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Vitamin E Administration Improves Impairment of Endothelium-Dependent Vasodilation in Patients With Coronary Spastic Angina

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Objectives. **We examined the effects of oral administration of vitamin E, an antioxidant, on endothelium-dependent vasodilation in patients with coronary spastic angina.**

Background. **We have recently reported that endothelium-dependent vasodilation is impaired in patients with coronary spastic angina (CSA). Furthermore, it is known that oxidative stress may play an important role in the impairment of endothelium-dependent vasodilation in cardiovascular diseases.**

Methods. **With the ultrasound technique, flow-dependent vasodilation of the brachial arteries during reactive hyperemia was examined before and after treatment for a month with either oral administration of vitamin E (α-tocopherol acetate, 300 mg/day) or placebo, which is randomly assigned, in patients with CSA (n = 60).**

Results. **Before treatment, patients with CSA had impaired flow-dependent vasodilation, lower plasma levels of α-tocopherol and higher plasma levels of thiobarbituric acid reactive substances (TBARS), as compared with age- and sex-matched control subjects (n = 60) (flow-dependent vasodilation: 3.1 ± 1.8 vs. 7.1 ± 2.5%, $p < 0.001$; α-tocopherol levels: 8.9 ± 1.8 vs. 10.8 ± 1.8 μg/ml, $p < 0.001$). In patients with CSA, treatment with vitamin E restored flow-dependent vasodilation (3.1 ± 1.7 vs. 8.3 ± 2.0%, $p < 0.001$), and this improvement was associated with the decreases in plasma TBARS levels and anginal attacks.**

Conclusions. **The results indicate that vitamin E treatment improved endothelium-dependent vasodilation and decreased plasma TBARS levels in patients with CSA. Thus, increased oxidative stress may contribute to endothelial dysfunction and anginal attacks in patients with CSA.**

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Coronary spasm plays an important role in the pathogenesis of not only variant angina but also ischemic heart disease in general, including other forms of angina pectoris, acute myocardial infarction and sudden death (1–4). We have previously shown that endothelial nitric oxide (NO) activity is decreased in patients with coronary spastic angina (CSA) (5), leading to hyperconstrictive response of coronary arteries to acetylcholine and impairment of flow-dependent vasodilation in coronary arteries (6). Furthermore, we showed that flow-mediated endothelium-dependent vasodilation was impaired in the brachial arteries (7), as well as coronary arteries, in patients with CSA (6). However, the precise mechanism(s) of the decrease in endothelial NO and/or the endothelial dysfunction in patients with CSA remains unknown.

Recently, there is increasing evidence that oxidative stress plays an important role in the mechanism(s) of endothelial dysfunction in cardiovascular diseases (8–10). A number of studies have shown that plasma levels of natural antioxidants are lower in cardiovascular diseases (11,12). Furthermore, supplementation of antioxidant vitamins has been shown to restore endothelial function in patients with coronary artery disease or patients with coronary risk factors (13–15). Thus, it is possible that increase in oxidative stress may also play a role in the mechanism(s) of endothelial vasomotor dysfunction in patients with CSA.

We examined the effects of vitamin E (α-tocopherol acetate) on endothelium-dependent vasodilation of the brachial arteries in patients with coronary spastic angina.

Methods

Study subjects. The study included 60 consecutive patients with CSA (mean age, 60.3 ± 7.3 years, ranging from 41 to 70 years, 31 men) in whom spontaneous angina occurred at rest. All of the patients with CSA had angiographically normal

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Abbreviations and Acronyms

ANOVA = analysis of variance
CSA = coronary spastic angina
NO = nitric oxide
TBARS = thiobarbituric acid reactive substances

coronary arteries and showed angiographically documented coronary spasm associated with ischemic ST segment changes after intracoronary injection of acetylcholine, as reported previously (16). The study also included 60 control subjects (mean age, 61.2 ± 6.6 years, ranging from 42 to 71 years, 28 men). These control subjects were selected to match the risk factors for atherosclerosis to those in patients with CSA, as shown in Table 1. The control subjects underwent diagnostic cardiac catheterization for evaluation of chest pain. They had angiographically normal coronary arteries and did not show coronary spasm after intracoronary injection of acetylcholine. Control subjects were studied to compare the baseline data with those in patients with CSA.

