Original Article

High plasma homocysteine is associated with the risk of coronary artery disease independent of methylenetetrahydrofolate reductase 677C→T genotypes

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Hyperhomocysteinemia is an independent risk factor for coronary artery disease (CAD). The aim of this study was to investigate the relations between the methylenetetrafolate reductase (*MTHFR*) 677C →T genotypes, B-vitamins (folate, vitamin B-12 and B-6), homocysteine and the risk of CAD. In this case-control study, patients who were identified by cardiac catheterization as having at least 50% stenosis of one major coronary artery were assigned to the case group (n = 121). Healthy individuals with normal blood biochemical values were assigned to the control group (n = 155). Healthy subjects were matched to case subjects for age. The concentrations of plasma homocysteine, serum folate, vitamin B-12, plasma pyridoxal 5'- phosphate (PLP) and *MTHFR* 677C→T gene polymorphism were obtained. The T-allele carriers had significantly higher plasma homocysteine concentration compared to subjects with the 677CC genotype. The *MTHFR* 677C→T genotypes were associated with plasma homocysteine after adjusting for various potential risk factors in the case and pooled groups. The *MTHFR* genotypes were found to have no associations with the risk of CAD. However, plasma homocysteine (≥ 12.5 μmol/L) (OR, 3.49; 95% CI, 1.23 – 9.88) had a significant association with increased risk of CAD even after additionally adjusted folate status. High plasma homocysteine concentration had a direct effect on the risk of CAD independent of *MTHFR* 677C→T genotypes.

Key Words: methylenetetrahydrofolate reductase, gene polymorphism, homocysteine, B-vitamins, coronary artery disease

INTRODUCTION

Epidemiological studies and clinical trials have shown that hyperhomocysteinemia is an independent risk factor for coronary artery disease (CAD).[1-3] In addition to B-vitamins (i.e., folate, vitamin B-6 and B-12) deficiencies, genetic defects are particularly interesting because of their association with the elevated plasma homocysteine concentrations.

Homocysteine can be remethylated to form methionine or transsulfurated to form cysteine. In the remethylation pathway, the 5, 10-methylenetetrahydrofolate reductase (*MTHFR*), a folate-dependent enzyme, catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. The *MTHFR* 677C→T mutation may contribute to hyperhomocysteinemia and has been considered to be a common genetic risk factor for CAD[4,5] because it is thermolabile and mildly dysfunctional *in vivo*. [6,7] The *MTHFR* 677C→T mutation leads to moderate hyperhomocysteinemia with low folate status.[4,8] A meta-analysis by Cronin et al.[9] concluded that the *MTHFR* 677C→T allele is a genetic risk factor for stroke. However, the inconsistency between this genetic defect and CAD has also been reported. [10] It might be worth to know whether this genetic defect is independent or involves a synergic effect with homocysteine or the B-vitamins, in the risk of CAD. Therefore, the purpose of this study was to investigate the relationship between genetic mutation, B-vitamins, homocysteine and the risk of CAD.

MATERIALS AND METHODS

Subjects

This study was designed as a case-control study. Patients were recruited from the cardiology clinic of Taichung Veterans General Hospital and were assigned to the case group through the identification of cardiac catheterization as representative of at least 50% stenosis of one major coronary artery (Case group, n = 121). Healthy subjects

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were matched to case subjects for age (± 2 years) and recruited from the physical examination unit of Taichung Veterans Hospital who exhibited normal blood biochemical values, including fasting blood glucose < 110 mg/dL, blood urea nitrogen (BUN) < 7.9 mmol/L, creatinine < 1.4 mg/dL, alkaline phosphates < 190 U/L, glutamic oxoloacetic transaminase (GOT) < 35 U/L, and glutamic pyruvate transaminase (GPT) < 45 U/L. Healthy subjects had no history of gastrointestinal disorder, cardiovascular disease, hypertension, hyperlipidemia, liver and renal disease, diabetes, cancer, alcoholism or other metabolic disease (Control group, n = 155). Informed consent was obtained from each subject. This study was approved by the Institutional Review Board of Chung Shan Medical University.

All subjects' age and gender were recorded. Body weight and height were also measured and the body mass index (BMI; kg/m^2) was then calculated. Blood pressure [systolic blood pressure (SBP), diastolic blood pressure (DBP)] was measured after a resting period of at least 5 min. All subjects were instructed as to how to complete a 24-hour diet recall, and the recall was obtained on the day blood samples were drawn. If subjects took vitamin or mineral supplements, the brand name, contents, dosage, and frequency of intake were also recorded to determine total nutrient intake. Nutrient composition was calculated with the use of Nutritionist Professional software (Kitchen Business Corporation, Taiwan), and the nutrient database was based on the Taiwan food composition table (Department of Health, 1998).

