Lack of carotid stiffening associated with MTHFR 677TT genotype in cardiorespiratory fit adults

Motoyuki Iemitsu,1,2 Haruka Murakami,1 Kiyoshi Sanada,2 Kenta Yamamoto,1 Hiroshi Kawano,3 Yuko Gando,3 and Motohiko Miyachi1
1Health Promotion and Exercise Program, National Institute of Health and Nutrition, Tokyo; 2Faculty of Sport and Health Science, Ritsumeikan University, Shiga; and 3Faculty of Sport Sciences, Waseda University, Saitama, Japan
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Iemitsu M, Murakami H, Sanada K, Yamamoto K, Kawano H, Gando Y, Miyachi M. Lack of carotid stiffening associated with MTHFR 677TT genotype in cardiorespiratory fit adults. Physiol Genomics 42: 259–265, 2010. First published April 20, 2010; doi:10.1152/physiolgenomics.00039.2010.—The TT genotype of C677T polymorphism in 5,10-methylenetetrahydrofolate reductase (MTHFR) induces elevation of homocysteine level and leads to atherosclerosis and arterial stiffening. Furthermore, cardiorespiratory fitness level is also associated with arterial stiffness. In the present study, a cross-sectional investigation of 763 Japanese men and women (18–70 yr old) was performed to clarify the effects of cardiorespiratory fitness on the relationship between arterial stiffness and MTHFR C677T gene polymorphism. Arterial stiffness was assessed by carotid β-stiffness with ultrasonography and tonometry. The study subjects were divided into high-cardiorespiratory fitness (High-Fit) and low-cardiorespiratory fitness (Low-Fit) groups based on the median value of peak oxygen uptake in each sex and decade. The plasma homocysteine level was higher in the TT genotype of MTHFR C677T polymorphism compared with CC and CT genotype individuals. MTHFR C677T polymorphism showed no effect on carotid β-stiffness, but there was a significant interaction effect between fitness and MTHFR C677T polymorphism on carotid β-stiffness (P = 0.0017). In the Low-Fit subjects, carotid β-stiffness was significantly higher in individuals with the TT genotype than the CC and CT genotypes. However, there were no such differences in High-Fit subjects. In addition, β-stiffness and plasma homocysteine levels were positively correlated in Low-Fit subjects with the TT genotype (r = 0.71, P < 0.0001), but no such correlations were observed in High-Fit subjects. In CC and CT genotype individuals, there were also no such correlations in either fitness level. These results suggest that the higher cardiorespiratory fitness may attenuate central artery stiffening associated with MTHFR C677T polymorphism.

peak oxygen uptake; arterial stiffness; homocysteine; 5,10-methylenetetrahydrofolate reductase

ELEVATED PLASMA HOMOCYSTEINE level is considered a risk factor for cardiovascular events and is associated with arterial stiffness and atherosclerosis in subjects with some cardiovascular risk factors (7, 15, 30, 36). High homocysteine levels may impair endothelial function, increase oxidative stress, and alter protein structure (5, 6, 37). Exposure of endothelial cells to elevated homocysteine levels results in decreased availability of nitric oxide (NO), which has vasodilatory and antiplatelet effects, and impaired vascular function, which are early events in atherogenesis (6, 29, 33, 35). Homocysteine metabolism represents an interesting model of gene-environment interaction (34, 38). Elevations in homocysteine may be caused by genetic and environmental factors and by gene-gene and/or gene-environment interactions. The enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (4). A polymorphism of C677T (Ala→Val) in the gene encoding MTHFR is associated with decreased activity of the enzyme due to thermolability (1). In individuals homozygous for the T (Val) allele, a relative deficiency in the remethylation process of homocysteine into methionine leads to mild to moderate hyperhomocysteinemia, a condition recognized as an independent risk factor for arterial stiffness and atherosclerosis (1, 34). Thus the variation in MTHFR genetic sequence was shown to be associated with differences in the development of cardiovascular disease and related conditions, such as arterial stiffness and atherosclerosis.

