Vitamin C Attenuates Abnormal Vasomotor Reactivity in Spasm Coronary Arteries in Patients With Coronary Spastic Angina

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Objectives. This study sought to examine the effect of vitamin C, an antioxidant, on the abnormal vasomotor reactivity in spasm coronary arteries.

Background. Oxygen free radicals generated in the arterial walls have been shown to cause endothelial vasomotor dysfunction.

Methods. Responses of the epicardial arterial diameters of the left coronary arteries to the intracoronary infusion of acetylcholine (ACh) (10 and 50 μg/min) were measured by quantitative coronary angiography before and during combined intracoronary infusion of vitamin C (10 mg/min) or saline as a placebo in 32 patients with coronary spastic angina and in 34 control subjects.

Results. Vitamin C infusion suppressed the constrictor response of the epicardial diameter to ACh in spasm coronary arteries but had no significant effect in the control coronary arteries (percent change in distal diameter in response to 10 μg/min of ACh [constriction (−), dilation (+), mean ± SEM] before vitamin C: −8.2 ± 2.9% in spasm arteries, +8.4 ± 2.9%* in control arteries; during vitamin C: +0.2 ± 3.8%* in spasm arteries, +7.2 ± 1.3%* in control arteries [*p < 0.01 vs. spasm arteries before vitamin C]). The coronary sinus–arterial difference in plasma thiobarbituric acid reactive substances during ACh infusion, an indicator of lipid peroxidation in coronary circulation, was higher in patients with coronary spastic angina than in control subjects (p < 0.01) but was suppressed in patients with coronary spastic angina to comparable levels in control subjects by combined infusion of vitamin C. Saline infusion had no effect.

Conclusions. The results indicate that vitamin C attenuates vasomotor dysfunction in epicardial coronary arteries in patients with coronary spastic angina. Oxygen free radicals may at least in part play a role in the abnormal coronary vasomotor reactivity in response to ACh in spasm coronary arteries.

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We recently showed (1,2) that the impairment of endothelium-dependent vasodilation as well as the hypercontractile response of smooth muscle in coronary arteries may play an important role in the genesis of coronary spasm (1,2). It has been recently shown (3–5) that reactive oxygen molecules generated in arterial walls and in circulating blood cells might cause endothelial dysfunction and modify the arterial tone. Enhanced production of superoxide anions in vascular cells has been shown (5,6) to inactivate endothelium-derived nitric oxide, leading to impairment of endothelium-dependent vasodilator response in atherosclerotic arteries. Recent clinical studies from our and other laboratories (7–10) showed that supplementation of vitamin C, an antioxidant, restored the impairment of endothelium-dependent vasodilation in cigarette smokers and in patients with coronary artery disease in whom oxidative stress is suggested to be increased (11,12). Therefore, we hypothesized that oxygen-derived free radicals may cause endothelial dysfunction or inactivate endothelium-derived nitric oxide, leading also to the abnormal vasomotor reactivity in spasm coronary arteries of patients with coronary spastic angina. To test this hypothesis, we examined the effects of intracoronary infusion of vitamin C on the coronary vasomotor reactivity in patients with coronary spastic angina compared with those in control subjects.

Methods

Study subjects. Patients. The study included 32 consecutive patients with coronary spastic angina (mean age 60 years, range 42 to 75; 18 men, 14 women). The patients with coronary...
spasm angiina fulfilled all the following inclusion criteria: 1) spontaneous attacks of chest pain associated with ST segment elevation or depression on the 12-lead electrocardiogram (ECG) or ambulatory ECG at rest, usually in the middle of the night or early morning; 2) coronary artery spasm (total or subtotal occlusion) in the left coronary arteries, demonstrated angiographically during the anginal attack of chest pain with the ST segment changes during the intracoronary infusion of acetylcholine (ACh), as previously reported (1,13–15); 3) no angiographic organic stenosis (<10% stenosis) in coronary arteries.

