Inflammation, Infection, and Cardiovascular Risk
How Good Is the Clinical Evidence?

Paul M. Ridker, MD, MPH

Despite substantial gains in the prevention and treatment of acute myocardial infarction, many atherothrombotic events occur among individuals without readily apparent risk factors. Several lines of basic research indicate that inflammation and perhaps chronic infection may play important roles in the initiation and progression of atherosclerosis. For example, pathological studies demonstrate that atherosclerotic lesions are heavily infiltrated with cellular components associated with inflammation, influx of neutrophils into the walls of the epicardial vessels has been demonstrated in response to acute ischemia, and sites of acute plaque rupture are preferentially associated with inflammatory components. Further, proinflammatory cytokines as well as cellular adhesion molecules involved in the attachment of monocytes to the endothelial wall appear to be critical in early atherogenesis. With regard to chronic infection, evidence of prior exposure to Chlamydia pneumoniae, cytomegalovirus, and Helicobacter pylori has been detected within human atherosclerotic tissues, and it has been hypothesized that these organisms may activate vessel-associated leukocytes or lead to a transformation of vascular smooth muscles or endothelial cells. In addition, animal studies suggest that infection with cytomegalovirus and perhaps other agents can lead to endothelial lesions similar to that of human atherosclerosis.

See p 1675

From an epidemiological perspective, however, the role of inflammation and infection as potential cardiovascular risk factors is far from certain. Although several studies have reported associations between exposure to various infectious agents and prevalent coronary disease, these data derive almost exclusively from cross-sectional or retrospective studies that cannot establish a temporal relation between exposure and disease. Furthermore, it is difficult for cross-sectional and retrospective studies to exclude the possibility that observed associations are the result of inadvertent selection bias or residual confounding on the basis of age, smoking pattern, and socioeconomic status. For example, individuals with greater inflammatory and infectious burdens may be at increased coronary risk simply because they are older, have poorer health habits, and have less access to care. In addition, both inflammation and infection are more prevalent among smokers. Thus, whether relationships between inflammation, infection, and atherosclerosis are causal or largely due to confounding requires careful consideration.

Fortunately, prospective epidemiological studies that can control for many of these effects have recently become available, at least with respect to clinical evidence of inflammation. In particular, several prospective studies have been presented that indicate that mildly elevated levels of C-reactive protein, a nonspecific marker for systemic inflammation, are present among individuals with stable and unstable angina at risk for future myocardial infarction, elderly patients at risk for symptomatic coronary heart disease, those at high risk for infarction primarily because of smoking, and apparently healthy middle-aged men at risk for first-ever myocardial infarction or stroke.

Data from the prospective Physicians Health Study (PHS) have been particularly informative because that study evaluated a group of low-risk men with no prior history of cardiovascular disease and low rates of cigarette consumption. Overall, data from the PHS indicate that initially healthy men with baseline levels of C-reactive protein in the highest quartile had a threefold increase in risk of developing future myocardial infarction (relative risk, 2.9; P<.001) and twice the risk of developing stroke (relative risk, 1.9; 0.02). These risk estimates were stable over an 8- to 10-year follow-up period, were not modified by smoking status, and were independent of other cardiovascular risk factors, including total and HDL cholesterol, triglycerides, lipoprotein(a), and fibrinogen. Moreover, measurement of C-reactive protein adds to the predictive value of lipids in determining vascular risk. For example, a fivefold increase in risk of future myocardial infarction was observed among those with high baseline levels of both C-reactive protein and total cholesterol, a risk estimate greater than the product of the risks associated with isolated elevations of either C-reactive protein or total cholesterol alone. Elevated baseline levels of C-reactive protein are also associated with a fourfold increase in the risk of developing clinically severe peripheral arterial disease, again independent of usual risk factors.

Whether C-reactive protein has direct vascular effects or is simply a marker for systemic inflammation remains uncertain. However, there appears to be no association between levels of C-reactive protein and risks of venous thrombosis, suggesting that this acute-phase reactant does not induce a hypercoagulable state. Furthermore, other acute-phase reactants, including fibrinogen and serum amyloid A, appear to be associated with vascular risk. Recent prospective data.
indicate that plasma concentrations of the soluble intercellular adhesion molecule (sICAM-1) are elevated many years in advance of a first-ever myocardial infarction and that levels of sICAM-1 correlate with C-reactive protein. Because cellular adhesion molecules, such as ICAM-1, are critical in the adhesion of circulating leukocytes to the endothelial cell and subsequent endothelial transmigration, these data provide further epidemiological evidence that cellular mediators of inflammation have a critical role in atherogenesis.

By contrast, prospective epidemiological data relating evidence of infection to future vascular risk are sparse. Thus, investigations evaluating whether infection is a cause of chronic inflammation and whether infection is a risk factor for cardiovascular disease have relied primarily on cross-sectional and retrospective approaches. Despite epidemiological limitations, these study approaches provide opportunities to generate new hypotheses and gain substantial pathophysiological insight.