None of the study patients had previous myocardial infarction, congestive heart failure or other serious diseases. Written informed consent was obtained from all patients before the study. The study was in agreement with the guidelines approved by the ethics committee at our institution.

Study protocol. Patients with CSA were randomly assigned to the two treatment groups, either vitamin E group (α-tocopherol acetate, 300 mg/day) or placebo group, by means of a computerized randomization, as shown Figure 1. All patients with CSA were treated with diltiazem (200 mg/day), a calcium antagonist. No other medications affecting the arterial vasomotor tone and plasma lipid peroxidation were administered to any of the study patients. Measurements of flow-dependent vasodilation and blood sampling for assays of thiobarbituric acid reactive substances (TBARS) and α-tocopherol were performed before and 4 weeks after treatment with either placebo plus diltiazem or vitamin E plus diltiazem in both treatment groups. Furthermore, the number of anginal attacks was also recorded before and 4 weeks after treatment in both groups.

Measurement of flow-dependent vasodilation in the brachial arteries was performed in a quiet and temperature-controlled (22°C to 24°C) room in the fasting state in the early morning. Measurements were taken in the exact same manner between the before and after the treatment. All medications except sublingal nitroglycerin were withdrawn for at least 24 hours before the measurements were taken. No study patients had taken nitroglycerin within 6 hours of the study. All subjects abstained from smoking for at least 8 hours before the studies. Heart rate and blood pressure were monitored continuously during the study period.

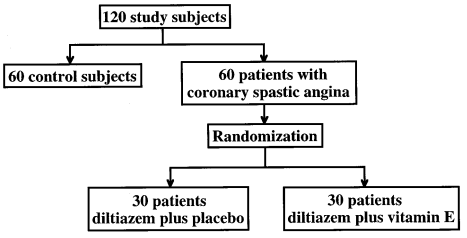


Figure 1. Diagram of the study.

Ultrasound studies. Vasodilator responses in the brachial arteries were measured by the ultrasound technique validated previously by our study and by others (7,17–20). Diameter of the brachial artery was measured from B-mode ultrasound images, using a 7.5-MHz linear array transducer (SSH-160A ultrasound system, Toshiba Corp., Japan). Flow velocity of the brachial artery was measured using a pulsed Doppler signal at a 70° angle to the vessel, with the range gate (1.5 mm) in the center of the artery. The brachial artery was scanned in the antecubital fossa in a longitudinal fashion. Gain setting was optimized at the beginning of the study and was kept constant throughout the recording period. When a satisfactory transducer position was found, the surface of the skin was marked, and the arm remained in the same position throughout the study.

The subjects lay quietly for 10 min before the scan. After baseline measurements of the diameter and flow velocity in the brachial artery, a blood pressure cuff placed around the forearm was inflated with a pressure of 250 to 300 mm Hg for 5 min, and then the cuff was released. Diameter and flow velocity were continuously measured during cuff inflation and

Table 1. Clinical Characteristics of Study Subjects

	Coronary Spastic Angina (n = 60)		
	Placebo Group (n = 30)	Vitamin E Group (n = 30)	Controls (n = 60)
Age (yr)	60.7 ± 7.3	59.9 ± 7.4	61.2 ± 6.6
Men/Women	16/14	15/15	28/32
No. of smokers (%)	16 (53.3)	14 (46.7)	29 (48.3)
Total cholesterol (mg/dl)	178.0 ± 42.8	174.4 ± 40.7	178.5 ± 49.8
HDL cholesterol (mg/dl)	46.6 ± 10.6	47.0 ± 10.1	48.3 ± 12.1
Fasting blood sugar (mg/dl)	86.3 ± 9.4	83.9 ± 11.5	83.1 ± 11.2
Body-mass index (kg/m^2)	22.8 ± 4.0	23.0 ± 3.7	23.3 ± 3.8

Values are expressed as mean value ± SD. HDL: high density lipoprotein.

after cuff deflation. Flow-mediated dilator response was used as a measure of endothelium-dependent vasodilation. Thereafter, the subjects lay quietly for 15 min, by which time the diameter and flow velocity had returned to baseline levels. Then, sublingal nitroglycerin (300 μg) was administered, and 3 min later the last measurements were performed. Response to nitroglycerin was used as a measure of endothelium-independent vasodilation.

