Prevalence of Familial Hyperhomocyst(e)inemia in Men With Premature Coronary Artery Disease

Jacques J. Genest Jr., Judith R. McNamara, Barbara Upson, Deeb N. Salem, Jose M. Ordovas, Ernst J. Schaefer, and M. Rene Malinow

Elevated plasma levels of homocyst(e)ine have been reported to be more prevalent in patients with coronary artery disease (CAD) than in controls. The purpose of this study was to determine whether this elevation was genetic. We determined homocyst(e)ine levels in 176 men with premature CAD (>50% stenosis of a major epicardial coronary artery occurring before the age of 60 years) and in 255 controls free of cardiovascular disease. Homocyst(e)ine levels were higher in the CAD group compared with controls (13.9 ± 6.7 versus 10.9 ± 4.9 nmol/ml, p < 0.001); in addition, 28% of CAD patients had homocyst(e)ine levels above the 90th percentile of controls. Statistical analysis revealed that homocyst(e)ine levels were not related to the presence of hypertension or diabetes, smoking, or plasma levels of lipoprotein cholesterol and apolipoproteins A-I and B. The families of 71 CAD patients were sampled (selected on the basis of availability of relatives) and included 60 spouses and 239 first-degree relatives; 370 subjects were thus sampled. Spearman correlations between probands and spouses (r = 0.264, p = 0.041) and between mean values for parent and offspring (r = 0.356, p = 0.002) for homocyst(e)ine levels indicated that homocyst(e)ine levels are in part genetically determined. In 20 families (28.2%), the proband had homocyst(e)ine levels greater than the 90th percentile; familial segregation was observed in 10 of these kindreds. Therefore, 14% of CAD patients had familial hyperhomocyst(e)inemia. In conclusion, our data suggest that plasma homocyst(e)ine is a risk factor for the development of CAD, independent of other cardiovascular risk factors, and that this elevation is in part genetically determined. (Arteriosclerosis and Thrombosis 1991;11:1129–1136)

Hyperhomocyst(e)inemia (elevated plasma levels of homocyst(e)ine) has been associated with the development of peripheral vascular disease, cerebrovascular disease, and more recently with premature coronary artery disease (CAD).1–10 Extreme elevations of homocyst(e)ine are seen in cases with inborn errors of metabolism that affect transsulfuration reactions. Homocystinuria is a rare disorder associated with ocular (ectopia lentis and myopia), skeletal (osteoporosis), central nervous system (mental retardation and psychiatric disturbances), and vascular (thrombosis) abnormalities.11 Homocystinuria may be caused by an abnormal transsulfuration reaction, a deficiency of cystathionine β-synthase,10 or an impaired activity of 5-methyltetrahydrofolate–homocysteine methyltransferase; the latter may be due to a vitamin B12 deficiency, a failure of the conversion of cobalamin to methylcobalamin,12,13 or abnormal activity of 5,10-methylenetetrahydrofolate reductase.14 The heterozygous state for cystathionine β-synthase deficiency has been seen more frequently in men with cerebrovascular or peripheral vascular disease than in those with CAD.4

The vascular events in homocystinuria include venous thrombosis with pulmonary embolism, stroke, and myocardial infarction. Although vascular complications are often the cause of death in patients with homocystinuria, survival into adulthood is often seen, especially in those patients who respond to vitamin B12 therapy.15

Milder elevations of homocyst(e)ine may occur in the absence of the clinical manifestations of homo-
cystinuria. The etiology of mild homocyst(e)ine elevation is for the most part unknown. Deficiencies of vitamin B₁₂, vitamin B₉, or folate may underlie some cases of elevated homocyst(e)ine levels, and the heterozygous state of cystathionine β-synthase deficiency may also be found. Other causes of elevated plasma homocyst(e)ine levels include medications (methotrexate and antiepileptics), kidney or liver failure, and the postmenopausal state. It is unclear whether moderate hyperhomocyst(e)inemia is in part due to genetic factors or is an acquired disorder. We and others have previously shown that moderately elevated levels of homocyst(e)ine (>90th percentile of an age- and gender-matched control group) are more frequent in patients with premature CAD than in controls. Furthermore, homocyst(e)ine levels have been shown to be independent of lipid and lipoprotein cholesterol levels.