Blood analyses

Fasting venous blood samples (15 mL) were obtained to estimate hematological and vitamin status. Blood specimens were collected in Vacutainer tubes (Becton Dickinson, Rutherford, NJ, USA) containing EDTA as an anticoagulant or no anticoagulant as required. Serum and plasma were prepared and then stored frozen (-80℃) until analysis. Plasma homocysteine was measured by using high-performance liquid chromatography (HPLC) according to the method of Araki and Sako.[11] The intra- and inter-assays of fasting plasma homocysteine variabilities were 1.6% (n = 3) and 4.3% (n = 15), respectively. Plasma pyridoxal-5'-phosphate (PLP), the biologically active form of vitamin B-6, was determined by HPLC based on the method of Bates et al.[12] and conducted under yellow light to prevent photo-destruction. The intra- and inter-assays of plasma PLP variabilities were 2.0% (n = 4) and 3.6% (n = 4), respectively. Serum folate and vitamin B-12 were analyzed by using standard competitive immunochemiluminometric methods on a Chiron Diagnostics ACS: 180 Automated Chemiluminescence System (Chiron Diagnostics Corporation, East Walpole, MA, USA). All analyses were performed in duplicate. Hematological entities [i.e., BUN, serum creatinine, GOT, GPT, total cholesterol, triacylglycerol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL)] were measured by using an automated biochemical analyzer. Automated high sensitivity C-reactive protein (hs-CRP) measurements were performed by particle-enhanced Immunonephelometry with an Immage analyzer. [13] DNA was extracted from frozen peripheral blood lymphocytes by use of a genomic DNA purification kit (Pharmacia GFX spin column, USA). The *MTHFR* 677C→T gene polymorphism was amplified by polymerase chain reaction. The amplified DNA fragment (198 bp) was then digested by the H*in*FI restriction enzyme (New England BioLabs, Ipswich, MA) and subsequent electrophoresis in a 4% agarose gel.[14,15]

Statistical analyses

Data were analyzed with SigmaStat statistical software (version 2.03; Jandel Scientific, San Rafael, CA). Differences in subjects' demographic data and hematological measurements were analyzed by Student's t-test or Mann-Whitney rank sum test between the two groups. For categorical response variables, differences between two groups were assessed by Chi-square test. Differences in subjects' plasma homocysteine and B-vitamins concentration after stratification by *MTHFR* 677C→T genotypes were analyzed by one-way analysis of variance (ANOVA) with the Tukey post hoc test or Kruskal-Wallis one-way analysis of variance on ranks. To examine the association of *MTHFR* 677C→T gene polymorphism and B-vitamins with plasma homocysteine concentrations, multiple linear regression analyses were performed with adjustment for potential confounders. Adjusted odds ratios (ORs) with 95% confidence intervals (CI) for CAD were calculated from unconditional logistic regression models according to the *MTHFR* 677C→T genotypes and plasma homocysteine. Results were considered statistically significant at $p < 0.05$. Values presented in the text are means ± standard deviation (SD).

RESULTS

Table 1 shows the demographic data and health characteristics of the study subjects. Subjects in the case group had significantly higher BMI, SBP, LDL, total cholesterol/HDL ratio, triacylglycerol, hs-CRP but lower serum creatinine and HDL than subjects in the control group. With regard to the three variants distribution of the *MTHFR* 677C→T genotypes, there were no significant differences between two groups. The genotypes distribution between the two groups of subjects was consistent with that calculated from the Hardy-Weinberg equilibrium.

Unexpectedly, case subjects had a significantly higher serum folate concentration and intake than that of control subjects (Table 1) and even after stratification by the *MTHFR* 677C→T genotypes (data not shown). There were 53.7% of CAD subjects (31.4% 677CC, 19% 677CT and 3.3% 677TT) compared to 26.5% of control subjects (15.5% 677CC, 9% 677CT and 2.4% 677TT) who had adequate folate intake (> 400 μg/d). There were no significant differences in serum vitamin B-12 concentrations between the two groups. However, subjects in the case group consumed significantly lower amounts of vitamin B-12 than did subjects in the control group. Control subjects had significantly higher mean plasma PLP concentration than that of case subjects. However, there were no significant differences on vitamin B-6 intakes between the two groups.

