

The Role of C-Reactive Protein in Percutaneous Coronary Intervention

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Endast den som inte uträttar något i praktiken
kan undgå att göra fel.

(Lenin)

To Mima, Niga, Lana and my parents

Abstract

An elevated preprocedural plasma or serum C-reactive protein (CRP) level in patients undergoing percutaneous coronary intervention (PCI) is associated with short-, intermediate- and long-term outcome. Furthermore, the procedure itself has been shown to provoke an inflammatory reaction as shown by increased plasma CRP levels after PCI. The research programme resulting in this thesis focus on the role of CRP and inflammation in patients undergoing PCI.

In study I 400 consecutive patients with serum levels of troponin T ≤ 0.03 $\mu\text{g/l}$ presenting with stable or unstable angina pectoris were investigated. Twenty-one percent of the patients experienced a myocardial infarction during PCI. The median value of CRP before the procedure was 1.83 (0.12-99.7) mg/l. No difference was seen in CRP levels before PCI between patients without or with myocardial infarction during PCI. Multivariate analysis identified stent implantation, procedure time and complications during the procedure as independent predictors of myocardial infarction during PCI.

In study II 121 patients with stable angina pectoris were enrolled. 100 patients were treated with a thrombin-based (Duett sealing) femoral artery closure device and 121 patients were treated with the FemoStop device. Irrespective of femoral artery closure device serum CRP and serum amyloid A (SAA) levels increased significantly after PCI. The increase was more pronounced in the Duett sealing device group compared with the FemoStop device group.

In study III 100 patients with stable angina pectoris scheduled for elective PCI were prospectively enrolled. Antibodies against different pathogens were examined. Plasma CRP and IL-6 levels were measured before and 6, 24, 48, 72 hours after PCI. Neither infection with single or multiple pathogens nor a minor troponin T elevation after PCI was associated with plasma CRP or interleukin-6 (IL-6) area under the curves (AUCs). Patients treated with stent implantation had higher plasma CRP and IL-6 AUCs compared with patients treated with balloon angioplasty alone

Study IV 891 consecutive patients presenting with stable or unstable angina pectoris undergoing a variety of PCIs were investigated. Serum concentrations of CRP and troponin T were determined before and the day after PCI. The mean follow-up time after PCI was 2.6 years. In multivariate analysis, patients in the highest tertile of CRP, induced by PCI, had an increased risk (risk ratio (RR) 2.48 [95% confidence interval (CI) 1.42-4.33]) for death or non-fatal myocardial infarction. Furthermore, patients in the second (RR 1.75 [95% CI 1.14-2.75]) and third (RR 2.15 [95% CI 1.37-3.36]) tertiles of the CRP response had an increased risk for coronary revascularization. Patients with periprocedural myocardial infarction with a postprocedural troponin T > 0.14 $\mu\text{g/l}$ had an increased risk for death or non-fatal myocardial infarction (RR 2.65 [95% CI 1.02-6.83]).

Conclusion: Periprocedural factors, whereas not the preprocedural CRP were associated with the risk of myocardial infarction during PCI. However, an elevated serum CRP concentration in response to PCI is a strong independent predictor of death or non-fatal myocardial infarction and coronary revascularization independent on myocardial injury during the procedure. Factors related to the procedure are influenced the CRP response to PCI. The results emphasize the role of CRP in coronary artery disease (CAD), and the need to develop treatments that block the increase in CRP in CAD.

Keywords: C-reactive protein, Duett sealing device, FemoStop, interleukin-6, pathogen burden, percutaneous coronary intervention, prognosis, myocardial infarction, serum amyloid A, troponin T.

LIST OF ORIGINAL PAPPERS

This thesis is based on the following studies, which will be referred to by their Roman numerals.

I

Saleh N, Svane B, Velander M, Nilsson T, Hansson LO, Tornvall P.
C-reactive protein and myocardial infarction during percutaneous coronary intervention.
J Intern Med. 2004;255:33-39.

II

Saleh N, Olausson A, Nilsson T, Hansson LO, Tornvall P
Comparison of effects of a thrombin-based femoral artery closure device with those of a mechanical compression device on serum C-reactive protein and amyloid A after percutaneous coronary intervention. Am J Cardiol. 2003;92:324-327.

III

Saleh N, Svane B, Jensen J, Hansson LO, Nordin M, Tornvall P. Stentimplantation, but not pathogen burden, is associated with plasma C-reactive protein and interleukin-6 levels after PCI in patients with stable angina pectoris. Submitted.

IV

Saleh N, Svane B, Hansson LO, Jensen J, Nilsson T, Danielsson O, Tornvall P.
Serum C-reactive protein response to percutaneous coronary intervention has a prognostic value.
Submitted.

ABBREVIATIONS

ACC	The American College of Cardiology
AHA	The American Heart Association
ASA	Acetyl salicylic acid
AUC	Area under the curve
BMI	Body mass index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CK	Creatine kinase
CKMB	Creatine kinase-MB
CMV	Cytomegalovirus
CPN	Chlamydia pneumoniae
CRP	C-reactive protein
DCA	Directional atherectomy
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eNOS	Endothelial nitric oxide synthase
ESC	The European Society of Cardiology
HDL	High density lipoprotein
HPY	Helicobacter pylori
HSV	Herpes simplex virus
ICAM-1	Intercellular cell adhesion molecule-1
Ig	Immunoglobulin
IL	Interleukin
LDL	Low density lipoprotein
MACE	Major advanced cardiac events
MCP	Monocyte chemoattractant protein
MCSF	Macrophage colony-stimulating factor
NO	Nitric oxide
PAI-1	Plasminogen activator inhibitor-1
PCI	Percutaneous coronary intervention

PTCA	Percutaneous transluminal coronary angioplasty
SAA	Serum amyloid A
SAP	Serum amyloid P
SMC	Smooth muscle cell
sPLA2	Secretory type II phospholipase A2
SVG	Saphenous vein graft
TNF	Tumor necrosis factor
tPA	Tissue plasminogen activator
TVR	Target vessel revascularization
VCAM-1	Vascular cell adhesion molecule-1
VLDL	Very low density lipoprotein

Introduction

Despite a major decline in death rates from myocardial infarction, coronary artery disease (CAD) still remains the leading cause of morbidity and mortality in the Western world (Chockalingam 1999). Much of the decline in CAD related mortality is a result of better understanding of the pathophysiology of atherosclerosis and advent of new therapies. Furthermore, several new risk factors, which contribute to the pathogenesis of CAD, have been identified. Recently, emphasis has been placed on the presence of inflammation and infection in atherosclerosis as potential pathogenic factors.

Atherosclerosis is a chronic disease that progress over decades (Fuster 1992). Atherogenesis represents a series of highly specific cellular and molecular responses to vascular injury and lipid infiltration into the intima and that can be described as an inflammatory process (Ross 1999). The two major theories of atherogenesis; i.e., oxidation of lipids and response to injury, may well be interrelated.

A number of circulating indicators of vascular inflammation has been proposed such as acute phase reactants (C-reactive protein, fibrinogen and serum amyloid A), cytokines, leukocyte count and soluble adhesion molecules (Ridker 1999, Pearson 2003). The clinical utility of these markers depend on the ability to measure levels in plasma or serum accurately and reliably, and on their predictive value as demonstrated in clinical studies.

Laboratory and clinical evidence favours CRP as the marker of preference for clinical application (Pearson 2003, Yeh 2003). It is the only analyte with acceptable laboratory standards considering assay availability, stability, World Health Organization standardization and precision. Furthermore, it has the largest database to support its clinical utility for assessing cardiovascular risk (Ridker 2003).

Percutaneous coronary intervention (PCI) is an established coronary revascularization procedure. In the 27 years since the introduction of PCI, there has been an enormous increase in the volume of cases, number of operators and sites performing coronary angioplasty. Although the introduction of stents and adjunctive antithrombotic therapy has substantially reduced complications, including restenosis, a significant proportion of successfully treated patients experience early and late nonfatal or fatal ischemic events. The pathophysiologic mechanisms for these events include periprocedural myocardial infarction, in-stent restenosis or CAD progression in lesions that have not been subjected to intervention. The identification of these high-risk patients is essential in everyday clinical practice and remains a challenge. To more accurately risk stratify these patients, several clinical and angiographic characteristics as well as biochemical markers have been suggested. A previous study has shown that activation of inflammatory cells before PCI may play a role in the modulation of vessel wall response to the injury induced by balloon dilatation (Pietersma 1993). This possibility is supported by experimental and clinical studies showing that acute phase reactants and proinflammatory cytokines promote leukocyte, endothelial and smooth muscle cell activation, resulting in an increase in procoagulant activity, metalloproteinase release and neointimal proliferation (Cermak 1993, Galis 1995, Ikeda 1991).

The research programme resulting in this thesis focus on the role of CRP and inflammation in patients undergoing PCI.

Background

Inflammation and atherosclerosis

Atherosclerotic lesions occurs principally in large and medium-sized elastic and muscular arteries and can result in ischemia of the heart, brain or extremities, resulting in infarction. Lesions of a varying degree might develop throughout an individuals lifetime. The pathogenesis of atherosclerosis is multifactorial and is influenced by hypercholesterolemia, hypertension, diabetes mellitus, smoking, and many other, as yet unidentified risk factors. Hypercholesterolemia plays a dominant role in the

initiation and progression of the fatty streak, the earliest atherosclerotic lesion. Indeed, hypercholesterolemia induces fatty streaks in humans as early as during fetal development and seems to be essential for lesion development in animal models (Witztum 1999).

The endothelium is an active, dynamic tissue that controls many important functions, including maintenance of blood circulation and fluidity as well as regulation of vascular tone, coagulation, and inflammatory responses (Gonzalez 2003). The arterial endothelium responds to flow and shear forces via a pathway that leads to phosphorylation of endothelial nitric oxide synthase (eNOS), that results in nitric oxide (NO) production (Gonzalez 2003). NO is one of the most important substances in preserving a normal vascular function. NO inhibits expression of adhesion molecules and cytokines (peng 1998). NO also possesses antithrombotic properties through its antiplatelet properties and inhibition of expression of tissue factor (Oeckler 2000). Furthermore, NO inhibits migration and proliferation of endothelial and smooth muscle cells (SMC), and diminished eNOS gene expression in atherosclerosis leads to increased proliferation and remodeling of the vessel wall (Oeckler 2000).

The presence of CAD risk factors and/or atherosclerosis will result in impairment of the response of endothelium to flow and shear forces (Gonzalez 2003). Possible causes of endothelial dysfunction include elevated low density lipoprotein (LDL), cigarette smoking, hypertension, diabetes mellitus, genetic alterations, elevated plasma homocysteine concentrations, hypertriglyceridemia and infection. Loss of the endothelium-dependent anticoagulant defence results in a procoagulant state with increased platelet aggregation, shortened platelet survival time, decreased tissue plasminogen activator (tPA), and increased plasminogen activator inhibitor-1 (PAI-1) secretion. Furthermore, impaired endothelial function is characterized by expression of leukocyte adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), intercellular cell adhesion molecule-1 (ICAM-1), and P-selectin (Price 1999).