In this study, we extended our original findings and studied the families of patients with premature CAD to determine whether the hyperhomocyst(e)inemia was familial. We also performed discriminant analysis between CAD patients and controls with regard to conventional cardiovascular risk factors and plasma lipid, lipoprotein cholesterol, apolipoprotein, and homocyst(e)ine levels. We provide new information about elevated homocyst(e)ine as an independent risk factor for CAD and its underlying familial nature.

Methods

Patients

Patients (n=176) were selected from those undergoing coronary angiography at the New England Medical Center Hospital, Boston, Mass., for the diagnosis and determination of the extent of CAD. The referral base of the cardiac catheterization laboratory included the greater Boston area and northeastern Massachusetts. CAD was defined as a 50% or greater cross-sectional stenosis of at least one of the main epicardial coronary arteries on multiple projections (75% lumen reduction). Angiograms were reviewed by three cardiologists, two of whom were unaware of the patients' inclusion in the study; the latter scored the angiogram for diagnostic purposes. All patients were men who were less than 60 years of age at the time of their cardiac catheterization. Patients with a history of myocardial infarction, major surgery, or trauma in the 6 weeks preceding their catheterization were excluded from the study, as were those with minimal CAD (<50% stenosis) or with angiographically normal coronary arteries. Information on cardiovascular risk factors (smoking, hypertension, and diabetes) as well as medication use (especially β-adrenergic-blocking agents and diuretics) was obtained for all patients. None of the patients had renal failure requiring dialysis. Information on vitamin B₉, folate, and vitamin B₉ intake was not obtained for either patients or controls, nor was an estimate made of ethanol consumption. All patients gave written consent; the protocol for patient sampling and family studies was approved by the Human Investigation Review Board of the New England Medical Center Hospital.

Family Studies

From the group of 176 probands, families were sampled for 71 of them (40%). An attempt was made to contact all those patients with a nuclear family and to sample all first-degree relatives. In addition to the probands, there were 60 genetically unrelated spouses and 239 first-degree relatives. On average, there were 3.37 first-degree relatives per proband. A total of 370 subjects were thus examined. Parental consent for those under 18 years of age was obtained. We defined an affected family if 1) the proband had a homocyst(e)ine level greater than the 90th percentile and 2) at least one first-degree relative was so affected.

Controls

The control group consisted of 255 men from cycle 3 of the Framingham Offspring Study. These control subjects were selected as being free of clinical or electrocardiographic manifestations of CAD and were free of peripheral vascular or cerebrovascular disease. None of the control subjects were taking β-blockers by design. Based on this control group of middle-aged men, the 90th percentile for homocyst(e)ine was determined to be 15.02 nmol/ml and the 95th percentile to be 19.03 nmol/ml.

Lipid, Lipoprotein Cholesterol, and Apolipoprotein Determinations

Blood was collected in tubes containing EDTA to a final concentration of 1.2 mg/ml after an overnight (1–14-hour) fast. Plasma was isolated by centrifugation (3,000 rpm, 4°C, 20 minutes); multiple aliquots were stored at −80°C until measurement of apolipoproteins and homocyst(e)ine was performed. Total cholesterol and triglyceride levels were measured enzymatically, with high density lipoprotein (HDL) cholesterol similarly determined after dextran-Mg²⁺ precipitation. Low density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula. In cases where the triglyceride level was greater than 400 mg/dl, LDL cholesterol was determined after plasma ultracentrifugation at d=1.006 g/ml. Apolipoproteins (apo) A-I and B were determined by enzyme-linked immunosorbent assays. We have previously shown that inhospital sampling is associated with lower HDL cholesterol and apo A-I levels compared with sampling in the free-living state. We have therefore corrected HDL cholesterol and apo A-I values for those patients who were sampled in the hospital.

