Increased Serum Homocysteine and Sudden Death Resulting from Coronary Atherosclerosis With Fibrous Plaques

Allen P. Burke, V. Fonseca, Frank Kolodgie, Arthur Zieske, Louis Fink, Renu Virmani

Introduction—Moderate elevations of total homocysteine have been associated with increased risk for coronary atherosclerosis but correlation between elevated homocysteine and plaque morphology has not been described in humans.

Methods—We determined serum homocysteine at postmortem from 87 men with coronary thrombus (62 of whom were diagnosed as acute), from 35 men with severe coronary disease without thrombus, and from 46 controls. In coronary deaths, atherosclerotic plaques at the sites of maximal luminal narrowing of the four epicardial coronary arteries were classified as fibrous plaques, fibrous cap atheromas, thin-cap atheromas, and healed ruptures, and macrophage infiltration was assessed semiquantitatively.

Results—Median serum homocysteine postmortem as a result of acute thrombus was 10.4 µmol/L (P=0.4 versus controls), 12.1 µmol/L in men with organized thrombi (P=0.1 versus controls), 15.6 µmol/L in men without thrombus (P=0.007 versus controls), and 9.8 µmol/L in controls. The median homocysteine was 12.1 µmol/L in 65 men with healed infarcts (P=0.03 versus controls). The number of fibrous plaques was associated with log-normalized homocysteine (P=0.004), independent of age, albumin, smoking, hypertension, and serum cholesterol. Homocysteine levels in the upper tertile (>15 µmol/L) were associated with sudden death without acute or organized thrombus (odds ratio 3.8, P=0.03) independent of age and other risk factors; the coexistence of diabetes increased the association (odds ratio 25.1, P=0.009, versus lowest tertile ≤8.5 µmol/L).

Conclusions—Increased serum homocysteine is associated with sudden death in the absence of acute coronary thrombosis, especially with concomitant diabetes, and with the presence of lipid-poor, fibrous plaques. (Arterioscler Thromb Vasc Biol. 2002;22:1936-1941.)

Key Words: homocysteine ■ diabetes ■ coronary artery disease ■ sudden death ■ thrombosis

Homocysteinuria is a rare inborn error of metabolism that is a result of cystathionine β-synthase deficiency and results in a high (>100 µmol per liter) plasma homocysteine and premature mortality resulting from thromboembolic events. The mechanism of thrombosis is unclear but may be related to an effect of homocysteine on coagulation, decreased resistance of the endothelium to thrombosis, and inhibition of nitric oxide–mediated vasodilation. In contrast, modest elevations of total homocysteine between 10 to 100 µmol per liter are due to variations in vitamin B intake and genetic factors, particularly 5,10-methylenetetrahydrofolate reductase polymorphism. There has been a link between modest elevations of total homocysteine with acute myocardial infarction, stroke, aortic atherosclerosis, and mortality in patients with known coronary artery disease. Because thrombosis is a component of the progression of atherosclerosis, small increases in total homocysteine may accelerate atherosclerosis by a thrombotic mechanism. However, mechanisms independent of thrombosis may play a role in homocysteine-mediated atherogenesis, and unstable coronary syndromes are not always associated with elevations of total homocysteine.

There has as yet been no study measuring total homocysteine in sudden coronary death victims or studies correlating total homocysteine with coronary plaque morphology. In patients who die suddenly of coronary artery disease, the coronary findings are heterogeneous. Potential mechanisms for sudden death caused by severe coronary disease include plaque rupture or erosion with luminal thrombosis and nonthrombotic mechanisms in patients without arterial thrombi, which may include myocardial factors such as hypertrophy and healed infarcts and coronary spasm overlying stable plaque. The purpose of this study was to compare homocysteine levels in men who died suddenly with coronary thrombosis or with severe coronary artery disease without thrombosis to a control set of men who died of noncoronary causes. In addition, the types of coronary plaque are be correlated with homocysteine levels using a recent classification adapted from morphological studies of sudden-death victims. The results of these data will demonstrate whether...
elevations of homocysteine that have been seen in patients with severe coronary disease correlate with coronary thrombosis or stable plaque and whether homocysteine is elevated in patients who die suddenly with severe coronary disease compared with controls.

