Link Between Infection and Atherosclerosis
Who Are The Culprits: Viruses, Bacteria, Both, or Neither?

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On the basis of an examination of 400,000 sections from 40 autopsy cases in 1935, Leary\(^1\) used the term “abscess” to describe atheromatous plaques, because leukocyte infiltration suggested an inflammatory process. A substantial body of evidence has since implicated inflammation and immune activation in the pathogenesis of atherosclerosis, thrombosis, and neointimal thickening after arterial injury.\(^2\)\(^-\)\(^3\) A number of potential triggers capable of inducing proinflammatory cellular responses have been identified; these include modified lipoproteins, cytokines, chemokines, angiotensin II, hypertension, hyperglycemia, smoking, oxidative stress, and others.\(^2\)\(^-\)\(^3\) However, one of the most interesting developments in recent years has been the hypothesis that one or more infectious agents may play a role in atherothrombosis, either through a direct proinflammatory effect on the vessel wall or through a less specific, long-distance proinflammatory effect.\(^2\)\(^-\)\(^6\)


The possibility of infections contributing to atherosclerosis was suggested in the late 1800s and early 1900s by several authors\(^7\)\(^-\)\(^8\) and, in fact, in 1911, Frothingham suggested that “The sclerosis of old age may simply be a summation of lesions arising from infectious or metabolic toxins.”\(^9\) Specific organisms that have been implicated include viruses such as herpes simplex virus (HSV-1), cytomegalovirus (CMV), hepatitis virus, and bacteria such as Chlamydia pneumoniae, Helicobacter pylori, and porphyromonas gingivalis.\(^2\)\(^-\)\(^6\) The evidence implicating infection in atherothrombosis includes the following: (1) seroepidemiological data, (2) the identification of viruses and bacteria in atherosclerotic plaques, (3) a strong association between specific infections such as CMV with transplant atherosclerosis, (4) experimental models showing an induction or acceleration of atherosclerosis by viruses or bacteria, (5) the ability of infectious organisms or their structural components to induce proatherogenic and prothrombotic responses in cells relevant to atherogenesis (smooth muscle cells, monocyte-macrophages, T-cells, and endothelial cells), and (6) provocative data from pilot clinical trials using anti-Chlamydia antibiotics.\(^2\)\(^-\)\(^6\),\(^10\)\(^-\)\(^11\)

Despite all the evidence to date, the concept that infection in general and/or specific pathogens in particular may contribute to atherothrombosis in humans, although extremely intriguing, is far from established. In fact, several prospective, seroepidemiological studies have failed to confirm the results of retrospective studies that had identified a positive association between serological evidence of C pneumoniae infection and coronary heart disease events.\(^12\)\(^-\)\(^14\) Although negative serology may not necessarily rule out infection, substantial inconsistencies should, nevertheless, raise questions about the validity of the hypothesis.

In a recent issue of Circulation, Siscovick et al\(^15\) reported the results of a prospective, nested, case-control study of elderly subjects >65 years who were recruited from the ongoing Cardiovascular Health Study. The authors examined the differences in serology (IgG antibodies) for HSV-1 (positive versus negative), CMV (positive versus negative), and C pneumoniae (positive versus negative and low versus high titers) in 213 cases who experienced a nonfatal myocardial infarction or cardiovascular death during a median follow-up of 2.1 years after initial blood sampling and in a group of 405 matched controls. After adjustment for a number of relevant covariates, positive serology for HSV-1 was associated with a 2-fold higher risk for adverse events. In contrast, there was no difference in the overall prevalence of positive serology for CMV or C pneumoniae between cases and controls. Taken at face value, these results would support a potential link between HSV-1 and atherothrombosis while raising doubts about a similar role for CMV and C pneumoniae.

