Introduction – Our Traditional View of Atherosclerosis
When I started Medical School, my lecturers told me that atherosclerosis was predominantly a disease of lipid deposition and smooth muscle proliferation. An injury to the endothelium initiates the process. As the lipids and cells in the growing plaque built up they encroach on the lumen of the affected vessel. When the fibrous cap overlying that wad of gruel got thin enough and you held your tongue just the right way, the cap would crack, exposing juicy bits beneath that are irresistible to platelets passing by. This initiates the coagulation cascade. The body clots the fissured plaque just like a cut on the back of your hand. Stuffing a narrowed pipe full of clot doesn’t do much good to blood flow, and unstable angina or a non-ST-elevation or ST-elevation myocardial infarction develops. If you were too fat, too male, too lazy (sounding a lot like your humble author), smoked too much, never controlled your diabetes or blood pressure and chose your parents poorly, their defective genes predisposed you to a fate of premature coronary artery disease (CAD).

The Incomplete Puzzle – Something is Missing
That theory worked for me: it was simple, made scientific sense and more importantly, I passed my exams with it. Those traditional risk factors for premature CAD injure the endothelium through mechanisms that are not 100% clear. Nonetheless, scientists told us that if you had those traditional risk factors you were this or that many times more likely to develop CAD than that other healthy fellow on the street beside you. Our current guidelines\(^1\) extol the virtues of this thinking by suggesting routine use of the Framingham Risk Score for predicting who develops clinical CAD. The problem is that half of all heart attacks in North America occur in people with normal cholesterol levels and half of all heart attack patients have no preceding unstable angina\(^2\). In reality, many people present with sudden cardiac death. With our current risk assessment tools, we have trouble predicting who will develop clinically significant CAD and when.

Atherosclerosis as Inflammation
Over the last couple of decades, a significant body of work has suggested this simple hypothesis of the pathogenesis of atherosclerosis is too simple. What has resulted is a richer view analogous to a chronic inflammatory state. Inflammation can be thought of as the body’s response to a noxious, damaging stimulus. It is usually self-limited. As the inflammatory response is deployed and the mess is cleaned up and eliminated, the response wanes to zero. Let’s use the same example as the cut on the back of the hand: hyperemia increases blood flow to the area, bringing inflammatory cells and mediators, providing nutrients and removing waste and cellular debris (redness and swelling). Thrombosis effects hemostasis, stopping the bleeding (the scab). Eventual healing occurs via extracellular matrix deposition, cell proliferation and remodeling of the damaged tissue (the scar). If the noxious stimulus is not eliminated due to persistence or the injury is repeated over and over, chronic inflammation develops. Often this is maladaptive or injurious like the resultant thickened scarred skin from constantly scratched itchy eczematous skin.

Classic chronic inflammatory diseases include rheumatoid arthritis, pulmonary fibrosis and chronic pancreatitis. All are the result of chronic or recurrent noxious stimuli. All are
mediated by inflammatory white cells: monocytes, macrophages and lymphocytes. All produce proliferation of connective-tissue cells: smooth muscle cells or fibroblasts. All produce extracellular matrix: collagen, elastin and proteoglycan. Finally, all are coordinated by the language of inflammation: immediate cell-cell signaling via expression and binding of intercellular adhesion molecules (ICAM-1, VCAM-1), and distant cell signaling via cytokines (tumor necrosis factor [TNF-α], interleukins [IL-1 & IL-6], and others).

In atherosclerosis, the chronic noxious stimulus results from exposure to the traditional damaging risk factors: hypertension, smoking, hypercholesterolemia, diabetic hyperglycemia, obesity and their damaging effects to the endothelium. The same white blood cells, connective tissue cells, extra-cellular matrix deposition and mediators implicated in the other chronic inflammatory diseases have been implicated in this process. As examples, in genetically modified mice that lack apolipoprotein E and thus are hypercholesterolemic, ICAM-1 expression is increased at lesion-prone arterial branch points. VCAM-1 is normally absent in normal mice but is heavily expressed at the same sites as ICAM-1 in the hypercholesterolemic mice. Both produce exuberant atherosclerosis. In mice bred to be entirely deficient in ICAM-1, smaller lesions of atherosclerosis develop than in regular hypercholesterolemic mice. Numerous other studies show the link between the players and mediators of inflammation and the atherosclerotic process.

From Bench to Bedside – The Search for Inflammatory Markers

If we accept that atherosclerosis is best described as an inflammatory process and that inflammatory mechanisms run the show, how do we reconcile this with our currently imperfect models for risk prediction in CAD? Our traditional risk factors are all the usual suspects that damage our endothelium. But what about all the other future and undiscovered villains out there that may be silently wreaking havoc – the undiscovered and future risk factors that cause endothelial damage? Whether they are, elevated homocysteine levels, apo-lipoprotein(a), chronic infection with Chlamydia species or any of the other prospective pledges in the fraternity of CAD, they all result in the same thing – initiating and ongoing-damage to normal or vulnerable endothelium. They may be the missing pieces in our currently imperfect risk prediction models.

The beauty of the inflammatory hypothesis is that it offers a final common pathway for the stimulus to inflict its damage. Regardless of how many other causative agents and risk factors are out there to fill out the atherosclerotic mosaic, if the net result is inflammation, assessing net inflammation would seemingly provide the best insight into net atherosclerosis and net risk. This allows for some elegant concepts to tantalize us: 1. If we accept that inflammation causes atherosclerosis, can we monitor inflammation to monitor the activity of atherosclerosis? 2. By monitoring inflammation, can we predict who will have events and when they will occur? 3. Can we intervene at the final common pathway, inflammation, to prevent its atherosclerotic sequelae and clinical CAD endpoints?