Materials and Methods
Cardiac Dissection
Hearts from 122 men who died suddenly of severe coronary artery disease were studied. Risk factor data without homocysteine analysis, definitions of sudden coronary death, and cardiac dissection techniques have been reported previously for these cases. In addition, sera and risk factor data were obtained from 46 male control noncoronary deaths. The epicardial arteries of the study patients were evaluated at 3- to 4-mm intervals and each segment with a gross estimation of >50% cross-sectional luminal narrowing or evidence of thrombus were studied histologically.

Morphological Analysis
We assessed the relationship of homocysteine levels to the nature of the “culprit lesion,” whether a fibrous plaque, acute thrombus (rupture or acute plaque erosion), organized thrombus, or no significant coronary lesion in the case of control patients. Stable culprit plaque was defined as one or more segments with ≥75% cross-sectional area luminal narrowing (severe coronary disease) in the absence of acute coronary thrombus. Coronary deaths with stable culprit plaque were subclassified as cases of healed infarcts (area of fibrosis >1 cm in greatest diameter) with or without organizing or organized thrombi; stable plaque with or without organizing or old coronary thrombi but absence of healed infarction; and ≥75% cross-sectional area luminal narrowing and absence of healed infarction and organizing or organized thrombi. Acute ruptures and erosions were defined as previously reported.12

We also assessed the relationship of homocysteine to quantitation of types of plaques in hearts with severe coronary disease. Plaques were classified as predominantly fibrous plaque when the plaque consisted of fibrous tissue, smooth muscle cells, few macrophages with or without calcification, fibrous cap atheroma with a lipid-rich necrotic core, thin-cap atheroma, recanalized thrombus, and healed plaque rupture, as previously described. In the coronary cases, 11 ± 4 sections (excluding acute thrombi) were examined. Fibrous plaque denoted an absence of a lipid-rich core and 0 to 1+ semiquantitative analysis of macrophage infiltrates (see below). Fibroatheroma, in contrast, demonstrated a core filled with cholesterol clefts and macrophage cellular debris. Thin-cap atheroma denoted an area of thinning over the lipid core and was focially <65 μm in thickness, as previously defined. A semiquantitative assessment of macrophage infiltration, assessed by avidin–biotin immunohistochemical staining for CD68 (Dako, Carpinteria, Calif; 1:200), was assessed as follows: 0, rare or few macrophages; 1+, isolated macrophages limited to surface plaque; 2+, isolated macrophages present throughout the plaque and surrounding lipid core; 3+, focal clusters of macrophages within the fibrous cap and within lipid core; and 4+, sheets of macrophages within the fibrous cap and diffuse CD68 staining within lipid core. Healed ruptures were determined by staining with Sirius Red and assessing breaks in the fibrous cap using polarized light.7 The numbers of each of these plaques were counted in each specimen, and these values compared among groups of men with and without the serum homocysteine elevation.

Determination of Homocysteine
Total serum homocysteine–cysteine, mixed disulfides, and protein-bound homocysteine was measured by high-performance liquid chromatography, coupled with fluorescence detector, on autopsy sera. In all cases, blood was centrifuged and separated into serum at the time of autopsy and frozen at −70°C and batched for measurement of homocysteine.

Determination of Other Risk Factors
In addition to homocysteine, the interaction of other traditional risk factors was assessed. Diabetes mellitus was determined based on history and percent glycated hemoglobin determination on postmortem red blood cells. Greater than 8% glycated hemoglobin indicated glucose intolerance and >10% indicated overt diabetes.14 Cigarette smoking was determined based on history and postmortem evaluation of thiocyanate. Total and HDL cholesterol and serum albumin were measured as previously described.15,16 Hypertensive renovascular changes were identified based on previous criteria.7,10,16–18 For determination of increased left ventricular mass, hearts were weighed to the nearest gram before fixation, after removal of intracavitary blood, pericardium, and great vessels 2 to 3 cm above the aortic root.

