Association of Elevated Homocysteine Levels With a Higher Risk of Recurrent Coronary Events and Mortality in Patients With Acute Myocardial Infarction

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Background: Despite the prothrombotic and proinflammatory effects associated with elevated homocysteine levels, only limited data exist regarding the effect of homocysteine levels on outcome of patients with acute myocardial infarction.

Methods: Homocysteine levels were determined within 24 hours of presentation in 157 consecutive patients with acute myocardial infarction. Patients were allocated to 2 groups: those with homocysteine levels of 2.7 mg/L (20 μmol/L) or more (n=22 [14%]) and those with homocysteine levels of less than 2.7 mg/L (n=135 [86%]).

Results: Female and diabetic patients had significantly lower homocysteine levels than males (P<.01) and non-diabetic patients (P=.005), respectively, with no significant correlation with age (r=0.07, P=.42) or other risk factors. Patients with homocysteine levels greater than or equal to 2.7 mg/L and less than 2.7 mg/L did not differ significantly regarding extent of coronary artery disease as reflected by prevalence of multivessel disease (54% vs 61%; P=.87), and their in-hospital course. However, in a mean ±SD follow-up of 30±10 months, patients with homocysteine levels greater than or equal to 2.7 mg/L had a higher incidence of recurrent coronary events (36% vs 17%; P=.04) and death (18% vs 5%; P<.05). Homocysteine levels greater than or equal to 2.7 mg/L remain a significant determinant of recurrent coronary event and/or death after controlling for potential cofounders by multivariate analysis (odds ratio, 3.8; 95% confidence interval, 1.3-11.0).

Conclusions: In patients with acute myocardial infarction, elevated homocysteine levels are associated with a higher risk of recurrent coronary events and death, independent of other risk factors and the extent of coronary artery disease.

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During the past decade, hyperhomocysteinemia has been recognized by most prospective studies to be a primary risk factor for coronary events and/or cardiovascular mortality, although not uniformly. More recently, elevated levels of homocysteine were found to be an independent predictor of long-term mortality in patients with angiographically documented coronary artery disease (CAD) and of restenosis after percutaneous coronary intervention. In patients with an acute coronary event, elevated levels of homocysteine are associated with hypercoagulability and increased platelet aggregation. Despite this, there are limited data regarding the association between homocysteine levels and the clinical outcome of patients with acute coronary events. Moreover, in each of these studies, homocysteine levels were not correlated with the extent of the underlying coronary disease.

In the present study, we investigated the correlation between admission homocysteine levels and other risk factors for CAD, clinical characteristics, and angiographic findings, and prospectively studied their effect on the 30-month outcome in patients with acute myocardial infarction (AMI).

Methods

Study Population

The study population comprised 157 consecutive patients with AMI, admitted within 12 hours of symptom onset. The diagnosis of AMI was based on the presence of ischemic chest pain of at least 30 minutes' duration and creatine kinase (CK) elevation of at least twice the upper normal limit, with CK-MB isoenzyme concentration of at least 6% of the peak CK value, accompanied by dynamic ST-segment elevation or depression of 1 mm or more in at least 2 adjacent leads. Patients who had hypothyroidism, malignant disease, or renal failure (creatinine level, ≥1.5 mg/dL [≥133...
µmol/L), or who were treated with anticonvulsant therapy, theophylline, or niacin (which might influence homocysteine levels), were excluded from the study.

A blood sample for homocysteine determination was obtained from each patient after 12 hours fasting, as soon as possible within the first 24 hours.

**HOMOCYSTEINE DETERMINATION**

Venous blood for homocysteine levels was collected in tubes containing EDTA. The blood was centrifuged immediately and the obtained plasma was then frozen at −70°C. Total plasma homocysteine level was determined by the high-performance liquid chromatography method with fluorescence detection.18

**CLINICAL FOLLOW-UP**

During hospitalization, patients were followed up prospectively for adverse events, including recurrent ischemia, reinfarction, congestive heart failure (Killip class ≥II), atrial fibrillation, and malignant ventricular arrhythmias (ventricular tachycardia and fibrillation). Reinfarction was diagnosed on the basis of the recurrence of persistent ischemic chest pain, followed by CK reelevation of at least twice the last measured value. Any recurrent ischemic chest pain that was accompanied by ST-T-segment changes or led to otherwise unscheduled catheterization was considered recurrent angina.

