Infection, Endothelial Dysfunction, and Atherogenesis

To the Editor:

Khairy et al reported a lack of association between chronic infection and endothelial function in healthy young men. The study population was highly selective and, therefore, excluded women, individuals aged ≥45 years, and subjects with any conventional risk factors of coronary artery disease (CAD). The authors assumed that serum antibodies against the various infectious agents investigated represented evidence of chronic infection.

The results of Khairy et al are indirectly supported by findings of other authors, who reported that seropositivity to infectious agents was not associated with increased atherothrombotic risk. However, they contrast with data by Prasad et al, who found a significant correlation between total infectious burden to five infectious agents and decreased intracoronary endothelial function. Khairy et al suggest that the discrepancies between studies are due to different patient populations, different infectious agents, and different methods of assessing outcome. Moreover, they point out that interactive effects between conventional risk factors and infectious agents could have played a role in the Prasad et al study. The findings of Khairy et al contrast also with the results of a recent study by Parchure et al, which showed that antibiotic treatment with azithromycin had a favorable effect on endothelial function in patients with CAD and seropositivity to Chlamydia pneumoniae. This randomized, prospective, double-blind, placebo-controlled trial showed that endothelial function was significantly improved by azithromycin treatment compared with placebo. Unfortunately, Khairy et al omitted any mention of this article, probably because the patients had CAD.

Khairy et al selected a “pure study population,” in which factors potentially able to affect endothelial function were absent. This stringent selection represents one of the major limitations of the study. Conceivably, this population constitutes a group in which protective factors, genetic or otherwise, operate, making these subjects less susceptible to developing vascular disease. Individuals in this study are unlikely to be a sample representative of the general population. Therefore, extrapolation of these results to other individuals may not be straightforward.

Also of concern is that seroprevalence was taken as evidence for chronic infection. IgG antibodies do not necessarily indicate duration or activity of infection. Although I concur that infectious agents may not be entirely responsible for initial endothelial injury, I do not believe that the Khairy et al results categorically indicate that chronic, low-grade infection is unlikely to be responsible for the initiation of CAD. A more appropriate conclusion should perhaps be that in selected healthy individuals without CAD risk factors, seropositivity is not associated with systemic endothelial dysfunction. The suggestion that infectious agents are not implicated as early etiologic triggers of CAD is purely speculative.

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Response

We thank Dr Kaski for his interest in our manuscript. Issues regarding the nature of the study population, chronicity of infection, and potential interactive effects between conventional risk factors and infectious agents were fully recognized, addressed, and elaborated on in the Discussion section of our report.

Dr Kaski’s perception that a “pure study population” represents a “major limitation” contrasts with basic epidemiologic principles regarding study designs for potential etiologic factors. In fact, it is far more important to restrict admissibility to individuals comparable with respect to other risk factors for the outcome under investigation than to attempt to select subjects representative of an entire population, to allow the greatest degree of generalizability. We summarized these thoughts as follows: “At the expense of generalizability, a relatively homogeneous population was deliberately selected to increase precision regarding inference about disease etiology and offer some protection against unmeasured variables that may contribute to variability in endothelial function but are less likely associated with seropositivity status” (p 1970). In further support of this design, numerous studies have demonstrated that all traditional and many nontraditional risk factors for coronary artery disease (CAD) are individually associated with impaired endothelial function. The concept that endothelial dysfunction is an early initiating event is supported by the demonstration that children and young subjects with risk factors for CAD have measurable endothelial dysfunction.

We recognize the important contribution of the study by Parchure et al. However, our findings neither support nor refute their results, as the studies address two entirely different questions in mutually exclusive patient populations. Whereas one study attempts to isolate a potential trigger for endothelial dysfunction in otherwise healthy individuals, the other explores potential therapy in patients with established CAD and chronic angina. We agree with the authors’ Discussion that their study “cannot provide clear evidence as to whether the beneficial effects of azithromycin therapy on endothelial function are due to the anti-chlamydial action of the drug, its anti-inflammatory properties, a direct effect on endothelium, or a combination of all three” (p 1302).

Accounting for limitations previously discussed, we believe our results suggest that a chronic low-grade infection with these agents is not likely to be responsible for initiating CAD, but they do not preclude a role in later stages of the pathophysiologic process such as acceleration of atherosclerosis or plaque rupture.

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Circulation. 2003;108:e171-e172
doi: 10.1161/01.CIR.0000108169.26553.D7
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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/108/25/e171

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