Statistical Analysis
Univariate comparisons of serum homocysteine were performed by Mann–Whitney unpaired two group test. Because homocysteine levels are not distributed normally, log-transformed values were used for Student t test and ANOVA. In correlating culprit plaques with homocysteine tertiles, multivariate analysis was performed using logistic regression with dependent variable in the presence or absence of morphological finding (e.g., presence of sudden death with stable plaque). For determination of odds ratios, serum homocysteine levels were grouped into lowest (≤8.5), middle (8.5 to 15), and upper tertiles (>15 μmol/L). The odds ratios are presented comparing the highest versus the lowest tertile. The correlation of numbers of nonculprit plaque types with log-transformed homocysteine levels, multiple linear regression was used. Software from SAS Institute (Statview, Cary, NC), was used.

Results
Patient Age and Presence of Infarct
The mean age of the 122 men with coronary disease was 50 ± 10 years. Of these, there were 62 acute coronary thrombosis (aged 48 ± 9 years), of which 46 were plaque ruptures (49 ± 9 years) and 16 plaque erosions (46 ± 9 years). An additional 25 men who died with coronary disease demonstrated organized thrombi, and 15 of the men with acute thrombi had organized thrombi as well. The mean age of the 25 men with organized thrombi was 50 ± 11 years. Thirty-five hearts in the severe coronary disease group showed no thrombi, acute or organized (mean age 53 ± 11 years, Table 1). Healed infarcts were present in 65 hearts and were distributed in all groups (mean age 52 ± 10 years) but were especially frequent in hearts with organized thrombi (Table 1). The control men were aged 51 ± 12 years and died of unnatural traumatic causes (n = 36) and noncoronary cardiac causes (n = 10); in no case was there >50% cross-sectional area luminal area narrowing by atherosclerotic plaque.

Effect of Postmortem Interval on Homocysteine Levels
By simple regression, there was no effect of postmortem interval on log-normalized homocysteine using all samples (r² = 0.005) or values <15 μmol/L (r² = 0.004).

Analysis of Homocysteine Levels of Coronary and Control Deaths by Culprit Plaque
By univariate analysis, serum homocysteine levels were elevated in men who died with coronary disease compared with controls (median 1.05 μmol/L versus 9.8 μmol/mL, P = 0.05, Table 1). When analyzed by culprit plaque morphology, homocysteine was especially elevated in the absence of acute or organized thrombus compared with controls (median
9.8 μmol/L/L versus 15.6 μmol/L/L, \( P=0.007 \), controls versus coronary deaths without thrombus). The median and mean log-transformed homocysteine levels were intermediate in the organized thrombus group, reaching borderline statistical significance \( (P=0.05 \) using log-transformed data, Table 1). Mean and median homocysteine levels were only slightly increased over controls in the acute thrombus group \( (P>0.1, \) Table 1). Although there was a significant correlation between maximal percent cross-sectional luminal narrowing and log-transformed serum homocysteine levels \( (P=0.03) \), the correlation was weak \( (r^2=0.03) \).

### Univariate Analysis of Serum Homocysteine and Other Risk Factors

There was a significant weakly positive correlation between log-transformed homocysteine and age \( (P=0.03, r^2=0.04) \) and a positive but insignificant correlation with heart weight \( (r^2=0.004) \), glycohemoglobin \( (r^2=0.006) \), albumin \( (r^2=0.006) \), presence or absence of diabetes \( (P=0.4) \), and presence of hypertension \( (P=0.3) \). There was a negative, insignificant correlation between serum homocysteine and body mass index \( (r^2=0.01) \), total/HDL cholesterol ratio \( (r^2=0.03) \), and cigarette smoking \( (P=0.7) \).