Once adherent to the endothelium leukocytes penetrate into the intima. Recent research has identified candidate chemoattractant molecules responsible for this transmigration. Monocyte chemoattractant protein-1 (MCP-1) appears responsible for the direct migration of monocytes into the intima at sites of lesion formation (Gu 1998, Bohring 1998) whereas a family of T-cell chemoattractants may likewise stimulate lymphocyte migration into the intima (Match 1999). Transendothelial migration of monocytes is followed by transformation to macrophages. These macrophages express scavenger receptors that binds and take up modified lipoproteins, permitting macrophages to ingest lipid and become foam cells. Macrophage colony-stimulating factor (MCSF) contributes to differentiation of blood borne monocytes to macrophages (Smith 1995, Qiao 1997). T cells likewise encounter signals that cause them to elaborate inflammatory cytokines such as γ -interferon and tumor necrosis factor [TNF]- β that in turn can stimulate macrophages as well as vascular endothelial and smooth muscle cells (Hansson 1996). As this inflammatory process continues, activated white blood cells secrete cytokines and growth factors that promote migration and proliferation of SMCs. SMCs located in the media express metalloproteinases that can degrade elastin and collagen in response to inflammatory stimulation. This degradation of the arterial extracellular matrix permits migration of SMCs through the elastic laminae and collagenous matrix of the growing plaque (Ross 1999).

The inflammatory process do not only promote initiation and evolution of atheroma, but do also contribute to precipitate acute thrombotic complications of atheroma. About two thirds of coronary arterial thrombi that cause fatal acute myocardial infarction arise because of a physical disruption of the atherosclerotic plaque. The activated macrophages, abundant in the atheroma, produces metalloproteinases capable of degrading collagen that lends strength to the plaque's protective fibrous cap. Thus the cap become thin and weak, and susceptible to rupture. Furthermore, γ -Interferon arising from activated T lymphocytes in the plaque can halt collagen synthesis by SMCs, limiting its capacity to renew the collagen that reinforces the plaque (Libby 1996, Libby 2001). Macrophages also produce tissue factor, the major procoagulant and trigger to thrombosis found in plaques. Inflammatory mediators regulate tissue factor expression by plaque macrophages, demonstrating an essential link between arterial inflammation and thrombosis (Libby 2001).

C-reactive protein (CRP)

Structure and function

CRP is a member of the phylogenetically ancient and highly conserved pentraxin family of proteins (Figure 1), which also includes serum amyloid P (SAP), a constituent of amyloid desposits (Volanakis 2001).

Human CRP is a calcium-dependent ligand binding protein that binds with high affinity to phosphocholine residues, a constituent of many bacterial and fungal polysaccharides and of most biological cell membranes (Volanakis 2001). When human CRP is ligand bound, it activates the classical complement pathway (Volanakis 2001). The secondary effects of CRP that follow ligand binding resemble some of the key properties of antibodies, suggesting that under various circumstances CRP may contribute to host defence against infection (Volanakis 2001). CRP-mediated phagocytosis may be indirect, through activation of complement and complement receptors, or direct, through receptors for the Fc portion of immunoglobulin G (IgG; Fcγ receptors) (Tornvall 2003) (Figure 1).

Phosphocholine is prevalent also in circulating plasma lipoproteins that are intimately involved in the pathogenesis of atherosclerosis. The specific binding of CRP to LDL and very-low-density lipoproteins (VLDL) and to the membranes of damaged cells has long been recognised (Pepys 1985, de Beer 1982, Rowe 1984), and more recently it has been observed that CRP also binds to apoptotic cells in a Ca^{2+} -dependent manner, enhancing their opsonization and phagocytosis by macrophages (Gershov 2000). Plasma CRP is produced by hepatocytes (Figure 2)

(Volanakis 2001), although other sites for CRP synthesis and possibly secretion have been suggested (Hirschfield 2003). CRP may thus have a local role in particular microenvironments, such as the arterial wall, as well as function via the systemic circulation. CRP production is induced predominantly by the cytokine IL-6, but IL-1 or TNF- α might also contribute (Mackiewicz 1991). The genes for both CRP and SAP are on chromosome 1 (Hirschfield 2003). Control of CRP expression is principally at the level of transcription, and in vitro studies in hepatocyte cell lines have identified some of the intracellular signalling pathways and also shown that secretion is more efficient during an acute-phase response (Hirschfield 2003). Healthy subjects tend to have rather stable, unstimulated CRP concentrations that are significantly (35–40%) heritable (Hirschfield 2003).

In healthy adult volunteer blood donors the median serum baseline CRP concentration was 0.8 mg/l (Shine 1981) but following an acute-phase stimulus, values may increase by as much as 1000-fold, with de novo hepatic synthesis starting very rapidly. Concentrations begin to rise at about 6 h, and peak around 48 h after a single stimulus (Kushner 1978). In a healthy unselected population, the median unstimulated CRP values are higher and tend to increase with age. Females have higher circulating CRP concentrations (Hutchinson 2000). The plasma half-life of CRP is the same (about 19 h) under all conditions, and the sole determinant of the plasma or serum level is the synthesis rate, which, in turn, reflects the intensity of the pathological process(es) stimulating CRP production (Vigushin 1993). In vivo turnover studies of human CRP in man did not demonstrate any detectable tissue deposition of CRP, even in inflamed or infected foci (Vigushin 1993).

Liver failure impairs CRP production, but no other intercurrent pathology and very few drugs reduce CRP values, unless they also affect the underlying acute-phase stimulus. Circulating CRP is thus a very useful non-specific biochemical marker of inflammation, a measurement of which contributes to screening for organic disease and monitoring the response to treatment of inflammation and infection (Hirschfield 2003).

In order to use CRP as a cardiac risk marker in healthy subjects or in patients with CAD an accurate measurement of CRP within the conventional reference range (< 5 mg/l) is needed. The existing turbidimetric and nephelometric methods do not cover the required range and thus expensive, time-

consuming and labour-intensive enzyme immunoassays have been used for the clinical studies focusing on CAD risk. A new method based on microparticle enhanced turbidimetry or nephelometry, which attained the required limit of detection, while keeping the upper measuring limit comparable to the existing turbidimetric and nephelometric methods has been developed. The analytical detection limit of this type of method is approximately 0.2 mg/l (Eda 1998).

Interestingly, evidence has recently accumulated that CRP might be a direct participant in the atherothrombotic process capable of augmenting the innate inflammatory response by triggering expression of adhesion molecules and MCP-1, attenuating expression of eNOS, inducing PAI-1, and having a direct effect on arterial thrombosis (Lagrand 1999, Pasceri 2000, Fichtlscherer 2000).

CRP and CAD

Elevated plasma or serum CRP levels have been reported in patients with stable angina pectoris compared with healthy controls and it has been shown that CRP can predict long-term prognosis in these patients (Haverkate 1997, Zebrack 2002). The definition of elevated CRP in patients with CAD has been variable (range 3 to 25 mg/l) (Haverkate 1997, Heeschen 2000, Lindahl 2000, Morrow 1998, de Winter 1999) but generally higher than cut-off levels generated in primary prevention studies (range 0.6 to 8.5 mg/l) (Ridker 1997,1998 and 2000).

In patients with unstable angina pectoris increased levels of plasma or serum CRP are associated with a worse outcome. Furthermore, it has been suggested that CRP contribute to the transition from a clinically stable to an unstable coronary atherosclerotic plaque (Haverkate 1997, Zebrack 2002, Lindahl et al 2000, Liuzzo 1999, James 2003, Berk 1990).

The increase in circulating CRP following myocardial infarction is a typical acute phase response to cell death and inflammation, mediated by the action on the liver of the cytokine cascade, especially IL-6, triggered by the event. The magnitude of CRP response reflects the extent of myocardial necrosis (Kushner et al 1978, de Beer 1982). Furthermore, peak CRP values at around 48 h after the onset, predict outcome after myocardial infarction (Pietilä 1996, Ueda 1996, Anzai 1997). Importantly, CRP is deposited within all acute myocardial infarcts (Kushner 1963, Lagrand 1997) and compelling experimental evidence now suggests that the CRP response not only reflects tissue damage in this context, but may also contribute significantly to the severity of ischaemic myocardial injury (Griselli 1999).

CRP and cardiovascular risk factors

The relationship between CRP and CAD raises the question of how risk factors for CAD relate to this marker. Those with well-known risk factors for cardiac events, including the elderly, smokers, patients with hyperlipidemia, hypertension, obesity and diabetes mellitus may have a greater risk of CAD if their plasma CRP concentration is increased.

Age

The plasma CRP concentration increase with age. A survey of CRP levels in 5748 healthy subjects of all ages from the MONICA trial showed median levels double from the second to the sixth or seventh decade of life (Koenig 1999). Furthermore, the European Concerted Action on Thrombosis and Disabilities (ECAT) Angina pectoris Study showed that for patients 45–69 years old, CRP levels increased by 2% for each incremental year (Haverkate 1997).

Smoking

Plasma CRP concentrations are increased in smokers. An association between CRP and smoking was first described by Das in 1985, unfortunately CAD status was not recorded in that study. Many trials have documented that plasma or serum CRP concentrations are increased in smokers, including the ECAT (Haverkate 1997) and MONICA studies where CRP concentrations were twice as high in smokers as in non-smokers (Koenig 1999). Analysis of smoking in the Cardiovascular Health Study found that the plasma CRP value was strongly associated with smoking status (Tracy 1997). The

MRFIT study of middle-aged men without CAD showed that an increased plasma CRP concentration was associated with an increased risk of mortality from CAD, with a relative risk of approximately 3. In this trial the association between CRP and CAD was true only for smokers (Kuller 1996). Furthermore, in the Helsinki Heart Study, smokers with a CRP in the highest quartile had a CAD risk of 9 compared with smokers with a low CRP that had a CAD risk of 1.5 (Roivainen 2000). However, the PHS showed that the risk of CRP was independent of smoking (Ridker 1997).

Hyperlipidemia

Several studies have shown that the risk of an increased plasma CRP concentration is independent of lipid levels both in healthy individuals and those with known CAD. In the Physicians' Health Study (PHS) in individuals without a known history of CAD, the risk of a first myocardial infarction was more accurately predicted by baseline CRP than by plasma cholesterol or high density lipoprotein (HDL) cholesterol concentrations (Ridker 1997). The ECAT study found that the risk of coronary events in patients with stable angina pectoris with a high plasma cholesterol concentration was low if their CRP was low. A plasma CRP level of >3.6 mg/l increased the risk twofold for a coronary events compared with patients with CRP in the lowest quintile (Haverkate 1997). In patients with unstable angina patients and a high plasma cholesterol level, CRP predicted re-admission (Meier-Ewert 2001). Furthermore, although baseline values of plasma and HDL, cholesterol and CRP, all were associated with a first myocardial infarction, CRP and plasma cholesterol together increased the relative risk more than plasma cholesterol, plasma cholesterol/HDL ratio or CRP alone, by a factor of more than 2. Controlling for smoking habits, obesity, hypertension and diabetes mellitus did not affect these results (Ridker 1998). Similar results were found for women in the Women's Health Study (WHS), which showed that CRP and plasma cholesterol/HDL-C independently raised the risk of CAD (Ridker 2003). Women with high plasma CRP levels but normal LDL concentrations (<3.37 mmol/l) had a four times increased risk of a cardiovascular events compared with those with a low plasma CRP (Ridker 2000) suggesting that CRP can identify individuals at increased risk who otherwise would be missed if only lipid screening was used.