Images were recorded on a super-VHS videocassette recorder (model BR-S601M, Victor Corp., Japan), and brachial arterial diameters were measured from the tape with ultrasonic calipers by two observers who were blinded as to the protocols of the study and the subject grouping. Measurements were taken from the anterior to the posterior "m" line (the interface between media and adventitia) at end diastole, incident with the R wave on a continuously recorded electrocardiogram (7,17–21). Diameter at four cardiac cycles was analyzed for each scan, and the measurements were averaged. Diameter measurements for the reactive hyperemia were taken 45 to 90 s after cuff deflation. Responses of the vessel diameters to the reactive hyperemia and nitroglycerin were expressed as a percent increase of the baseline value of the diameter. Blood flow was calculated by multiplying the velocity-time integral of the Doppler flow signal by heart rate and the vessel cross-sectional area. Increase in brachial blood flow was calculated as a maximum flow recorded in the first 15 s after cuff deflation and was expressed as a percent increase of the baseline value of the flow.

In our studies, the interobserver variability for repeated measurement of resting arterial diameter was 0.06 ± 0.03 mm. The intraobserver variability for repeated measurement of resting arterial diameter was 0.01 ± 0.09 mm. Furthermore, when these studies were performed at the same time on two separate days in 20 controls, the between-occasions, within-patients difference for measurement of the percent increase in arterial diameter during reactive hyperemia was 1.4 ± 1.2%.

Coronary angiography. Quantitative coronary angiography was performed to examine correlation of endothelium-dependent vasodilation between brachial arteries and coronary arteries, according to a validated technique (5,6). The method of injecting acetylcholine for provocation of coronary spasm has been detailed previously (5,16). Endothelium-dependent vasodilator responses of epicardial coronary arteries to acetylcholine at a dose of 50 μg/min was evaluated to compare with the endothelium-dependent vasodilation of brachial arteries.

Biochemical assays. Blood sampling was performed just before the ultrasound studies. The plasma levels of α-tocopherol were determined by high performance liquid chromatography (22). Levels of lipid peroxides in plasma were determined by measuring the TBARS (20,23). Briefly, 2.0 ml of trichloroacetic acid-thiobarbituric acid (TBA)-HCl reagent was added to 1.0 ml of sample and vortexed. To minimize peroxidation during the assay procedure, butylated hydroxytoluene was added to the TBA reagent mixture. The results were expressed as malondialdehyde equivalent content (nmol MDA/ml plasma).

Statistical analysis. The changes in hemodynamic parameters, percent increase in brachial arterial diameter, plasma α-tocopherol levels, plasma TBARS levels and number of anginal attacks were assessed by two-way analysis of variance (ANOVA) with repeated measures followed by post hoc testing with Sheffe's test by computer statistical software package SAS, version 6.12. Comparisons of data between patients with CSA and control subjects were performed by two-tailed unpaired t test for continuous variables, or chi-square test for categorical variables. Comparisons of data before treatment between placebo group and vitamin E group in patients with CSA were performed by two-tailed unpaired *t* test for continuous variables, or chi-square test for categorical variables.

Correlation between the percent increases in brachial arterial diameter during reactive hyperemia before treatment versus the changes of coronary arterial diameter in response to acetylcholine at a dose of 50 μg/min was made using linear regression analysis.

Statistical significance was defined as $p < 0.05$. Data are expressed as mean ± SD.

Results

Data Before Treatment in All Study Subjects

Clinical characteristics. There were no significant differences in the clinical characteristics between patients with CSA and controls (Table 1) and between placebo group and vitamin E group in patients with CSA (Table 1).