Table 2 shows the concentration of plasma homocysteine and B-vitamins according to different *MTHFR*

Table 1. Demographic and health characteristics of study subjects[1]

Characteristics	Case (n = 121)	Control (n = 155)	p-value
Male / Female	77 / 4	85 / 70	0.418
Age (y)	59.1 ± 8.43	58.8 ± 7.08	0.789
MTHFR 677C→T (n)			
CC/CT/TT	66 / 47 / 8	88 / 57 / 10	0.675
BMI (kg/m^2)	25.9 ± 3.33	23.9 ± 3.01	< 0.001
Blood pressure			
SBP (mmHg)	131 ± 20.6	121 ± 17.3	< 0.001
DBP (mmHg)	76.1 ± 12.8	75.0 ± 9.70	0.365
Cholesterol (mmol/L)			
Total	4.80 ± 1.10	4.84 ± 0.83	0.719
LDL	3.14 ± 1.06	2.65 ± 0.82	< 0.001
HDL	1.07 ± 0.30	1.66 ± 0.40	< 0.001
Total cholesterol/HDL ratio	4.70 ± 1.40	3.10 ± 0.90	< 0.001
Triacylglycerol (mmol/L)	1.73 ± 0.93	1.15 ± 0.55	< 0.001
hs-CRP (mg/L)	8.04 ± 21.6	1.45 ± 29.2	< 0.001
Serum creatinine (μmol/L)	79.6 ± 35.4	88.4 ± 17.7	< 0.001
Plasma homocysteine (μmol/L)	10.7 ± 5.60	9.60 ± 2.20	0.799
Folate			
Serum (nmol/L)	36.3 ± 17.2	25.4 ± 12.0	< 0.001
Intake (μg/d)	488 ± 282	317 ± 188	< 0.001
Vitamin B-12			
Serum (pmol/L)	381 ± 135	380 ± 150	0.617
Intake (μg/d)	4.88 ± 9.79	6.68 ± 11.2	0.048
Vitamin B-6			
Plasma PLP (nmol/L)	39.9 ± 48.6	69.4 ± 61.4	< 0.001
Intake (mg/d)	1.45 ± 1.18	1.70 ± 2.04	0.586

[1]Values are means ± standard deviation. BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein

677C→T genotypes. There was no significant difference with regard to plasma homocysteine concentrations among three genotypes, in both case and control groups. However, carriers of the T-allele had significantly higher plasma homocysteine concentration than subjects with the 677CC genotype in the pooled (case plus control) group. Subjects with the 677TT genotype had slightly lower serum folate (p = 0.05) and significantly lower vitamin B-12 concentration when compared with subjects with the 677CC genotype in the case group; while there was no significant difference in plasma PLP concentration among three different genotypes in the case group.

The associations between plasma homocysteine with *MTHFR* 677C→T genotypes and B-vitamins are listed in Table 3. The plasma homocysteine concentration were significantly and positively associated with *MTHFR* 677C→T genotypes after adjusting for potential risk factors and even after additionally adjusting for three B-vitamins in the case and pooled groups. Plasma homocysteine was significantly negatively associated with serum folate only in the case group. Serum vitamin B-12 and plasma PLP were significantly negatively associated with the plasma homocysteine concentration in the control and pooled groups.

We then calculated the risks of CAD (Table 4). The *MTHFR* 677C→T genotypes had no associations with the risk of CAD. After additional adjustments for homocysteine and three B-vitamins, the relations with the risk of CAD were still non significant. Plasma homocysteine (≥ 12.5 μmol/L), however, showed a significant association with the risk for CAD (OR, 2.95) after the potential confounders were adjusted for. The OR for CAD (OR, 3.49) was even much greater after additionally adjusting for the *MTHFR* 677C→T genotypes and serum folate. When *MTHFR* 677C→T genotypes and plasma homocysteine were simultaneously considered in the logistic regression model, subjects with plasma homocysteine ≥ 12.5 μmol/L increased the risk of CAD independent of the *MTHFR* 677C→T genotype.