Homocyst(e)ine Measurement

Plasma levels of homocyst(e)ine, that is, free and bound homocystine, homocysteine, and cysteine—homocysteine mixed disulfide, were performed on plasma aliquots after storage at −80°C. Samples were coded and sent packed in dry ice to the Oregon.
TABLE 1. Lipid, Lipoprotein Cholesterol, Apolipoproteins A-I and B, and Homocyst(e)ine Levels in Cases Versus Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>CAD patients</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>71</td>
<td>All</td>
<td>255*</td>
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<tr>
<td>Chol (mg/dl)</td>
<td>50±7</td>
<td>50±7</td>
<td>49±6</td>
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<tr>
<td>TG (mg/dl)</td>
<td>196±33</td>
<td>208±52</td>
<td>212±36</td>
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<tr>
<td>LDL (mg/dl)</td>
<td>175±89</td>
<td>190±103</td>
<td>136±106</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>137±34</td>
<td>139±51</td>
<td>141±34</td>
</tr>
<tr>
<td>Apo B (mg/dl)</td>
<td>35±10</td>
<td>35±10</td>
<td>46±13</td>
</tr>
<tr>
<td>Apo A-I (mg/dl)</td>
<td>104±25</td>
<td>105±24</td>
<td>137±34</td>
</tr>
<tr>
<td>H(e) (nmol/ml)</td>
<td>13.7±6.1</td>
<td>13.9±6.7</td>
<td>10.9±4.9</td>
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</table>

Values are mean±SD. Probability differences are between all CAD cases and controls.

CAD, coronary artery disease; Chol, cholesterol; TG, triglycerides; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; Apo, apolipoprotein; H(e), homocyst(e)ine.

*See Reference 10.

Statistical Analysis

Data were stored on a VAX/VMS 11/785 computer (Digital Equipment Corp., Maynard, Mass.) by use of the database RS/1 (BBN Software, Cambridge, Mass.) and were analyzed with the SAS statistical package (Statistical Analysis System, Cary, N.C.). Comparisons of means were performed by t test; triglyceride and homocyst(e)ine levels were logarithmically transformed (base 10) to approximate a normal distribution. Mann-Whitney U tests were also performed on variables that did not have a normal distribution. Spearman's correlation coefficients between homocyst(e)ine and plasma lipid, lipoprotein cholesterol, and apolipoprotein levels were determined. Proband-spouse, proband-mean level of offspring, spouse-mean level of offspring, and mean level of parent-mean level of offspring correlations for homocyst(e)ine were performed by Spearman's rank correlations. Stepwise discriminant analysis was performed with a forward/backward procedure and sequential addition of hypertension, smoking, diabetes, plasma lipid, LDL and HDL cholesterol, and homocyst(e)ine into the statistical model. A second model was analyzed in which risk factors, apo A-I and B (in lieu of HDL and LDL cholesterol, respectively), and homocyst(e)ine were entered. Homocyst(e)ine was entered last in each model.

Results

Mean values for cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, apo B, and apo A-I for the 176 subjects compared with control subjects are shown in Table 1. These parameters were determined in the 71 patients for whom family members were available and were found to be not significantly different from the entire patient group. Cases had significantly higher triglyceride (190±33 versus 127±33 mg/dl, p<0.001), apo B (127±33 versus 105±24 mg/dl, p<0.001), and homocyst(e)ine (13.9±6.7 versus 10.9±4.9 nmol/ml, p<0.001) levels and significantly lower HDL cholesterol (35±10 versus 46±13 mg/dl, p<0.001). Mean levels of parent-mean level of offspring were significantly different from the entire parent group.

*Low density lipoprotein cholesterol triglyceride levels did not enter the model at p<0.1.

†Diabetes did not enter the model at p<0.1.

**Spearman's rank correlations.

TABLE 2. Stepwise Discriminant Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Partial r²</th>
<th>Model r²</th>
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<th>p</th>
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<td></td>
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<tr>
<td>Smoking</td>
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<td>0.294</td>
<td>198.56</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>0.135</td>
<td>0.429</td>
<td>100.20</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.078</td>
<td>0.507</td>
<td>67.51</td>
<td>0.001</td>
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<tr>
<td>Homocyst(e)ine</td>
<td>0.009</td>
<td>0.517</td>
<td>8.53</td>
<td>0.004</td>
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<tr>
<td>Diabetes</td>
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<td>0.521</td>
<td>6.16</td>
<td>0.051</td>
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<td>Risk factors and apolipoproteins†</td>
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<tr>
<td>Smoking</td>
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<td>0.295</td>
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<td>0.001</td>
</tr>
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<td>0.001</td>
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<tr>
<td>Hypertension</td>
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<td>0.504</td>
<td>70.55</td>
<td>0.001</td>
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<tr>
<td>Homocyst(e)ine</td>
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<td>0.517</td>
<td>10.72</td>
<td>0.002</td>
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<tr>
<td>Apo B</td>
<td>0.011</td>
<td>0.528</td>
<td>9.88</td>
<td>0.002</td>
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</table>

HDL, high density lipoprotein cholesterol; Apo, apolipoprotein.

