Hyperhomocyst(e)inemia
A Common and Easily Reversible Risk Factor for Occlusive Atherosclerosis

M.R. Malinow, MD

Homocysteine (HCY) is a thiol-containing amino acid that results from the demethylation of methionine. HCY is readily oxidized in body fluids to the disulfides homocystine (HCY-HCY) and HCY-cysteine (CYS) mixed disulfide (MDS) (see Figure 1). Free and protein-bound forms in plasma are collectively designated homocyst(e)ine [H(e)], and their total concentration is expressed as HCY in nanomoles per milliliter (i.e., micromoles per liter).

The normal concentration of H(e) in plasma is ~10 nmol/ml, but it may attain levels of 200 nmol/ml in homocystinuria. This rare genetic condition is usually associated with serious thromboembolic complications at an early age; thrombosis of extracranial and intracranial arteries, veins, and sinuses as well as coronary occlusion are common fatal occurrences. In young homocystinuric patients, occlusion of peripheral arteries often results in renovascular hypertension, intermittent claudication, or mesenteric ischemia, and peripheral venous thrombosis may be followed by pulmonary embolism. Premature atherosclerotic lesions in most large and medium-sized arteries are common in these patients (i.e., thickened intima resulting in narrowing of the vascular lumen with microscopic intimal fibrosis and often disruption, fragmentation, and thickening of elastic fibers). Patients may also exhibit mental retardation as well as other abnormalities resembling the unrelated Marfan’s syndrome (i.e., ectopia lentis and skeletal deformities). Several abnormalities in single enzymes controlling the metabolism of HCY have been described in homocystinuric subjects, mainly impairment of cystathionine β-synthase—which regulates an early step in the transsulfuration of HCY to CYS—and of 5,10-methylenetetrahydrofolate reductase, which provides substrate for the B12-dependent remethylation of HCY to methionine.

Many investigators have demonstrated that HCY levels may be elevated in adult patients with occlusive atherosclerosis lacking other characteristics of homocystinuric patients, and it has been suggested that heterozygosity for cystathionine β-synthase may be implicated. However, it is not known how hyperhomocyst(e)inemia affects atherogenesis and thrombosis. High concentrations of HCY in vitro damage cultured endothelial cells, perhaps through hydrogen peroxide generated by the oxidation of HCY to the disulfides. But it is difficult to extrapolate from the concentrations necessary to obtain cytotoxic effects in vitro to the H(e) levels present in atherosclerotic patients.

Table 1 summarizes results in 11 series with more than 2,000 patients almost equally divided into cases and controls; results have been reported as MDS, free HCY, HCY-HCY, or H(e). Methionine load was used to elicit the abnormality in four series, whereas basal levels of H(e) were measured in the remaining observations. Because of the recent development of an automated method to measure basal levels of H(e), approximately one half of the subjects were studied in our laboratory. Values of the sulfur-containing amino acids were higher in patients with cerebrovascular or peripheral arterial diseases than in controls; the same was true in patients with coronary artery disease, with a single exception in a series involving only a small number of patients. Because of the simultaneous occurrence of peripheral and coronary artery diseases, the former was excluded in one series; however, elevated levels of H(e) were still observed in the coronary patients. Defining normality as the 95th percentile distribution of controls, cases frequently exhibited abnormal H(e) values in the 20–40 nmol/ml range. The prevalence of abnormally high levels of the sulfur-containing amino acids in atherosclerotic patients was between 20% and 30%; therefore, a great overlap between cases and controls is not unexpected because 70–80% of patients had “normal” levels.

Homocyst(e)inemia showed no significant correlation with other factors associated with atherosclerosis, including plasma levels of cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, cigarette smoking, hypertension,
and diabetes (see Table 1); in one series, though, hypertensive patients had slightly higher H(e) levels than normotensive controls. Moreover, H(e) correlated significantly with age in women; this might be related to increased HCY levels observed after the menopause. In several series, homocyst(e)inemia correlated positively with serum uric acid and creatinine levels, perhaps indicating some kidney impairment because H(e) levels are increased in renal failure.

There are probably multiple mechanisms involved in the pathogenesis of hyperhomocyst(e)inemia; they include heterozygosity for metabolic defects involved in the enzymatic control of HCY metabolism as well as conditions resulting in low levels of involved cofactors (i.e., folate, vitamin B-12, and vitamin B-6). These cofactors may have a large role in the pathogenesis of hyperhomocyst(e)inemia in view of the high prevalence of probably suboptimal intakes of folate and pyridoxine in selected U.S. subpopulations. In addition, hyperhomocyst(e)inemia may be observed during bile acid sequestrant plus niacin therapy, which may impair folate absorption, and other instances may be secondary to abnormal kidney function or to other mechanisms not yet characterized.