Such is the case for an intriguing paper in this issue of Circulation in which Pasceri and colleagues present data describing an association between virulent Helicobacter pylori strains and prevalent ischemic heart disease. In a thoughtful retrospective case-control study design, the prevalence of infection with Helicobacter pylori among 88 case subjects with a history of ischemic heart disease was compared with the prevalence of infection among a group of 88 age- and sex-matched control subjects of similar social background who were free of coronary disease. On an a priori basis, Pasceri and colleagues also sought to determine whether Helicobacter pylori strains associated with increased inflammatory virulence caused by possession of the cytotoxin-associated gene-A (Cag-A) might confer a particularly high risk of ischemic heart disease.

Three findings in this study are particularly noteworthy. First, overall prevalence of Helicobacter pylori infection was significantly higher among patients than control subjects (62% versus 40%, P = .004), data consistent with prior observational studies relating prevalence of Helicobacter pylori to coronary disease. Second, much of this effect appeared to be mediated through Cag-A positivity, an intriguing finding because this genetically mediated virulence factor may be associated with a greater inflammatory burden. Specifically, patients with ischemic heart disease had a significantly higher prevalence of Cag-A positive strains of Helicobacter pylori (43% versus 17%, P = .001) compared with patients without ischemic heart disease. In contrast, prevalence of Cag-A-negative Helicobacter pylori strains was similar between patients and control subjects (19% versus 23%, P = .8). Third, despite an association between Helicobacter pylori positivity and ischemic heart disease, there was no association between seropositivity and severity of coronary disease defined at angiography.

These data provide yet another potential link between inflammation, infection, and vascular disease. Prior work suggests that Cag-A positivity may be associated with an increased inflammatory response, at least in the setting of duodenal ulcer disease. Thus, if the association between Helicobacter pylori and vascular disease proves valid and indeed relates to the virulence of this bacterium, then infection with Helicobacter pylori may influence atherosclerosis through the generation of a persistent low-grade inflammatory stimulus. The fact that C-reactive protein levels increase with increasing prevalence of exposure to Helicobacter pylori provides indirect support for this hypothesis.

Pasceri and colleagues note that their data must be interpreted cautiously. Despite attempts to draw case and control subjects from a similar social background, case subjects with Helicobacter pylori positivity were of lower socioeconomic status than were those without evidence of infection, once again raising the possibility that Helicobacter pylori seropositivity may be a surrogate for reduced access to care and poorer health outcomes. Pasceri and colleagues further note that their results require confirmation in prospective controlled populations. To date, at least three such studies have been presented. In the first of these, IgG antibodies directed against Helicobacter pylori were determined among residents of 24 British towns who were then prospectively followed for myocardial infarction and stroke. In that study, unadjusted analysis suggested a positive association. However, Helicobacter pylori infection was also associated with lower social class, increased cigarette consumption, and several traditional cardiovascular risk factors. When these confounding factors were adjusted for, no statistically significant association was found between Helicobacter pylori and risk (P = .4 for myocardial infarction, P = .9 for stroke). Similarly, in the large-scale British United Provident Association (BUPA) study as well as in the Atherosclerosis Risk in Communities (ARIC) study, no associations between Helicobacter pylori seropositivity and future ischemic heart disease or coronary mortality were observed. However, in each of these studies, prevalence of infection was again associated with lower socioeconomic status. Although none of these three prospective studies specifically evaluated for Cag-A positivity, they do indicate that retrospective associations must be interpreted with caution.

How good, then, is the clinical evidence relating inflammation, infection, and cardiovascular risk? With regard to inflammation, the available prospective data are highly consistent and provide strong evidence that inflammatory parameters are independent risk factors for coronary disease that may well add to our ability to predict risk, even among otherwise low-risk individuals. Moreover, clinical evidence relating inflammation to vascular risk complements a large body of basic laboratory and experimental work demonstrating a fundamental role for inflammatory mediators in the atherothrombotic process. The strength of these observations suggests that ongoing work evaluating therapies that interfere with the inflammatory component of atherosclerosis is a potentially important line of research.

With regard to infection, provocative hypotheses such as that raised by Pasceri and colleagues concerning Cag-A positivity and vascular disease deserve careful consideration, as do hypotheses concerning Chlamydia pneumoniae and cytomegalovirus. At a minimum, large-scale prospective studies evaluating early life infection with these agents and subsequent vascular disease need completion, preferably in...
populations homogenous for socioeconomic status and with long-term follow-up.

Until such studies are completed, the role of infectious pathogens in coronary disease will remain uncertain. However, in the wake of two small studies that suggest that macrolide antibiotics might reduce cardiovascular event rates, it is increasingly difficult to ignore the possibility that infection may be a novel cardiovascular risk factor. Large scale clinical trials will provide direct evidence as to whether eradication of infection has a role in cardiovascular disease prevention. If appropriately designed, such trials will enable scientists to clearly discern whether associations between infection and ischemic heart disease are causal or due to residual confounding.

Acknowledgment

Dr Ridker is supported by an Established Investigator Grant from the American Heart Association.

References

4. van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation. 1994;89:36–44.


**Key Words:** Editorials ▪ inflammation ▪ infection ▪ Helicobacter pylori ▪ Chlamydia pneumoniae ▪ C-reactive protein
Inflammation, Infection, and Cardiovascular Risk: How Good Is the Clinical Evidence?
Paul M. Ridker

Circulation. 1998;97:1671-1674
doi: 10.1161/01.CIR.97.17.1671

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/97/17/1671

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at: http://circ.ahajournals.org//subscriptions/