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<th>Model r²</th>
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HDL, high density lipoprotein cholesterol; Apo, apolipoprotein.

*Low density lipoprotein cholesterol triglyceride levels did not enter the model at p<0.1.

†Diabetes did not enter the model at p<0.1.

TABLE 3. Parent-Offspring Correlations* for Homocyst(e)ine

<table>
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<th>Groups compared pairwise</th>
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<tr>
<td>Mean level of parent-mean level of offspring</td>
<td>0.356</td>
<td>0.002</td>
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<tr>
<td>Proband-spouse‡</td>
<td>0.264</td>
<td>0.041</td>
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<td>Proband-mean level of offspring</td>
<td>0.248</td>
<td>0.037</td>
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<tr>
<td>Spouse-mean level of offspring</td>
<td>0.224</td>
<td>0.084</td>
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</table>

*Spearman's rank correlations.

†n=71; ‡n=60.
FIGURE 1. Pedigrees of families with familial hyperhomocyst(e)inemia. Homocyst(e)ine (H[e]) levels are indicated in nmol/ml within the symbols. The proband is indicated by an arrow. Circles denote females, and squares denote males. $\varpi$, $\varphi$, Deceased. Family members who participated in the study are denoted by heavy-lined symbols.
sus 46±13 mg/dl, p<0.001) and apo A-I (105±24 versus 137±34 mg/dl, p<0.001) levels than did controls. No significant differences were observed for total (208±52 mg/dl versus 212±36 mg/dl, p=NS) or LDL (139±51 versus 141±34 mg/dl, p=NS) cholesterol levels in cases versus controls. No significant differences in homocyst(e)ine levels were noted in CAD patients who were or were not taking β-blockers. Twenty-eight percent of patients had homocyst(e)ine levels greater than the 90th percentile and 9% had such levels above the 95th percentile of controls.

**Discriminant Analysis**

Spearman’s rank correlation coefficients between homocyst(e)ine and cholesterol (r=0.032, p=NS), triglycerides (r=−0.096, p=NS), LDL cholesterol (r=0.034, p=NS), HDL cholesterol (r=0.009, p=NS), apo B (r=−0.012, p=NS), and apo A-I (r=0.099, p=NS) indicate that plasma cholesterol, triglyceride, LDL and HDL cholesterol, and apo A-I and B levels do not predict homocyst(e)ine levels. Stepwise discriminant analysis was performed on cases versus controls by inserting smoking, hypertension, diabetes, LDL and HDL cholesterol, triglycerides, and homocyst(e)ine levels in the first statistical model and including apo A-I and B in a second model by use of a forward/backward procedure (Table 2). Smoking, HDL cholesterol, hypertension, homocyst(e)ine, and diabetes, in descending order, were significantly associated (at the p<0.05 level) with the presence of CAD. Triglycerides and LDL cholesterol did not enter the model at p<0.1. In a second model apo B and A-I were used in lieu of LDL and HDL cholesterol, respectively; homocyst(e)ine was still associated with the presence of CAD (Table 2).

**Family Studies**

There were 71 probands for whom sufficient family members were available for analysis. A comparison of correlation coefficients between proband and spouse and between parents and offspring for homocyst(e)ine levels serves as an index of environmental (shared household and diet) and genetic factors, respectively. Table 3 shows the Spearman’s correlation coefficients between mean level of parent–mean level of offspring (r=0.356, p=0.002) and proband–spouse (r=0.264, p=0.041) for homocyst(e)ine levels. Proband–mean level of child (r=0.248, p=0.037) and spouse–mean level of child (r=0.224, p=0.084) correlations indicate that parental levels of homocyst(e)ine determine in part the levels in children. The higher correlation coefficient between mean level of parent–mean level of offspring suggests that the genetic contribution of plasma homocyst(e)ine levels may be more than that due to environmental causes.

