

Coronary Artery Disease and High-Sensitivity C-Reactive Protein

Coronary Artery Disease (CAD), as a form of generalized atherosclerosis, continues to be the leading cause of death in the world. In the US, though the incidence of death from CAD has declined after peaking in the 1960s, morbidity continues unabated. Though the increased CAD risk in association with diabetes mellitus, hyperlipidemia, tobacco use, and family history have been well defined, up to one-half of patients presenting with a CAD event have no history of or apparent risk factors associated with atherosclerosis. It is the search for reliable markers of increased risk for early atheromatous plaque development that motivates much cardiovascular research today.

Atheromatous plaques (APs) have been intensely studied for many years, yet the inciting event(s) in their pathogenesis are still largely hypothetical. Much is known about the structure and evolution of APs and renewed interest in the last few years has led to new avenues of research. The atherosclerotic plaque develops as an accumulating mass of smooth muscle cells, inflammatory cells and macrophages loaded with lipids, and multiple chemicals of intracellular and extracellular origin, within a chemically complex matrix lying underlying the intimal lining of the involved artery. Though unknown definitively, the first thing that likely happens is an injury of some type to the intimal lining. The body's apparent first response is to render the immediate area of trauma chemically "sticky". From here on, the process seems quite variable, depending on genetics, current disease state, chemical nature of the blood, etc. It is clear that the body's response to the initial insult plays a major determinative role in how the intimal damage is repaired, whether by minimal inflammatory response and rapid "scar" formation or by a more exuberant, multifaceted chemical and cellular response that ultimately ends in the development of an atheromatous plaque. It is this inflammatory response that is one current focus of cardiovascular research interest.

It has been established that there is an inflammatory component to the development and progression of CAD. This relationship appears to be a major factor in the syndrome of unstable angina, thus linking this syndrome to the recent "vulnerable plaque" discussions. A number of blood markers have been recently evaluated in investigating the role of inflammation in the AP, including levels of serum amyloid A, several interleukins, "soluble intercellular adhesion molecule type 1" (sICAM-1), homocysteine, and C-reactive protein (CRP).

With the recent advent of a more sensitive laboratory test for CRP (termed high-sensitivity or hs-CRP), several studies have shown that the serum hs-CRP level is directly related to the risk of future CAD in healthy men and women, even with normal lipids, and to the risk of recurrent myocardial infarction, stroke, and peripheral vascular disease. Early evidence is that the hs-CRP serum level is an independent risk factor, unrelated to diabetes, family history, etc. Current research in this area focuses on the many questions surrounding this newly defined relationship. One central question under intense investigation is whether elevated serum CRP is one of the bodily inflammatory responses to some infectious agent, or whether it causes damage on its own. To address the second possibility first, there is evidence that the CRP molecule binds complement C1q at the damage site, initiating the complement sequence.

Regarding the first hypothesis, that an infective agent may be at work in AP formation, several studies have identified DNA in plaques from a number of bacterial and viral agents, by far the most common of which were Chlamydia pneumoniae and Helicobacter pylori. As you will recall, C. pneumoniae causes persistent pulmonary infections, while H. pylori causes ulcers in gastric mucosa. In one study of cardiovascular specimens, 46 endarterectomy specimens (carotid and abdominal) and 39 adjacent segments of artery (controls) were evaluated for DNA of these two organisms by polymerase chain reaction (PCR). Twenty-six percent of the 46 endarterectomy specimens were positive for C. pneumoniae DNA and thirty-seven percent were positive for H. pylori, while the control specimens were all negative. Six of the specimens were positive for both C. pneumoniae and H. pylori DNA.

CRP is one of the more abundant blood proteins and is a non-specific marker of inflammation. Its concentration is significantly increased in infections, inflammation (acute or chronic), malignancy, and tissue trauma. Instrumentational and methodological improvements have made measuring low, "normal", levels reproducible and practical, so-called high sensitivity-CRP (hs-CRP) methodology. In a "normal" adult population, age and gender do not appear to be significant variables in CRP levels, though post-menopausal women on hormone replacement therapy have higher levels. Ninety percent of the "healthy" subjects in a large study had hs-CRP levels, using the method of measurement that PRL uses, of 0.169 mg/dL or less, with most values being equal to or less than 0.3mg/dL. CRP levels

above 1.0 to 1.5 mg/dL are commonly associated with acute or chronic inflammation. There is significant (around 40%) individual variation in CRP levels, so for values above 0.5 mg/dL, a repeat test is recommended, to avoid inappropriate interpretation. It is further recommended to wait at least 2 weeks after an acute or chronic inflammatory event or tissue trauma to measure hs-CRP.

Studies have shown that a more meaningful way to look at individual hs-CRP levels is through assignment to quartiles (25% segments) or quintiles (20% segments) of the population, then relating these segments to relative risk. Several studies have shown that, in apparently healthy adults, a hs-CRP value that places an individual in the highest quartile or quintile of the otherwise "healthy" population is associated with a 2-4 times higher risk of atherosclerosis, stroke, myocardial infarction or peripheral vascular disease. But, it must be remembered that the relative risk for the disease states noted above increases as the hs-CRP level increases, particularly within the upper quartiles/quintiles of the otherwise "healthy" population. Further studies indicate that combining the risk-assignment quintiles from hs-CRP levels and the total cholesterol/HDL cholesterol ratio (TC/HDL-C) has the best capability for predicting future cardiovascular disease (Rifai and Ridker, Clin . Chem., 47, No.1, 2001).

Quintile	hs-CRP (mg/dL)	Relative Risk of CV Disease (risk associated with hs-CRP alone)
1	<0.07	1.0
2	0.07 - 0.11	1.2
3	0.12 - 0.19	1.4
4	0.20 - 0.38	1.7
5	0.39 - 1.50	2.2

If one adds to the above data, the statistical impact of a total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C) ratio of >3.4 for either sex, the relative risk for the above mentioned diseases increases dramatically, such that for a male in hs-CRP quintile 5 who has a TC/HDL-C ratio of >5.5, the relative risk jumps to 8.7.

As indicated above, post-menopausal women on hormone replacement therapy have higher hs-CRP levels. It has been shown that aspirin, the "statin" drug pravastatin, glucocorticoids, and non-steroidal anti-inflammatory drugs can decrease the hs-CRP blood level significantly and it is believed that these medications may decrease the increased risk noted above.

Obviously, the answers are not in on the pathogenesis and evolution of atheromatous plaques. But researchers around the world are nibbling away at that one-half of primary myocardial infarctions without previous demonstrable risk factors. There is increasing evidence that the blood level of hs-CRP should be treated as an independent risk factor for coronary artery disease, as the lipid profile, family history, diabetes mellitus, and possibly blood homocysteine are currently. As with blood homocysteine, the possibility that the hs-CRP blood level is an independent risk factor is particularly exciting because these levels may be amenable to therapeutic modification, possibly altering the risk of future CAD. Research is underway, using several different antibiotics as well as other anti-inflammatory agents, to determine whether this risk modification is possible.