Relationship Between Plasma Homocysteine Levels and Congestive Heart Failure in Patients With Acute Myocardial Infarction

Homocysteine and Congestive Heart Failure

Takehiko Washio,1 MD, Kazumiki Nomoto,1 MD, Ikuyoshi Watanabe,1 MD, Shigemasa Tani,1 MD, Ken Nagao,1 MD, and Atsushi Hirayama,2 MD

Summary

Heart failure after acute myocardial infarction (AMI) is an important factor in determining clinical outcome. We examined whether the plasma homocysteine level was a predictor of heart failure in patients with AMI. A series of 96 patients without renal failure who were admitted to our hospital because of AMI between January 2003 and December 2005 were assigned to two groups: a group with a high homocysteine level (group H: n = 48) and a group with a low homocysteine level (group L: n = 48) based on a median homocysteine level. Congestive heart failure was defined as Killip Class II or higher at the time of admission or the development of congestive heart failure after hospitalization. The mean brain natriuretic peptide (BNP) level at the time of admission in group H was higher than that of group L (175.3 pg/mL versus 89.9 pg/mL; P = 0.068). The incidence of heart failure in group H was significantly higher than that in group L (43.7% versus 12.5%; P < 0.001, log-rank test; hazard ratio: 2.92). Multivariate Cox regression analysis indicated that a high plasma homocysteine level of 10.8 μmol/L or higher was a risk factor for the development of heart failure (HR: 7.175, P < 0.01). The plasma homocysteine level in patients with AMI may be related to the development of heart failure. (Int Heart J 2011; 52: 224-228)

Key words: Homocysteine, Congestive heart failure, Acute myocardial infarction

Since the publication of a report describing juvenile atherosclerotic and thrombotic lesions in patients with homocysteinuria caused by an inborn error of metabolism,1 research in this area has focused on the relationship between high plasma levels of homocysteine and cardiovascular disease. In 1984, Brattstrom, et al2 demonstrated that moderate hyperhomocysteinemia was a risk factor for cerebrovascular diseases, and a relationship between hyperhomocysteinemia and arteriosclerotic diseases has been reported in the United States, Europe and Japan.3-8) A high plasma homocysteine level has been shown to promote arteriosclerosis and to be an independent risk factor in the development of cardiovascular disease.9,10) In a cohort of patients in the Framingham Heart study, a high plasma homocysteine level was shown to be a predictor of heart failure in adults who had not yet experienced myocardial infarction.11) However, the relationship between heart failure and homocysteine levels in patients with AMI has not been reported. Here, we examined whether the plasma homocysteine level, a risk factor for arteriosclerosis and cardiovascular disease, was also related to the development of heart failure in patients with AMI.

Methods

Patients: The subjects comprised 96 consecutive patients admitted to our coronary care unit (CCU) between January 2003 and December 2005. All patients had been admitted within 24 hours of the onset of their conditions and met at least two of the following criteria; 1) chest pain persisting for 30 minutes or more; 2) an elevated ST on at least two leads; and 3) a peak creatine kinase level that was twice the normal upper limit. At the time of hospital admission, the plasma homocysteine, BNP, creatine kinase, and troponin T levels were measured. Patients with renal failure exhibit high homocysteine levels,16 patients with an estimated glomerular filtration rate (eGFR) of 30 mL/minute/1.73 m² or lower (indicating severe chronic kidney disease) were excluded from the present study. The creatine kinase and troponin T levels were measured at the time of hospital admission and at 3, 6, 12, 18, and 24 hours thereafter; the peak values obtained during this 24-hour period were recorded and used in subsequent analyses. At the time of hospital admission, echocardiography was conducted to assess the left ventricular ejection fraction (LVEF). All patients underwent an emergency coronary angiography and percutaneous coronary intervention (PCI), as necessary. The patients were classified into two groups: a group with a high homocysteine level (group H: n = 48) and a group with a low homocysteine level (group H: n = 48).
Patients with Killip Class II or higher at the time of admission to the CCU or with Killip Class I at admission who subsequently developed heart failure symptoms, including pulmonary congestion, effusion on chest X-rays, and ankle edema during hospitalization were defined as having heart failure. The present study was approved by the ethical committee of our hospital. All subjects provided written informed consent with regard to the measurement of their homocysteine levels and other parameters prior to their enrollment in the present study.

The plasma homocysteine levels were determined using high performance liquid chromatography (LC-9A; Shimadzu Corporation) (normal range: 3.7 to 13.5 μmol/L). Statistical analysis: All values are expressed as the mean ± standard deviation (SD). Parametric variables and nonparametric variables were compared using the t-test and the Mann-Whitney U test, respectively. Multivariate analyses were conducted using the Cox proportional hazard model. The incidence of heart failure and the survival rate were analyzed using the Kaplan-Meier method. These analyses were performed using Statview (ver. 5.0) computer software, and a value of P < 0.05 was regarded as significant.