Hemodynamic variables. There were no significant differences in the baseline values of heart rate, blood pressure, resting arterial diameter, resting arterial blood flow and percent increase in arterial blood flow during reactive hyperemia between patients with CSA and controls (Table 2) and between placebo group and vitamin E group in patients with CSA (Table 2).

Flow-dependent vasodilation of the brachial artery. Flow-dependent vasodilation was significantly decreased in patients with CSA as compared with controls (3.1 ± 1.8 vs. 7.1 ± 2.5%, $p < 0.001$) (Fig. 2, A). There was no significant difference in percent increase in arterial diameter after nitroglycerin administration between patients with CSA and controls (Table 2). Flow-dependent vasodilation and percent increase in arterial diameter after nitroglycerin administration were not significantly different between placebo group and vitamin E group in patients with CSA before treatment (Fig. 3, Table 2).

Plasma levels of vitamin E and TBARS. Plasma levels of α-tocopherol were lower in patients with CSA than in controls (8.9 ± 1.7 vs. 10.8 ± 1.8 μg/ml, $p < 0.001$) (Fig. 2, B). Plasma levels of TBARS were higher in patients with CSA than in controls (6.6 ± 1.3 vs. 4.7 ± 1.0 nmol/ml, $p < 0.001$) (Fig. 2, C). The levels of α-tocopherol and TBARS were not significantly different between placebo group and vitamin E group in patients with CSA before treatment (Fig. 4 and 5).

Table 2. Hemodynamic Variables of Study Subjects

	Coronary Spastic Angina (n = 60)				
	Placebo Group (n = 30)		Vitamin E Group (n = 30)		Controls (n = 60)
	Before	After	Before	After	
Heart rate (beats/min)	63.4 ± 5.8	57.0 ± 5.9	64.0 ± 6.2	57.9 ± 5.8	63.1 ± 7.0
Mean blood pressure (mm Hg)	88.0 ± 4.6	82.1 ± 4.1	87.2 ± 4.5	80.9 ± 4.2	82.5 ± 8.1
Arterial diameter at rest (mm)	3.86 ± 0.20	3.88 ± 0.17	3.85 ± 0.19	3.87 ± 0.18	3.88 ± 0.49
Arterial diameter after cuff deflation (mm)	3.98 ± 0.20	4.09 ± 0.21	3.97 ± 0.22	4.19 ± 0.22	4.16 ± 0.53
Resting arterial blood flow (ml/min)	177.9 ± 13.2	181.4 ± 10.3	175.8 ± 11.9	181.0 ± 11.3	183.9 ± 68.8
Increase in arterial blood flow (%)	264.9 ± 34.7	257.6 ± 23.4	268.4 ± 37.5	261.6 ± 24.1	249.3 ± 84.4
Increase in diameter after nitroglycerin administration (%)	18.3 ± 1.5	17.9 ± 1.7	18.4 ± 1.8	18.0 ± 1.7	18.1 ± 4.1

Measurements of hemodynamic variables in patients with coronary spastic angina were performed before and after treatments with either placebo plus diltiazem or vitamin E plus diltiazem. Values are expressed as mean value ± SD.

Effect of Treatment in Patients With Coronary Spastic Angina

Hemodynamic variable. There were no significant differences in the magnitude of changes in hemodynamic variables (heart rate, mean blood pressure, resting arterial diameter, resting blood flow and percent increase in arterial blood flow during reactive hyperemia) between vitamin E group and placebo group (p = NS, ANOVA). Heart rate and mean blood pressure decreased after treatment in both groups (Table 2), probably due to the effects of diltiazem.

Flow-dependent vasodilation of the brachial artery. Flow-dependent vasodilation was greater after treatment as compared with before treatment in both groups (placebo group: 3.0 ± 1.9 vs. 5.5 ± 2.3%, $p < 0.001$; vitamin E group: 3.1 ± 1.7 vs. 8.3 ± 2.0%, $p < 0.001$) (Fig. 3). Flow-dependent vasodilation after treatment was greater in the vitamin E group than in the placebo group ($p < 0.001$) (Fig. 3). The magnitude of increase in flow-dependent vasodilation was significantly greater in the vitamin E group than in the placebo group ($p < 0.001$, ANOVA) (Fig. 3).