All patients had a complete echo examination (including 2-dimensional echo and Doppler) before discharge.

After discharge, patients were interviewed via the telephone for recurrent ischemic events and recurrent hospitalization information. Hospital records were reviewed for the causes and course of hospitalization. The criteria used for the diagnosis of AMI and unstable angina in the index myocardial infarction were applied. Mortality data from the National Population Register at the Ministry of the Interior were also obtained, and cause of death was based on the death certificate and/or medical records. The investigators who conducted the clinical follow-up were blinded to patients’ homocysteine levels.

**ANGIOGRAPHY**

Patients were catheterized at the discretion of the attending physician. Angiograms were assessed by 2 experienced angiographers, who were blinded to the patients’ homocysteine levels.

A stenosis was considered significant if the coronary artery was narrowed by 70% or more. The infarct-related artery was narrowed by 70% or more. The infarct-related artery was considered as proximal culprit lesions, and otherwise, as distal. Culprit lesions proximal to the first septal branch in the left anterior descending coronary artery, first obtuse marginal in the circumflex coronary artery, and before the first right ventricular branch in the right coronary artery were defined as proximal culprit lesions, and otherwise, as distal.

**STATISTICAL ANALYSIS**

Homocysteine levels were skewed to the right (long tail toward the high levels) and presented as median (first and third quartiles). The comparison of homocysteine levels according to sex, existence of other risk factors, and number of diseased coronary arteries was performed by Wilcoxon rank sum test. To study the effect of homocysteine levels on clinical outcomes, patients were stratified by means of a homocysteine cutoff point, which was determined by empirical receiver operating characteristics analysis. The optimal cutoff point was determined on the basis of the assumption that type II error is more important than type I error, and the actual frequency of recurrent coronary events and/or mortality is the same as in the sample. In this comparison, categorical variables were compared with Pearson χ² or Fisher exact test and continuous variables by unpaired, 2-tailed t test. Backward logistic regression was used to determine the independent predictors of recurrent coronary events and/or mortality. The initial list of potential covariates included age, sex, previous myocardial infarction or cerebrovascular event, risk factors for CAD, administration of reperfusion therapy, infarct location (anterior vs nonanterior), Q wave myocardial infarction, existence of heart failure during hospitalization, and left ventricular ejection fraction. All statistical analyses were performed with SAS (version 8) software (SAS Institute Inc, Cary, NC). Data are given as mean ± SD unless otherwise indicated.

**RESULTS**

**AGE, SEX, RISK FACTORS FOR CAD, AND HOMOCYSTEINE LEVELS**

Blood for homocysteine was drawn, on the average, 9.6 ± 3 hours after admission. Homocysteine levels ranged from 0.3 to 11.8 mg/L (2–87 µmol/L), and the median homocysteine level in the entire study population was 1.5 mg/L (1.0, 2.2 mg/L) (11.4 µmol/L [7.6, 16.0 µmol/L]).

Men had significantly higher homocysteine levels than women: 1.6 mg/L (1.1, 2.4 mg/L) (12 µmol/L [8.5, 17.7 µmol/L]) vs 1.0 mg/L (0.7, 1.6 mg/L) (7.6 µmol/L [5.4, 11.6 µmol/L]) (P < .01). There was no significant correlation between patients’ ages and homocysteine levels (r = 0.07, P = .42). Diabetic patients had significantly lower homocysteine levels: 1.2 mg/L (0.9, 1.7 mg/L) (8.7 µmol/L [7, 12.3 µmol/L]) vs 1.6 mg/L (1.1, 2.4 mg/L) (11.8 µmol/L [8, 18.4 µmol/L]) (P = .005). Diabetes mellitus remained significantly associated with lower homocysteine levels, independent of age and sex (P = .003, P for interaction by analysis of variance = .60). A similar trend was noted with hypercholesterolemia: 1.3 mg/L (0.99, 1.82 mg/L) (9.4 µmol/L [7.2, 13.2 µmol/L]) vs 1.7 mg/L (1.1, 2.5 mg/L) (12.4 µmol/L [7.9, 18.4 µmol/L]) (P = .045). However, this trend did not exist after adjustment for sex differences (P by analysis of variance = .47). Among patients with hypercholesterolemia, there was no effect of previous statin use on the admission homocysteine levels (P = .97). We found no significant correlation between smoking (P = .22), hypertension (P = .45), family history of premature CAD (P = .16), and homocysteine levels.

**CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS**

On the basis of the receiver operating characteristics analysis, optional homocysteine threshold for the prediction of a recurrent coronary event and/or death was 2.7 mg/L (20 µmol/L). Twenty-two patients (14%) had homocysteine levels of 2.7 mg/L or more (mean ± SD, 4.6 ± 1.2 mg/L [34 ± 9 µmol/L]) and 135 patients (86%) had lower levels (1.4 ± 0.05 mg/L [10 ± 0.4 µmol/L]). Patients with homocysteine levels of 2.7 mg/L or more were less likely to have diabetes mellitus (9% vs 28%; P = .06) and a history of previous anginal syndrome (18% vs 37%; P = .09) than those with homocysteine levels less than 2.7 mg/L.
A larger number of patients in the group with higher homocysteine levels had a history of cerebrovascular event (18% vs 4%; \( P = .02 \)). Both groups of patients were comparable regarding other baseline demographic (Table 1) and initial clinical (Table 2) characteristics. Patients with higher and lower homocysteine levels also had similar peak CK values (690±598 U/L vs 591±635 U/L; \( P = .47 \)) and predischarge left ventricular ejection fraction (44%±11% vs 46%±9%; \( P = .45 \)). Patients with higher and lower homocysteine levels had a similar incidence of multivessel \( \text{CAD} \) (54% vs 61%; \( P = .87 \)) and mean number of diseased coronary arteries (1.7±0.8 vs 1.8±0.8; \( P = .90 \)).

**Clinical Outcome**

Patients with homocysteine levels of 2.7 mg/L or more and less than 2.7 mg/L did not differ significantly with regard to their in-hospital course (Table 3). Patients were followed up for a mean period of 30±10 months after discharge, without differences in length of follow-up between patients with higher and lower homocysteine levels. Two patients (1%) with lower homocysteine levels were lost to follow-up. The incidences of the major adverse clinical events during a mean ± SD follow-up of 30±10 months after acute myocardial infarction according to homocysteine level. All differences were statistically significant (\( P < .05 \)) except for the difference in urgent revascularization (\( P = .18 \)). CVS indicates cardiovascular system.

as well as a similar distribution of the culprit lesion within the infarct-related artery (proximally located culprit lesions [64% vs 60%; \( P = .80 \)]). In addition, a comparable number of patients with higher and lower homocysteine levels underwent percutaneous coronary interventions during hospitalization (59% vs 67%; \( P = .60 \)).
Homocysteine levels had a higher mortality rate than those with lower values (4 [18%] vs 7 [5%]; P < .05). All deaths in patients with higher homocysteine levels were due to cardiac causes, as were 6 of 7 deaths in patients with lower homocysteine levels. In multivariate analysis, higher homocysteine levels remained independent predictors of recurrent coronary event and/or death (odds ratio, 3.8; 95% confidence interval, 1.3-11.0) along with diabetes mellitus (odds ratio, 3.1; 95% confidence interval, 1.4-9.0), heart failure during hospitalization (odds ratio, 3.5; 95% confidence interval, 0.9-14.0), and reperfusion therapy (odds ratio, 0.1; 95% confidence interval, 0.005-0.6).