Control group. The study also included 34 consecutive control patients with atypical chest pain (mean age 58 years, range from 41 to 78; 18 men, 16 women) who were selected to match the risk factors for coronary artery disease with those in patients with coronary spastic angina. Control patients underwent diagnostic cardiac catheterization for evaluation of atypical chest pain and fulfilled all the following inclusion criteria: 1) no significant ST segment changes during the chest pain on the 12-lead ECG and ambulatory ECG at rest, usually in the middle of the night or early morning; 2) no chest pain or ST segment changes during the intracoronary infusion of acetylcholine (ACh), as previously reported (1,13–15); 3) no angiographic organic stenosis (<10% stenosis) in coronary arteries.

The clinical characteristics of the study patients are shown in Table 1. All medications except sublingual nitroglycerin were withdrawn at least 3 days before the study. No study patient had pharmacologic doses of antioxidants at least 1 month before the study. No study patient had taken nitroglycerin within 6 h of the study. No patient had a previous myocardial infarction, congestive heart failure, cardiomyopathy, valvular heart disease or other serious disease. Written informed consent was obtained from all patients before the study. The study was approved by the ethics committee of our institution.

Study protocol. The study protocol is shown schematically in Figure 1. Coronary angiographic study was performed with the Judkins technique using contrast material (Iopromide, Schering AG) in the morning, when the patients were fasting. After baseline measurements of systemic hemodynamic variables, angiography of the left and right coronary arteries was performed. Incremental doses of ACh were then infused into the left anterior descending (LAD) and left circumflex (LCx) coronary arteries (10, 50, 100 µg/min) and subsequently into the right coronary artery (RCA) (20 and 50 µg/min) until coronary spasm was induced or the maximal doses were reached in all patients of both groups. The infusion of ACh at the dose of 10 µg/min into the left coronary arteries was performed for 2 min, and other doses were infused for 1 min with a 5-min interval between consecutive doses. Measurement of systemic hemodynamic variables and angiography of the LAD and LCx were repeated at the end of each infusion. Coronary spasm induced by this method resolved spontaneously within 2 to 3 min without use of nitroglycerin and allowed further studies in all patients with coronary spastic angina.

Fifteen minutes after the completion of the intracoronary infusion of ACh, measurement of systemic hemodynamic variables and control angiography of the left coronary arteries were performed. Vitamin C (10 mg/min at a rate of 2 ml/min for 5 min) was then infused into the LAD and LCx through the Judkins catheter in 20 patients with coronary spastic angina and in 23 control patients. In the other 12 patients with coronary spastic angina and in the other 11 control patients, saline (0.9%) as a placebo of vitamin C was infused (at a rate of 2 ml/min for 5 min) into the LAD and LCx in the same manner as vitamin C. This dose of vitamin C yielded 708 ± 48 µmol/liter of vitamin C plasma concentration in the coronary sinus (determined by high performance liquid chromatography), levels of which have been reported to be effective as an antioxidant and have little prooxidant effect (16,17). Measure-

![Figure 1. Schematic representation of infusion protocol. Control = control patients; CSA = patients with coronary spastic angina.](image-url)
mements of systemic hemodynamic variables and coronary angiography were performed before and at the end of the infusion. Subsequently, the infusion of vitamin C or saline was continued for an additional 10 min, and incremental doses of ACh (10 and 50 μg/min) were simultaneously infused into the LAD and LCx in exactly the same manner as performed before the infusion of vitamin C or saline. Measurements of systemic hemodynamic variables and coronary angiography were repeated at the end of the combined infusion of each dose of ACh with vitamin C or saline. ACh infusion at the dose of 50 μg was not repeated in patients with coronary spastic angina who had coronary spasm during the ACh infusion at the dose of 50 μg before the infusion of vitamin C or saline. After an additional 10 min, intravenous injection of nitroglycerin (250 μg) was performed, and 2 min thereafter coronary angiography was performed in multiple projections in all study patients. All drugs were dissolved in 0.9% saline in a sterile manner and kept at 37°C. Vitamin C (ascorbic acid) was purchased from Takeda Pharmaceutical Company (Tokyo, Japan).