Hypertension

Hypertension is a risk factor for CAD that does not have a clearly understood pathophysiology. Some have speculated that the increased risk may be mediated through vessel wall inflammation, perhaps related to the renin-angiotensin system (Chae 2001). One small study found that the plasma CRP concentration in patients with essential hypertension was increased compared with healthy controls (Dodson 1984). It is unknown whether CRP values correlate with renin or angiotensin II levels in patients with essential hypertension, or whether these patients are more likely to develop cardiovascular events.

Obesity

The plasma CRP concentration is increased in patients with a high body mass index (BMI) as shown in several of the large studies (Haverkate 1997). The MONICA study showed that CRP was twice as high in those with an BMI > 30 compared with those with a normal BMI < 25 (Koenig 1999). In trials focusing on this issue, CRP was associated with measures of central obesity in women and men, a form of obesity that has previously been connected with a high CAD risk (Yudkin 1999. Hak 1999). The largest data base connecting CRP with obesity is the Third National Health and Nutrition Examination Survey of the US population performed between 1988 and 1994. Being obese conferred an increased odds ratio for having an increased CRP (2.13 for men and 6.21 for women) after controlling for other variables (Visser 1999). The association between an increased the plasma CRP concentration and obesity is prevalent in a wide range of individuals. Even in childhood, CRP is higher in those with an increased BMI (Cook 2000). Although the exact mechanism for the increased plasma CRP levels in obesity is not well-characterized, it is known that the liver synthesizes CRP in response to IL-6, and that IL-6 is released by adipose tissue (Mohamed-Ali 1997).

Diabetes mellitus

In a cross-sectional study by Ford (Ford Diabetes care 1999) the association between CRP, and BMI and diabetes mellitus among 16,573 participants aged ≥ 20 years was examined. Serum CRP values

were lowest among individuals with a BMI < 18.5 without diabetes or impaired fasting glucose and increased with increasing BMI categories and was highest among those with newly or previously diagnosed diabetes mellitus after adjustment for age, sex, race or ethnicity, education, and BMI (Ford 1999).

There is evidence indicating that a low-grade inflammation has as a potential role in the pathogenesis of type 2 diabetes. Recently, data from the PHS (Pradhan 2001) and by Freeman and coworkers (Freeman 2002) identified elevated plasma levels of CRP as a predictor for the development of diabetes mellitus in women and men independent of risk factors such as BMI, fasting triglycerides and blood glucose. Potential mechanisms for this association might be direct or indirect. For example, cytokines such as TNF- α may produce insulin resistance by influencing the function of the insulin receptor or by stimulating adipocyte lipolysis. Alternatively, endothelial dysfunction may link inflammation to insulin resistance. It is also noteworthy that established mechanisms to decrease insulin resistance, such as weight loss and thiazolidinediones have significant anti-inflammatory effects (Ridker 2003). Finally, an intracellular link between the inflammation cascade and insulin signaling has been reported in a recent study showing that salicylates prevents obesity and diet-induced insulin resistance (Ridker 2003).

CRP, Infection and CAD

Several studies have shown an association between antibodies against chronic infections such as cytomegalovirus (CMV), *Chlamydia pneumoniae* (CPN), Epstein-Barr virus (EBV), *Helicobacter pylori* (HPY), herpes simplex virus type 1 (HSV1) and 2 (HSV2) and coronary artery disease (CAD) (Blankenberg 2001, Danesh 2000, Ridker 2001, Hajjer 1987). Recent investigations have suggested that the CAD risk of infection is related to the pathogen burden i.e. the number of significant titres of antibodies against infectious pathogens, rather than to a specific pathogen (Zhu 2000, Espinola-Klein 2002, Choussat 2000). It has been speculated that the increased risk for CAD associated with pathogen burden is mediated by inflammation (Zhu 2000, Georges 2003). However, the results of studies relating multiple antibodies against infectious pathogens to CAD have been inconsistent. First, Zhu and coworkers have shown, in women and men referred to coronary angiography, that CRP was associated with atherosclerosis and the aggregate number of antibodies against pathogens (Zhu 2000). More recently, De Backer and coworkers have shown that seropositivity against four infectious pathogens was not associated with CAD in a case-control study of middle-aged men (De Baker 2002). The results of studies concerning the impact of infectious burden on prognosis in CAD have also been contradictory. Two prospective studies of patients, a majority of men with coronary atherosclerosis documented by angiography, have shown that the risk of myocardial infarction or cardiovascular death was related to the pathogen burden independently of CRP (Espinola 2002, Zhu 2001). In contrast, Ridker and coworkers have shown that multiple antibody titres against infectious pathogens were not associated with the subsequent risk for CAD in a prospective nested case-control study in apparently healthy postmenopausal women (Ridker 1999). The importance of pathogen burden for the outcome after PCI has been investigated in one study only. Horne and coworkers have shown in patients with stable angina pectoris or ACS that pathogen burden was associated with clinical restenosis after PCI (Horne 2002). Because infection is a cause of inflammation it may contribute to persistently elevated plasma levels of CRP. Results from previous studies investigating the association between single or multiple antibodies against infectious pathogens and inflammation in patients with CAD have been somewhat contradictory. Pathogen burden has been shown to be associated with increased plasma CRP levels in studies by Zhu and coworkers (Zhu 2000) and Georges and coworkers (Georges 2003) whereas studies by De-Backer and coworkers (De Baker 2002) and Ridker and coworkers (Ridker 1999) failed to show any association between seropositivity against multiple infectious pathogens and inflammatory markers. Furthermore, Choussat and coworkers showed in patients with ACS that acute phase proteins increased during the first 2 days of hospitalization but failed to demonstrate any association between the presence of seropositivity against multiple infectious pathogens and the inflammatory response (Choussat 2000).

Troponin

The troponin complex is formed by three different forms of structural proteins (troponin C, I and T) located in the thin filament of the contractile apparatus of both skeletal and myocardial myocytes regulating the calcium dependent interaction between actin and myosin. Cardiac isoforms of troponin I and T are expressed solely in myocardial cells and released from the cytoplasm after disintegration of the cell membrane caused by myocardial necrosis. Accordingly, measurable plasma or serum levels of troponin I or T are highly specific for myocardial injury indicating even microscopic areas of necrosis irrespective of the cause (Collinson 2001). The initial rise of troponin concentration occurs 3 to 4 hours after the ischemic injury with a persistent elevation up to two weeks after the event.

Increased plasma troponin values have been shown to be more powerful prognostic indicators than CK-MB (Bahit 2002), and serial sampling enhances the likelihood of identifying myocyte necrosis among patients presenting at different stages of the myocardial infarction process (Newby 1998).

While several manufactures have produced antibody-based assays for troponin I with different antigens, patent protection has meant that only Roche Diagnostics (Basel, Switzerland; formerly Boehringer Mannheim of Mannheim, Germany) has produced a troponin T assay. Using the current generation of troponin T assay, the discrimination value for the detection of myocardial infarction is 0.03 µg/l, which is higher than the 99th percentile of values of a healthy reference group. At 0.03 µg/l the coefficient of variation is $\leq 10\%$ which meets the levels of precision specified in the European Society of Cardiology (ESC)/American College of Cardiology (ACC) definition (The Joint European Society of Cardiology/American College of Cardiology Committee. 2000).

Apart from ACS, the most frequent causes of elevated circulating troponin concentrations are tachycardia, pulmonary emboli with right ventricular infarction (Perna 2002), and cardiac failure with myocardial necrosis caused by neurohumoral changes and elevated left ventricular end diastolic pressure. Other causes of increased troponin values include cardiac surgery, myocarditis, and renal failure in which the cause of myocyte necrosis yet has to be elucidated (Aviles 2002).

Troponin and clinical outcomes

In both short (30-day) and long (up to 3 years) term follow-up studies, the magnitude of troponin elevation has correlated consistently with the risk of death or the composite risk of death or non-fatal myocardial infarction, irrespective of whether the patients had ST-elevation or non-ST elevation ACS (Klein 1997, Stubbs 1996, Ohman 1996, Antman 1996). In the global use of strategies to open occluded coronary arteries in acute coronary syndromes (GUSTO)-IIa troponin T substudy, the baseline troponin T value correlated with the risk of mortality at 30 days, and was the second most powerful prognostic predictor after electrocardiographic changes (Bahit 2002). The thrombolysis in myocardial infarction (TIMI) group reported similar findings using a troponin I assay (Dade-Behring), with a linear increasing risk ratio for mortality at 42 days with increasing troponin values (Antman 1996).

Percutaneous coronary intervention (PCI)

Historical perspective

The introduction of PCI in 1977 by Andreas Gruntzig and two years later in Sweden at the Karolinska Hospital by Alfred Szamozsi has had a dramatic impact on the practice of cardiology conceptually expanding the traditional role of the invasive cardiologist from diagnostician to "therapist" and providing an opportunity to learn more about coronary pathology and pathophysiology (Tornvall 2002). In the first 50 patients who underwent PCI, the primary success rate was only 64% and emergency coronary bypass surgery (CABG) was required in 14% of the cases. Subsequently, as a result of greater operator experience and refinements in catheter and imaging technology, acute complication rates of PCI steadily decreased. However, acute thrombotic complications, restenoses

and the need for repeat interventions occurring in up to 50% of cases, remained a severe limitation. This led to a search for more efficient catheter-based approaches such as directional atherectomy (DCA) (Baim 1993) and rotational atherectomy (Rihal 1998). An alternative strategy was placement of a permanent metallic intravascular scaffold or coronary stent. The first implantation of coronary stents in humans was performed in 1986 by Ulrich Sigwart in Switzerland. Because stent thrombosis occurred frequently during the first weeks after stent implantation, an intense search for the optimal antithrombotic therapy after stenting was instituted.

Techniques of PCI

Since coronary angioplasty encompassed the use of both balloons and other devices such as stents, the generic term of coronary angioplasty was changed from percutaneous transluminal coronary angioplasty (PTCA) to percutaneous coronary intervention (PCI). PCI results in lumen enlargement with dissection of the arterial intima and media, and stretching of the vessel circumference. Success of balloon angioplasty depends on both clinical and angiographic factors (Ellis 1988). Despite the improved initial success rate of balloon angioplasty, restenosis continued to occur in up to 40% of cases. Moreover, coronary lesions with bulky atherosclerotic plaques seemed to be less suitable for PCI. The DCA technique removes atheroma using a cutting and retrieval system. The initial encouraging results could not be confirmed in the randomized trials comparing DCA with balloon angioplasty (Topol 1993, Holmes 1995). DCA is currently used in certain bifurcation and ostial lesions, and for bulky eccentric plaques (Simonton 2000). Rotational atherectomy involves cutting and ablation of inelastic plaques by means of a high speed burr. It is usually used as debulking before stent placement in calcified lesions (Moussa 1997). Cutting balloon angioplasty is a strategy of atherotomy rather than atherectomy. It uses balloons with microsurgical blades that incise atherosclerotic plaque resulting in a controlled dissection. The main indications for this technique are restenosis including in-stent restenosis and ostial lesions (Ajani 2001).

