Editorial Comment

Inflammation, infection and coronary heart disease

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It has become clear that inflammation is an important component of coronary heart disease. Atherosclerotic disease usually begins with injury to endothelial cells. This injury can occur upon exposure to many injurious agents such as high levels of low density lipoprotein cholesterol (LDL-C), hypertension, diabetes mellitus, and tobacco smoke as well as infectious agents. Once the injury occurs, lipoproteins and inflammatory cells are attracted to the area. Activated macrophages and T lymphocytes contribute to the inflammatory process and release cytokines into the circulation attracting further inflammatory cells to the area of injury. Many of these inflammatory cytokines can be measured in the plasma and correlate with both the extent of coronary disease and complications of the disease.

High levels of inflammatory cytokines have correlated with plaque rupture and acute coronary events. High sensitivity C-reactive protein (hsCRP) has been studied in a number of different clinical conditions. C-reactive protein is a marker for ongoing inflammation and may be directly involved in the atherosclerotic process. C-reactive protein may directly cause endothelial dysfunction leading to a progression of coronary heart disease.

Evidence is emerging that chronic inflammatory conditions may lead to the development and progression of coronary heart disease. For example, chronic arthritis and periodontal disease have been implicated in increasing the risk of coronary heart disease. Infectious agents including Chlamydia pneumoniae and cytomegalovirus have also been suggested as a cause of endothelial damage. Once this damage has occurred, a typical inflammatory response is initiated that may persist long after the initial infection is gone.

The study by Kazar and colleagues in this issue of the Journal of Geriatric Cardiology shows an increase in prevalence of antibodies to cytomegalovirus and Chlamydia in patients with documented coronary heart disease and in patients undergoing vascular surgery. In addition, these patients were more likely to have positive inflammatory markers, including C-reactive protein and interleukin-6, in their sera.

The presence of antibodies to infectious agents was also commonly measured in the control patients as well, suggesting that the presence of these antibodies be not very useful to discriminate patients with active disease. It remains to be determined if these infectious agents are just innocent bystanders or are actively involved in the atherosclerotic process. It is also possible that certain individuals may be more susceptible to endothelial damage from these agents than others.

The high prevalence of antibodies to infectious agents in patients with atherosclerotic disease raises the question if active infection may be present in these individuals and if treatment directed against the infection may modify the course of the disease. A number of studies have used antibiotic therapy to see if it can modify the natural history of coronary heart disease. Cannon et al. enrolled 4162 patients hospitalized for an acute coronary syndrome and evaluated the long term treatment with the antibiotic gatifloxin, an antibiotic known to be effective against Chlamydia. There was no difference in the rate of events between the gatifloxin and placebo group at two years. Grayston et al. assigned 4012 patients with documented stable coronary disease to either azithromycin or placebo for one year and found no difference in cardiac events among the two groups. From these studies, there does not appear to be a role for antibiotics in the treatment of coronary heart disease.

It is possible that exposure to certain infectious agents may lead to endothelial dysfunction and the development of atherosclerotic disease in genetically susceptible individuals. The atherosclerotic plaque may continue to develop long after the initial infection has resolved. The infectious agent may cause the initial damage setting up a wound healing process and ongoing inflammation that leads to progression of the disease. If this is the case antibiotic therapy would no longer be expected to be of any use long after the infection has resolved. Instead treatment aimed at turning off the inflammatory process will be needed to allow plaque healing and prevent future acute events.

There is emerging evidence that aggressive therapy using statins to lower LDL-C can reduce future coronary events in part by reducing inflammation. In the TIMI-22 study, two doses of statin medication were used in patients presenting with an acute coronary syndrome. One group received a standard dose of statin medication, pravastatin 40 mg once daily,
and the second group received high doses statin therapy, atorvastatin 80 mg once daily. The high dose group had a significant reduction in events compared to the standard therapy group. The high dose group also achieved a significant reduction in C-reactive protein compared to the standard dose group suggesting that the reduction in inflammation have helped reduce events.

It has become clear that there are multiple insults to the vasculature that can lead to damage, inflammation and the development of atherosclerosis. Regardless of the damage, the vasculature acts in a stereotypical fashion attracting inflammatory cells to the area of injury setting up a wound healing process that leads to the development of atherosclerotic disease. Treatment will need to focus on turning off this wound healing process allowing plaques to stabilize and become less prone to rupture. Systemic inflammation may be an additional risk to endothelial cells. Ongoing research will need to be done to see if a reduction in systemic inflammation can change the natural history of coronary heart disease. Unfortunately treatment with systemic antibiotics has not been shown to be beneficial. Antibodies to infectious agents may give us an historical perspective to injury but do not necessarily indicate ongoing infection.

References