Habitual exercise results in higher cardiorespiratory fitness and reduced risk of cardiovascular disease, such as arterial stiffness and atherosclerosis (8, 11, 12, 31). There have been several cross-sectional studies regarding the relationship between cardiorespiratory fitness and homocysteine status. These factors were reported to be independent regardless of sex (10) or to be negatively associated in women but not in men (19). Therefore, genetic variations in MTHFR, such as C677T polymorphism, may influence the effects of regular exercise and plasma homocysteine status on arterial stiffness. Recently, plasma homocysteine levels were shown not to be associated with cardiorespiratory fitness after controlling for potential confounders, including MTHFR C677T, in a cross-sectional study of Swedish children and adolescents (26). However, it remains unclear whether cardiorespiratory fitness level affects the relationship between arterial stiffness and genetic variations in MTHFR.

We hypothesized that single-nucleotide polymorphism (SNP) genotypes of C677T (Ala→Val) in exon 5 of MTHFR on chromosome 1 and cardiorespiratory fitness level may affect arterial stiffness in healthy Japanese subjects. The present study represents a cross-sectional investigation of 763 Japanese men and women (18–70 yr) to clarify the effects of cardiorespiratory fitness on the relationship between arterial stiffness and MTHFR C677T gene polymorphism.

METHODS

Subjects. A total of 763 Japanese subjects (239 men and 524 women) between 18 and 70 yr of age participated in this cross-sectional study (mean: 40 ± 1 yr). The study population consisted of sedentary or moderately active subjects who participated in swimming, stretching, and healthy gymnastics programs (at least 60 min/wk) and did not participate in any other vigorous sports activities. Subjects were divided into low-cardiorespiratory fitness (Low-Fit) and high-cardiorespiratory fitness (High-Fit) groups, with the dividing line set at the median value of peak oxygen uptake (V̇O₂peak), as an
index of cardiorespiratory fitness, in each sex and decade [median value of VO$_2$peak (ml·kg$^{-1}$·min$^{-1}$) for 18–30 yr old: men 47.1, women 36.7; 31–40 yr old: men 37.1, women 35.6; 41–50 yr old: men 34.7, women 31.9; 51–60 yr old: men 31.8, women 29.3; 61–70 yr old: men 31.0, women 27.2]. The median values of VO$_2$peak in the present study were similar to the reference values included in the exercise guidelines established by the Ministry of Health, Labor, and Welfare of Japan for prevention of lifestyle-related diseases (http://www.nih.go.jp/eiken/programs/pdf/epar2006.pdf). Subjects were recruited for the present study by advertisement. All subjects were free of any overt signs or symptoms of chronic disease, and all were nonsmokers. Carotid β-stiffness (β-stiffness) and common carotid intima-media thickness (ccIMT) were determined as indexes of arterial stiffness in all subjects. Systolic blood pressure (SBP), diastolic blood pressure (DBP), percent body fat, and MTHFR gene C677T polymorphism were determined in all subjects. Body fat mass was determined for the whole body with dual-energy X-ray absorptiometry (DXA) (Hologic QDR-4500A scanner, Hologic, Waltham, MA). SBP and DBP were measured at rest with a vascular testing device (Colin Medical Technology, Tokyo, Japan). Serum cholesterol, triglyceride, and folic acid levels and plasma glucose and homocysteine levels were also measured.

The study was approved by the Ethical Review Board of the National Institute of Health and Nutrition. Written informed consent was obtained from all subjects before inclusion in the study.

**Measurement of VO$_2$peak.** VO$_2$peak was measured by an incremental cycle exercise test using a cycle ergometer (828E; Monark, Varberg, Sweden). The incremental cycle exercise began at a work rate of 90 W (60–120 W) in men and 60 W (30–90 W) in women, and power output was increased by 15 W/min until the subjects could not maintain a fixed pedaling frequency of 60 rpm. The subjects were encouraged during the ergometer test to exercise at the level of maximum intensity. Heart rate and rating of perceived exertion (RPE) were monitored during the last 30 s of each increase in work rate. Subjects breathed through a low-resistance two-way valve, and the expired air was collected in Douglas bags. Expired O$_2$ and CO$_2$ gas concentrations were measured by mass spectrometry (ARCO-1000A; Arco System, Chiba, Japan), and gas volume was determined with a dry gas meter (DC-5C; Shinagawa Seiki, Tokyo, Japan). VO$_2$peak was assessed by the attainment of three of the following four criteria: 1) a plateau in VO$_2$ with increases in external work, 2) maximal respiratory exchange ratio $\geq$ 1.1, 3) maximal heart rate of the age-predicted maximum [208 − 0.7 × age (yr)] $\geq$ 90% (32), and 4) RPE $\geq$ 18; the highest value of VO$_2$ during the exercise test was then designated as VO$_2$peak.