### Multivariate Analysis of Homocysteine Levels by Culprit Plaque

Using multivariable analysis, including as covariates age, body mass index, serum albumin, hypertension, history of smoking, and total/HDL cholesterol ratio in all cases examined, men in the highest tertile (>15 μmol/L/L) of homocysteine were significantly more likely to have stable plaque without acute or organized thrombus (odds ratio 3.8, range 1.1 to 12.9, \( P=0.03 \), versus lowest tertile). When the additive effect of diabetes and homocysteine was examined, diabetic men with serum homocysteine in the upper tertile as compared with the lowest tertile (≥8.5 μmol/L/L) were more likely to die with stable plaque (odds ratio 25.1, range 2.2 to 281, \( P=0.009 \)). When the percentage of men who died without acute thrombus was plotted against the presence of diabetes and elevated homocysteine in the highest tertile, there appeared to be an additive effect of diabetes and homocysteine elevation for men who died with stable plaque without acute thrombus (Figure 1).

### Homocysteine Levels and the Presence of Myocardial Infarction

Table 2 shows that the presence of healed infarcts was associated with elevated homocysteine. There was no difference in the control and acute infarct groups.

### Association Between Types of Nonculprit Plaques and Serum Homocysteine

The numbers of recanalized thrombi (Figure 2A) and fibrous cap atheromas (Figure 2B) did not significantly vary by homocysteine tertile. Thin-cap atheromas were more frequent in lower tertiles of homocysteine (Figure 2C). Fibrous plaques were the most numerous in the highest tertile (Figure 2D). There were fewer healed plaque ruptures in the highest serum homocysteine tertile compared with the lowest (Figure 2E). Mean macrophage index was least in the highest tertile of homocysteine (Figure 2F). By multivariate analysis, numbers of fibrous plaques was associated with log-normalized homocysteine \( (P=0.0045, r=2.9) \), independent of age, albumin, smoking, renovascular changes of hypertension, and total/HDL cholesterol.

### Discussion

**Homocysteine Levels in Sudden-Death Victims**

The current study demonstrates that homocysteine is elevated in sudden death as a result of severe coronary artery disease without acute or organized coronary thrombosis. In addition, this association seems to be increased if there is concomitant diabetes mellitus. Whether these data suggest that reduction of serum homocysteine may reduce the rate of sudden coronary death in men remains unknown. Whether elevated serum homocysteine may be causally associated with sudden death is an important question for future research.

**Figure 1.** The relationship of diabetes and homocysteine elevation to stable plaque. The proportion of deaths resulting from stable plaque was increased with homocysteine and diabetes, with an additive effect.
death or merely a marker of a process related to sudden death is unclear. A prospective clinical study linked elevated serum homocysteine to all mortality in patients with clinically documented coronary disease, suggesting that the association between homocysteine and sudden death may not be coincidental. Folsom et al. however, did not show a relationship between serum homocysteine and acute coronary events independent of serum vitamin levels and vitamin use.

Cross-sectional studies have demonstrated an increased risk for coronary events in patients with elevated serum homocysteine. The association between healed myocardial infarct and elevated serum homocysteine in the current study is consistent with clinical findings relating elevated serum homocysteine with a history of previous myocardial infarction. The association between homocysteine and acute infarction has been questioned because of the apparent acute phase reactant effect of homocysteine, which has been suggested in a study comparing serum homocysteine at days 1 and 3 after acute infarction. Other studies have suggested, however, that homocysteine is independent of C-reactive protein levels and may reflect the degree of myocyte necrosis. The current study demonstrates that instantaneous deaths with stable plaque in the absence of an acute or organized thrombus, which demonstrated necrosis in 2% of cases, were associated with increased homocysteine levels, unlike death as a result of acute coronary thrombi, which was associated with myocyte necrosis in 17% of patients. Therefore, it seems likely that homocysteine is a marker for stable coronary plaque, as opposed to a marker for an acute response to an inflammatory reaction secondary to acute ischemia.