Coronary stents

Metallic stents are balloon-expandable or self-expandable scaffolds. Balloon-expandable stents are made of stainless steel whereas self-expanding stents are typically made of a memory metal such as self-expandable nitinol stents (Harnek 2002). Stents differ in length and diameter, flexibility, radiopacity, strut thickness, interunit geometry, size of strut windows and surface area coverage. They may either be passively or actively coated. An example of passive coating is covalently bound heparin, used to prevent thrombosis in high-risk patients (Serruys 1998). An example of active coating is drug-eluting stents coated with antiproliferative agents, which inhibit intima hyperplasia and reduce restenosis (Sousa 2001). Two randomized trials have been performed to compare stent implantation with balloon angioplasty: the STent REStenosis Study (STRESS) and the BELgium Netherlands STENT (BENSTENT) (Fischman 1994, Serruys 1994). Binary restenosis (defined as > 50% diameter stenosis) and a composite clinical end-point consisting of death, myocardial infarction, stroke, and the need for CABG or repeat PCI at 6 months was reduced in both trials. Long-term outcome of stent placement has been evaluated up to 3 years after implantation. Loss of initial gain of lumen diameter was limited to the first 6 months, after which minimal lumen diameter remained unchanged through 1 year, and actually increased significantly by 3 years (Kimura 2002).

Stent thrombosis

Stent thrombosis is the most serious complication of stent implantation. It is associated with 30-day mortality rates of 21% to 26% in recent series (Levine 2003). Stent thrombosis most frequently occurs in the first days to weeks after stent implantation. Patients usually present with severe chest pain and often have ST-segment elevation on electrocardiogram (ECG). Randomized comparisons of antiplatelet and anticoagulation regimens were performed in the Intracoronary Stenting and Antithrombotic Regimen Study (ISARS) and Stent Antithrombotic Regimen Study (STARS) (Schomig 1996, Leon 1998) trials. There was a 7-fold reduction in the rate of stent thrombosis with aspirin and ticlopidine compared with anticoagulation with warfarin. Major adverse cardiac events (MACE), including myocardial infarction and repeat target vessel revascularization (TVR), as well as

bleeding were reduced (Schomig 1996, Leon 1998). More recently, clopidogrel has been shown to be as effective as ticlopidine in preventing stent thrombosis, with a lower incidence of skin rash and neutropenia and has therefore largely replaced ticlopidine (Bertrand 2000). Recent pooled analyses have confirmed the reduced stent thrombosis rate (0.9%–2.0%) (Cutlip 2001, Schulen 2001).

The use of another group of adjunctive agents, intravenous glycoprotein IIb/IIIa inhibitors, have resulted in an absolute reduction of 1.5% to 6.5% in the 30-day risk of death, myocardial infarction, or urgent TVR, with some variability in the treatment effect among the agents tested (abciximab, eptifibatide and tirofiban) (Lincoff 2000). In the Evaluation of Platelet IIb/IIIa Inhibition for STENTing (EPISTENT), the primary end point of death, myocardial infarction, and TVR at 1 month was reduced from 10.8% to 5.3% by abciximab. This was mainly due to a reduction in large (CK >5 times the upper limit of normal) non-Q-wave myocardial infarction (The EPISTENT investigators 1998). In randomized trials, eptifibatide has also been shown to decrease ischemic complications in patients undergoing stenting (O'Shea 2001) while tirofiban was equal to abciximab in reducing MACE 6 months after the index coronary intervention (Moliterno 2002).

Patients treated with bare-metal stents should receive 4 weeks of clopidogrel, in addition to aspirin, to prevent stent thrombosis. Because of a concern that late stent thrombosis may develop in patients treated with drug-eluting stents, recent trials have extended clopidogrel treatment to 3-6 months after PCI (Levine 2003).

Restenosis

Restenosis is a process by which a PCI-treated arterial narrowing reoccurs over time. The restenosis process is believed to occur because of a constrictive negative arterial remodeling (arterial "constriction") and intimal hyperplasia (Levine 2003). Diabetes mellitus, unstable or severe angina pectoris at the time of PCI, are associated with an increased risk of restenosis. Furthermore, restenosis is associated with factors related to the procedure such as intervention in the left anterior descending artery or in a saphenous vein graft, total length and diameter of the lesion treated, chronically occluded arteries, previously treated lesions, and factors related to technical aspects of the procedure itself, most notably minimum luminal diameter immediately after the procedure (Levine 2003). The restenotic process occurs over the first one to 8 months after PCI (Levine 2003). The presenting symptom for most patients with restenosis is exertional angina (25% to 85%) while few patients (11% to 41%) present with unstable angina pectoris. Presentation with acute myocardial infarction is rare (1% to 6%) (Levine 2003). Stents reduce restenosis by providing a larger initial lumen and eliminate "arterial constriction" rather than reducing intimal hyperplasia (Levine 2003). The most promising therapy for prevention of restenosis is the use of drug-eluting stents. Several randomized trials are currently comparing the efficacy of drug-eluting stents with bare stents (Arjomand 2003). Initial reports showed a lack of angiographic restenosis at 1- and 2-year follow-up in the First-In-Man studies and RAndomized study with sirolimus-coated bx VELOCITY stent (RAVEL), respectively (Fajadet 2002, Sousa 2002). In the SIROLImUS eluting stent in de novo native coronary lesions (SIRIUS) trial, which included a more diverse patient group than the initial trials, angiographic restenosis occurred in 3% of patients treated with sirolimus-eluting stents compared with 35% of patients treated with bare stents (Moses 2002). A stent coated with paclitaxel has also been shown to be effective for decreasing neointimal proliferation within the stented segment and reducing the incidence of clinically significant in-stent or edge restenosis. Three randomised trials: the ASian Paclitaxel-Eluting Stent Clinical Trial (ASPECT) (Park Circulation 2001), the European evaluation of pacliTaxel Eluting Stent (ELUTES) trial (Gershlick Circulation 2001) and TAXUS (Grube Circulation 2003) found that paclitaxel-coated stents significantly reduced angiographic restenosis at 6 months (0-4% vs. 10-27% for bare stent). If these results are confirmed, the application of drug-eluting stents will be most beneficial in groups of patients at high risk for restenosis (ie, patients with small vessels, diabetes, chronic total occlusions, SVG lesions, and multivessel disease) (Arjomand 2003).

Indications for PCI

Indications for PCI have been suggested by the ACC/American Heart Association (AHA) Task Force (Smith 2001).

Stable angina pectoris:

Patients who are asymptomatic or have only mild symptoms are generally best treated with medical therapy unless one or more significant lesions, cause ischemia in a large area of viable myocardium confirmed by non-invasive testing and PCI can be performed with a high chance of success and a low likelihood of complications (Smith 2001). Patients with moderate or severe angina pectoris, particularly those who are refractory to antianginal therapy are suitable candidates for PCI, provided that the lesion, cause ischemia in a moderate to large area of viable myocardium as determined by non-invasive testing. Patients with recurrent symptoms while receiving antianginal therapy are candidates for PCI even if they have a moderate risk for an adverse outcome during revascularization (Smith 2001).

Acute coronary syndrome

In patients with unstable angina pectoris or non-Q-wave myocardial infarction, coronary revascularization might improve prognosis. The TIMI IIIB trial found no difference in death or myocardial infarction at 1 year in patients undergoing routine angiography and revascularization for recurrent ischemia. However, patients treated invasively experienced less angina and were rehospitalized less than those treated with a conservative approach (Anderson 1995). Patients assigned to early catheterization and revascularization in the Veterans Affairs Non-Q-Wave Infarction Strategies In-Hospital (VANQWISH) trial experienced no reduction in the rate of death or the composite end-point of death or myocardial infarction at 1 year when compared with patients assigned to cardiac catheterization and intervention only for recurrent ischemia (Boden 1998). There are several other notable features of the VANQWISH trial. First, although the frequency of multivessel coronary artery disease was high (74% of patients in the invasive group had multivessel disease), only 44% of the patients assigned to invasive therapy actually underwent coronary revascularization, suggesting that the potential benefits of coronary revascularization were not completely realized. Second, although this study was performed before the widespread use of coronary stents and glycoprotein IIb/IIIa inhibitors, the clinical outcomes associated with PCI was quite favorable. Finally, coronary artery bypass graft surgery was performed in nearly 50% of the patients who underwent revascularization in the invasive arm. The 12% mortality rate in these patients exceeds the experience in this group of patients in other series (TIMI IIB 1994, FRISC II 1999, Cannon 2003) and is not fully explainable from the baseline clinical features. Thus, it is quite likely that the very high perioperative surgical mortality rate influenced the overall results of the trial. In contrast to the VANQWISH trial, the Fragmin during Instability in Coronary Artery Disease (FRISC-II) trial demonstrated a significant reduction in death or myocardial infarction at 6 months in patients with non-ST-elevation ACS assigned to routine catheterization and revascularization versus those assigned to a conservative approach (The FRISC-II Investigators 1999). Furthermore, in Treat Angina with tirofiban and determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS) study, patients with unstable angina and myocardial infarction without ST-segment elevation who were treated with the glycoprotein IIb/IIIa inhibitor tirofiban, the use of an early invasive strategy significantly reduced the incidence of death or myocardial infarction at 6-month follow up (Cannon 2003). In the Randomized Intervention Treatment of Angina (RITA-3) trial (Fox 2002), patients with non-ST-elevation ACS were randomized to early intervention or a conservative strategy. At 4 months patients in the intervention group had a lower rate of the combined end-point of death, non-fatal myocardial infarction or refractory angina, compared with patients in the conservative group (10% vs 14%). This difference was mainly due to a reduction of refractory angina in the intervention group. Death or non-fatal myocardial infarction were similar in both treatment groups at 1 year (7.6% vs 8.3%, respectively). Symptoms of angina improved and use of antianginal medications was significantly reduced with the interventional strategy (Fox 2002).

Troponin T and PCI

Myocardial necrosis, indicated by an elevation of a cardiac marker, occurs frequently in the absence of a clearly definable clinical event after an otherwise successful PCI and is associated with an adverse clinical outcome, including death (Davis 2003). Detectable rises in CK-MB occurs following 5–30% of all PCI procedures, and have been associated with adverse outcomes (death, myocardial infarction or TVR) in both short (6-month) and long (up to 3 years) term follow-up studies (Califf 1998, Tardiff 1999, Harrington 1995, Kong 1997). The relation between periprocedural CK-MB elevations and late mortality is approximately linear, and myocardial necrosis has a similar prognostic significance whether it is caused by a "spontaneous" ischaemic event or by PCI (Akkerhuis 2002).