There was no significant difference in the magnitude of changes of the percent increase in arterial diameter after nitroglycerin administration between the vitamin E group and the placebo group (p = NS, ANOVA). The percent increase in arterial diameter after nitroglycerin administration was comparable between the before and after treatment in each treatment group (Table 2).

Plasma levels of vitamin E. Plasma α-tocopherol levels were increased after treatment as compared with before treatment in both groups (placebo group: 8.9 ± 1.3 to 9.2 ± 1.3 μg/ml, $p < 0.02$; vitamin E group: 8.9 ± 2.1 to 20.3 ± 4.7 μg/ml, $p < 0.001$) (Fig. 4). Plasma α-tocopherol levels after treatment were significantly higher in the vitamin E group than in the placebo group ($p < 0.001$) (Fig. 4). The magnitude of increase of plasma α-tocopherol levels was significantly greater in the vitamin E group than in the placebo group ($p < 0.001$, ANOVA) (Fig. 4).

Plasma levels of TBARS. Plasma TBARS levels decreased after treatment as compared with before treatment in both groups (placebo group: 6.8 ± 0.6 vs. 6.3 ± 0.9 nmol/ml, $p < 0.03$; vitamin E group: 6.6 ± 1.3 vs. 4.7 ± 1.0 nmol/ml, $p < 0.001$) (Fig. 5). Plasma TBARS levels after treatment were significantly lower in the vitamin E group than in the placebo

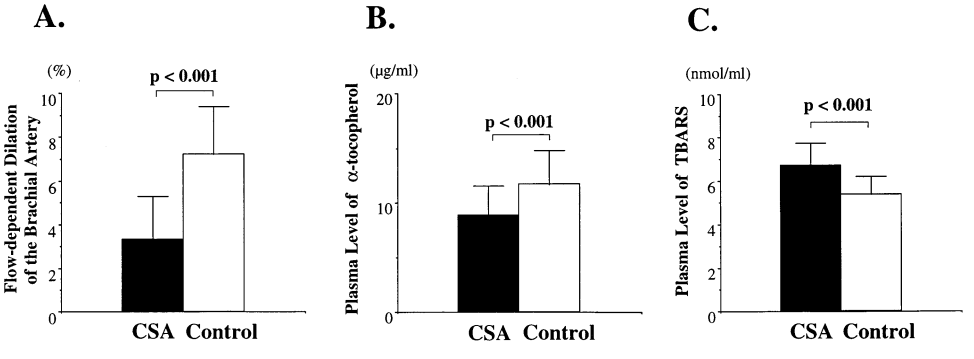


Figure 2. **(A)** Bar graphs showing the percent increase in brachial arterial diameter during reactive hyperemia before treatment in patients with coronary spastic angina (CSA) **(solid bar)** and controls **(open bar)**. **(B)** Bar graphs showing the plasma α-tocopherol levels before treatment in patients with CSA **(solid bar)** and controls **(open bar)**. **(C)** Bar graphs showing the plasma TBARS levels before treatment in patients with CSA **(solid bar)** and controls **(open bar)**.

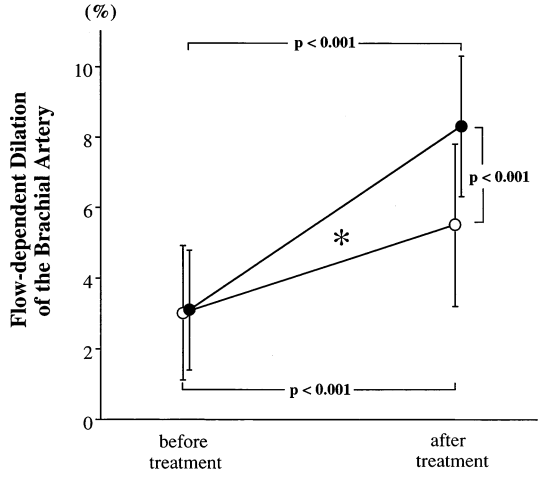


Figure 3. Percent increase in brachial arterial diameter during reactive hyperemia in patients with coronary spastic angina before and after treatment in the placebo group and the vitamin E group. *Significant effect of vitamin E treatment compared with values in placebo group, $p < .001$ by ANOVA. ⊖, diltiazem + placebo; ●, diltiazem + vitamin E.

