Prognostic Value of Plasma Levels of High Sensitivity C-Reactive Protein in Chronic Systolic Heart Failure of Ischaemic Origin

Protocol of Thesis

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Abbreviations

CHF	Congestive heart failure
LV	left ventricle
CRP	C- Reactive protein
HSCRP	high sensitivity C-Reactive protein
ACS_s	Acute coronary syndromes
LDL	low density lipoprotein
VLDL	very low density lipoprotein
TNF	Tumour Necrosis factor
IL6	Interleukin-6
MPO	Myeloperoxidase
MI	myocardial infarction
AHA	American Heart Association
CV	Cardiovascular
DM	Diabetes Mellitus
SNPS	Single Nucleotide Polymorphisms
CHD	Coronary Heart disease
HDL	High density lipoprotein
CI	Confidence interval
ADHF	acute decompensated heart failure
CDC	Centers for disease control and prevention
NCEP	National cholesterol education program
P value	propability value
RA	rheumatoid arthritis
SAA	serum amyloid A
ICAM-1	Intercellular adhesion molecule
PNV	Predictive negative value
PPV	Predictive Positive value

Introduction

Heart failure is a complex clinical syndrome characterized by impaired myocardial performance and progressive activation of the neuroendocrine system leading to circulating insufficiency and congestion.

Despite significant improvement in medical treatment, congestive heart failure (CHF) remains a major clinical problem with high morbidity and mortality. Risk stratification is therefore an important step for the selection of patients that may benefit from pronounced follow-up in addition to intensive educative programs, and also from alternative therapeutic approaches such as cardiac transplantation or left ventricular (LV) assist devices or cardiac resynchronization therapy.

The concept that biological markers may accurately predict the outcome of CHF patients is an attractive one. Several reports have indicated that elevated blood levels of inflammatory markers are associated with an adverse prognosis in CHF patients ***(Tsutamoto et al., 1998).***

C-reactive protein is a sensitive marker of inflammation. When compared with other more sophisticated measures of cytokine activity, C-reactive protein determination may be more appropriate for routine clinical use. High-sensitivity (hs) assays for C-reactive protein have been standardized across many commercial platforms;

moreover, C-reactive protein is highly stable, allowing measures to be made accurately in both fresh and frozen plasma without requirements for special collection procedures ***(Ridker et al., 2003)***. hs C-reactive protein levels have been shown in multiple prospective epidemiological studies to predict vascular risk (myocardial infarction, stroke, or peripheral arterial disease) but few data are available regarding the prognostic impact of hs C-reactive protein levels in patients with CHF ***(Lamblin et al., 2005).***

Inflammation plays an important role in the progression of atherosclerosis ***(Libby et al., 2002).*** High-sensitivity C-reactive protein (CRP) has emerged as an important risk factor for systemic atherosclerosis and is related to its clinical complications ***(Ridker et al., 2002)***. Activation of the immune system may also play a role in the pathogenesis of heart failure (HF) ***(Seta et al., 1996)***. Small studies have shown that plasma CRP is elevated in patients with HF. In several community studies, plasma CRP predicted the development of HF and other adverse events. However, clinical data on the prognostic value of CRP in patients with established HF are limited, inconsistent, and obtained in modest sample sizes ***(Anand et al., 2005).***

The serum concentration of C-reactive protein (CRP) is mildly elevated in patients with chronic congestive heart failure (CHF), but this level falls well within the range found in healthy subjects. Standard clinical assays for CRP lack

sensitivity within the low reference range and thus cannot be used effectively for routine clinical risk prediction. Because assays for high-sensitivity CRP (hsCRP) are now available, we can measure hs-CRP to determine its predictive value for the prognosis of patients with CHF ***(Yin et al., 2004).***

Aim of the Study:

Our aim to investigate the relationship between hs-CRP and prognosis in patients with CHF and LV systolic dysfunction of ischaemic origin.

C-Reactive Protein and Hs-CRP

CRP and cardiovascular disease: New insights from an old molecule:

The classical acute-phase protein C-reactive (CRP) is an exquisitely sensitive systemic marker of disease with brand clinical utility for monitoring and differential diagnosis. inflammation, the key regulation of CRP synthesis, plays a pivotal role in atherothrombotic cardiovascular disease.

There is a powerful predictive association between raised serum CRP values and the outcome of ACSs and remarkably, between even modestly increased CRP production and future atherothrombotic events in otherwise healthy individuals.

Baseline CRP values also reflect metabolic states associated with atherothrombotic events. The presence of CRP within most atherosclerotic plaques and all acute myocardial infarction lesions, couplet with binding of CRP to lipoproteins and its capacity for pro-inflammatory complement activation, suggests that CRP may contribute to

the pathogenesis of complications of cardiovascular disease thus CRP may be a novel therapeutic target.