### Table 2. Homocysteine Levels by Presence of Infarct

<table>
<thead>
<tr>
<th>Infarct (n; age, y±SD)</th>
<th>Hcy, Median</th>
<th>Hcy±SD</th>
<th>Log Hcy</th>
<th>Hcy±SD</th>
<th>Albumin, mg/dL±SD</th>
<th>% htn</th>
<th>% Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary disease, no infarct (49; 48±11)</td>
<td>10.4</td>
<td>0.39</td>
<td>1.06±0.26</td>
<td>0.26</td>
<td>4.2±0.8</td>
<td>33</td>
<td>57</td>
</tr>
<tr>
<td>Coronary disease, acute infarct (8; 45±9)</td>
<td>9.9</td>
<td>0.21</td>
<td>1.11±0.24</td>
<td>0.22</td>
<td>4.1±0.7</td>
<td>25</td>
<td>63</td>
</tr>
<tr>
<td>Coronary disease, healed infarct (65; 52±10)</td>
<td>12.1</td>
<td>0.03</td>
<td>1.13±0.31</td>
<td>0.02</td>
<td>4.0±0.7</td>
<td>42</td>
<td>54</td>
</tr>
<tr>
<td>Controls (46; 51±12)</td>
<td>9.8</td>
<td>–</td>
<td>1.00±0.23</td>
<td>–</td>
<td>4.0±0.7</td>
<td>46</td>
<td>48</td>
</tr>
<tr>
<td>Total (168)</td>
<td>11.1</td>
<td>–</td>
<td>1.07±0.27</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</table>

Figure 2. Nonculprit plaque types by homocysteine tertiles. For homocysteine, the lowest tertile was ≤8.5, the middle 8.5 to 15, and the upper tertile >15 μMol/L. There was no significant difference in numbers of recanalized thrombi (A) or fibrous cap atheromas with lipid cores (B). Thin-cap atheromas decreased with increasing homocysteine (C); the difference between mid- and highest tertile was significant to P=0.04 (ANOVA means table, Fisher’s post hoc test). Stable plaques were increased with elevated homocysteine (D); the difference between lowest tertile with the highest tertile was significant (P=0.01). There was a decrease in healed plaque ruptures with increasing homocysteine (E). Macrophage index was significantly decreased in highest tertile of homocysteine (P=0.01 versus lowest tertile) (F). Values are mean±SD.
Homocysteine Is Not Associated With Acute Atherothrombosis But With Fibrous Plaque

Although the current study did not measure serum levels of pyridoxal 5’-phosphate and folate, which are inversely proportional to homocysteine levels, or gather data regarding vitamin use, it provides morphological data establishing a link between homocysteine and a specific type of coronary plaque, namely fibrous plaque. In particular, there was no association in our study between fatal acute coronary thrombosis and serum homocysteine. The implications of these findings are unclear, but they may explain in part negative studies showing no association between homocysteine and acute coronary events, which are presumably triggered by atherothrombosis.9,23

The weak association between homocysteine and organized thrombus appears contradictory, given the lack of link between homocysteine and acute thrombus. It is likely that this association is due to the fact that organized thrombi were very prevalent (84%) in hearts with healed myocardial infarcts. The same mechanism associating hyperhomocysteinemia with fibrous plaque formation may be at play in scar formation in the myocardium, but this hypothesis remains speculative.

Until recently, it was debated whether hyperhomocysteinemia results in increased atheroma formation, that is, is atherogenic, or whether the increased susceptibility to coronary events in patients with elevated serum homocysteine is mediated by functional abnormalities such as vasospasm.24 Animal studies have suggested the former because apoE-null mice develop larger lesions in the aorta when the diet is modified to increase serum homocysteine compared with normal levels.25,26 Interestingly, the lesions described by Zhou et al26 were fibrous-rich, similar to the human lesions described in the current study. The association between elevated homocysteine and fibrous plaques hearkens back to the seminal observations of McCully,27 who described fibrocalcific plaques in patients with congenital homocysteinemia.

