Tech Review

High-sensitivity C-Reactive Protein (hs-CRP)

Introduction

Numerous studies have demonstrated the importance of risk factors such as advanced age, diabetes, male sex, tobacco use, family history of premature heart disease, hypertension, and hyperlipidemia in predicting risk of cardiovascular disease (CVD). These established risk factors are largely absent, however, in approximately half of those who develop CVD.[1] Improvement in risk assessment is, therefore, dependent on identification of additional factors to identify more effectively those at risk who might benefit from more aggressive preventive health measures.

CRP and the Role of Inflammation in Atherosclerosis

C-reactive protein (CRP) is an acute phase reactant that has long been considered a classic marker for inflammation. Although normally circulating at low levels, acute inflammation, infection, or tissue injury induces a marked increase in hepatic synthesis of CRP, which can raise the serum level a hundredfold or more. It is now known that atherosclerosis, the process underlying CVD, which includes coronary heart disease (CHD), myocardial infarction (MI), and ischemic stroke, as well as peripheral vascular disease (PVD), is due at least in part to a chronic, low-level inflammation of the vascular endothelium.[2]

At autopsy in patients who have died from MI, inflammation is evident from the accumulation of monocytes and macrophages at the sites of plaque rupture. Such observations suggest that serum CRP levels may reflect the development and progression of atherosclerosis. The prospect of using CRP as a marker for vascular inflammation was initially thwarted by the insufficient sensitivity of existing assays to measure low concentrations of CRP in serum reliably. With the recent development of high-sensitivity assays (hs-CRP), however, investigations have been conducted to evaluate the role of CRP as a risk factor for CVD.

CRP and CVD Risk

Several prospective clinical case-controlled studies in the US on middle-aged men (Physicians Health Study,[3-6] Multiple Risk Factor Intervention Trial[7]), postmenopausal women (Women's Health Study[8,9]), and elderly men and women (Cardiovascular Health Study, Rural Health Promotion Project[10]) have identified CRP as a strong, independent risk factor for CVD. This finding receives additional support from studies in Germany (Monitoring Trends and Determinants in Cardiovascular Disease,[11] Finland Helsinki Heart Study[12]), and the UK[13], all conducted on middle-aged men.

Although specific details of these studies vary, they have some important elements in common, which facilitate a summary of the findings. Study subjects did not have CVD at entry but may have had other risk factors (eg, hypercholesterolemia, hypertension, diabetes, tobacco use).

Table 1.—Prospective Studies of CRP as a Risk Factor for Future Cardiovascular Disease[14]

Study	Endpoint	Relative Risk*
Physician's Health Study[4,5]	MI	2.9
	Stroke	1.9
	PVD	2.1
Women's Health Study[9]	CVD	4.4
MRFIT[7]	CHD Death	4.3
CHS/RHPP[10]	CHD	2.3
MONICA[11]	CHD	2.7
Helsinki Heart Study[12]	CHD	3.6

*Upper vs Lower Quartile

Baseline blood specimens collected at entry were assayed for various analytes, including C-reactive protein. (For the older studies, specimens collected at baseline and stored frozen at -70° were assayed using a high-sensitivity CRP method.)

Subjects were followed over time (3 to 17 years, depending on the study) and were monitored for development of cardiovascular disease. Subjects who experienced various CVD endpoints (eg, CHD, MI, stroke) or peripheral vascular disease were randomly paired against age-matched control subjects who remained disease-free, and baseline levels of CRP were compared in the two groups.

Subjects were assigned to quartiles (or quintiles) based on their CRP values. Relative risk was estimated by comparing

the frequency of occurrence of a given CVD endpoint in the highest vs the lowest quartile (quintile). The major findings are summarized below.

- CRP levels showed statistically significant positive correlations with other established risk factors including age, number of cigarettes smoked per day, body mass index, systolic and diastolic blood pressure, total cholesterol (TC), triglycerides, homocysteine, fibrinogen, and D-dimers; CRP levels correlated inversely with exercise frequency and high density lipoprotein cholesterol (HDL-C).[3] Nevertheless, when multivariate analysis was performed to control for these associations, **CRP emerged as a strong, independent risk factor in its own right.**

- Median baseline CRP levels ranged from 30% to twofold higher among subjects who subsequently developed CVD compared to subjects who remained disease-free.[4,5,8,9] **The degree of elevation varied with the CVD endpoint, follow-up interval, and other study variables.**

- Baseline CRP levels were a significant independent risk factor for CVD. In middle-aged men CRP was a risk factor for fatal and nonfatal MI,[4,7,11,12] ischemic stroke,[4] and PVD[5] but not venous thrombosis, suggesting its value in risk assessment may be limited to the arterial system. In postmenopausal women CRP was a risk factor for CHD death, nonfatal MI, and stroke.[8,9] Similar but less definitive conclusions were drawn from two limited studies on elderly men and women.[10] The relative risk values from these studies are summarized in Table 1, above.[14]

- In a subset of middle-aged male subjects taking aspirin to reduce CVD risk, those in the highest CRP quartile experienced a 56% reduction in MI compared to a statistically insignificant reduction for those in the lowest quartile.[4] This finding suggests that **CRP levels may be useful in identifying those high-risk patients most likely to benefit from aspirin therapy.**

- CRP levels were reduced by the lipid lowering drug pravastatin (Prevacol®) showing that **CRP is a modifiable risk factor** and suggesting that an anti-inflammatory activity may contribute to the drug's therapeutic efficacy.[15,16]

- In addition to assessing future CVD risk in asymptotic individuals, **CRP also appears to have predictive value in patients with acute coronary ischemia[14] and in the chronic phase following acute MI.[15]**

- **The addition of CRP to other CVD risk factors increased the overall predictive value.** In particular, when CRP and the TC:HDL-C ratio were used together, a significant improvement in risk assessment was achieved compared to the use of each separately.[6]

With regard to this last finding, it has been proposed that CRP be measured routinely along with other risk factors to identify better those patients at risk for CVD.[17] A proposed risk assessment algorithm based on CRP and lipid levels is shown in Figure 1, below.