DISCUSSION

Similar to the results of previous studies regarding the relationship between the *MTHFR* 677C→T genotypes and the risk of CAD,[4,9,10] our results failed to support the implication that the *MTHFR* 677C→T gene mutation is associated with the risk of CAD. Though *MTHFR* 677C→T gene mutation was associated with increased homocysteine concentration in those with a low folate status (control group), the association of this genetic defect might be compensated by adequate folate intake.[16,17] Nutritional compensation may make a substantial difference in homocysteine concentrations in those with

Table 2. Homocysteine and B-vitamins concentration according to the methylenetetrahydrofolate reductase 677C→T genotypes[1]

	Case (*n* = 121)				Control (*n* = 155)				Pooled (n = 276)			
	CC (n = 66)	CT (n = 47)	TT (n = 8)	T-allele[2] (n = 55)	CC (n = 88)	CT (n = 57)	TT (n = 10)	T-allele (n = 67)	CC (n = 154)	CT (n = 104)	TT (n = 18)	T-allele (n = 122)
Homocysteine (μmol/L)	10.2 ± 4.8	10.3 ± 3.1	16.6 ± 14.6	11.2 ± 6.4	9.4 ± 2.3	9.8 ± 2.2	10.3 ± 1.8	9.9 ± 2.1	9.8 ± 3.6[d]	10.1 ± 2.7	13.1 ± 10.0	10.5 ± 4.6
Folate (nmol/L)	38.5 ± 17.0[a,b]	35.3 ± 17.7[a]	24.5 ± 11.1[a]	33.8 ± 17.2[a]	24.9 ± 11.8	26.1 ± 12.7	26.3 ± 10.9	26.1 ± 12.5	30.6 ± 15.6	30.4 ± 15.9	25.4 ± 10.7	29.7 ± 15.2
Vitamin B-12 (pmol/L)	402 ± 143[c]	367 ± 118	275 ± 114	353 ± 121	378 ± 151	388 ± 154	348 ± 128	382 ± 150	389 ± 147	379 ± 140	316 ± 124	370 ± 139
PLP (nmol/L)	35.9 ± 41.2[a]	40.6 ± 37.8[a]	68.9 ± 118.7	44.7 ± 56.1 [a]	63.2 ± 53.3	79.3 ± 73.6	66.2 ± 47.6	77.4 ± 70.2	51.5 ± 50.2	61.8 ± 62.9	67.4 ± 83.7	62.6 ± 66.0

[1]Values are means ± standard deviation. [2]T-allele means subjects carried CT or TT genotypes.
[a]Calculated with Student's *t*-test between case and control groups within the genotype, $p < 0.05$. [b]Calculated with Kruskal-Wallis one-way analysis of variance on ranks in the case group (CC v.s. TT) , $p = 0.05$. [c]Calculated by one-way ANOVA with the post hoc test of Tukey in the case group (CC v.s. TT) , $p < 0.05$. [d]Calculated with Mann-Whitney rank sum test in pooled groups (CC v.s. T-allele), $p < 0.05$.
MTHFR, methylenetetrahydrofolate reductase; PLP: pyridoxal 5'-phosphate.

Table 3 Multiple linear regression analysis with plasma homocysteine concentrations as the dependent variable after adjusting for potential confounders

	Case (n = 121)			Control (n = 155)			Pooled (n = 276)		
	β [1]	SE [2]	p	β	SE	p	β	SE	p
MTHFR 677C→T genotypes[3]									
Model 1[4]									
CC	Reference	—	—	Reference	—	—	Reference	—	—
CT	-0.55	1.38	0.693	0.49	0.33	0.133	0.13	0.49	0.795
TT	8.32	2.52	0.002	0.10	0.67	0.876	3.20	0.96	0.001
Model 2[5]									
CC	Reference	—	—	Reference	—	—	Reference	—	—
CT	0.12	1.44	0.933	0.63	0.33	0.054	0.55	0.47	0.235
TT	8.74	2.53	0.001	0.42	0.68	0.539	3.67	0.93	<0.001
T-allele[6]									
Model 1	1.08	1.39	0.438	0.44	0.31	0.162	0.60	0.47	0.206
Model 2	1.64	1.48	0.273	0.60	0.31	0.054	0.99	0.46	0.030
Serum folate (nmol/L)									
Model 1	-0.10	0.04	0.020	-0.00	0.01	0.895	-0.03	0.02	0.056
Model 3[7]	-0.06	0.04	0.114	0.00	0.01	0.860	-0.02	0.02	0.231
Serum vitamin B-12 (pmol/L)									
Model 1	-0.01	0.01	0.059	-0.00	0.00	0.010	-0.01	0.00	0.003
Model 3	-0.01	0.01	0.121	-0.00	0.00	0.041	-0.00	0.00	0.016
Plasma PLP (nmol/L)									
Model 1	0.00	0.02	0.828	-0.01	0.00	0.008	-0.01	0.00	0.043
Model 3	0.01	0.03	0.756	-0.01	0.00	0.068	-0.01	0.00	0.085

[1]β, regression coefficient. [2]SE, standard errors. [3]*MTHFR*, methylenetetrahydrofolate reductase; CC = 0, 0; CT = 1, 0; TT = 0, 1. [4]Adjusting for age, gender, body mass index, total cholesterol to high density lipoprotein ratio, creatinine, systolic blood pressure and C-reactive protein. [5]As for model 1 and additionally adjusting for B-vitamins (folate, vitamin B-6 and vitamin B-12). [6]T-allele means subjects carried CT or TT genotypes. [7]As for model 1 and additionally adjusting for *MTHFR* and the other two B-vitamins.

