Homocysteine and Arteriosclerosis:
Subclinical and Clinical Disease Associations

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In 1969, the clinical observations of McCully1 first linked marked hyperhomocysteinemia (ie, equivalent to total homocysteine [tHcy] levels of 100 to 450 μmol/L by current assays) to precocious arteriosclerotic disease in autopsied children who died from distinct metabolic forms of homocystinuria. Intermittent reports of severe thrombotic outcomes specifically involving the extracranial carotid arteries in homocystinuric patients have been reported dating back at least 20 years.2–4 Excepting 2 small but notable studies,5,6 overall a rather consistent body of published data has emerged linking plasma tHcy levels to extracranial carotid artery wall thickening in young adults homozygous7 or heterozygous8 for cystathionine synthase deficiency, among young heterozygotes for familial hypercholesterolemia,9 and in general population samples of middle-aged, asymptomatic individuals free of clinical cardiovascular disease (CVD).10–13 In addition, tHcy levels have also been associated with more advanced extracranial carotid artery arteriosclerosis (ie, percentage of luminal stenosis) in elderly subjects14–17 and those with prevalent cerebrovascular disease.18

Thirty years after McCully’s initial report,1 a burgeoning amount of clinical evidence has accumulated that indicates that mild to moderate fasting, nonfasting, or post–methionine loading (PML) hyperhomocysteinemia (ie, tHcy levels ≥12 to ≤100 μmol/L fasting or nonfasting or ≥50 to ≤140 μmol/L 6 hours PML) is an independent risk factor for hard, arteriosclerotic outcomes. A recent series of pooled observational studies examining the relationship between homocysteine and CVD19–21 has been updated through the end of 1998 (Dr S.A.A. Beresford, personal communication). These meta-analyses indicated that the best estimate for the increased risk of arteriosclerotic coronary heart disease morbidity and mortality comparing fasting and nonfasting tHcy levels of ≥15 to ≤10 μmol/L, after adjustment for established CVD risk factors, was 1.4. This estimate is unaffected when only prospective studies are analyzed (7 studies, ≈1400 incident events), including the recently reported Atherosclerosis Risk in Communities22 and British United Provident Association23 cohort studies. More recent prospective data not included in these meta-analyses from the Scottish Heart Health Study24 and US Nurses Health Study25 indicate that tHcy levels were independently predictive of incident coronary heart disease in Scottish women and men, as well as of incident total CVD among middle-aged US women. Three additional prospective studies also not included in these meta-analyses examined the potential association between tHcy levels and CVD mortality. The first 2 of these reports found strong, independent links between tHcy levels and subsequent CVD death in patients with angiographically confirmed coronary artery disease26 or symptomatic peripheral vascular disease,27 whereas the third study found a more modest but significant independent association between tHcy levels and CVD mortality in the elderly population–based Framingham cohort.28 Furthermore, a large, multicenter, European case-control study has confirmed that PML hyperhomocysteinemia confers a risk for prevalent CVD equal in magnitude to and independent of fasting hyperhomocysteinemia.29 Initial prospective follow-up (≈4.5 years) of this cohort with prevalent CVD has revealed that postload hyperhomocysteinemia may independently predict subsequent CVD death.30 Finally, 3 prospective studies31–33 conducted among persons with end-stage renal disease have yielded concordant findings indicating a significant independent association between baseline tHcy levels and subsequent CVD occurrence in this high-CVD-risk population.

In light of all these data, one could reasonably infer that homocysteine appears to be an independent risk factor for arteriosclerosis across the continuum from subclinical to clinical disease. However, it has been proposed that clinical or even subclinical arteriosclerosis itself somehow raises tHcy levels, resulting in a spurious association between mild hyperhomocysteinemia and clinical CVD due to reverse causality.22,34,35 Devoid of any plausible biological mechanism, this reverse causality hypothesis is not supported by the pooled epidemiological evidence from all published observational studies reviewed above (as opposed to the highly selective citation methods exercised in the studies reported in References 22, 34, and 35) and the following reported findings from additional human and animal studies:

1. Despite the absence of any traditional CVD risk factors, 50% of untreated children and young adults with homocystinuria due to cystathionine synthase deficiency experience a major atherothrombotic event by the age of 30 years.36

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Furthermore, strategies designed solely to reduce tHcy levels in these patients have been shown to decrease atherothrombotic event rates.\textsuperscript{36,37} 

2. In adults (n=38; mean age, 58±12 years) with mild hyperhomocysteinemia, tHcy-lowering treatment may have reduced the rate of progression of ultrasound-determined extracranial carotid artery plaque area.\textsuperscript{38} 

3. Young, healthy subjects free of clinical arteriosclerosis or CVD risk factors who have normal baseline flow-mediated brachial arterial reactivity experience a dramatic “dose-response” reduction in their flow-mediated brachial artery reactivity after acute hyperhomocysteinemia produced by an oral 1-methionine load.\textsuperscript{39} 

4. Randomized, controlled studies have revealed that mild, dietary-induced hyperhomocysteinemia resulted in abnormal vascular reactivity among nonhuman primates,\textsuperscript{40} as well as increased arterial stiffness and frank atherothrombotic sequelae in minipigs.\textsuperscript{41} 

Although we do not believe the reverse causality hypothesis is tenable, we certainly agree that simultaneous pursuit of 2 related areas of investigation will be required to confirm a causal relationship between hyperhomocysteinemia and CVD: (1) randomized, placebo-controlled trials of the effect of tHcy lowering on recurrent (and perhaps, de novo) CVD outcomes and (2) elucidation of the basic biological mechanism linking hyperhomocysteinemia to arteriosclerosis. As described in detail elsewhere, well-designed tHcy-lowering trials for secondary CVD outcome prevention are currently under way\textsuperscript{42} in Europe as well as the United States. The data of McQuillan et al\textsuperscript{13} in this issue of Circulation suggest the potential use of changes in extracranial carotid artery intimal-medial thickness score as a surrogate end point to gauge the efficacy of tHcy-lowering treatment in clinical trials conducted among individuals free of symptomatic cerebrovascular disease. Analogous studies of lipid lowering that used this noninvasive surrogate end point have added to our understanding of the role of dyslipidemia in the progression of asymptomatic carotid arteriosclerosis.\textsuperscript{43} Currently, however, in the absence of any data from randomized, controlled trials demonstrating a reduction in CVD outcomes or the progression of subclinical carotid arteriosclerosis with successful treatment of mild hyperhomocysteinemia, we do not believe screening and treatment recommendations for mild hyperhomocysteinemia can or should be provided. This suggestion is concordant with the recently published American Heart Association position paper on homocysteine,\textsuperscript{44} which emphasized that screening and treatment recommendations for hyperhomocysteinemia in the general population were premature and must await the results of clinical trials of tHcy lowering for secondary or primary CVD outcome prevention.

Acknowledgments

Support for this work was provided in part by the National Heart, Lung, and Blood Institute (grant No. ROI-HL-56908-01A1) and the US Department of Agriculture, Agricultural Research Service contract 53-3K06-01.

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KEY WORDS: Editorials | atherosclerosis | homocysteine | risk factors