A postprocedural rise in plasma troponin concentrations occurs in up to 40% of PCI procedures (Cantor 2002, Davis 2003) and appears to have a prognostic significance similar to that of elevated CK-MB values. In one study, 26% of the patients with normal troponin values before PCI were found to have concentrations above the upper limit of the reference range after PCI (Cantor 2002). Of these patients the 90 day mortality rate was 5% compared with 0% in patients without elevated troponin I after PCI (risk ratio 4.3, 95% CI 1.4 to 13.5). Another recent study of 1872 PCI patients found that 32% developed elevated plasma troponin I concentrations after the procedure. Elevated troponin I values, the presence of diabetes mellitus, and age were all independent predictors of 1 year mortality (Abizaid 2001). However, the association between increased periprocedural troponin levels and outcome for more than 1 year has not been investigated.

Many studies have attempted to explore the aetiology of myocardial infarction during PCI. Clearly, patients who experience complications during PCI (side-branch occlusion, intimal dissection, coronary spasm and distal embolization) are more likely to have elevated troponin T after PCI (Davis 2003). Glycoprotein IIb/IIIa receptor antagonists have been shown to reduce the incidence of periprocedural myocardial infarction, and the reduction in long term mortality seen with abciximab treatment supports the clinical importance of distal embolization (Chew 2001). There is controversy as to whether the adverse long term prognosis associated with periprocedural myocardial infarction is due to small areas of myocyte necrosis, or whether periprocedural cardiac marker elevations reflect a large atherosclerotic burden in the coronary arteries and elsewhere (Tardiff 1999). The majority of deaths occurring after periprocedural myocardial infarction has been reported as being sudden, which suggests an arrhythmogenic mechanism possibly related to multiple small areas of myocardial necrosis (Brenner 2002).

In a study by Akkerhuis and coworkers (2002) the relative increase in 6-month mortality was similar for CK-MB elevations after PCI and those occurring spontaneously in the setting of ACS. These data support the hypothesis that, regardless of aetiology, any myocyte necrosis has prognostic implications (Akkerhuis 2002).

CRP and PCI

Several studies have suggested that an elevated preprocedural (baseline) plasma or serum CRP level in patients undergoing percutaneous coronary intervention (PCI) is associated with short-, intermediate- and long-term outcome (Table 1). Furthermore, the procedure itself has been shown to provoke an inflammatory reaction as shown by increased plasma CRP levels after PCI. However, the role of CRP response to PCI for prognosis has been investigated only in a few small studies (Table 2). To further explore the role of CRP and the factors that determine CRP in the setting of PCI, the following hypothesis and aims for this thesis was formulated.

Hypothesis and Aims

Hypothesis

In the setting of PCI, CRP is an important prognostic factor that is influenced by pre- and peri-procedural factors.

Aims

- to investigate the impact of a baseline serum CRP determination, medication, and factors related to the procedure for the risk of myocardial infarction during PCI.
- to investigate the influence of a thrombin-based femoral artery closure device on the serum CRP response to PCI.
- to investigate the impact of pathogen burden on the CRP and IL-6 response to PCI.
- to investigate the association between the CRP response to PCI and the long-term risk of death or non-fatal myocardial infarction and coronary revascularization during mean 2.6 years of follow-up.

Material and methods

This thesis consist of 4 studies including patients recruited between Maj 1999 and June 2003. All included patients have undergone PCI at the Karolinska University Hospital in Sweden. Inclusion was performed during office hours, with breaks during weekends, Christmas and summer holidays. Details of inclusion and representativity are given in Figure 3 and Table 3.

Study subjects

Study I

Between May 1999 and April 2001, 400 patients with stable or unstable angina pectoris and with normal serum troponin T levels, undergoing PCI at Karolinska University Hospital were prospectively recruited. Patients undergoing intervention in saphenous vein grafts (SVG) and patients treated with directional or rotational atherectomy were excluded in this study.

Study II

From a cohort of 685 patients admitted for PCI during office hours between January 2000 and October 2002, 221 patients were retrospectively selected for this study. Patients with unstable angina pectoris, treatment with directional or rotational atherectomy, PCI performed through the radial artery, and patients with incomplete CRP and SAA data were excluded. Of the remaining, 100 patients were treated with a thrombin-based femoral artery closure device (Duett sealing device, Vascular Solutions, Minneapolis, Minnesota, USA) and 121 patients were treated with the FemoStop device (RADI Medical Systems, Uppsala, Sweden).

Study III

One hundred patients with stable angina pectoris scheduled for elective PCI at the Karolinska University Hospital were prospectively enrolled in the study between February 2001 and June 2003. Patients with acute infections, chronic inflammatory conditions and patients treated with drug-eluting stents or with a thrombin-based femoral artery closure device were excluded.

Study IV

A total of 891 consecutive patients undergoing PCI at the catheterization laboratory at the Karolinska University Hospital were prospectively investigated. Patients had stable or unstable angina pectoris with a normal serum troponin T ($\leq 0.3 \mu\text{g/l}$) before PCI.

Follow-up

Information about mortality and hospitalization was obtained from a registry kept by the Stockholm County Council. Data about myocardial infarction and coronary revascularization were obtained from hospital records. In cases where patients moved from Stockholm during the follow-up period (20 patients) information was obtained by a telephone interview.

Definitions

Complications during PCI: side-branch occlusion, intimal dissection, coronary spasm and distal embolization.

Myocardial infarction: combination of symptoms of myocardial infarction and elevated troponin I or T levels according to national guidelines.

Periprocedural myocardial infarction: serum troponin elevation the day after PCI to a level > 0.05 µg/l based on the recommendation for definition of myocardial infarction from the joint ESC/ACC committee (2000).

Successful PCI: percentage of residual stenosis of < 50% in the worst of two orthogonal views.

Laboratory procedures

Blood sampling

Study I-II and IV. Five ml of venous blood was collected immediately before PCI and at 6 a.m. the day after PCI (15-20 hours after PCI) for analysis of biochemical markers.

Study III. Before and 6, 24, 48 and 72 hours after PCI, venous blood samples were collected in vacuum tubes and centrifuged immediately (plasma) or after 30 minutes (serum) at 2000 x g for 20 minutes. Both plasma and serum samples were frozen at -80 °C until analyses.

Analyses

C-reactive protein and Serum amyloid A. CRP and SAA concentrations were assayed in serum by a high sensitive method using particle-enhanced immunonephelometry with BN II analyzer reagent (Dade Behring, GmbH, Mamburg, Germany). In study III, CRP was measured in plasma by a high sensitive nephelometric method using particle-enhanced reagent (Dade Behring, Deerfield, IL, USA) in a Behring BN ProSpec analyzer (Dade Behring). The lower detection limit was 0.16 mg/L.

Troponin T. In all studies troponin T levels were measured in serum except in study III where it was analysed in plasma. Measurements were performed with a Troponin T STAT, Cardiac T reagent (Roche Diagnostics, Mannheim, Germany) on a Elecsys 2010 immunoassay analyzer (Roche Diagnostics). The lower detection limit was 0.010 µg/l.

Interleukin-6. Plasma IL-6 levels were determined using a high sensitive ELSA kit (HS600, R&D Systems, Minneapolis, MN, USA). The lower detection limit was 0.1 pg/ml.

Serology. Antibodies of IgG-class (for *Chlamydia pneumoniae* (CPN) also antibodies of IgA-class) against different pathogens were examined by commercially available ELSA kits with the exception for cytomegalovirus where an inhouse ELISA was used. For CPN IgA EIA and IgG EIA (AniLabsystems Ltd. Oy, Helsinki, Finland), for Epstein-Barr virus (EBV) Anti-EBV VCA IgG ELISA (Biotest AG, Dreieich, Germany), for *Helicobacter pylori* (HPY) Pyloriset® EIA-G III (Orion Corporation Orion Diagnostica, Espoo, Finland). IgG-antibodies for HSV-1 and HSV-2 by HerpeSelect® 1 ELISA IgG and HerpeSelect® 2 ELISA IgG (FOCUS Technologies, California, USA). Results were interpreted as positive or negative according to the manufactures' instruction. All equivocal results were regarded as a negative results.

Anticoagulation therapy

Patients undergoing PCI were in general treated with acetyl salicylic acid (ASA). In a few cases, patients had clopidogrel because of contraindications to ASA or warfarin when anticoagulation therapy was indicated for other reasons such as prevention of systemic or venous embolism e.g. in mechanical heart valve prosthesis, myocardial infarction, atrial fibrillation, deep venous thrombosis or

pulmonary embolism. None of the patients in the studies received clopidogrel or ticlopedine in combination with ASA before PCI. Anticoagulation at the time of the procedure was administered as unfractionated heparin (bolus 5000-15000 U aiming at an activating clotting time >300 s) or enoxaparin (0.5 mg/kg bodyweight) intravenously or intraarterially at the start of, or enoxaparin 1 mg/kg bodyweight subcutaneously within the last 6 hours before the procedure. Antithrombotic treatment with glycoprotein IIb/IIIa inhibitors were given as "bail out" if visible thrombus during the procedure. If stentimplantation, ticlopedine 250 mg were given twice or clopidogrel 75 mg once daily for 4 weeks in combination with ASA. All treatment before, during and after PCI was decided by the treating cardiologist.

Femoral artery closure after PCI

Duett sealing device is a non-mechanical femoral artery closure device. It contains a procoagulant mixture, comprised of 250 mg of bovine microfibrillar collagen (Avitene, Davol, Woburn, MA) and 10000 units of bovine thrombin (Gentrac, Middleton, WI) reconstituted in 5 ml of phosphate buffered water for optimal viscosity, osmolarity and pH. This mixture is delivered after positioning of a ballooncatheter. The balloon is inflated within the artery and retracted initially against the sheath and subsequently together with the sheath against the vessel wall. An attempt of aspiration through the sheath is made after 5 mm of retraction and thereafter the procoagulant mixture is injected through the sheath, with the intention of covering the external surface of the artery and sealing the track from the artery to the skin surface. After the end of the injection the balloon is deflated and removed through the sealed track. *FemoStop device* is a compression arch with a pneumatic dome that serve as a mechanical compression after inflation that permits removal of the sheath.

Analysis of lesion morphology

The ACC/AHA grading system (Table 4) (Ellis et al 1990) were used to classify the severity of lesions. Angiograms were evaluated by two interventional cardiologists. In case of disagreement, a third cardiologist was consulted. The cardiologists were blinded to the biochemical results. The lesion type of the most severe stenosis was evaluated in the statistical analysis in the case of intervention of more than one lesion.