The algorithm was constructed from data obtained on middle-aged men (aged 40 to 84) followed for nine years and postmenopausal women followed for three years.[4,6,9] A relative risk of 1.0 was assigned to individuals falling into the lowest quintiles of both CRP and TC:HDL-C ratio.

hs-CRP value (mg/L)	TC/HDL-C ratio	
	Women	Men
0.1-0.7	<3.4	<3.4
0.7-1.1	3.4-4.1	3.4-4.0
1.2-1.9	4.1-4.7	4.0-4.7
2.0-3.8	4.7-5.8	4.7-5.5
3.9-15.0	>5.8	>5.5

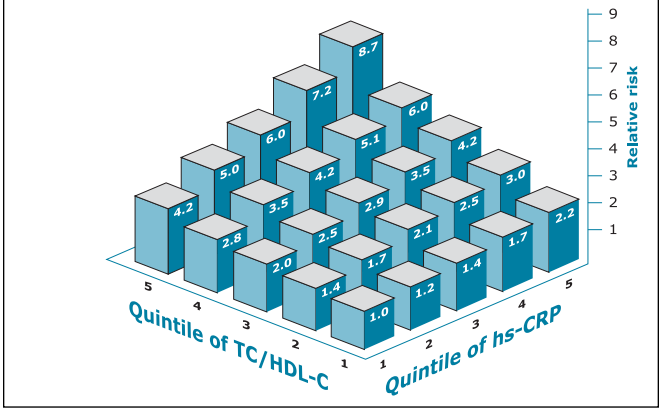

Figure 1.—Proposed CVD Risk Assessment Algorithm Based on Serum CRP and TC:HDL-C Ratio[17]

The CRP reference intervals that appear on the LabCorp report form represent CRP quartiles within middle age to older males and females. The associated relative risks are derived from clinical studies referenced above[4,8] and apply when CRP alone is used to assess risk.

Limitations

- In the epidemiological studies conducted to date, most subjects have been Caucasian.

- Although several high-sensitivity CRP assays are currently available for assessing CVD risk, some variation between assays has been observed.[18,19] It is often optimal to use the same assay (or laboratory) when monitoring a patient's CRP over time.

- Increases in CRP levels are nonspecific. CRP is an indicator for a wide range of disease processes and should not be interpreted without a complete clinical history. Recent medical events resulting in tissue injury, infections, or inflammation, which may cause elevated CRP levels should also be considered when interpreting results. Testing should not be performed for at least two weeks following the resolution of a known acute inflammation or infection. When using CRP to assess risk of CVD and PVD, measurements should be compared to previous values.

C-Reactive Protein (CRP), Cardiac 120766

CPT 86140

Related Information C-Reactive Protein (CRP), Quantitative

Synonyms Cardiac C-Reactive Protein (CRP); Cardiac CRP; Cardio C-Reactive Protein (CRP); Cardio CRP; C-Reactive Protein (CRP), High Sensitivity; C-Reactive Protein (CRP), HS; CRP, Cardiac; CRP, Cardio; CRP, High Sensitivity; CRP, HS; High Sensitivity CRP; HS CRP

Special Instructions State patient's sex on the test request form.

Specimen Serum or plasma

Volume 1 mL

Minimum Volume 0.5 mL

Container Red-stopper tube or serum-separator tube or lavender-stopper (EDTA plasma) tube or green-stopper (heparinized plasma) tube

Collection Separate serum or plasma from cells within 1 hour after collection.

Storage Instructions Refrigerate (maximum 8 days). May be frozen at -25°C or lower if samples are frozen within 24 hours after collection. Repeated freeze-thaw cycles are to be avoided.

Causes for Rejection Gross lipemia

Reference Interval Relative risk

Male:

CRP	>2.11 mg/L	future MI: 2.9; future stroke: 1.9
CRP	1.15-2.10 mg/L	future MI: 2.6; future stroke: 1.9
CRP	0.56-1.14 mg/L	future MI: 1.7; future stroke: 1.7
CRP	<0.55 mg/L	future MI: 1.0; future stroke: 1.0

Female:

CRP	>7.3 mg/L	future MI or stroke: 5.5
CRP	3.8-7.3 mg/L	future MI or stroke: 3.5
CRP	1.5-3.7 mg/L	future MI or stroke: 2.7
CRP	<1.5 mg/L	future MI or stroke: 1.0

Use Measurement of CRP by high sensitivity CRP assays may add to the predictive value of other markers used to assess the risk of cardiovascular and peripheral vascular disease.[5-7,9,11,16]

Limitations Increases in CRP values are nonspecific. CRP is an indicator for a wide range of disease processes and should not be interpreted without a complete clinical history. When using CRP to assess risk of cardiovascular and peripheral vascular disease, measurements should be compared to previous values. Recent medical events resulting in tissue injury, infections or inflammation, which may cause elevated CRP levels, should also be considered when interpreting results.

Methodology Latex immunonephelometry

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