More than 25 years ago, Fabricant et al\(^16\) and Benditt and Benditt\(^17\) proposed a potential role for viral infections in atherosclerosis. Since then, additional observations have bolstered such notions. These data include the identification of viral genomes in atherosclerotic vessels, cell-culture studies showing proatherogenic effects of viral infection, and experiments by Fabricant et al\(^16\) and Nicholson and Hajjar\(^5\) showing Marek’s virus (avian herpes virus)–induced fibroproliferative and lipid-laden atherosclerosis in animals with and without hypercholesterolemia and the atheroprotective effect of preimmunization with a turkey herpes virus. The findings reported by Siscovick et al\(^15\) provide additional, albeit indirect, evidence in support of this hypothesis. Further analysis of their data shows an intriguing interaction between smoking, HSV-1 serology, and cardiovascular risk. The increased risk associated with a positive HSV-1 serology was essentially confined to smokers (odds ratio, 2.0), because nonsmokers had an odds ratio of 1.0. Although these differences did not reach conventional levels of statistical signifi-
The possibility that specific patterns of infection with C pneumoniae or altered host immune responsiveness) may be more relevant possibly different serotypes with different immunogenicities may be due to reinfection, reactivation, or infection with C pneumoniae that result in a high-titer serological response (which mostly retrospective studies but in keeping with a number of recent prospective studies.12–14 Before dismissing a potential link between C pneumoniae infection and atherothrombosis, we must note the intriguing observation that a high-titer serology (>1:1024) for C pneumoniae was twice as frequent among cases than controls (15.1% versus 8.7%) and that a high-titer positive serology for C pneumoniae that result in a high-titer serological response (which may be due to reinfection, reactivation, or infection with possibly different serotypes with different immunogenicities or altered host immune responsiveness) may be more relevant to its potential pathophysiological role in atherothrombosis. It should also be noted that lack of a positive serology might not definitively rule out the presence of C pneumoniae infection in the vessel wall. Furthermore, the study by Siscovick et al15 only included elderly subjects and most previous studies have included younger and middle age subjects; thus, the data may or may not apply to all age groups.

Although evidence showing a relationship between certain viral and bacterial infections and atherothrombosis continues to accumulate, any causal link remains tantalizing but not fully proven. Furthermore, previous studies have produced inconsistent results with respect to the precise identity of the relevant pathogens (viruses, bacteria, or both). It has also been hypothesized that multiple pathogens may be involved and that total pathogen burden may be a more relevant marker of risk than evidence of individual viral or bacterial infections alone. It has not yet been determined whether and which infectious organisms are culprits or common innocent bystanders. Ongoing randomized, controlled trials of anti-Chlamydia antibiotics in subsets of patients with coronary artery disease may shed further light on the subject, although collateral anti-inflammatory effects of macrolide antibiotics, independent of their antibacterial effects, will certainly cloud the issue of causality.

Several large clinical trials of anti-Chlamydia antibiotic therapy in various subsets of patients with coronary artery disease are currently underway. The Weekly Intervention with Zithromax for Atherosclerosis and Related Disorders (WIZARD) trial, which involves 3500 patients with chronic coronary artery disease who are seropositive for C pneumoniae, has completed its enrollment. The 1400-patient Azithromycin in Acute Coronary Syndromes (AZACS) trial in patients with acute ischemic syndromes (regardless of positive or negative C pneumoniae serology) being conducted at Cedars Sinai Medical Center is near completion. The Azithromycin and Coronary Events Study (ACES), which is sponsored by the National Institutes of Health and plans to recruit 4000 patients with chronic coronary artery disease, is underway. Finally, the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, which plans to recruit 4200 patients, is in the final planning stages.

Even if a causal link were to be eventually demonstrated in terms of HSV-1 and atherothrombosis, any effective preventive and therapeutic strategies remain to be developed and tested, although immunization was shown to be protective in animals. Because nonsmokers seemed not to face an increased risk, despite evidence of HSV-1 infection, another way to eliminate HSV-1–related atherogenic risk, if one is eventually proven, may be to discourage smoking. Clearly, further investigation is required to establish a firm causal link between infection and atherothrombosis and the precise identity of the pathogen(s) involved. Time will tell whether the relevant pathogen(s) will include viruses, bacteria, both, or neither. Meanwhile, we all need to do a better job of educating our patients, colleagues, and other healthcare providers to adopt primary and secondary preventive measures that have already been proven to be beneficial.

References
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