C-reactive protein is an acute phase protein, synthesized by the liver and its concentration in serum rises rapidly in response to tissue injury, infection, inflammation, necrosis or neoplasm ***(Pepyes et al., 1981).***

It is formed by hepatocytes and normally only a trace is present in the plasma. It is a part of the protein response along with other plasma proteins such as anti-trypsin, ceruloplasmin and fibrinogen. The rate of synthesis and secretion of C-reactive protein increases within hours of acute injury or the onset of inflammation ***(Kushner et al., 1978)***. This is probably under the influence of several hormonal mediations called cytokines for example IL-6, IL-I or hepatocyte stimulating factor ***(Mauric et al., 1989).***

CRP was originally isolated as protein that binds to the C-polysaccharide of the cell wall of pneumococci ***(Tillet and Francis, 1930)***. It is made up of 5-identical non-glycosylated subunits arranged in a ring resembling a donut. For many years, CRP was known as an acute phase reactant that could raise its level 100-fold within 24 to 48 hours during an inflammatory process . CRP is synthesized and secreted

mainly by hepatocyte in response to cytokines such as interleukin-6 and has a plasma half-life of 19 hours - CRP are elevated in many inflammatory disorders and have been used to predict clinical outcomes. Thus, CRP level may reflect the degree of underlying inflammatory response and provide a useful measure of immune injury to tissue. Another possibility is that CRP could directly participate in amplifying the immune response, thus leading to further tissue damage.

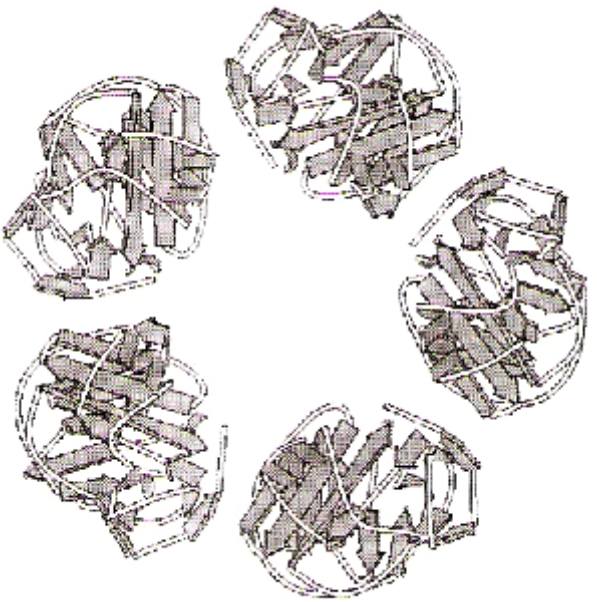

Figure (1): Molecular structure of CRP, viewed face-on showing the A face, displayed as a ribbon diagram ***(Thompson et al., 1999).***

CRP has been shown to bind to damaged tissue, to nuclear antigens, to lipoproteins and to apoptotic cells. It also participates in complement activation and tissue damage ***(Duclos et al., 2000).***

Interestingly, CRP is present in atherosclerotic plaques but not in the normal vessel wall and CRP deposits in early atherosclerotic lesions may precede the appearance of monocytes ***(Torzewski et al., 2000)***.

The median normal circulating concentration of C-reactive protein is 0.8 mg/L ***(Shine et al., 1981).*** CRP is synthesized exclusively in the liver and secreted in increased amounts within about 6-hours of an acute stimulus such as elective surgery or myocardial infarction. Thereafter the plasma level can double at least every 8 hours reaching a peak after about 50 hours.

Table (1): Routine and possible future clinical uses of CRP measurement of using standard and/or high sensitivity assay: ***(Hirschfield and Pepys, 2003)***

Screening assay for organic disease:

Assessing disease activity in inflammatory conditions

- **Juvenile chronic arthritis**
- **Rheumatoid arthritis**
- **Ankylosing spondylitis**
- **Reiter's syndrome**
- **Psoriatic arthropathy**
- **Vasculitides (Behçet's syndrome, Wegener's granulomatosis, polyarteritis nodosa, polymyalgia rheumatica)**
- **Crohn's disease**
- **Rheumatic fever**
- **Familial fevers including familial Mediterranean fever**
- **Acute pancreatitis**

Diagnosis and management of infections

- **Bacterial endocarditis**
- **Neonatal septicaemia and meningitis**
- **Intercurrent infection in systemic lupus erythematosus**
- **Intercurrent infection in leukaemia and its treatment**
- **Postoperative complications, including infection and thromboembolism**

Differential diagnosis/classification of inflammatory disease

- **Systemic lupus erythematosus versus rheumatoid arthritis**
- **Crohn's disease versus ulcerative colitis**

Risk prediction in cardiovascular disease

- **Long term future predictive value of CRP in healthy populations**
- **Outcome of patients with acute coronary syndromes and following invasive coronary procedures**
- **Initiation of statin therapy for the primary prevention of cardiovascular disease**

Table (2): Clinical disease and CRP response:

Major CRP response	
Infections	**Bacterial**
	Fungal
	Mycobacterial
	Viral (severe or systemic)
Hypersensitivity complications of infection	**Rheumatic fever**
	Erythema nodosum
Acquired and inherited inflammatory diseases	**Rheumatoid arthritis**
	Juvenile chronic arthritis
	Ankylosing spondylitis
	Psoriatic arthritis
	Systemic vasculitis
	Polymyalgia rheumatica
	Reiter's disease
	Crohn's disease
	Familial Mediterranean fever
Tissue necrosis	**Myocardial infarction**
	Tumour embolization
	Acute pancreatitis
Trauma	**Surgery**
	Burns
	Fractures
Neoplasia	**Lymphoma**
	Carcinoma
	Sarcoma
Modest/absent CRP response	**Systemic lupus erythematosus**
	Scleroderma
	Dermatomyositis
	Ulcerative colitis
	Leukaemia
	Graft-vs.-host disease

(Hirschfield and Pepys, 2003)

C-reactive protein and the pathogenesis of atherosclerosis:

Our original identification of the possibility that CRP may contribute to the pathogenesis of atherosclerosis ***(Pepys***