ANGIOGRAPHIC RESULTS

During the in-hospital course, 112 patients (71%) were catheterized. There was no significant difference in homocysteine levels between these patients and the remaining 45 noncatheterized patients: 1.6 mg/L (0.9, 2.4 mg/L) (11.6 µmol/L [6.7, 17.7 µmol/L]) vs 1.5 mg/L (1.1, 1.4 mg/L) (10.8 µmol/L [8.10 µmol/L]), P = .47. Among those catheterized, there was no correlation between homocysteine levels and the angiographic extent of the coronary disease. The homocysteine levels in patients with 1-, 2- and 3-vessel CAD were 1.3 mg/L (1.1, 2.2 mg/L) (9.3 µmol/L [7.6, 12.6 µmol/L]), 1.5 mg/L (1.1, 2.2 mg/L) (11.4 µmol/L [8.16.2 µmol/L]), and 1.5 mg/L (1.1, 1.9 mg/L) (10.8 µmol/L [8.2, 13.9 µmol/L]), respectively (P = .4). No correlation was found between homocysteine levels and angiographic findings was made. Nygard et al10 demonstrated a strong positive correlation between homocysteine levels and mortality in patients with angiographically confirmed CAD. Nevertheless, consistent with our findings, they found only a weak correlation between homocysteine level and the angiographic extent of the underlying coronary disease. Similarly, in the physician study, elevated homocysteine levels (2.2-4.2 mg/L [16-31 µmol/L]) were significant predictors of AMI and/or death,1 but were not associated with the risk of developing severe stable angina.19 These findings suggest that homocysteine levels are more strongly associated with the likelihood of coronary events than with the extent of the CAD.

In vitro models, elevated homocysteine levels induced a hypercoagulable state by reducing thrombomodulin level, protein C activity,20-22 and heparin sulfate level,23 as well as inhibiting the binding of tissue plasminogen activators to endothelial cells.24 In addition, they activated factors V and XII,25 increased tissue-factor expression on endothelial cells,26 and induced platelet adhesiveness and aggregation.13 Yet, it is important to note that the homocysteine levels in these studies were much higher than the levels usually encountered in a clinical setting. In clinical studies, hyperhomocysteinemia was associated with activation of coagulation systems in patients with premature atherosclerotic arterial disease3 and with thrombin generation in patients with acute coronary syndrome.14 Hyperhomocysteinemia was also found to be an independent risk factor for venous thromboembolism.37,20 Furthermore, homocysteine induces expression and release of the inflammatory cytokines monocyte chemotactic protein 1 in human monocytes28 and monocyte chemotactic protein 1, vascular cell adhesion molecule 1, and interleukin 8 in endothelial cells,30-32 resulting in increased adhesion of T cells and monocytes to homocysteine-exposed endothelial cells.32,33 Both the prothrombotic and proinflammatory effects of elevated homocysteine levels may account for the increased risk of recurrent coronary events in patients with elevated levels of homocysteine, irrespective of the extent of the underlying coronary disease.

STUDY LIMITATIONS

1. Both the small sample size and the determination of the homocysteine cutoff point based on empirical receiver operating characteristics rather than prospective analysis call for cautious interpretation of the results, particularly regarding long-term mortality. However, the 2 study groups (homocysteine levels ≥ 2.7 and < 2.7 mg/L) were similar with respect to the major predictors of long-term outcome after a cardiac event, including age, left ventricular ejection fraction, and extent of CAD. Moreover, patients with homocysteine levels of 2.7 mg/L or more had a lower prevalence of diabetes mellitus, further decreasing the chance of false-positive results.

2. Our current study findings suggest that increased homocysteine levels are associated with a worse prognosis after AMI, irrespective of the extent of the CAD. This conclusion is limited, however, by the fact that only 71% of the patients were catheterized. Yet, the absence of statistically significant differences in levels of homocysteine, clinical characteristics, and outcomes between
catheterized and noncatheterized patients decreases the likelihood of a significant bias.

3. Previous studies have demonstrated higher homocysteine levels in the convalescent period compared with those determined 24 to 48 hours after myocardial infarction and stroke onset, suggesting an acute-phase reaction. However, a more recent study, in which homocysteine levels were determined within the first 24 hours of the acute coronary syndrome—as in the present study—showed no significant differences between homocysteine levels determined within 24 hours and 1 and 6 months later. Furthermore, Al-Obaidi et al demonstrated a significant decrease in homocysteine levels on the second day, which might explain the differences between this and previous studies.

Our findings corroborate the accumulating evidence that elevated levels of homocysteine confer an increased risk of a coronary event. Previous prospective studies have shown that hyperhomocysteinemia is an independent risk factor for coronary events in the general population and in patients with angiographically confirmed CAD. The present study supports other recently published studies that demonstrate the same relationship in patients who sustained an acute coronary event, and further expand these studies by showing that this relationship exists irrespective of the extent of the angiographic CAD.

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