Table 4. Adjusted odds ratios of coronary artery disease according to methylenetetrahydrofolate reductase genotypes and plasma homocysteine concentrations

	Factors adjusted[1]			Additional factors adjusted[2]		
	OR	95% CI	*p*	OR	95% CI	*p*
MTHFR 677C→T genotypes						
CC	1.00	–	–	1.00	–	–
CT	0.76	0.36 – 1.57	0.453	0.73	0.34 – 1.57	0.426
TT	1.16	0.55 – 2.44	0.697	1.14	0.48 – 2.71	0.774
T-allele[3]	0.80	0.40 – 1.59	0.524	0.75	0.36 – 1.54	0.427
Plasma homocysteine						
< 12.5 μmol/L	1.00	–	–	1.00	–	–
≥ 12.5 μmol/L	2.95	1.09 – 7.99	0.033	3.49	1.23 – 9.88	0.019
MTHFR genotypes + Plasma homocysteine						
677CC + homocysteine < 12.5 μmol/L	1.00	–	–	1.00	–	–
T-allele + homocysteine < 12.5μmol/L	0.92	0.43 – 1.97	0.829	0.90	0.42 – 1.95	0.794
677CC + homocysteine ≥ 12.5 μmol/L	3.62	1.02 – 12.9	0.047	3.99	1.06 – 15.1	0.041
T-allele + homocysteine ≥ 12.5 μmol/L	2.00	0.44 – 9.00	0.367	2.62	0.57 – 12.1	0.219

[1]Adjusting for age, gender, body mass index, total cholesterol to high density lipoprotein ratio, creatinine, systolic blood pressure and C-reactive protein. [2]Additionally adjusting for the genotypes, folate and/or homocysteine. [3]T-allele means subjects carried CT or TT genotypes. CI, 95% confidence interval; OR, odds ratio; *MTHFR*, methylenetetrahydrofolate reductase.

MTHFR 677C→T gene mutation. This might be a reason for the inconsistency between the *MTHFR* 677C→T genotypes and the risk of CAD.

Previous studies indicated that the plasma homocysteine concentration in the 677TT genotype might be more sensitive to folate status.[18,19] The results of our study showed that T-allele carriers had a significantly higher plasma homocysteine concentration. Although the *MTHFR* 677C→T genotypes did not have an association with the risk of CAD, this gene mutation significantly increased the homocysteine concentration even when folate was further adjusted for. In partial agreement with Meleady et al.[19] we support the finding that the *MTHFR* 677C→T genotype has no association with the risk of CAD but mediates it through high plasma homocysteine concentrations. Brattström et al.[10] indicated that the common *MTHFR* 677C→T genotype is accompanied by a small elevation of homocysteine concentration, but the mutation is not associated with increased cardiovascular risk that might be an epiphenomenon in vascular patients. It is also highly likely that our limited sample size of TT genotype is a major methodological limitation to determine the association between *MTHFR* 677C→T genotypes and the risk of CAD.

Schneider et al.[20] reported that the *MTHFR* C677T mutation had a different distribution among different ethnic groups. A meta-analysis showed that the distribution of TT homozygous was from 3.9% to 17% in the European and North American white populations.[21] The frequency of the TT genotype was 7% in the Taiwanese in our study and was similar to that of previous studies.[22-25] However, the TT genotype was much higher and was noted in 15-23% of other Asian populations (i.e., Korean, Japanese and Chinese)[26-28] when compared with whites and our study group. It seems that the frequency of the homozygous mutation varies, even among Asian populations.

In addition to the ethnic issue, age and gender may also confound the relationship between the *MTHFR* 677C→T genotypes and the risk of CAD. Age and gender were associated with the elevated plasma homocysteine concentration [29] and CAD risk factors.[30, 31] Our male subjects also had a significantly higher homocysteine concentration than females (11.8 ± 5.4 vs. 8.7 ± 3.2 μmol/L). Since there were different gender distributions in the CAD and control groups, we further excluded the female data to minimize the gender effect. The results did not show any significant modification after female data were excluded; therefore, data from both genders were included in all statistical analyses. In addition, after we adjusted for age and gender, the differences did affect the results of this study.