**Quantitative coronary angiography.** Quantitative coronary angiographic studies were performed as described in our previous reports (1,14,15). In the control patients, each trunk of the LAD and LCx was divided into proximal and distal segments of equal lengths. The lumen diameter at the center of each segment was measured to analyze the effects of various drugs on the epicardial coronary diameter by means of the computer-assisted coronary angiographic analysis system (Cardio 500, Kontron Instruments). In patients with coronary spastic angina, the lumen diameter was measured at the site of coronary spasm induced by intracoronary injection of ACh (1,14). Coronary spasm was defined as total or subtotal occlusion of the epicardial coronary arteries associated with signs of myocardial ischemia, such as chest pain and ischemic ST segment changes. When subtotal occlusion occurred diffusely from the proximal to the distal segments of a coronary artery, the diameters were measured at both the proximal and distal segments of the spasm artery. The responses of the coronary diameter to various drugs were expressed as the percent change from baseline values on the angiogram taken just before each infusion of the drugs.

**Assays of plasma thiobarbituric acid reactive substances.** A 6F Goodale-Lubin catheter (USCI) for blood sampling was positioned in the coronary sinus through the right antecubital vein. EDTA plasma was obtained from the blood in the coronary sinus and the aortic root at baseline and during each infusion of various drugs. The lipid peroxidation product in plasma samples, into which butylated hydroxytoluene at a final concentration of 20 μmol/liter was added, was measured in terms of thiobarbituric acid reactive substances (TBARS) (18). TBARS is expressed using malondialdehyde (MDA) equivalents as a standard.

**Statistical analysis.** Results are expressed as mean value ± SEM, unless otherwise indicated. For comparison of coronary luminal diameters, systemic hemodynamic variables and TBARS levels during each infusion of the various drugs between patients with coronary spastic angina and control patients, two-way analysis of variance (ANOVA) for repeated measures, followed by the Bonferroni multiple comparison test, was used. Serial responses of systemic hemodynamic variables and TBARS levels in each study group to the intracoronary infusion of various drugs were compared using one-way ANOVA. Differences between two means were compared by paired or unpaired Student t test. The correlation between two continuous variables was examined using linear regression analysis. Difference in frequencies of risk factors between patients with coronary spastic angina and control patients was compared using the chi-square test. A p value <0.05 was considered statistically significant.

**Results**

**Provocation of coronary spasm.** In all patients with coronary spastic angina, spasm occurred in the coronary arteries into which ACh was infused, in association with both chest pain and ischemic ST changes. Coronary spasm was documented in 62 coronary arteries (31 LAD, 14 LCx and 17 RCA). Total occlusion occurred at the proximal segment in 10 coronary arteries and at the distal segment in 7, and subtotal occlusion occurred diffusely either at the proximal or the distal segments in the remaining 45 coronary arteries. Spasm was induced by ACh infusion at the dose of 20 μg in 5 coronary arteries (5 RCA), at 50 μg in 17 arteries (3 LAD, 2 LCx, 12 RCA) and at 100 μg in 40 arteries (28 LAD, 12 LCx). In contrast, intracoronary infusion of ACh did not induce coronary spasm associated with signs of myocardial ischemia in any control patient.