The current study shows a marked difference in the types of plaque in men with elevations of homocysteine compared with those with hypercholesterolemia. It has been demonstrated that elevated cholesterol is associated with features of plaques that are associated with ruptures, including thin-capped atheroma, acute plaque rupture, and healed plaque rupture.7,10 The current study demonstrates that features of plaque associated with rupture are less frequent in men with elevated homocysteine levels, suggesting a different method of plaque progression. These data suggest that homocysteine may not result in plaque instability as currently understood. Therefore, efforts to reduce serum homocysteine may be complementary to lipid reduction because plaque fibrosis may occur via a distinct mechanism. One possible mechanism that may contribute to sudden death in hyperhomocysteinemic patients without overt thrombosis may be endothelial dysfunction. Endothelial dysfunction is well known to occur in hyperhomocysteinemia and can be corrected by folate supplementation.28

Interaction Between Diabetes and Hyperhomocysteinemia

The observed interaction between diabetes and hyperhomocysteinemia in our study is interesting and compatible with other report in the literature. Recent studies have demonstrated that total homocysteine is an important risk factor even in patients who are already at high risk, such as those with type 2 diabetes.29,30 In the Hoorn study, hyperhomocysteinemia increased the risk of death in all subjects,29 but the effect was greater in patients with type 2 diabetes. Total homocysteine is frequently elevated in patients with type 2 diabetes who have coexistent cardiovascular disease.31 In contrast, patients with diabetes without vascular disease may have low total homocysteine, but total homocysteine is still a predictor of mortality. In patients with diabetic nephropathy, the risk of mortality may be even greater30 and recent data suggest complex derangement of homocysteine metabolism in these patients.31 It is possible that recently described effects of glucose and insulin on homocysteine metabolism play a role in elevating homocysteine levels in diabetic patients.32

Mechanism of Atherogenesis and Increased Homocysteine

Although the current study does not address mechanisms, the observation linking increased homocysteine with fibrous plaques with or without calcification suggests, as mentioned above, a distinct mechanism of atherogenesis from that induced by hyperlipidemia, which is believed to be mediated largely by inflammatory cells, especially macrophages. Experimental studies have shown that homocysteine upregulates endothelial endoplasmic reticulum stress-response genes,33 which may induce proliferation of smooth muscle cells,8 and results in upregulation of nuclear factor κB in smooth muscle cells.34 Although further studies relating risk factors and plaque morphology are necessary, the current study suggests, similar to previous work, that plaque morphology may reflect distinct mechanisms of atherogenesis induced by different risk factors, underscoring the heterogeneity of the atherosclerotic process.

Study Limitations

Because the current study uses autopsy specimens, there are inherent errors in postmortem risk-factor determinations. Although homocysteine levels increase with the duration of blood cells in contact with serum, between 1% and 25% in a 4-hour interval,35–37 we were unable to demonstrate significant increases in overall homocysteine levels with increasing postmortem intervals. Another potential confounding effect is the increase in homocysteine seen in patients with renal failure.38 The association, however, between homocysteine and renal failure in patients with acute coronary syndromes has been shown to be minor,39 and in the current study the association between homocysteine and fibrous plaques appeared to be independent of renovascular hypertensive changes and serum albumin.

Conclusion

Elevated serum homocysteine is associated with sudden unexpected death in men and is especially associated with
diabetes. Although hyperhomocysteinuria is associated with unstable coronary syndromes, the mechanism of sudden coronary death in men with modest elevations of homocysteine does not seem to be mediated via a thrombotic mechanism. Elevated serum homocysteine is associated with an increase in fibrous plaques and a relative decrease in thin-cap atheromas, suggesting a different mechanism of atherogenesis from that of hypercholesterolemia.

References

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Correction

In the November 2002 issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, in the article by Burke et al (Increased Serum Homocysteine and Sudden Death Resulting From Coronary Atherosclerosis With Fibrous Plaques; pp 1936–1941), there is an error in the text and in Table 1. On page 1937, line 3 of the last paragraph should read “median 11.05” and not “median 1.05.” Likewise, in Table 1, 2nd column, 6th row, the value should be “11.05.” The authors apologize for this error.