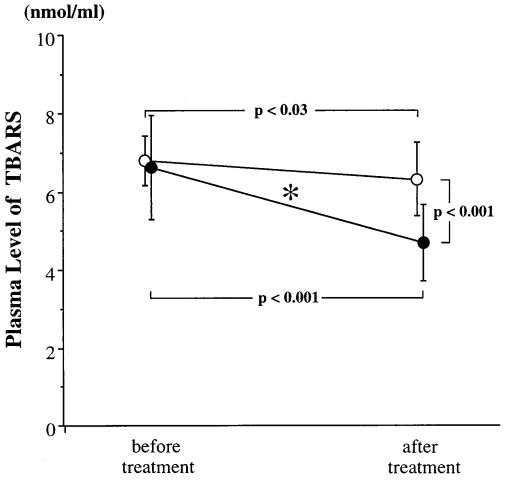
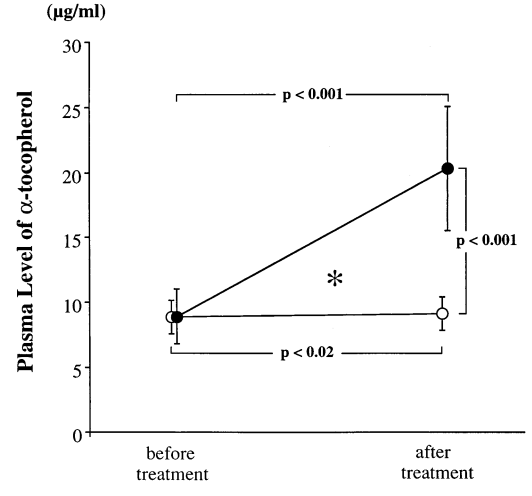


Figure 5. Plasma TBARS levels in patients with coronary spastic angina before and after treatment in the placebo group and the vitamin E group. *Significant effect of vitamin E treatment compared with values in the placebo group, $p < .001$ by ANOVA. ⊖, diltiazem + placebo; ●, diltiazem + vitamin E.

group ($p < 0.001$) (Fig. 5). The magnitude of decrease of plasma TBARS levels was significantly greater in the vitamin E group than in the placebo group ($p < 0.001$, ANOVA) (Fig. 5).

Number of anginal attacks. The number of anginal attacks before treatment was comparable between the placebo group and the vitamin E group (placebo group: 6.8 ± 4.3 vs. vitamin E group: 6.9 ± 4.3 times). The number of anginal attacks decreased after treatment as compared with before treatment in both groups (placebo group: 6.8 ± 4.3 vs. 0.9 ± 1.1 times; vitamin E group: 6.9 ± 4.3 vs. 0.2 ± 0.5 times). The number of anginal attacks after treatment was smaller in the vitamin E group than in the placebo group (0.2 ± 0.5 vs. 0.9 ± 1.1 times).

Figure 4. Plasma α-tocopherol levels in patients with coronary spastic angina before and after treatment in the placebo group and the vitamin E group. *Significant effect of vitamin E treatment compared with values in placebo group, $p < .001$ by ANOVA. ⊖, diltiazem + placebo; ●, diltiazem + vitamin E.



However, the difference in the magnitude of decrease of number of anginal attacks per previous week between the vitamin E group and the placebo group did not reach a significant level when tested by ANOVA.

