

Homocysteine Levels in Patients Undergoing Open-Heart Surgery

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ABSTRACT

Background: The aim of this prospective study was to determine the levels of plasma homocysteine (HCY) in patients who have undergone open-heart surgery for ischemic heart disease (IHD) or nonischemic heart disease (NIHD) and to evaluate whether an association is present between hyperhomocysteinemia and coronary artery disease.

Material and Methods: We investigated prospectively 30 patients who underwent open-heart surgery. Of these patients, 15 had IHD, and 15 had NIHD such as mitral and/or aortic valve disease. The 2 groups were well matched for age, sex, body mass index, and blood pressure. In all patients HCY was assayed by high performance liquid chromatography preoperatively and on the first, second, and third day postoperatively.

Results: The mean age of the patients was 57.2 years in group IHD and 52.6 years in group NIHD. The male:female ratio was 8:7 in group IHD and 7:8 in group NIHD. Of 15 patients in group IHD, 13 had hyperhomocysteinemia and 2 had normal plasma HCY levels. Of 15 patients in NIHD group, 1 had hyperhomocysteinemia and the others had normal plasma HCY levels. Preoperative plasma HCY levels of all patients in the IHD group were significantly lower during all subsequent time periods, whereas preoperative plasma HCY levels in the NIHD group were lower only on the first day post-surgery ($P < .05$).

Conclusions: Our data suggest that plasma HCY levels in patients with IHD are associated with the development of atherogenesis and coronary artery disease. For this reason, HCY levels should be measured routinely and treated appropriately in patients with risk factors for atherosclerosis.

Presented at the 52nd International Congress of the European Society for Cardiovascular Surgery, Istanbul, Turkey, November 7-10, 2003.

Received September 30, 2004; received in revised form November 3, 2004; accepted November 18, 2004.

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INTRODUCTION

One third to one half of the variation in vascular disease occurrence remains unexplained by traditional risk factors such as smoking, hypercholesterolemia, hypertension, and diabetes mellitus [Eikelboom 1999, Smith 2000]. Epidemiological and experimental evidence suggests that chronic hyperhomocysteinemia is an independent risk factor for the development of atherosclerosis, thrombosis, and other cardiovascular diseases, perhaps because of impaired fibrinolysis or increased platelet reactivity [Chao 1999, Li 2002, Bozkurt 2003, Hughes 2003].

The aim of the present prospective study was to determine the plasma homocysteine (HCY) levels in ischemic heart disease (IHD) and nonischemic heart disease (NIHD) patients to evaluate a possible relationship between hyperhomocysteinemia and coronary artery disease.

MATERIALS AND METHODS

We prospectively investigated 30 patients who underwent open-heart surgery in our clinic. In these patients, there were no additional diseases such as diabetes mellitus or renal failure. The patients were divided into 2 groups: a coronary artery disease (IHD) group ($n = 15$) and an NIHD group ($n = 15$), with the latter including patients with conditions such as mitral and/or aortic valve disease. The 2 groups were well matched for age, sex, body mass index, blood pressure, and history of smoking and chronic alcohol and coffee consumption. Blood samples were taken from all patients during the preoperative period and on the first and third day of the postoperative period.

The 5-mL fasting blood samples were drawn into EDTA-containing vacuum glass tubes for determination of the HCY. The EDTA samples for HCY measurement were immediately placed on ice and centrifuged at 3500g for 5 minutes. The plasma was separated and stored at -20°C until analysis. The resultant sample is stable for at least 4 weeks under these conditions. The plasma total HCY concentration was measured by an isocratic system with HPLC (HP 1100) at the following instrument settings: pump flow rate of 1.7 mL/min, injection volume of 20 μL , analytical run time of 4 to 5 minutes, and detection with fluorescence detector (Ex, 385 nm; Em, 515 nm).

We calculated matched odds ratio as estimates of the relative risk of atherosclerosis for HCY values above a given

Mean Plasma Homocysteine Values Obtained in Patients in the Ischemic Heart Disease (IHD) and Nonischemic Heart Disease (NIHD) Groups*

Parameters	IHD Group (n = 15)	NIHD Group (n = 15)
Preoperative	19.83 ± 3.92	10.98 ± 3.13†
Postoperative day 1	17.41 ± 2.30‡	9.76 ± 2.45†,§
Postoperative day 3	17.52 ± 2.46‡	9.04 ± 3†

*Numerical results are given as mean ± SD.

† $P < .001$ versus plasma homocysteine concentrations in IHD group patients.

‡ $P < .05$ versus preoperative plasma homocysteine levels in NIHD group patients, by Bonferroni test.

§ $P < .05$ versus Preoperative plasma homocysteine levels in of IHD group patients by Bonferroni test.

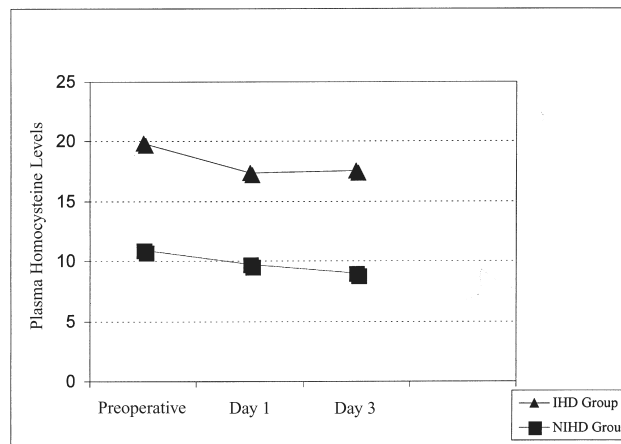
point, with the matching factor taking into account. The normal value of HCY is between 5 and 15 $\mu\text{mol/L}$. Plasma HCY levels $>15 \mu\text{mol/L}$, were considered to be hyperhomocysteinemia.