**Measurement of ccIMT.** Carotid artery IMT was measured from the images obtained with a Vivid i ultrasound system (GE Medical Systems, Milwaukie, WI) equipped with a high-resolution linear array broadband transducer as described previously (12, 18, 24). Ultrasound images were analyzed with image analysis software (Image J; National Institutes of Health, Bethesda, MD). At least 10 IMT measurements were taken at each segment, and the mean values were used for analysis. This technique has excellent day-to-day reproducibility (coefficient of variation 3 ± 1% for ccIMT).

**Measurement of β-stiffness.** A combination of ultrasound imaging of the pulsatile common carotid artery with simultaneous planimetry of tonometrically obtained arterial pressure from the contralateral carotid artery permits noninvasive determination of arterial compliance (31). The carotid artery diameter was measured from images obtained with an ultrasound system equipped with a high-resolution linear array transducer. A longitudinal image of the cephalic portion of the common carotid artery was acquired 1–2 cm proximal to the carotid bulb. All image analyses were performed by the same investigator.

Pressure waveforms and amplitudes were obtained from the common carotid artery with a pencil-type probe incorporating a high-fidelity strain gauge transducer (SPT-301; Millar Instruments; Houston, TX) (31). Because baseline levels of blood pressure are subject to hold-down force, the pressure signal obtained by tonometry was calibrated by equating the carotid mean arterial and diastolic blood pressures to the brachial artery value (12, 18, 24, 31). The β-stiffness indexes were calculated with the equation [ln(P1/P0)]/(D1 − D0)/D0, where D1 and D0 are the maximal (systolic) and minimal (diastolic) diameters and P1 and P0 are the highest (systolic) and lowest (diastolic) blood pressures, respectively. The day-to-day coefficients of variation for carotid artery diameter, pulse pressure, and β-stiffness were 2 ± 1%, 7 ± 3%, and 5 ± 2%, respectively.

**SNP genotyping.** Genomic DNA was extracted from plasmauffy coats and buccal cells with a QIAamp DNA Blood Maxi Kit (Qiagen, Tokyo, Japan). MTHFR SNP genotypes were determined by real-time PCR with TaqMan probes and an ABI Prism 7700 Sequence Detector (Perkin-Elmer Applied Biosystems, Foster City, CA) as described previously with minor modifications (16, 23). The gene-specific primers and TaqMan probes for each SNP were synthesized with Primers Express v.1.5 software (Perkin-Elmer Applied Biosystems) according to the published DNA sequences for each SNP as follows: C677T (Ala→Val) in exon 5 of MTHFR (NCBI accession no. rs1801133). The sequences of the oligonucleotides used were as follows: MTHFR forward: 5′-GCACTTGAAGGAGAAGTGTCT-3′, MTHFR reverse: 5′-CCTCAAGAAAGAGCTGGTGATG-3′, MTHFR/G probe: 5′-ATGAAATCGGCTCCCGC-3′, MTHFR/A probe: 5′-ATGAAATCGACTCCCGC-3′.

PCR 96-well plates were read on an ABI-7700 with the end-point analysis mode of the SDS v.1.7a software package (Perkin-Elmer Applied Biosystems). Genotypes were determined automatically by the signal processing algorithms in the software.

**Measurements of serum cholesterol, triglyceride, and folic acid levels and plasma glucose and homocysteine levels.** Fasting serum concentrations of cholesterol and triglycerides and plasma concentrations of glucose were determined by standard enzymatic techniques. Plasma homocysteine level was analyzed by gas chromatography-mass spectrometry. Serum folic acid level was determined by microbiological methods.

**Statistical analysis.** The MTHFR allele frequencies were calculated with a gene-counting method, and Hardy-Weinberg equilibrium was confirmed with the $\chi^2$-test. Student’s $t$-test for unpaired values was used to evaluate differences between High-Fit and Low-Fit groups, and ANOVA was used to evaluate differences among geno-type groups. Furthermore, the β-stiffness, ccIMT, and plasma homocysteine level comparisons between the genotype groups in each High-Fit and Low-Fit group were assessed by an analysis of covariance (ANCOVA) model that included age as covariates. Values are expressed as means ± SE, and $P < 0.05$ was taken to indicate significance.