Of the 71 probands, 20 (28.2%) had homocyst(e)ine levels greater than the 90th percentile; of those, eight (11.3%) were greater than the 95th percentile. In 10 families (14%), at least one first-degree relative had homocyst(e)ine levels greater than the 90th percentile (Figure 1). Thus, based on these 71 families the prevalence of hyperhomocyst(e)inemia in men with premature CAD is 28%, with half (14%) having a familial form of hyperhomocyst(e)inemia. In three of these 10 families, data for several first-degree relatives other than children were used to determine the familial nature of the disorder (families 064, 198, and 208). There were equal numbers of children in the families of probands designated as having familial hyperhomocyst(e)inemia and in the families not so designated (30 and 29 children, respectively). However, there were 10 siblings and parents in the former and none in the latter. In our study, this may have contributed to an underestimation of the familial nature of the disorder.

Plasma lipid, lipoprotein cholesterol, and apo A-I and B levels in the affected and unaffected probands (homocyst[e]ine level >90th percentile) and affected and unaffected children are shown in Table 4. In affected probands the mean plasma cholesterol level was 200±32 mg/dl, similar to that of unaffected probands (194±34 mg/dl, p=NS). There were no significant differences in triglyceride levels (170±67 versus 177±94 mg/dl, p=NS), LDL cholesterol (132±30 versus 125±35 mg/dl, p=NS), HDL cholesterol (35±6 versus 35±11 mg/dl, p=NS), apo B (103±31 versus 108±26 mg/dl, p=NS), and apo A-I (111±17 versus 113±28 mg/dl, p=NS) between affected and unaffected probands. Homocyst(e)ine levels by selection

**Figure 1. Continued.**
criteria were significantly higher in affected probands (20±7 versus 11±2 nmol/ml, p<0.001).

Offspring

No significant differences in levels of total cholesterol, triglyceride levels, LDL and HDL cholesterol, or apo A-I and B were seen in affected male and female offspring compared with unaffected offspring (Table 4). Homocyst(e)ine levels in affected versus unaffected offspring were, by selection, significantly different (p<0.005). Mean levels of homocyst(e)ine in all offspring were not significantly different from those of the control group.

The percentage of offspring with homocyst(e)ine levels greater than 15 nmol/ml in the children of affected probands is 25% (Figure 2), indicating that in addition to genetic predisposition other factors play a role in the determination of homocyst(e)ine levels in children. In the present study half of the probands had a familial form of hyperhomocyst(e)inemia. Based on a segregation ratio of 25% in affected families, one would expect that only 12.5% (25% of 50%) of the offspring of patients with elevated plasma homocyst(e)ine levels would also have hyperhomocyst(e)inemia. However, the determination of such a segregation ratio is based on cutoff levels for homocyst(e)ine in adult men and thus may not be valid for women and children.

Discussion

The clinical manifestations of homocystinuria have been discussed in detail.24-28 The vascular complications seen in this disorder include arterial and venous thrombosis and venous and systemic embolization. The presence of emboli both in arteries and veins has been almost universally reported. Fibrous thickening of the arterial and venous intima, with disruption of the internal elastic lamina and increased collagen in the interstitial space, is seen throughout the vascular tree.11

Elevation of plasma homocyst(e)ine levels is a risk factor for the development of CAD and other vascular complications, including stroke and peripheral vascular disease.1-10 Stepwise discriminant analysis of cardiovascular risk factors, lipoprotein cholesterol, and apolipoprotein levels reveals that homocyst(e)ine levels are an independent risk factor for the development of CAD. The cause of mild to moderate elevations of homocyst(e)ine may be related to the heterozygous state for cystathionine β-synthase deficiency,4 the thermolability of 5,10-methylenetetrahydrofolate reductase,14 nutritional deficiencies of folate and vitamins B12 and B6, or other factors,16 including antineoplastic therapy.30

The familial nature of moderate hyperhomocyst(e)inemia has not been reported previously. Our data suggest that at least half of probands with moderate homocyst(e)ine have a familial disorder, with an affected first-degree relative. The elevation of homocyst(e)ine in CAD probands in whom no first-degree relative was affected may be due to other factors, as mentioned above, or to a genetic trait that is not detected because of insufficient family members. It is likely that the distribution of homocyst(e)ine levels is age and gender dependent. Case-control studies have revealed a slight difference in homocyst(e)ine levels in men and women, with women having slightly lower levels than men.7,16 Large population norms for homocyst(e)ine have not been published. Thus, our cutoff point of 15.02 nmol/ml for the 90th percentile may be inappropriately stringent when applied to offspring.