**Responses of epicardial coronary arteries to ACh.** As shown in Table 2, baseline values of heart rates and mean blood pressure in patients with coronary spastic angina were not significantly different from those in control patients. In patients with coronary spastic angina, the coronary diameter responses to the infusion of ACh alone and in combination with vitamin C or saline were analyzed in the LAD and LCx with the ACh-induced spasm, and this analysis was performed at the subthreshold concentrations of ACh that did not provoke spasm in the respective coronary arteries with spasm (i.e., 31 LAD and 14 LCx at 10 μg of ACh; 28 LAD and 12 LCx at 50 μg of ACh) because the diameter of the coronary arteries during total or subtotal occlusion due to coronary spasm cannot be accurately measured. In control patients, the diameter responses of 34 LAD and 34 LCx to ACh at 10 and 50 μg were analyzed as referenced control coronary arteries. Most of the spasm coronary arteries showed a constrictor response to the concentrations of 10 and 50 μg of ACh, whereas the control coronary arteries as a whole showed a slightly dilator response to both 10 and 50 μg of ACh, as shown in Figure 2. In the subgroup analysis of the patients with lifelong nonsmoking and no passive smoking, most of the spasm coronary arteries also showed a constrictor response to ACh infusion, whereas the control coronary arteries showed a dilator response (see later). There were no significant changes in
systemic hemodynamic variables from baseline values during infusion of ACh into the LAD and LCx in both patients groups, as shown in Table 2.

**Responses to vitamin C alone and in combination with ACh.** The effects of vitamin C infusion on the coronary lumen diameters were analyzed in all coronary segments with spasm in 20 patients with coronary spastic angina (i.e., 40 spasm sites in 17 proximal [11 LAD, 6 LCx] and 23 distal segments [15 LAD, 8 LCx] of the 31 spasm arteries). The analysis was also performed at 46 proximal (23 LAD, 23 LCx) and 46 distal segments (23 LAD, 23 LCx) of the 46 control arteries in 23 control patients.

The epicardial coronary diameters were not significantly changed after the infusion of vitamin C alone in both spasm and control coronary arteries (diameters at proximal segment of spasm arteries [n = 17]: 2.3 ± 0.2 mm before vitamin C vs. 2.3 ± 0.1 mm after vitamin C, p = NS; diameters at proximal segments of control arteries [n = 46]: 2.7 ± 0.2 mm before vitamin C vs. 2.7 ± 0.1 mm after vitamin C, p = NS). However, the constrictor response to ACh in spasm coronary arteries was significantly attenuated by the combined infusion of vitamin C, whereas the response to ACh in control coronary arteries was not affected by vitamin C, as shown in Figures 3 and 4. In the subgroup analysis of the nonsmokers, vitamin C infusion significantly converted the constrictor response to ACh to the dilator response in the spasm arteries but had no effect on the response to ACh in control arteries (percent change in distal segment from baseline [constriction (–), dilation (+)] in spasm arteries [n = 12]: −7.7 ± 3.6% during 10 µg of ACh alone vs. +6.5 ± 4.7% during vitamin C plus 10 µg of ACh, p = 0.01; in control arteries [n = 26]: +9.9 ± 3.2% during 10 µg of ACh alone vs. +7.5 ± 1.8% during vitamin C plus 10 µg of ACh, p = NS [^p = 0.0001 vs. spasm arteries during 10 µg of ACh alone]). Vitamin C infusion did not significantly affect systemic hemodynamic variables, as shown in Table 2.

**Responses to combined infusion of saline with ACh.** Effects of the saline infusion on the response of the coronary lumen diameters to ACh infusion were analyzed in all distal coronary segments with spasm in 12 patients with coronary spastic angina (i.e., 13 spasm sites at distal segments [12 LAD, 1 LCx]). The analysis was also performed at 22 distal segments (11 LAD, 11 LCx) of the 22 control arteries in 11 control patients. Intracoronary infusion of saline did not affect the response of the epicardial coronary diameters to ACh in both spasm and control coronary arteries (percent change of distal segment from baseline in spasm arteries [n = 12]: −16.6 ± 4.7% during 50 µg of ACh alone vs. −18.1 ± 5.7% during saline plus 50 µg of ACh, p = NS; in control arteries [n = 22]: +2.8 ± 0.8% during 50 µg of ACh alone vs. +3 ± 0.7% during saline plus 50 µg of ACh, p = NS). Saline infusion did not significantly affect systemic hemodynamic variables (data not shown).