Effect of treatment in nonsmoking patients with coronary spastic angina. In the subgroup analysis of the nonsmokers with CSA, flow-dependent vasodilation was greater after treatment as compared with before treatment in both groups (placebo group: 3.3 ± 1.9 vs. 5.4 ± 2.4%, $p < 0.01$; vitamin E group: 3.3 ± 2.0 vs. 8.4 ± 2.4%, $p < 0.001$), and the magnitude of increase in flow-dependent vasodilation was significantly greater in the vitamin E group than in the placebo group ($p < 0.01$, ANOVA). Plasma TBARS levels were decreased after treatment as compared with before treatment in both groups (placebo group: 6.8 ± 0.5 vs. 6.4 ± 0.2 nmol/ml, $p < 0.03$; vitamin E group: 6.7 ± 1.5 vs. 4.6 ± 1.1 nmol/ml, $p < 0.001$), and the magnitude of decrease of plasma TBARS levels was significantly greater in the vitamin E group than in the placebo group ($p < 0.01$, ANOVA).

Relation in the magnitude of endothelium-dependent vasodilation between brachial arteries and coronary arteries. A significant correlation existed between the flow-dependent vasodilation of brachial artery versus the changes of coronary arterial diameter in response to acetylcholine ($r = 0.596$, $p < 0.001$) (Fig. 6).

Discussion

The present study showed that flow-mediated endothelium-dependent vasodilation was impaired in patients with coronary spastic angina, a result that is in agreement with our previous reports (5–7). The present study further showed that oral vitamin E administration improved impairment of endothelium-dependent vasodilation in patients with CSA,

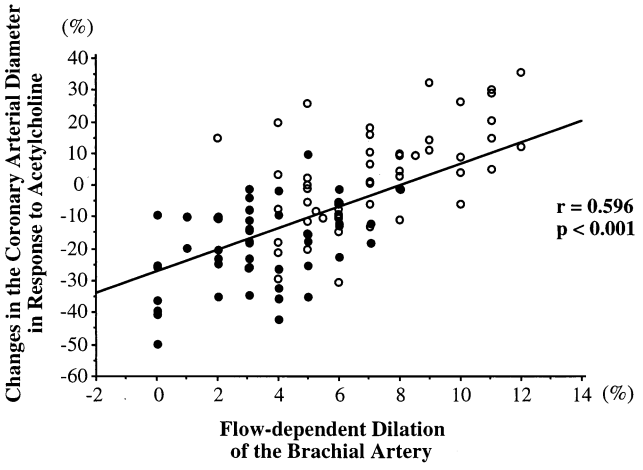


Figure 6. Correlation between the percent increases in brachial arterial diameter during reactive hyperemia versus the changes of coronary arterial diameter in response to acetylcholine at a dose of 50 μg/min in patients with coronary spastic angina **(squares)** and controls **(circles)**.

whereas it had no effect on the dilator response to nitroglycerin, an endothelium-independent vasodilator. These results indicate that vitamin E restored the endothelial dysfunction in patients with CSA. These results are in agreement with previous in vitro studies of experimental hypercholesterolemia and atherosclerosis (24,25).

Recently, there is increasing evidence that oxidative stress may play an important role in the mechanism(s) of endothelial dysfunction in cardiovascular disease (8–10). In the present study, plasma levels of α-tocopherol were lower in patients with CSA than in controls, which is in agreement with the previous report of Miwa et al. (12). Plasma TBARS levels, an indicator of lipid peroxidation, were higher in patients with CSA than in controls. Furthermore, the improvement of endothelial dysfunction by vitamin E administration was associated with a decrease in plasma TBARS levels, suggesting that vitamin E was effective as an antioxidant and suppressed oxygen free radicals in patients with CSA.

Possible mechanism of increase in oxidative stress. However, the precise mechanism of the increased oxidative stress in patients with CSA still remains undetermined in the present study. Cigarette smoking is a major risk factor for coronary spasm (26,27), and it has been shown that cigarette smoke contains large amounts of free radicals, such as superoxide anions and hydroxyl radicals (28,29), which could degrade endothelium-derived nitric oxide (NO) (30,31). Our previous study showed that increased oxidative stress may contribute to endothelial dysfunction in the brachial arteries in smokers (20). Therefore, oxygen free radicals in smoke may have at least partly contributed to increased oxidative stress in smokers with coronary spastic angina. However, the beneficial effects of vitamin E in patients with CSA cannot be completely explained by the suppression of oxidative stress due to cigarette smoking; the beneficial effects of vitamin E were also shown in nonsmokers in the present patients with CSA.

