artery and subsequent myocardial infarction.

The significant increase of C-reactive protein plasma levels after stent implantation (P<0.0001) might reflect a reactive inflammatory process during the period of intimal healing. The significantly higher C-reactive protein plasma levels in type C lesions (P=0.035) might, on the other hand, indicate a larger amount of pre-existing plaque inflammation in complex lesions in our patients despite clinical stability. As was demonstrated, C-reactive protein plasma levels in patients with subsequent restenosis were found to have taken a different course within the first 120 h after stent implantation, compared to patients without restenosis. C-reactive protein elevation lasted longer and C-reactive protein peak levels were significantly higher. These findings may reflect a shorter period of inflammatory reaction after stent implantation and/or less pre-existing local plaque inflammation in the group without restenosis. The prolonged elevation of C-reactive protein plasma levels may reflect an ongoing inflammatory response, leading to enhanced neointimal proliferation and subsequently to increased late lumen loss and angiographic restenosis. In our study, the observation period of 120 h after stent implantation describes only the acute and subacute phase after stent implantation. There are currently no data available in the literature measuring C-reactive protein plasma levels continuously over a longer time period after PTCR. This may be largely due to the fact that patients after elective and successful coronary interventions are discharged from hospital early, because this has been shown to be safe[32] and cost effective[33]. Further investigation will be needed to investigate the duration of persistence of C-reactive protein plasma levels during the follow-up after PTCR.

Both antithrombotic and antiplatelet drug regimens used had no influence on the course of C-reactive protein plasma levels or restenosis rate, as also confirmed recently[34], suggesting that the reactive inflammatory processes after stent implantation is not influenced by the antithrombotic and platelet inhibiting drugs used.

Limitation of the study

Firstly, this study is limited by the relatively small number of patients included. However, inclusion criteria were firm and all patients were enrolled prospectively and consecutively and completed follow up angiography. Secondly, C-reactive protein plasma levels were only evaluated over 120 h after coronary stenting because a longer stay at hospital was not reasonable for patients after a successful procedure and data about the length of course of elevated C-reactive protein plasma levels in patients after a successful procedure and data about the length of course of elevated C-reactive protein plasma levels in patients after stent implantation are not available. Thirdly, C-reactive protein is an unspecific marker of inflammation and might reflect a periprocedural reaction which is not necessarily only related to the intimal reaction of balloon dilatation and the stent implantation. However, patients with subsequent restenosis after stent implantation had significantly higher and prolonged C-reactive protein elevation, which may be a strong indicator of a relationship with the prior coronary intervention and/or the composition of the pre-existing plaque.

Figure 3 C-reactive protein mean plasma levels (SEM) in patients who remained free from restenosis (○) and patients with restenosis (●) at follow up angiography 6 months after stent implantation (P=0.038).

Figure 4 C-reactive protein mean plasma levels (SEM) in patients with lesion-types A (○), B (□), and C (●) according to the ACC/AHA guidelines (P=0.035).
Clinical implication

These findings suggest that restenosis after intracoronary stenting may be related to a process that is, at least in part, inflammatory in nature. Elevated C-reactive protein plasma levels, particularly when persisting for more than 48 h after coronary stenting appear to be indicative of an increased risk for angiographic restenosis 6 months after the procedure.

References


