Role for Chronic Infections in Atherosclerosis?

To the Editor:

The study by Espinola-Klein et al1 showed a significant association between infectious burden (C pneumoniae, H pylori, cytomegalovirus, herpes simplex virus 2) and the extent of atherosclerosis; moreover, the risk for future death was increased by the number of infectious pathogens, especially in patients with advanced atherosclerosis. The specific IgG or IgA antibodies used in the study, however, do not necessarily distinguish between persistence of infections and only a previous contact. Other more sensitive markers of actual infections are available: specific IgG-containing immune complexes for C pneumoniae2; the 13C-urea breath test for H pylori3; specific polymerase chain reaction for cytomegalovirus and herpes simplex virus 2 infections.4

Because of these limitations, the present data do not really indicate that these infectious agents per se play a direct role in atherosclerosis. On the other hand, the high prevalence of a seropositivity to multiple infectious agents in atherosclerotic patients may rather suggest a “bystander activation” of the immune system.5 Autoreactive T cells may exist in these subjects, representing a potential reservoir of pathogenic effectors that, when stimulated by microbial adjuvants, could trigger an autoimmune phenomenon. The induction of cross-reactivity does not require a replicating agent, and immune-mediated injury can occur after the immunogen has been removed. In our opinion, this mechanism could better explain the significant association found among seropositivity to multiple different infectious agents, extension of atherosclerosis, and long-term prognosis of atherosclerotic patients.

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Response

We thank Gabrielli et al for their interest in and valuable comments about our article in Circulation. We agree that not all antibodies used in our trial necessarily indicate persistent infections. However, this was not our intention. We measured IgG and/or IgA antibodies to 8 pathogens (Chlamydia pneumoniae, Helicobacter pylori, Haemophilus influenzae, Mycoplasma pneumoniae, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus type 1 and 2) to evaluate the total pathogen burden of each individual.1,2 According to the hypotheses of Zhu and Epstein,3,4 it is unlikely that one single pathogen is involved in the pathogenesis of atherosclerosis. This is supported by our findings, showing a significant relation between the number of infectious pathogens to which an individual has been exposed and the extent of atherosclerosis.1

Gabrielli et al point out in their letter that autoreactive T cells may represent a potential reservoir of pathogenic effectors. Indeed, infection by multiple pathogens, contributing to pathogen burden, may trigger an immune response with pathogen-targeted antibodies and/or T cells, and these mechanisms may be involved in the pathogenesis and progression of atherosclerosis.5

Furthermore, we agree that these immune-mediated mechanisms may occur after the pathogen has been removed. This theory confirms the results of our study—namely, that infectious burden does play a role in the pathogenesis of atherosclerosis and that various immune mechanisms are involved in these processes.

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