**RESULTS**

**Comparison of characteristics in low- and high-cardiorespiratory fitness groups.** In the High-Fit group, body weight, %Fat, and triglyceride levels were significantly lower than those in the Low-Fit group. High-density lipoprotein (HDL) level was significantly higher in the High-Fit group than in the Low-Fit group (Table 1). There were no significant differences in age, height, SBP, DBP, β-stiffness, ccIMT, total cholesterol, glucose, homocysteine, or folic acid levels between the High-Fit and Low-Fit groups (Table 1).

**Comparison of characteristics between genotypes.** We analyzed the MTHFR genotypes of the study subjects (Table 2), and no significant differences were found in the frequency of these polymorphisms between sexes. In addition, the allele frequencies did not deviate from the expected Hardy-Weinberg equilibrium.
We next compared the characteristics of subjects with different gene polymorphisms (Table 3). In the MTHFR C677T genotypes, plasma homocysteine level was significantly higher in the TT genotype than in the CC and CT genotypes. There were no significant differences in age, body weight, height, %fat, SBP, DBP, β-stiffness, AU, common carotid intima-media thickness, HDL, high-density lipoprotein; V˙O2peak; peak oxygen uptake. *P < 0.05 vs. Low-Fit.

To further explore the possible relationship between arterial stiffness (%stiffness) and plasma homocysteine levels, we performed regression analyses between %stiffness and plasma homocysteine level (Fig. 3). In the Low-Fit group, there were positive and significant correlations between %stiffness and plasma homocysteine level in the individuals with the TT genotype of MTHFR (y = 0.78x + 2.80, r = 0.71, P < 0.0001). There were no significant correlations for the CC and CT genotypes. In the High-Fit group, there were no significant correlations for any of the MTHFR genotypes (Fig. 3). The slopes of the regression lines were significantly different between High-Fit and Low-Fit groups in TT genotype of MTHFR (P < 0.05). There was a slight significant correlation between plasma homocysteine and V˙O2peak (y = 0.04x + 6.06, r = 0.16, P < 0.05).

DISCUSSION

The present cross-sectional study demonstrated the associations among arterial stiffness, cardiorespiratory fitness, and polymorphisms in the MTHFR gene in Japanese subjects. Plasma homocysteine concentrations were significantly higher in individuals with the TT genotype of MTHFR than in those with the CC and CT genotypes in each fitness group. Interestingly, in the Low-Fit subjects carotid β-stiffness was higher in the TT genotype individuals than in those with the CC and CT genotypes.
Table 4. Characteristics of subjects in each cardiorespiratory fitness and genotype of MTHFR C677T group