**Figure 2.** Percent change in coronary lumen diameter of spasm and control arteries from baseline values at proximal (left) and distal segments (right) in response to ACh.

**Figure 3.** Percent changes in coronary lumen diameter of spasm arteries from baseline values at proximal (left) and distal segments (right) in response to ACh with (open circles) or without vitamin C (solid circles) in patients with coronary spastic angina.

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**Table 2.** Systemic Hemodynamic Variables

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<th>Baseline</th>
<th>ACh 10 µg</th>
<th>ACh 50 µg</th>
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<th>Vitamin C + ACh 10 µg</th>
<th>Vitamin C + ACh 50 µg</th>
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* ^p < 0.01 versus baseline value. Data presented are mean value ± SD. ACh = acetylcholine; CSA = coronary spastic angina; HR = heart rate; MBP = mean blood pressure; NTG = nitroglycerin.
Baseline coronary diameter and response to nitroglycerin.

Baseline diameters of the spasm arteries in patients with coronary spastic angina were significantly smaller than those of the control arteries in control patients (2.4 ± 0.2 mm [n = 13] vs. 2.7 ± 0.1 mm [n = 34], p < 0.05 at the proximal segment; 1.4 ± 0.1 mm [n = 27] vs. 1.6 ± 0.1 mm [n = 34], p < 0.05 at the distal segment, respectively, of the LAD). The percent increase in the coronary diameter after nitroglycerin was significantly greater in the spasm arteries than in the control arteries at both the proximal and distal segments (percent increase from baseline values: 33 ± 3% in spasm arteries [n = 21] vs. 24 ± 2% in control arteries [n = 68] at the proximal segment, p < 0.05; 31 ± 2% in spasm arteries [n = 36] vs. 22 ± 2% in control arteries [n = 68] at the distal segment, p < 0.05). The dilator response of the epicardial diameter to nitroglycerin after the vitamin C infusion was not significantly different from that after the saline infusion in both spasm and control coronary arteries (percent dilation of the distal segment from the baseline: 30 ± 2% after vitamin C [n = 23] vs. 32 ± 3% after saline infusion [n = 13] in spasm arteries, p = NS; 23 ± 2% after vitamin C [n = 46] vs. 20 ± 3% after saline infusion [n = 22] in control arteries, p = NS). Coronary diameters of the spasm arteries after nitroglycerin administration were not different from those of the control arteries at either the proximal or the distal segment (3.2 ± 0.1 mm [n = 13] vs. 3.2 ± 0.1 mm [n = 34] at the proximal segment; 1.8 ± 0.1 mm [n = 27] vs. 1.9 ± 0.1 mm [n = 34] at the distal segment, p = NS, respectively, of the LAD). Thus, the basal tone of the epicardial coronary arteries was increased in the spasm arteries compared with that in the control arteries. The difference between the coronary diameter responses to the infusion of ACh alone and ACh plus vitamin C, reflecting the magnitude of the vitamin C-induced improvement of vasomotor reactivity to ACh, was not significantly correlated with the basal coronary diameter, dilator response to nitroglycerin and constrictor response to ACh in spasm coronary arteries (difference between the responses of distal segments to 50 μg of ACh alone and 50 μg of ACh plus vitamin C [n = 23]: r = −0.09 vs. the basal diameter, p = NS; r = 0.28 vs. the dilator response to nitroglycerin, p = NS; r = 0.09 vs. the constrictor response to 50 μg of ACh alone, p = NS).