Statistics

In study I a sample size of 400 patients made it possible to detect a difference in baseline CRP of 0.3 mg/l between patients without or with myocardial infarction during the procedure with 80% power and $p < 0.05$. In study II, a sample size of 214 patients made it possible to detect a difference in CRP response to PCI of 0.3 mg/l between patients treated with the FemoStop device or Duett sealing device with 80% power and $p < 0.05$. In study IV, a sample size of 1000 patients was calculated to show a 4% absolute difference in death between patients with or without a periprocedural myocardial infarction with 80% statistical power and a one-sided significance level of < 0.05 . During the study the primary end-point had to be modified to death or non-fatal myocardial infarction due to the low number of deaths. Continuous data were expressed as mean \pm SD when normally distributed and as median (range) when skewed and group differences compared using non-parametric statistical methods with the exception of study 1 where continuous parameters were tested with Student's unpaired *t*-test or with ANOVA with Scheffé as the post-hoc analysis after logarithmic transformation. Categorical data were expressed as frequencies (percentages) and differences between groups were tested by Chi-square test. In Study III, area under the curves (AUCs) were constructed for CRP, IL-6 and troponin T values

obtained at 0, 24, 48 and 72 hours. AUCs were divided into tertiles and correlations between AUCs tertiles and pathogen burden were tested by Friedman ANOVA and Kendall's concordance (multiple independent variables) otherwise Spearman rank correlation test was used to test associations between variables. In Study IV, CRP values were divided into tertiles while troponin T values were categorized into 3 categories; no myocardial infarction, small and large myocardial infarctions with a cut-off value of 0.14 µg/l obtained by using the median of the troponin T value the day after PCI of patients with myocardial infarction. Cox proportional hazard regression was performed to evaluate the effects of troponin T and CRP on outcome. The analysis also controlled for other important factors that could influence the results. The assumption of time independent hazard ratio was investigated by including the covariates as a function of time. A backward selection procedure was used for assessing which factors to include in the models. Multivariate analyses were performed by SAS 8.2 statistical software otherwise StatSoft, Inc. (2001). STATISTICA (data analysis software system), version 6, was used. A p value < 0.05 was considered to indicate statistical significance.

Results and Discussion

Study I

This study was performed to evaluate the prognostic information of a preprocedural serum CRP determination to predict myocardial infarction during PCI.

The study patients mean age was 63 years \pm 10.7 and 28% were women. One third of the patients presented with unstable angina pectoris. The vast majority of patients were treated with ASA and cardioselective betablockers, whereas statins were used in more than two thirds of the patients prior to PCI. The majority of patients had one- or two-vessel disease with B-type stenoses according to the ACC/AHA classification. Approximately half of the interventions were in the left anterior descendent artery. Stents were used in 82% of the PCIs and complications during the procedure occurred in 9% of the procedures. Eighty three patients (21%) developed a myocardial infarction during the procedure with a median troponin T value 0.11 μ g/l (0.06-5.0) after PCI. No association was found between preprocedural serum CRP levels and myocardial infarction during PCI (Figure 4). Furthermore, there were no differences between patients without or with myocardial infarction during PCI in terms of treatment with betablockers or statins. However, complexity of the stenosis and factors related to the procedure such as number of dilated vessels, stent use, complication during PCI and duration of the procedure were all associated with the risk of myocardial infarction during PCI. Patients with complications during the procedure had a longer procedure time and more complex lesions than those without complications. Abciximab use tended to be higher in patients with myocardial infarction during PCI.

In multivariate logistic regression analysis, lesion type among preprocedural factors and stent implantation, complications during the procedure and duration of the procedure among periprocedural factors were associated with myocardial infarction during PCI. When all these independent pre- and periprocedural factors were included in the same model, stent implantation, complications during PCI and procedure length, but not lesion type, remained independently associated with myocardial infarction during the procedure (Table 5).

The cardiac troponins I and T have emerged as highly sensitive and specific markers of myocardial cell injury (Adams 1993, Apple 1997). The ability of cardiac troponins to detect myocardial injury is considerably higher than CK-MB (Davis 2003). Percutaneous coronary interventions (PCI) are associated with a risk of myocardial infarction with a varying incidence depending on the method of detection and reference values (Davis 2003). Cardiac troponins have shown to provide important prognostic information, which allows risk stratification of patients presenting with ACS (Lindahl 1996, Galvani 1997) and in patients undergoing PCI (Davis 2003, Nallamothu 2003). These data supports the consensus document recommendation from the ESC/ACC (The Joint European Society of Cardiology/American College of Cardiology Committee 2000) that emphasize that any increase in cardiac troponins results in an adverse prognosis. The incidence of myocardial infarction during PCI has been higher (40-60%) in previous reports using troponin I (Cantor 2002, Ricchiutti 2000) or troponin T (Abbas 1996, Karim 1995) than that observed in the present study (21%). Differences in baseline and procedural characteristics and inclusion of patients with elevated preprocedural troponin may be responsible for part of this discrepancy. Accordingly, the incidence of myocardial infarction during PCI in the study by Cantor and coworkers was 26% after exclusion of patients with increased or missing preprocedural troponin I values that is more in agreement with our findings. Furthermore, in a recent study by Nallamothu and coworkers (Nallamothu 2003) of 1157 patients with normal troponin I before PCI the incidence of periprocedural myocardial infarction was 29%.

Several case-control studies have shown that patients with CAD have increased plasma or serum CRP levels compared with healthy controls. Furthermore, CRP can predict future CAD in healthy individuals and is associated with future cardiac events in patients with established CAD (Ridker 1997 and 2000, James 2003). However, previously only one study has focused on the association between degree of inflammation, determined by plasma CRP, using a high sensitive method, before the

procedure and the occurrence of myocardial infarction during PCI using troponin I as a (Saadeddin 2002). Saadeddin and coworkers demonstrate marker of myocardial injury in 85 patients with stable angina pectoris undergoing elective PCI that an increased preprocedural serum CRP concentration was a independent determinant of myocardial infarction during the procedure, which is in disagreement with the results of the present study. The small patient sample of that study (85 vs 400 patients in our study), inclusion of patients with stable angina pectoris only and lack of estimation of risk ratios for increased CRP levels and other risk factors for myocardial infarction during PCI, makes it difficult to fully evaluate the results of the study by Saadeddin and coworkers. The possible explanation for our finding might be that elevated serum troponin T levels after the procedure reflects a thrombotic complication, due to downstream embolization with myocardial infarction as a consequence (Lindahl 2001) while a low-grade inflammation, as determined by an elevated preprocedural CRP, might reflect the process of atherosclerosis and is therefore related to later adverse cardiac events. This speculation is supported by the study by Heeschen and coworkers (Heeschen 2000) that investigated the predictive values of serum CRP and troponin T in patients with unstable angina pectoris. They could not show that elevated plasma CRP levels increased the risk of cardiac events during the first 72 hours after admission to hospital.

Statin therapy prior to PCI has been shown to improve short- and intermediate-term outcome (Chan 2002, Bunch 2002). The results of the present study showed no association between medication with statins at the time of PCI and myocardial infarction during the procedure. One recent study has shown that statins attenuates the increased risk of major adverse cardiac events in patients with elevated CRP levels undergoing PCI with stentimplantation (Walter 2001). In this context, our results raise the possibility that the improvement of outcome seen with statins is mediated by decreasing the inflammatory response to PCI rather than decreasing the thrombotic activity responsible for myocardial infarction during the procedure. To better understand the mechanisms of how statins improve outcome after PCI randomized trials would be of great value.

The role of prior medication with betablockers on short- and intermediate outcome in patients undergoing PCI is not clear. First, Sharma and coworkers (2002) showed that betablocker treatment at the time of PCI reduced CK-MB elevations after PCI and improved intermediate-term prognosis. However, in a larger study, Ellis and coworkers (Ellis 2001) found no relationship between betablocker use and subsequent rise in CK or CK-MB after PCI. The result of the current study confirm the finding of the latter study. An important limitation of the former two studies and our study is that betablocker treatment was not randomly assigned. Furthermore, 86% of the patients were treated with betablockers in the present study, hence it lacked sufficient statistical power to test the hypothesis of a possible positive effect of betablockers on the incidence of myocardial infarction during PCI.

Complexity of the coronary artery stenosis has been associated with elevated plasma or serum troponin concentrations and adverse clinical outcome in unstable angina pectoris and after PCI (Bugiardini 1991, Kastrati 1999, Benemar 1999). In these studies, the ACC/AHA lesion classification scheme (Ellis 1990) was utilized for classification of the coronary lesion. However, the validity of this scheme for evaluation of PCI outcome has been questioned (Tan 1995). In the present study, we found a univariate association between lesion complexity determined according to ACC/AHA lesion classification and elevated serum troponin T concentrations after PCI. However, this association failed to be significant in multivariate analysis.

Factors related to the procedure (number of dilated vessels, stent implantation, duration of and complications during the procedure) were more reliable to predict the risk of myocardial infarction during the procedure. Complications during the procedure were associated with periprocedural myocardial infarction both in uni- and multivariate analysis. These results are in agreement with results of previous studies (La Vecchia 1996, Talasz 1992, Oh 1980, Bertinchant 1999, Johansen 1998). However, complications did only explain part of the risk of myocardial infarction during the procedure. Other factors related to the procedure such as stent use and duration of the procedure were also associated with an increased risk of periprocedural myocardial infarction.

Our result regarding a role of stent implantation in periprocedural myocardial infarction is in agreement with results of previous reports. Shyu and coworkers (Shyu 1998) showed in 120 consecutive patients with stable or unstable angina pectoris undergoing PCI with or without stent implantation, that the frequency of increased plasma troponin T levels were higher than that of CK-MB mass after the procedure (21% vs. 7%) and higher after stenting when compared with angioplasty alone (29% vs. 13%). In another study, elective PCI with stent implantation was associated with greater release of CK-MB mass than balloon angioplasty alone (Genser 1997). In contrast, a third report claims that the incidence of myocardial damage associated with stent implantation is low and comparable to that associated with balloon angioplasty and that measurement of both troponin T and CK-MB mass concentrations is essential in assessing minor myocardial damage (Ohnishi 1998).

In summary, our results indicate that the risk of myocardial infarction during PCI cannot be predicted by determination of CRP before the procedure. Furthermore, the risk of periprocedural myocardial infarction is increased in patients with a long duration of the procedure and in patients treated with stentimplantation. These finding might provide useful information regarding the decision of the antithrombotic regime before, during and after the procedure, and the suitable grade of care needed after the procedure.

Study II

The present study was performed to evaluate whether the closing procedure of the femoral artery after PCI influences the degree of inflammation related to the procedure as measured by CRP and SAA. A thrombin-based device (Duett sealing device) was retrospectively compared with a mechanical compression device (FemoStop) in patients with stable angina pectoris.

The mean age of the study patients was 66 years (± 10.2) and 23% were women. More than one third of the patients had treatment for hypertension and the majority were on ASA and statin therapy (91% and 76% respectively). Stents was used in 86% and complications during the procedure were reported in 7% of the interventions. Patients with femoral artery closure by the Duett sealing device were younger (64 vs 67 years), had a lower degree of significant CAD and less dilated vessels than those with femoral artery closure by the FemoStop device (1.12 ± 0.36 vs 1.25 ± 0.47). No differences existed in serum CRP and SAA values before and after PCI. Irrespective of femoral artery closure device serum CRP and SAA levels increased significantly after PCI. The increase was more pronounced in the Duett sealing device group compared with the FemoStop device group (Figure 5 and 6).