<table>
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<tr>
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<tr>
<td>Age, yr</td>
<td>39 ± 1</td>
<td>38 ± 1</td>
<td>37 ± 2</td>
<td>38 ± 1</td>
<td>38 ± 1</td>
<td>41 ± 2</td>
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<tr>
<td>Body weight, g</td>
<td>60 ± 1</td>
<td>60 ± 1</td>
<td>61 ± 2</td>
<td>59 ± 1</td>
<td>58 ± 1*</td>
<td>57 ± 1*</td>
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<tr>
<td>Height, cm</td>
<td>164 ± 1</td>
<td>162 ± 1</td>
<td>164 ± 1</td>
<td>164 ± 1</td>
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<tr>
<td>%Fat</td>
<td>25.3 ± 0.7</td>
<td>26.9 ± 0.5</td>
<td>27.1 ± 1.1</td>
<td>20.7 ± 0.6*</td>
<td>21.0 ± 0.5*</td>
<td>22.7 ± 0.8*</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>111 ± 1</td>
<td>112 ± 1</td>
<td>115 ± 3</td>
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<td>111 ± 2</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>66 ± 1</td>
<td>66 ± 1</td>
<td>69 ± 1</td>
<td>66 ± 1</td>
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<td>cIMT, mm</td>
<td>0.60 ± 0.01</td>
<td>0.59 ± 0.01</td>
<td>0.58 ± 0.01</td>
<td>0.58 ± 0.01</td>
<td>0.58 ± 0.01</td>
<td>0.60 ± 0.02</td>
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<tr>
<td>Total cholesterol, mg/dl</td>
<td>190 ± 3</td>
<td>189 ± 3</td>
<td>193 ± 6</td>
<td>189 ± 3</td>
<td>191 ± 3</td>
<td>195 ± 5</td>
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<tr>
<td>HDL cholesterol, mg/dl</td>
<td>65 ± 1</td>
<td>63 ± 1</td>
<td>65 ± 1</td>
<td>67 ± 1</td>
<td>70 ± 1*</td>
<td>70 ± 2*</td>
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<tr>
<td>Triglycerides, mg/dl</td>
<td>75 ± 3</td>
<td>70 ± 2</td>
<td>75 ± 4</td>
<td>68 ± 3</td>
<td>67 ± 2</td>
<td>64 ± 4*</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>89 ± 1</td>
<td>90 ± 1</td>
<td>90 ± 1</td>
<td>90 ± 1</td>
<td>89 ± 1</td>
<td>89 ± 1</td>
</tr>
<tr>
<td>Folic acid, ng/ml</td>
<td>9.8 ± 0.4</td>
<td>9.2 ± 0.3</td>
<td>8.4 ± 0.8</td>
<td>9.9 ± 0.4</td>
<td>9.9 ± 0.4</td>
<td>9.0 ± 0.6</td>
</tr>
<tr>
<td>VO_{2peak}, ml·kg^{-1}·min^{-1}</td>
<td>31.1 ± 0.8</td>
<td>30.6 ± 0.5</td>
<td>32.9 ± 1.4</td>
<td>41.4 ± 0.9*</td>
<td>41.2 ± 0.8*</td>
<td>38.1 ± 1.1†</td>
</tr>
</tbody>
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Values are means ± SE. *P < 0.05 vs. each genotype in Low-Fit; †P < 0.05 vs. CC and CT in High-Fit.

genotypes of MTHFR C677T. However, there were no such differences in High-Fit subjects. In addition, β-stiffness and plasma homocysteine levels were positively correlated in the Low-Fit subjects with the TT genotype (r = 0.71, P < 0.0001) but were not correlated in the other groups.

The TT genotype at C677T of the MTHFR gene was associated with elevated plasma homocysteine level but showed no effect on carotid arterial stiffness in the present study. Elevated plasma homocysteine level is associated with vascular function and increased risk of arterial stiffness (7, 15, 30, 36), because exposure of endothelial cells to elevated homocysteine levels leads to decreased availability of NO and results in impairment of endothelium-dependent vasodilation in humans (6, 29, 33, 35). In subjects with lower fitness, the TT genotype at C677T of the MTHFR gene increased arterial stiffness only in lower-fitness subjects with the TT genotype. Regular exercise improves endothelial function through increased NO production and decreased endothelin-1 concentration (22). Hayward et al. (14) reported that exercise training improved endothelium-dependent vasodilation under conditions of homocysteine exposure, and this may contribute to the increased endothelial nitric oxide synthase (eNOS) protein levels and eNOS activity in the aorta of rats. Exercise training induced changes in expression levels of vasodilation-related molecules, including eNOS, in the aorta of rats with improvement of arterial stiffness (21). Therefore, regardless of elevated homocysteine level induced by the T allele of the MTHFR C677T polymorphism, regular exercise is considered to decrease stiffening in the central artery via improvement of endothelial function. Thus regular exercise, which can maintain and obtain sufficient cardiorespiratory fitness, may be needed to cancel the genetic negative effects of MTHFR polymorphism in subjects with the TT genotype at C677T of the MTHFR gene.