There are a lot of “ifs” here. Does an inflammatory marker exist that meets this conditions and allows this type of prognostication? Numerous inflammatory markers have been sampled and studied. The ideal marker should be independent of other traditional risk factors, equally represented in both sexes, easily and cheaply assayed, accurate and precise.
Global white blood cell count, erythrocyte sedimentation rate, assays of various interleukins and cell adhesion molecules have all failed for one reason or another. The recent volumes of work by Dr. Paul Ridker and others may just have yielded our holy grail: C-reactive protein (CRP).

**The CRP Story**

CRP is a hepatically-derived pentraxin composed of five 23-kDa subunits. It gained its name by binding the C-polysaccharide of pneumococcal cell walls. It belongs to a group of acute phase reactants that rise and are measurable in circulation as a result of a physiological inflammatory response. CRP has a long plasma half-life, is highly stable allowing assays to be taken from fresh or frozen plasma and stable over long periods of time (even decades). It is not affected by food intake and has essentially no circadian variation.

Despite being an acute phase reactant, its level of variation within an individual is comparable to that of LDL-cholesterol measurements and clinical ranges for its measurements have been established and validated in the literature. Traditional CRP assays do not have the sensitivity required for vascular disease prediction but high-sensitivity CRP assays (hs-CRP) are commercially widely available and are comparable in cost to cholesterol assays. CRP is an ideal inflammatory marker from a technical standpoint.

Recent publication of event-free survival data has become available and has allowed stratification of hs-CRP levels into low, intermediate and high risk strata at levels of <1.0, 1.0-3.0 and >3.0mg/L respectively. Event free survival in healthy individuals over 8 years was approximately 99%, 98% and 96% for each of the three groups, based on baseline CRP levels. Over a dozen prospective epidemiological studies have now used CRP to predict myocardial infarction, stroke, sudden cardiac death; recurrent ischemia and death in stable and unstable angina, those undergoing percutaneous transluminal coronary angioplasty procedures and those presenting to the emergency room with acute coronary syndromes.

Further, these predictions add prognostic value at all levels of LDL, are independent of LDL-cholesterol levels and are stronger predictors than LDL levels themselves. CRP has also been shown to add prognostic information at all levels of the Framingham Risk Score for traditional risk factors. CRP adds prognostic value to all levels of the metabolic syndrome and may predict incident Type 2 diabetes mellitus.

So yes, we can: 1. Monitor inflammation and indirectly assess the activity of atherosclerosis and 2. Predict in whom events will occur with a predictive power greater than that of traditional risk factors alone and additive to them. Predicting when events will occur is a bigger trick that CRP cannot yet do. But can we 3. Intervene at the final common pathway, inflammation, to prevent its atherosclerotic sequelae and clinical CAD endpoints?

**The Future...Therapeutic Targets?**

There is currently no definitive evidence that lowering CRP will necessarily reduce event rates. Almost all the data is thus far from prospective population-based epidemiological studies and animal models in the lab. However, studies addressing this issue are currently being designed and we should have these answers in the near future. Several pharmacological agents proven to reduce cardiovascular endpoints have an effect on CRP levels. Statins, other anti-hyperlipidemics, ASA, clopidogrel, abciximab and thiazolidinediones all have been shown to decrease CRP. Currently the most robust of that
data is with the statins. Additionally, angiotensin converting enzyme inhibitors and statins have demonstrated other anti-inflammatory properties acutely and with chronic use\textsuperscript{5}. Agents such as NSAIDS and immune modulators are being tested. Again, well-designed studies will be needed to test these agents in a prospective randomized trial setting.

The last and most provocative line of thinking in the CRP saga is in CRP’s role as not just marker, but mediator\textsuperscript{2}. CRP has demonstrated pro-atherogenic properties. CRP activates endothelial cells to express ICAM-1, VCAM-1, selectins and monocyte chemotactic protein-1. It also induces the secretion of IL-1 and IL-6. It activates macrophages to express cytokine and tissue factor and enhances the uptake of LDL. All these CRP actions enhance atherogenesis through inflammatory mechanisms. Is it possible that CRP is not only the bearer of bad news, but that it is part of the bad news itself? Can we envision a CRP-blocker in the future drug regimen of CAD patients?

Conclusions

The old hypothesis of atherosclerosis as a disorder of lipid accumulation and smooth muscle proliferation has gone by the wayside. Atherosclerosis is essentially established as an inflammatory process coordinated by inflammatory mechanisms. This has encouraged the investigation of inflammatory markers of atherosclerosis and CRP has emerged as the marker to watch. CRP has been shown prospectively to predict cardiovascular endpoints in large population studies. Although we currently have no definitive evidence that lowering CRP will reduce cardiovascular events, the supportive data is strong. We await large randomized trials to test this hypothesis.

In the meantime, lest we get seduced by the cult of CRP, do not forget the lesson recently reviewed in the hormone replacement therapy (HRT) arena. Prospective population based studies, retrospective analyses and subset analyses simply generate hypotheses. Clinicians and scientists the world over thought HRT in postmenopausal women prevented cardiovascular disease. Large well-designed trials proved that to be bunk and suggested HRT might be harmful to some.

Keep your eye on CRP. We have interesting times ahead.

References

6 Ridker PM et al: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. NEJM 2002; 347:1557-1565.