Various devices have been developed to replace standard manual or mechanical compression at the arterial puncture site to shorten bed rest following coronary angiography and PCI. Unfortunately the risk of peripheral vascular complications, such as hematoma and pseudoaneurysm formation, is slightly measured with the use of these devices compared with local compression at the puncture site (Koreny 2004). Several of these techniques deposit bovine microfibrillar collagen together with a high-dose of bovine thrombin directly above the femoral artery puncture site to obtain haemostasis. Thrombin has in addition to its role to promote hemostasis, proinflammatory activity through stimulation of release of proinflammatory cytokines (Johnson 1998). The biochemical mechanisms for such a response are still unclear. The results of this study support the notion that thrombin stimulates inflammation.

The differences in baseline and procedural characteristics between the two groups are not likely to influence the results of the study. Patients in the FemoStop group were older which probably resulted in an underestimation of the differences in the inflammatory parameters because age has been associated with increased cytokine production upon stimulation (Roubenoff 1998). Recently, it has been shown that degree of CAD was not associated with CRP and therefore the differences regarding the degree of CAD between the two groups is not likely to have influenced our results (Veselka 2002). Finally, the number of dilated vessels were higher in the FemoStop group that something might have resulted in an increased of the inflammatory response to PCI, resulting in underestimation of the results.

In summary, this study confirms that PCI triggers a systemic inflammatory response characterized by increased serum CRP and SAA levels after PCI (Azar 1997) and that this response was more pronounced when the arterial puncture is closed by a thrombin-based device than with a mechanical compression device. This effect of a thrombin-based device should be taken into consideration when deciding on the type of femoral artery closure device to be used after PCI.

Study III

The present study was performed to investigate the role of pathogen burden of infection in determining the magnitude of CRP and IL-6 response to PCI in patients with stable angina pectoris.

The study patients had a mean age of 65 years (± 9.7) and 15% were women. More than 90% of the patients were treated with ASA or betablockers and 83% with statins. Seventy-four patients were dilated in one vessel and the remaining in two vessels. More than one third of the lesions was type B2/C and half of the patients were dilated in the LAD and 8% in SVG. Stent were used in 84 patients and only 2 patients had complications during PCI. Baseline plasma CRP increased from 1.2 mg/l (0.65-2.15) to a peak value at 48 hours of 6.45 mg/l (2.98-9.04) (Figure 7). Plasma IL-6 concentrations increased from 1.4 pg/ml (1.0-2.5) to a peak value at 24 hours of 6.1 pg/ml (3.9-9.9) (Figure 8).

The pathogen burden, expressed as the number of seropositives distribution among the study group is shown in Figure 9. Pathogen burden was not associated with plasma CRP or IL-6 AUCs (Figure 10). This result did not differ when IgA antibodies were substituted for IgG antibodies against *Chlamydia pneumoniae*. No associations were found between individual pathogens and plasma CRP or IL-6 AUCs.

Patients with periprocedural myocardial infarction (21%) had a higher CRP AUC, however there was no correlation between plasma CRP and troponin T ($r = 0.09$) AUCs or IL-6 and troponin T AUCs ($r = 0.009$). Patients treated with stentimplantation had higher plasma CRP and IL-6 AUCs compared with patients treated with balloon angioplasty alone (Figure 11 and 12). None of the other baseline or procedural factors were associated with CRP or IL-6 AUCs.

Increased levels of systemic markers of inflammation, induced by PCI, may be a predictor of clinical outcome (Gaspardone 1998, Versaci 2000). The extent of such an inflammatory response has been suggested to be influenced by traditional cardiovascular risk factors, preprocedural treatment with ASA, statins and glycoprotein IIb/IIIa inhibitors or procedural factors. An association between seropositivity against bacterial or viral pathogens and CAD has been suggested (Blankenberg 2001, Danesh 2000, Ridker 2001, Hajjer 1987). Recently, the concept of pathogen burden has been proposed, i.e. exposure to multiple infectious agents might enhance the risk of CAD compared with a single exposure (Zhu 2000, Espinola-Klein 2002, Choussat 2000). Furthermore, it has been shown that CRP increase with the number of significant antibody titres and prediction of CAD by pathogen burden was limited to subjects with elevated CRP (Zhu 2000, Georges 2003). The present study is the first study to investigate the impact of pathogen burden on the magnitude of inflammatory response to PCI determined by plasma CRP and IL-6 levels. Our results could not confirm a role of pathogen burden in the inflammatory response to PCI. These results are in agreement with the result of a study by Choussat and coworkers (Choussat 2000). They showed, in patients with ACS, that acute phase proteins increased during the first 2 days of hospitalization but failed to demonstrate any association between the presence of seropositivity against multiple infectious pathogens and the inflammatory response.

Several studies of patients treated with stent implantation, have suggested an enhanced CRP response to PCI (Aggarwal 2003, Almagor 2003, Gottsauner-Wolf 2000, Gaspardone 1998). However, in these studies the impact of stent implantation on the CRP response to the procedure has been difficult to evaluate since only patients treated with stentimplantation were included. In our study group, patients treated with stentimplantation had a higher plasma CRP and IL-6 increase after PCI compared with those treated with angioplasty alone. Recently, Liu and coworkers (2003) were not able to show any association between stentimplantation and CRP response to PCI. However, the patients in their study

group had increased preprocedural CRP levels that might have obscured the results. Our results are more in agreement with the results of previous animal studies that have shown coronary artery stenting to cause a more severe arterial injury with a more intense inflammatory response within the vessel wall than balloon angioplasty alone (Hanke 1995, Kollum 1997, Hoffmann 1996, Hofma 1998). Another possibility for interpretation of our result is that the arterial overdilatation by a high-pressure balloon inflation in the case of stentimplantation in comparison with angioplasty alone might be a possible explanation for the increased inflammatory response to PCI in patients treated with stentimplantation (Hoffmann 1999, Roger 1999). The lack of data regarding inflation pressure and time of inflation might therefore be considered a limitation of the present study. A third possible explanation might be that exposure of the metal of the stent in the vessel wall, being a "foreign body", trigger an increased inflammatory response. Irrespective of the aetiology, our finding suggests the interesting possibility that the mechanism behind the low incidence of restenosis with drug-eluting stents might predominantly be by reducing the local inflammation induced by PCI with stentimplantation. Furthermore, treatment with high dose prednisolone has also been shown to reduce restenosis in patients with increased plasma CRP levels undergoing stent implantation (Versaci 2002).

Recently, a study by Bonz and coworkers (2003) aimed to investigate the effect of glycoprotein IIb/IIIa inhibitor on the inflammatory response to PCI. They stated that differences in the inflammatory response induced by the procedure are related to the presence or absence of troponin T release after the procedure. Their data are not consistent with our finding since we were not able to show any correlation between plasma CRP or IL-6 concentrations and plasma troponin T levels after PCI. However, after a careful review of their results, they were not able to demonstrate any significant difference in CRP levels between troponin-positive and troponin-negative patients. Our result add further information regarding the role of the inflammatory response in ACS as an independent risk factor not necessarily associated with myocardial injury.

In summary, our results indicate that the CRP response to PCI cannot be determined by neither infection with single or multiple pathogens nor a minor troponin T elevation after PCI. The inflammatory response to PCI was more pronounced in patients treated with stent implantation compared with angioplasty alone. These findings have implications for the mechanism of restenosis after stentimplantation and the cause of CRP and IL-6 increase seen in ACS.

Study IV

The present study was designed to determine whether the CRP response to PCI provide further information, in addition to a postprocedural increase in troponin T, to predict the risk for death or non-fatal myocardial infarction and coronary revascularization in patients undergoing PCI.

The study patients mean age was 63.6 years \pm 10.7 and they were predominantly men (73%). Seventeen of patients were current smokers and 14% had a previous diagnosis of diabetes mellitus. One third of the patients had presented with unstable angina pectoris. The majority of patients were treated with ASA and statins (92% and 77% respectively). Fifty-six percent of the patients had 1-vessel disease, and 23% and 5% had 2- and 3-vessel disease, respectively. The vast majority of patients underwent PCI in one vessel (84.5%). Half of the PCIs were performed in LAD and stent were used in 85% of the PCIs. Complications during the procedure were reported in 7% of interventions. The CRP concentration was 1.82 (0.88-4.36) mg/l at baseline and 3.98 (1.98-8.84) mg/l after PCI, respectively. The troponin T concentration was 0.01 (0.01-0.01) μ g/l before and 0.05 (0.01-0.05) μ g/l after PCI, respectively. There was no correlation between baseline CRP and troponin T after PCI (0.03, n.s.), while the CRP response to PCI were correlated to both baseline CRP (0.23, $p < 0.0001$) and troponin T after PCI (0.09, $p < 0.05$). Twenty-one percent of the patients had a periprocedural myocardial infarction. Myocardial infarction during the procedure was associated with lesion characteristics ($p < 0.001$), number of dilated vessels ($p < 0.001$) and complications during PCI ($p < 0.001$). Of baseline and procedural characteristics; female gender, smoking, hypertension, diabetes mellitus, degree of diseased vessels, unstable angina pectoris, medication with ASA (inverse relation) and interventions in LAD or SVG were associated with baseline CRP. Female gender, complication during PCI and interventions in SVG were associated with THE CRP response to PCI.

Baseline CRP levels was not associated with periprocedural myocardial infarction (1.76 mg/l [0.88-4.44] vs 1.83 mg/l [0.91-4.35]) , while the CRP response to PCI was higher in in patients with periprocedural myocardial infarction (1.85 mg/l [0.46-5.62] vs 1.34 mg/l [0.35-3.29], $p < 0.01$).

A primary end-points occurred in 76 patients (total 8.5%, 4.6% death and 3.9% non-fatal myocardial infarction), respectively and a secondary end-point occurred in 130 patients (total 15.0%, 12.0% PCI and 3.0% coronary artery by-pass graft operation), respectively at the end of follow-up period. Age, female gender, diabetes mellitus, unstable angina pectoris, number of diseased coronary arteries, treatment with glycoprotein IIb/IIIa inhibitor and ASA (inverse relation) were associated with death or non-fatal myocardial infarction. Unstable angina pectoris and stent use (inverse relation) were the only baseline or procedural parameters associated with coronary revascularization. An Increased preprocedural CRP serum concentration was associated with death or non-fatal myocardial infarction in univariate but not in multivariate analysis. The CRP response to PCI and periprocedural myocardial infarction were associated with death or non-fatal myocardial infarction in both uni- and multivariate analysis (Table 6, Figure 13 and 14). Revascularization only associated with the CRP response to PCI in univariate and after adjustment for age, stent, baseline CRP and troponin T after PCI, in multivariate analysis (Table 7 and Figure 15).

Preprocedural plasma or serum CRP levels have previously been shown to predict short- and intermediate-term outcome in patients undergoing balloon angioplasty with stent implantation (Table 1 introduction section). The association between baseline CRP and long-term outcome has been elucidated only in a few studies (Lenderlink 2003, de Winter 2002 and 2003). In the present study the serum baseline CRP concentration was associated with the risk of mortality and morbidity up to more than 2 years after PCI in univariate analysis. Differences in patients characteristics between previous studies and ours e.g. inclusion of patients with elevated preprocedural markers of myocardial injury or investigating patients with stent implantation or stable angina pectoris only in these studies, make our study result more reliable in assessing the role of preprocedural CRP for long-term prognosis.