The genetic factors modulating homocyst(e)ine levels within a family are not known. Boers et al4 reported that the prevalence of heterozygous cystathionine β-synthase deficiency in patients with vascular disease was 13.3% (10 of 75), based on in vivo

<p>| Table 4. Lipid, Lipoprotein Cholesterol, and Apolipoprotein Levels in Affected Probands and Offspring |
|-------------------------------------------------|---------------------------------|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age</th>
<th>Chol</th>
<th>TG</th>
<th>LDL</th>
<th>HDL</th>
<th>Apo B</th>
<th>Apo A-I</th>
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<td>Men</td>
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<tr>
<td>Men</td>
<td>97</td>
<td>26±12</td>
<td>171±35</td>
<td>112±129</td>
<td>106±29</td>
<td>44±11</td>
<td>85±34</td>
<td>131±26</td>
<td>9±2t</td>
</tr>
<tr>
<td>Women</td>
<td>109</td>
<td>26±11</td>
<td>170±36</td>
<td>75±37</td>
<td>103±31</td>
<td>52±11</td>
<td>76±29</td>
<td>155±31</td>
<td>8±3t</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD and are in mg/dl, except for age (yr) and H(e) (nmol/l). Chol, cholesterol; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; apo, apolipoprotein; H(e), homocyst(e)ine.

*Includes all offspring with homocyst(e)ine levels >15.02 nmol/ml.

tp<0.001 between affected and unaffected probands; tp<0.001 between affected and unaffected offspring.
methionine loading and reduced activity of cystathionine \( \beta \)-synthase determined from cultured skin fibroblasts. This prevalence (13.3%) of a genetic abnormality is similar to that observed in our families (14%). In this study we did not determine the activity of various enzymes involved in homocyst(e)ine metabolism. In addition to defects in cystathionine \( \beta \)-synthase, thermolabile 5,10-methylenetetrahydrofolate reductase may contribute to higher plasma levels of homocyst(e)ine in affected individuals. Kang et al.\(^1\) have shown that in patients with hyperhomocyst(e)inemia compared with control subjects, the activity of this enzyme is reduced after heating to 46°C. The molecular defect(s) underlying homocystinuria secondary to cystathionine \( \beta \)-synthase deficiency may be elucidated now that the gene for cystathionine \( \beta \)-synthase has been isolated.\(^{31-33}\) To date, the molecular variability of 5,10-methylenetetrahydrofolate reductase has not been determined.

The correlation coefficients between parents and children indicate that homocyst(e)ine levels are in part genetically determined and that environmental influences may also play a role in plasma level variability. We have not investigated the mechanisms involved in hyperhomocyst(e)inemia. To define the genetic etiology of familial forms of hyperhomocyst(e)inemia, the determination of enzymatic activity of cystathionine \( \beta \)-synthase and the thermolability of 5,10-methylenetetrahydrofolate reductase in skin fibroblasts or leukocytes of affected individuals must be performed. In addition, plasma levels of vitamin \( B_6 \), vitamin \( B_9 \), and folate as well as parameters of renal function should be determined for proper evaluation of secondary causes of hyperhomocyst(e)inemia.

The mechanisms by which homocyst(e)ine promotes atherosclerosis are uncertain. The studies of Harker et al.\(^{34-36}\) have revealed arterial endothelial cell denudation and decreased platelet survival in a nonhuman primate model of hyperhomocyst(e)inemia. These results have not been duplicated in other animal models. Whether homocyst(e)ine is indeed toxic to the endothelial cells must await further studies. This hypothesis is nevertheless appealing; endothelial cell denudation is found in experimental atherosclerosis in cholesterol-fed nonhuman primates.\(^ {37-40}\) The link between plasma homocyst(e)ine levels and CAD must now be evaluated in large prospective studies from which the caveats of case-control studies can be removed. Elevated levels of homocyst(e)ine respond to folate supplementation,\(^ {41}\) and such therapy in patients with elevated homocyst(e)ine levels may have relevance in further studies of cardiovascular risk reduction.

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KEY WORDS • homocyst(e)ine • coronary artery disease •
genetics • cardiovascular risk factors
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doi: 10.1161/01.ATV.11.5.1129

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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