In the present study, higher cardiorespiratory fitness did not seem to be associated with elevated plasma homocysteine...
levels in individuals with the TT genotype at C677T of the MTHFR gene. There have been several studies regarding the association with homocysteine status according to varied cardiorespiratory fitness levels and age. The relationship between \( V_{\text{O2peak}} \) and plasma homocysteine is unaffected in men or women aged 30–59 yr (10) and inversely associated in women (mean age 33.5 yr) but not in men (mean age 33.1 yr) (19). Moreover, the relationship was unaffected in children and adolescents (26), and a negative association was observed in women but not in men (27). Inconsistent results were also reported in athletes, in whom plasma homocysteine levels were elevated (25) or decreased compared with untrained control subjects (13). Thus the relationship between cardiorespiratory fitness and homocysteine status was not consistent. This discrepancy may be influenced by differences in physical fitness level, age, and genetic effects, such as MTHFR C677T, in each study. Although we extended our research effort to the association with MTHFR genotype, the present results could not account for the discrepancy. Therefore, further studies are required to examine differences in the relationship between different physical fitness levels and plasma homocysteine levels in various age groups.

In the present study, subjects were divided into Low-Fit and High-Fit groups, with the dividing line set at the median value of \( V_{\text{O2peak}} \) in each sex and decade, which were similar to the respective mean values for the Japanese population. It is considered that a higher level of exercise than the mean value for the Japanese population may be required to attenuate arterial stiffening in the TT genotype. However, further studies are necessary to determine the required amount of exercise.

Carotid \( \beta \)-stiffness was higher in the TT genotype at C677T of the MTHFR gene in subjects with lower cardiorespiratory fitness but was not altered in those with CC and CT genotypes. However, there were no effects of SNP on arterial stiffness in individuals with higher cardiorespiratory fitness. In contrast, ccIMT, evaluated as the thickness of the carotid arterial wall, was unaffected by the relationship between MTHFR C677T genotype and fitness level. Previous studies demonstrated the relationship between ccIMT and homocysteine levels in female smokers (17), whereas no relationship was observed in patients with atherosclerotic disease (28). de Bree et al. (10) reported no effect of ccIMT or pulse wave velocity on increases in plasma homocysteine levels in healthy middle-aged French subjects. Thus measurements using carotid \( \beta \)-stiffness may be a sensi-
tive means of detecting the effect of cardiorespiratory fitness on stiffening in the central artery induced by MTHFR C677T polymorphism in healthy subjects.

A previous study indicated the effects of plasma homocysteine level on the association between C677T and A1298C or G1793A (3). Further studies are required to determine the effects of fitness on the association between arterial stiffness and MTHFR haplotype. In addition, Labayen et al. (20) recently reported the effects of polymorphisms in the UCP3 gene on plasma homocysteine levels during youth. Plasma homocysteine level was higher in the TT and CT genotypes of the rs1800849 polymorphism in the UCP3 gene compared with individuals with the CC genotype after adjustment for sex, age, pubertal status, folate and vitamin B12 intake, and MTHFR C677T polymorphism. Moreover, the T allele of the rs1800849 polymorphism was associated with elevated homocysteine levels in young subjects with low fitness, but not with moderate or high cardiorespiratory fitness, indicating that cardiorespiratory fitness modifies the association between the rs1800849 polymorphism and homocysteine. The UCP3 gene polymorphism-induced increase in plasma homocysteine level in subjects with low fitness may affect arterial stiffness. Therefore, further studies are required to examine the effects of UCP3 gene polymorphism on the relationships among homocysteine, fitness, and arterial stiffness. Furthermore, although homocysteine is affected by endothelial function, we did not measure endothelial function, such as flow-mediated diameter, plasma NO, plasma endothelin-1, etc., in the present study. Therefore, further studies are required to determine the endothelial function parameters and the effects of gene polymorphism and fitness on homocysteine and endothelial function. Although it is well known that dietary folate intake is a major determinant of plasma homocysteine level, it could not be assessed in all subjects in the present study. Further studies are required to determine the effects of folate intake. Finally, the present study population included only Asian (Japanese) subjects; therefore, our data may not be applicable to other populations because genotypic distribution appears to show ethnic differences.

We investigated the associations among cardiorespiratory fitness, arterial stiffness, and C677T polymorphism of the MTHFR gene in healthy Japanese subjects. The results of this study indicated a lack of arterial stiffening associated with the TT genotype at C677T of the MTHFR gene in cardiorespiratory fit subjects. Thus habitual exercise-induced cardiovascular fitness may affect cardiovascular adaptations to molecular variation in the MTHFR gene in Japanese subjects. However, further studies are required to clarify the effects of fitness or physical activity on the risk of cardiovascular disease associated with genetic factors.

REFERENCES


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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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