The result regarding the association between increased preprocedural CRP and the need for coronary revascularization, has been inconsistent. In agreement with previous reports (Dibra 2003, Horne 2002, Lenderlink 2003, Zhou 1999), our study showed that a baseline CRP determination could not predict the risk for coronary revascularization. However, it is not clear why some earlier studies (Buffon 1999, Gaspardone 1998, Heeschen 2000, Versaci 2000) reported an association between baseline CRP and restenosis.

General discussion

In the studies included in this thesis the prognostic information of serum levels of CRP before and CRP response to PCI was investigated. Furthermore, the studies investigated if pre- and periprocedural factors determine the CRP response to PCI. The results show that serum CRP levels before the procedure were not associated with periprocedural myocardial infarction. Furthermore, the CRP response to PCI was an independent predictor of death or myocardial infarction and revascularization up to more than 2 years after PCI. The CRP response to PCI was more pronounced in patients treated with stent implantation or femoral artery closure using a thrombin-based device whereas the pathogen burden before the procedure was not associated with the CRP response to PCI.

Myocardial infarction during PCI occurs frequently in the absence of a clearly definable clinical event after an otherwise successful PCI, and is associated with an adverse clinical outcome, including death (Califf 1998, Ohman 1997, Tardiff 99). Thrombotic complications have suggested to be the major cause of the periprocedural myocardial infarction. In study I, an increased serum CRP level before PCI was not associated with myocardial infarction during the procedure. In contrast, Danenberg and coworkers (2003) demonstrated that arterial injury in mice transgenic for human CRP results in a higher rate of thrombotic occlusions compared with wild-type mice, which do not produce CRP. The authors concluded that CRP has a possible causal role for an increased rate of arterial thrombosis after controlled vascular injury. Our results could not support that this occurs in humans, PCI being a good model for vascular injury. However, an adverse impact of an increased preprocedural serum or plasma CRP concentration might be evident later after PCI. Periprocedural factors such as duration of the procedure, stent implantation and complications during the procedure seem to be more relevant than the preprocedural CRP for myocardial infarction during PCI. Distal protection devices during PCI has demonstrated the presence of embolic debris supporting the suggestion that distal embolisation during PCI is the most common pathophysiology behind myocardial infarction during PCI (Grube 2001). The utilisation of such devices and glycoprotein IIb/IIIa inhibitor might reduce the incidence of myocardial infarction during PCI.

PCI has consistently been shown to provoke an inflammatory reaction as shown by increased inflammatory markers after PCI. The results from study II showed that a femoral artery closure device containing bovine thrombin might enhance the inflammatory reaction induced by PCI. A proinflammatory activity of thrombin might be linked to its ability to costimulate the release of several inflammatory cytokines, including MCP, IL-1, IL-6, IL-8, TNF- α (Johnson 1998). Whether the local inflammatory response induced by thrombin in the thrombin-based device contribute to augment systemic inflammation and accelerate atherogenesis is unclear. However, it has been shown that local inflammation in the synovial tissue (synovitis) in rheumatoid arthritis can release cytokines into the systemic circulation. These circulating cytokines alter function of distant tissues including adipose, skeletal muscle, liver, and vascular endothelium to generate a spectrum of proatherogenic changes that include insulin resistance, dyslipidemia and endothelial dysfunction (Sattar 2003). The findings of our study needs to be verified in a prospective randomized trial with the focus on the long-term prognostic impact of an increased inflammatory response by a thrombin-based femoral artery closure device.

It has been suggested that there is an association between previous infection with cytomegalovirus (CMV), *Chlamydia pneumoniae* (CPN), Epstein-Barr virus (EBV), *Helicobacter pylori* (HPY), herpes simplex virus type 1 (HSV1) and 2 (HSV2) and CAD (Frishman 2002). The risk posed by infection might be associated to the aggregate number of pathogens (pathogen burden) rather than by one specific pathogen. Pathogen burden might contribute to CAD through an increased inflammatory response (Zhu 2000, Georges 2003). Much to our surprise, in study III we could not demonstrate any association between pathogen burden and the CRP response to PCI. Further investigations of factors that determine the inflammatory response to PCI are needed since animal and human studies suggest that host factors modulate the magnitude and extent of inflammatory response (Liao 1993, de Maat 1996, Pankow 2001). There is evidence of a substantial heritability (35–40%) of plasma CRP levels (Pankow 2001). Further efforts to identify gene loci affecting these traits are warranted. The role of genetic variation of inflammatory markers with PCI as a stimuli should be evaluated.

Over a 2-year follow-up, the risks of death or non-fatal myocardial infarction and revascularization were significantly higher in patients with an increased CRP response to PCI. In adjusted statistical analyses, the CRP response to PCI was a strong independent predictor of long-term mortality and morbidity in addition to a minimal troponin elevation after the procedure. The mechanisms behind the association between the CRP response to PCI and death or non-fatal myocardial infarction might be different than that between the CRP response to PCI and revascularization. The exact mechanisms behind these association are unclear. However, several experimental studies have revealed a broad range of potentially atherogenic properties of CRP (Yeh 2003). The results of study IV raises the question of whether the CAD risk associated with the CRP response to PCI is modifiable. Researchers have investigated the effects of interventions and medications already in use in CAD prevention including treatments that have anti-inflammatory effects, such as dietary changes, weight loss, exercise, ASA and statins (Lind 2003). Furthermore, the promising effect of drug-eluting stents to prevent restenosis (Arjomand 2003) might be mediated by attenuating the inflammatory response to PCI.

Future directions

Despite our findings regarding the strong independent role of CRP response to PCI on long-term prognosis, several issues have to be evaluated before measurement of CRP can be used for risk prediction in the setting of PCI in clinical practice. First, it has to be established if CRP is merely a marker for CAD or if it is actually directly involved in the pathogenic process of CAD and restenosis. Second, in an ideal prospective study a large number of inflammatory markers should be measured in order to evaluate if one of these markers are superior to others and whether the same inflammatory marker could be used to predict risk in both acute and chronic phases of CAD. Third, the effects of established therapies, directed towards conventional cardiovascular risk factors, on CRP should be further evaluated in randomized outcome trials. Fourth, in the future specific drugs that block the increase in CRP in CAD need to be developed and tested in outcome trials. This would be the ultimate test to evaluate if CRP is involved in the pathogenesis of CAD and restenosis, and thus CRP could serve as a surrogate biomarker for this process.

As early as 1997 Azar and coworkers showed that PCI by itself can induce an inflammatory response as expressed by increased serum CRP levels after the procedure (Azar 1997). Only two small studies have investigated the role of the CRP response to PCI for prognosis. In a study group consisting of 81 patients with stable angina pectoris and one vessel coronary artery disease undergoing PCI with stent implantation, Gaspardone and coworkers (1998) showed that persistent increased CRP levels at 72 hours after PCI were associated with a combined end-point of cardiac death, non-fatal myocardial infarction and recurrence of angina pectoris. In contrary to this finding, Liu and coworkers (2003) showed that elevated plasma concentrations of secretory type II phospholipase A2 (sPLA2) after PCI, which is involved in the production of various pro-inflammatory lipids, but not the CRP response to PCI, were associated with a combined end-point consisting of coronary death, non-fatal myocardial infarction and recurrence of angina pectoris in 247 patients. This discrepancy was found despite a high correlation between CRP and sPLA2. The elevated baseline CRP levels before PCI in that study might have obscured the increase in CRP stimulated by the procedure. In our large cohort of PCI patients we were able to study separate endpoints; death or non-fatal myocardial infarction and risk of coronary revascularization. Furthermore, our study is the first to investigate the combined prognostic value of baseline CRP, CRP response to PCI and periprocedural myocardial infarction determined by troponin T in a large consecutive group of patients without increased preprocedural troponin T concentrations undergoing PCI. The results clearly showed that the CRP response to PCI, in addition to that of a baseline CRP and periprocedural myocardial injury, had a strong prognostic value to predict the risk for death or non-fatal myocardial infarction and coronary revascularization.

The association between increased periprocedural troponin levels and outcome for more than 1 year has not been investigated. Furthermore, the cut-off of troponin concentration to identify PCI patients at

risk for adverse events is not clear. In a recent meta-analysis of 2605 patients who were followed up more than one year after PCI an increased troponin level after PCI using the recommended cut-off values according to ESC/ACC guidelines (The Joint European Society of Cardiology/American College of Cardiology Committee 2000), did not correlate with an increased incidence of a composite end-point consisting of cardiac death, non-fatal myocardial infarction and the need of revascularization (Wu 2002). It was difficult to interpretate the results of the majority of the reports included in this meta-analysis since the only abstract were published (Wu 2002). In the present study, also a minor periprocedural myocardial infarction (serum troponin T > 0.14 µg/l) was associated with an independent risk for death or non-fatal myocardial infarction. Of note an increased troponin T concentration of > 0.14 µg/l the day after PCI in combination with a CRP response to PCI in the highest tertile was associated with a more than 5 times increase in risk of death or non-fatal myocardial infarction up to more than 2 years after PCI.

Our results might have therapeutic implications. It can be speculated if it is possible to decrease the risk of future coronary events by lowering the CRP response to PCI. Observational studies have suggested that statin therapy decrease the risk for major adverse cardiac events in patients with elevated plasma CRP levels undergoing PCI with stent implantation (Chan 2002, Walter 2001). Contrary to this finding, our results showed no associations between baseline CRP or CRP response to PCI and prior medication with statins. Furthermore, treatment with statins was not associated with outcome. Controversy still exists regarding the benefit of ASA therapy in decreasing CRP levels and thus improving outcome (Feldman 2001, Feng 2000, Ikonomidis 1999). In the present non-randomized study medication with ASA was associated with a lower baseline CRP and with a decreased incidence of death or non-fatal myocardial infarction during follow-up. Furthermore, oral therapy with high dose prednisolone in patients with increased plasma CRP levels 72 hours after coronary artery stent implantation results in a reduction of restenosis (Versaci 2002). In order to better evaluate of the effects of various anti-inflammatory therapies on CRP levels and the associations with outcome in patients with CAD, large randomized studies are needed particularly in the setting of PCI.

In summary, an elevated serum CRP concentration in response to PCI is a strong independent predictor of death or non-fatal myocardial infarction and coronary revascularization independent on myocardial injury during the procedure. The result emphasize the role of CRP in CAD, and the need to develop treatments that block the increase in CRP in CAD.

CONCLUSIONS

Periprocedural factors such as duration of the procedure, stent implantation and complications during the procedure, whereas not the preprocedural CRP were associated with the risk of myocardial infarction during PCI. However, an elevated serum CRP concentration in response to PCI is a strong independent predictor of death or non-fatal myocardial infarction and coronary revascularization independent on myocardial injury during the procedure. Furthermore, the CRP response to PCI was more pronounced in patients treated with stent implantation or femoral artery closure using a thrombin-based device whereas the pathogen burden before the procedure was not associated with the CRP response to PCI.

Taken together, the results emphasize the role of CRP in CAD, and the need to develop treatments that block the increase in CRP in CAD.

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