The mean plasma homocysteine level of all the patients was 12.8 ± 8.3 μmol/L (range, 3.6 μmol/L - 51.4 μmol/L). The plasma homocysteine levels of groups H and L were 17.4 ± 1.4 μmol/L and 8.2 ± 0.3 μmol/L, respectively (P < 0.001). No differences in mean age (62.5 ± 2.0 years versus 64.5 ± 1.3 years; no significant difference [NS]) or gender (91.7% versus 77.1%; NS) were observed between the two groups. Further-
mine risk factors for the development of heart failure revealed that plasma homocysteine levels of 10.8 μmol/L or higher (HR: 7.175, \( P = 0.035 \)), the BNP level (HR: 1.005, \( P = 0.018 \)), and the peak creatine kinase level (HR: 1.001, \( P = 0.003 \)) were independent predictors of heart failure. However, no obvious relationship between heart failure and LVEF, age, CRP, or number of diseased vessels at the time of hospital admission was observed (Figure 2).

### Discussion

Homocysteine is an amino acid that is produced by the conversion of methionine to cysteine in two methionine metabolic pathways. One of these pathways requires vitamin B6 as a cofactor and the other requires vitamin B12. Hyperhomocysteinemia is induced by a deficiency of these vitamins, cystathionine β-synthase (a vitamin B6-dependent enzyme), and a genetic anomaly in methylenetetrahydrofolate reductase, all of which are essential for the above-mentioned metabolic pathways. Uremia is also known to alter the metabolism of homocysteine, leading to elevations in the plasma homocysteine level that are independent of the degree of renal homocysteine excretion. Hyperhomocysteinemia often accompanies renal dysfunction and sometimes occurs in hemodialysis patients. Therefore, in the present study, patients with eGFR levels of 30 mL/minute/1.73 m² or lower at the time of admission were excluded.

Hyperhomocysteinemia is an independent risk factor for arteriosclerotic and thromboembolic diseases, including myocardial infarction, cerebral infarction, and deep-vein thrombosis. Many issues regarding the mechanism of action of homocysteine in the pathogenesis of arteriosclerosis and thrombotic diseases remain unclear. However, possible causes include vascular endothelial dysfunction, smooth muscle cell growth, and an increase in blood clotting activity in vascular walls.

Elevated homocysteine levels may promote heart failure through 4 potential mechanisms. First, as described above, an elevated homocysteine level is widely considered a risk factor for coronary arteriosclerosis and myocardial infarction. Furthermore, homocysteine may cause myocardial ischemia in the absence of myocardial infarction by promoting endothelial dysfunction. Second, elevated homocysteine levels are related to high troponin levels in patients with acute coronary syndrome, suggesting that homocysteine might worsen myocardial injury. Third, homocysteine increases oxidative stress, a factor known to promote myocardial dysfunction. Finally, the development of myocardial fibrosis and matrix metalloproteinase activity was increased in rats with high levels of homocysteine.

In this study, however, no differences in the peak creatine kinase or troponin T levels, which indicate infarct size, were observed between the two groups. Therefore, heart failure was caused not only by direct myocardial damage resulting from AMI, but also occurred after AMI associated with potential cardiac dysfunction, including left ventricular remodeling, induced by elevated plasma homocysteine levels. May, et al. reported that hyperhomocysteinemia was independently associated with the presence of a low EF or a diagnosis of CHF, even after adjustments for the presence of coronary artery disease. Furthermore, Blacher, et al. demonstrated that significant associations were found between the plasma homocysteine level and the left ventricular mass. These correlations were independent of coronary artery disease, age, and sex.

In this study, the BNP level at admission was increased in the high homocysteine group. Some of the patients might have developed heart failure as a result of severe AMI at the time of admission; this would explain why the BNP levels were elevated. In an analysis of patients without signs of heart failure at the time of admission, no differences in infarct size (peak creatine kinase and troponin T levels) or BNP levels were observed between the groups. However, the incidence of heart failure was still higher in group H.

In the multivariate Cox regression analysis performed in the present study, hyperhomocysteinemia was independently associated with heart failure even after adjustments for CRP and the presence of recognized risk factors such as a low LVEF, age, and the number of diseased coronary vessels. High creatine kinase and BNP levels were independent risk factors.
for heart failure, but the hazard ratios for these parameters were not as high as that for hyperhomocysteinemia. Therefore, we concluded that hyperhomocysteinemia was more useful than infarct size for predicting heart failure.

**Limitations:** The results of this study suggest that a high homocysteine level may be a predictor of heart failure. However, the present data provide no insight regarding the associated pathogenic mechanisms. Some studies have proposed a mechanism whereby a high homocysteine level could cause heart failure. Additionally, some studies have reported that vitamin supplementation, including folic acid supplementation, improved the potency of vasodilation and decreased blood pressure.32,33 whereas others have suggested that such supplements are not effective.44,45 Therefore, in addition to evaluating the long-term outcome of the subjects in this study, further studies on the possible benefits of vitamin supplementation are necessary.

Our conclusions and interpretations of the findings in the present study were limited by the small study sample. Additional investigations in a larger number of patients are needed to validate our findings.

**Conclusion:** An elevated plasma homocysteine level in patients with AMI may be related to the development of heart failure. A high plasma homocysteine level also appears to be an independent predictor of other recognized risk factors of heart failure.

**REFERENCES**

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