Coronary spasm causes repeated myocardial ischemia and reperfusion, and this may also lead to production of free radicals (32,33). Previously, we have shown that endothelial NO bioactivity is decreased in coronary arteries of patients with coronary spastic angina, and this decrease in endothelial NO may lead to a hyperconstrictive response of coronary arteries to acetylcholine stimulation (5) and impairment of flow-dependent vasodilation of coronary arteries in patients with CSA (6). We have demonstrated that there are several mutations or polymorphisms in endothelial NO synthase in patients with CSA, and their mutations in endothelial NO synthase are significantly associated with patients with CSA (34). Thus, there is a possibility that the decrease in endothelial NO production may primarily occur and may be partly responsible for the increase in oxidative stress in patients with CSA because NO serves as a superoxide scavenger (8,10,35).

An increase in wall shear stress due to the increase in blood flow results in the production of NO (36). However, Laurindo et al. (37) recently reported that the increase in wall shear stress also triggers the production of free radical species, such as superoxide anions. Nitric oxide-dependent arterial dilation during increase in blood flow may be determined by the balance between endothelial NO and free radicals, both of which are released by an increase in blood flow. Thus, a weakening of some element in the antioxidant defense system, such as plasma vitamin E, intracellular glutathione (38) or superoxide dismutase, may reduce the activity of endothelium-derived NO released during the increase in blood flow, leading to impairment of flow-dependent vasodilation in patients with CSA.

Effects of diltiazem on endothelial function. It is important to note that endothelium-dependent vasodilation was also improved in the placebo group of patients with CSA. This improvement may be due to the adjunctive administration of diltiazem. Calcium antagonists, which are very effective in suppressing coronary spasm (3,4), act by interfering with the entry of calcium into smooth muscle cells and directly induce smooth muscle cell relaxation (39). Several reports show that calcium antagonists restored endothelial dysfunction and potentiated the activity of endothelium-derived NO (40–42). Furthermore, calcium antagonists are shown to have an antioxidant activity (43). Thus, adjunctive treatment with diltiazem also may have decreased oxidative stress, and it may have also improved endothelial dysfunction in the placebo group.

Clinical implications. Vitamin E plus diltiazem administration also reduced the number of anginal attacks in association with the improvement of endothelium-dependent vasodilation and decrease in plasma TBARS levels in patients with CSA in the present study. Thus, improvement of redox equilibrium in patients with CSA may lead to a reduction of ischemic events in association with the improvement of endothelium-dependent vasodilation of brachial arteries. A previous report showed a close relation in the magnitude of endothelium-dependent vasodilation between coronary arteries and brachial arteries (19), and in the present study, all the patients with CSA had coronary spasm induced by intracoronary injection of acetylcholine, an endothelium-dependent

vasodilator, and there was a significant correlation between the magnitude of endothelium-dependent vasodilation in brachial arteries and coronary constrictor response to acetylcholine in patients with CSA. Thus, it may be possible that redox equilibrium and endothelial dysfunction are related to the mechanism(s) of coronary artery spasm.

Study limitations. The effect of vitamin E alone on the attacks in patients with CSA could not be examined in the present study for ethical reasons. The treatment with placebo alone may cause severe myocardial ischemia, leading to fatal cardiac events such as acute myocardial infarction and ventricular tachycardia in patients with CSA; calcium antagonists have been shown to be very effective in suppressing coronary spasm (3,4).

In this study, diltiazem markedly reduced the number of attacks in both the vitamin E group and placebo group, and this may have contributed to no statistically significant difference in the magnitude of decrease in number of attacks between the two groups by ANOVA. Further studies are needed to prove whether vitamin E is effective in suppressing attacks in patients with CSA.

Conclusions. We conclude that endothelium-dependent vasodilation in the brachial arteries is impaired in patients with coronary spastic angina, and that this impairment is improved by vitamin E administration in association with the decreases in plasma TBARS levels and anginal attacks. These findings suggest that increased oxidative stress may contribute to endothelial dysfunction and anginal attacks in patients with CSA.

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