STATISTICAL ANALYSIS

Numerical results are expressed as means ± SD. The independent sample *t* test was used to compare the plasma HCY levels in patients with IHD and NIHD. The repeated measurement variance analysis (k-dependent group test) was used to determine whether there are differences between HCY levels during the preoperative period and on the first and third day of the postoperative period within each group. If differences were found, the Bonferroni test was used to assess these differences. The statistical differences were considered as significant if the *P*-value was .05 or less.

RESULTS

In IHD group, 8 patients were men and 7 were women, with ages ranging from 48 to 74 years (mean, 57.2 years). In NIHD group, 7 patients were men and 8 were women, with ages ranging from 38 to 65 years (mean, 52.6 years). All patients were similar in age, sex, and most other risk factors, but the patients in the NIHD group had a less frequent history of hyperlipidemia and hypercholesterolemia. The median plasma HCY levels in the patients with IHD (n = 15) and in the patients with NIHD (n = 15) are presented in the Table. Thirteen of 15 patients in the IHD group had hyperhomocysteinemia, and plasma HCY levels were normal in 2 patients. However, only 1 of 15 patients in the NIHD group had hyperhomocysteinemia, and plasma HCY levels were normal in the other patients (Table). The individual plasma HCY concentrations of patients with IHD and NIHD are shown in the Figure. The plasma HCY concentrations of the patients in the IHD group were found to be significantly higher than those in the NIHD group ($P < .001$). Preoperative plasma HCY levels of all patients in



The mean plasma homocysteine values of the ischemic heart disease (IHD) and nonischemic heart disease (NIHD) groups.

the IHD group significantly decreased during cardiopulmonary bypass and on the first and third day postsurgery ($P < .05$), whereas preoperative plasma HCY levels in the NIHD group significantly decreased only on the first day postsurgery ($P < .05$). In the NIHD group, postoperative third day plasma HCY levels were not significantly different from preoperative levels ($P > .05$).

DISCUSSION

Homocysteine is a sulfur-containing amino acid derived from methionine. Homocysteine metabolism involves remethylation, transsulfuration, and demethylation processes, which require folic acid, vitamin B₁₂, and vitamin B₆ [Prasad 1999]. The possible mechanisms for high plasma HCY levels leading to the development of atherosclerosis may be due to various factors including endothelial cell damage, smooth muscle cell proliferation, thromboembolism, and inability to sustain S-nitroso-homocysteine (a potent vasodilator and inhibitor of platelet aggregation) formation because of imbalance between nitric oxide production by dysfunctional endothelium and homocysteine [Prasad 1999, Milosevic-Tosic 2002]. Patients have severe hyperhomocysteinemia and a variety of abnormalities, including a high incidence of vascular pathology that may result in early death from myocardial infarction, stroke, or venous thromboembolism [Malinow 1999].

Hyperhomocysteinemia ($>15 \mu\text{mol/L}$) is caused by numerous factors including deficiencies in folic acid, vitamin B₁₂ and vitamin B₆, or enzymes (cystathione β -synthase, methionine synthase, methylenetetrahydrofolate reductase; the presence of certain drugs (methotrexate, phenitoin, nitrous oxide, theophylline, L-dopa, cholestamine, niacin); smoking; and chronic alcohol and coffee consumption [Prasad 1999, Li 2002]. For this reason, patients in our study did not receive the drugs that elevate plasma HCY levels or vitamins that decrease its levels. Also, all patients were well matched for blood pressure, smoking, and chronic alcohol and coffee consumption.

Modest increases in the concentration of HCY have been reported in patients with coronary artery disease, stroke, and peripheral vascular disease [Boushey 1995, Mayer 1996]. Our study showed that plasma HCY levels were high in 13 of 15 patients in the IHD group, whereas only 1 of 15 patients in NIHD group had hyperhomocysteinemia. The plasma HCY concentrations of the patients with IHD were found to be significantly higher than those in the NIHD group ($P < .001$). Levels of HCY were significantly elevated in the patients in the IHD group compared to patients in NIHD group. The present study confirmed the link between plasma HCY levels and coronary artery disease. In patients in IHD group, preoperative plasma HCY levels were significantly lower on both the first and third days postsurgery, whereas in patients in the NIHD group HCY levels were lower only on the first day postsurgery ($P < .05$). Our data suggest that plasma HCY levels in patients with IHD are associated with the development of atherogenesis and coronary artery disease. However, to confirm whether coronary revascularization is a factor affecting the levels of HCY, additional studies should be conducted, because of the relative small number of patients in our study.

The interaction of hyperhomocysteinemia with cholesterol, hypertension, and smoking is strong, and the combined effect of these factors is additive. Elevated homocysteine levels may result from low levels of folic acid, vitamin B₆, or vitamin B₁₂. It is well known that vitamin supplementation lowers homocysteine concentrations and reverses endothelial dysfunction in almost all subjects with hyperhomocysteinemia, regardless of the underlying cause [Woo 1997, Prasad 1999, Hackam 2000]. The observation of an association between a raised plasma homocysteine level and the occurrence of coronary atherosclerosis may imply the need for greater efforts to correct the nutritional factors that affect homocysteine metabolism [Wilcken 1997].

Our prospective and case-control study has shown that hyperhomocysteinemia is associated with coronary artery disease, and it is a risk factor for coronary atherosclerosis. We suggest that patients with elevated HCY should be treated with folic acid (1-2 mg/day), vitamin B₁₂, and vitamin B₆. In addition, it is recommended that the conditions that may elevate plasma homocysteine concentration, such as use of certain drugs, smoking, and chronic alcohol and coffee consumption, be avoided.

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