Treatment of elevated levels of H(e) is simple and innocuous. High doses of pyridoxine were first used with success in homocystinuric children; in most adult patients, small doses of folate (1–5 mg/day) are usually effective in rapidly reducing elevated levels of plasma H(e). Additional therapy of an equally innocuous character like small doses of pyridoxine, choline, betaine, or cyanocobalamin generally normalizes hyperhomocyst(e)inemic levels in folate-resistant patients.

In conclusion, multiple studies have demonstrated the occurrence of elevated levels of H(e) in patients with coronary, cerebrovascular, or peripheral arterial diseases; such an association is frequent and independent of most other risk factors for atherosclerosis.

### Table 1. Survey of Studies on Homocysteine and Atherosclerotic Disease

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Cases (n)</th>
<th>Controls (n)</th>
<th>Results</th>
<th>Correlation with other factors</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>After methionine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 22</td>
<td>MDS: CAD&gt;controls</td>
<td>a, j</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 17</td>
<td>MDS: CVD&gt;controls</td>
<td>a, j</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 25</td>
<td>Free HCYS: CVD&gt;controls</td>
<td>a, j</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 (25)</td>
<td>Free HCYS: PAD&gt;controls</td>
<td>a, j</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 (25)</td>
<td>Free HCYS: CAD&gt;controls</td>
<td>a, j</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>99 39</td>
<td>HCYS-HCYS: CAD&gt;controls</td>
<td>a, b, c, d, e</td>
<td>10</td>
<td></td>
<td></td>
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<tr>
<td>Basal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>347 202</td>
<td>H(e): CAD&gt;controls</td>
<td>b, m</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 36</td>
<td>H(e): CAD&gt;controls</td>
<td>a, b, d, f</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47 103</td>
<td>H(e): PAD&gt;controls</td>
<td>a, c, d</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>99 (31*)</td>
<td>H(e): CVD&gt;controls</td>
<td>a, b, c, n</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>99 259</td>
<td>H(e): CAD&gt;controls</td>
<td>a, b, c</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>170 255</td>
<td>H(e): CAD&gt;controls</td>
<td>b, c, d, e, f, g, h, l,</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 45†</td>
<td>H(e): CVD‡&gt;controls</td>
<td>a, d, e, f, k, l</td>
<td>b</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>20 (45†)</td>
<td>H(e): CVD§&gt;controls</td>
<td>a, e, f, k, l</td>
<td>d, b</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1,066</td>
<td>1,003</td>
<td></td>
<td></td>
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</tbody>
</table>

CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease; HCYS, homocysteine; HCYS-HCYS, homocysteine; MDS, HCYS-cysteine mixed disulfide; H(e), free and bound HCYS, HCYS-HCYS, and MDS.  

<table>
<thead>
<tr>
<th>Symbols</th>
<th>Meanings</th>
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<tr>
<td>a</td>
<td>cigarette smoking; b, hypertension; c, diabetes; d, total blood cholesterol; e, age; f, blood triglycerides; g, low density lipoprotein cholesterol; h, high density lipoprotein cholesterol; i, β-blocker medication; j, oral contraceptives; k, serum uric acid; l, serum creatinine; m, body weight; n, alcohol consumption.</td>
</tr>
<tr>
<td>*</td>
<td>Also reported in Reference 13.</td>
</tr>
<tr>
<td>†</td>
<td>Normotensive controls.</td>
</tr>
<tr>
<td>‡</td>
<td>Cerebral infarction.</td>
</tr>
<tr>
<td>§</td>
<td>Cerebral bleeding.</td>
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</table>
Further research is needed to better define involved mechanisms in the etiology and treatment of hyperhomocyst(e)inemia as well as in the pathogenesis of arteriosclerosis and thrombosis associated with high levels of H(e). Until more information is available, though, it might be desirable to screen atherosclerotic patients for this common abnormality; however, cost/benefit ratios and definition of populations to be targeted still need to be established. It is possible to rapidly normalize high H(e) levels using innocuous and inexpensive therapy; patients with undiagnosed pernicious anemia may require a different approach. Whether normalization of hyperhomocyst(e)inemia will result in changes in morbidity and mortality must be determined. Despite our lack of knowledge regarding the ultimate effects of treatment, it seems prudent to suggest that patients with hyperhomocyst(e)inemia be offered appropriate treatment on an individual basis, as occurs with other risk factors for atherosclerosis. Answers to many of the remaining questions in regard to H(e) must await the outcome of prospective epidemiologic observations and clinical trials; I hope these studies will be forthcoming soon.

References

28. Blankenhorn DH, Malinow MR (unpublished observations)
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