Folate status has been demonstrated to be a much stronger determinant of plasma homocysteine than vitamin B-12 and B-6.[32] Amouzou et al.[8] indicated that a high prevalence of moderate hyperhomocysteinemia was associated with folate deficiency. A low dose (0.5 mg/d) of folic acid has been shown to be effective in lowering plasma homocysteine concentration by 18% in CAD subjects[33] however the reduction was not significant with regard to the control group. Another large trial (the Norwegian Vitamin trial, NORVIT)[34] giving 3,749 men and women with acute myocardial infarction different combinations of B-vitamins, showed that although daily administration of 0.8 mg/d folic acid and 0.4 mg vitamin B-12 could reduce reduced plasma homocysteine concentration by 27%, such treatment had no beneficial effects on the primary end point and even resulted in an increased risk of recurrent CAD or death after acute myocardial infarction. [34] The Heart Outcomes Prevention Elevation 2 (HOPE-2) study[35] treated 5,522 vascular disease patients either with folic acid (2.5 mg/d) combined with vitamin B-6 (50 mg/d) and B-12 (1 mg/d) or with placebo for an average of five years; however, folic acid supplements did not reduce the risk of major cardiovascular events. The novelty of the present study is that our CAD subjects had higher serum folate concentration and intake compared to control subjects (Table 1), and the negative association of serum folate with plasma homocysteine was only observed in the case group (Table 3). It is worth noting that the amount of folate intake of our CAD subjects was reflected in their biochemical values. Dietary folic acid intake had significantly positive correlation with serum folate status (data not shown). It seems reasonable to assume that case subjects might tend to increase their folate intake after they have been diagnosed with CAD, since high folate intake has recently been shown to be beneficial in preventing CAD. The question is whether an increased dietary folate intake would reduce the risk of CAD. The review by Ubbink et al.[36] noted that late-in-life dietary folate changes can only produce limited effects since the development of atherosclerosis begins at a much earlier stage. The limitation of this study was that we did not exclude subjects who took vitamin supplements and we were also not aware of the folate status of CAD subjects before they were diagnosed with CAD. Therefore, conducting a prospective study (i.e., cohort study) might help researchers to better understand the association between folate status and the risk of CAD.

In conclusion, *MTHFR* 677C→T genotypes results in a significant increase in plasma homocysteine after the additional adjustment of serum folate, but it is not associated with the risk of CAD. Higher plasma homocysteine concentration (> 12.5 μmol/L) is associated with the risk of CAD independent of *MTHFR* 677C→T genotypes.

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Original Article

High plasma homocysteine is associated with the risk of coronary artery disease independent of methylenetetrahydrofolate reductase 677C→T genotypes

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同半胱胺酸而非甲基四氫葉酸還原酶(MTHFR 677C→T)基因多型性顯著獨立增加罹患冠狀動脈心臟病之危險性

高同半胱胺酸血症已被認為是冠狀動脈心臟病獨立危險因子之一。本研究為病例－對照組之研究，其目的為探討血漿同半胱胺酸（Hcy）及甲基四氫葉酸還原酶（MTHFR 677C→T）基因多型性與罹患冠狀動脈心臟病（CAD）之相關性。病例組由台中榮總心臟內科門診募集 CAD 受試者，並經心導管檢查發現冠狀動脈狹窄程度 ≥ 50%者（n = 121）；對照組受試者則於台中榮總健檢中心募集，經檢查有正常血清生化值者，且年齡與 CAD 受試者配對（n = 155）。結果發現攜帶 677TT 基因型之受試者，其血漿 Hcy 濃度顯著高於 677CC 者；而 MTHFR 677C→T 基因之多型性與 CAD 危險對比值卻無顯著相關性。邏輯式回歸顯示當血漿同半胱胺酸濃度大於 12.5 μmol/L 時，會顯著增加罹患 CAD 之危險對比值，即使調整血清葉酸後，此顯著性仍然存在（OR，3.49；95% CI, 1.23 – 9.88）。因此本研究認為高同半胱胺酸直接且顯著影響罹患 CAD 危險性。

關鍵字：五甲基四氫葉酸還原酶、基因多型性、同半胱胺酸、B-維生素、冠狀動脈心臟病。