TBARS levels in coronary circulation. There was no significant difference in TBARS plasma levels (nmol MDA/ml) in the aortic root at baseline and during each infusion between patients with coronary spastic angina and control patients (data not shown). The difference in TBARS levels between the coronary sinus and the aortic root (calculated by TBARS plasma level in the coronary sinus minus that in the aortic root), reflecting the generation of lipid peroxidation in the coronary circulation, was comparable at baseline between patients with coronary spastic angina and control patients, as shown in Figure 5. It was significantly increased from baseline values during ACh infusion in both patient groups, but the magnitude of the increase was greater in patients with coronary spastic angina than in control patients during infusion of ACh, even at the lower concentration that did not provoke coronary spasm. The coronary sinus–arterial difference of TBARS levels was further increased during myocardial ischemia due to coronary spasm provoked by the higher concentrations of ACh in patients with coronary spastic angina (0.6 ± 0.4 nmol MDA/ml at baseline; 3.2 ± 0.4* during infusion of 50 μg of ACh but without myocardial ischemia; 5.9 ± 0.6** during the myocardial ischemia; *p = 0.001 vs. baseline; **p < 0.001 vs. 50 μg of ACh). The coronary sinus–arterial difference of TBARS levels was not significantly changed from baseline by the infusion of vitamin C alone in both groups. However, the combined infusion of vitamin C significantly suppressed the increase in the coronary sinus–arterial difference of TBARS levels during ACh infusion in both patient groups to comparable values (Fig. 5), whereas the combined infusion of saline with ACh had no effect in both groups (patients with coronary spastic angina [n = 12]: 3.2 ± 0.5 nmol MDA/ml during 50 μg of ACh alone vs. 2.9 ± 0.5 nmol MDA/ml during saline plus

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**Figure 4.** Percent changes in coronary lumen diameter of control arteries from baseline values at proximal (left) and distal segments (right) in response to ACh with (open circles) or without vitamin C (solid circles) in control patients.

**Figure 5.** Coronary sinus-arterial difference in TBARS at baseline, during infusion of 50 μg of ACh alone and during infusion of vitamin C plus 50 μg of ACh in patients with coronary spastic angina (CSA, n = 17) and in control patients (Control, n = 23). Data from patients with coronary spastic angina in whom spasm in the LAD and LCx was provoked by infusion of 100 μg, but not 50 μg, of ACh were included in the analysis.
50 μg of ACh, p = NS; control patients [n = 11]: 1.8 ± 0.3 nmol MDA/ml during 50 μg of ACh alone vs. 1.9 ± 0.3 nmol MDA/ml during saline plus 50 μg of ACh, p = NS).

Discussion
To our knowledge, the present study is the first to show that the infusion of vitamin C attenuated the constrictor response of the epicardial spasm coronary arteries to ACh but had no effect on the response to ACh in control coronary arteries. The effect of vitamin C is unlikely to be due to the spontaneous change of the response to the repeated infusion of ACh because the saline infusion in the same protocol as the vitamin C infusion otherwise had no effect on the response of the epicardial diameter in the spasm coronary arteries to ACh. Also, the effect of vitamin C was not due to the higher basal tone and the hypercontractile response to ACh of spasm coronary arteries because the attenuation with vitamin C was not significantly correlated with the basal coronary diameter, the dilator response to nitroglycerin and the contractile response to ACh. Furthermore, the dilator response of spasm coronary arteries to nitroglycerin, an endothelium-independent relaxant, was not affected by vitamin C infusion. Thus, the effect of vitamin C on the vasomotor reactivity of spasm coronary arteries in response to ACh may be mediated at least in part by an improvement in endothelium-dependent vasodilation. The present study also showed that the beneficial effect of vitamin C on spasm coronary arteries was associated with a suppression of the increase in the production of TBARS, a marker of lipid peroxidation, in the coronary circulation during the ACh infusion, indicating that the intracoronary infusion of vitamin C effectively exerted an antioxidant effect on the coronary circulation. Therefore, the suppression of oxidative stress or oxygen-derived free radicals in the coronary arteries may contribute to the vitamin C-induced attenuation of the constrictor response to ACh in spasm coronary arteries.

We recently demonstrated (1) that the deficiency or decrease in endothelium-derived nitric oxide plays a role in the mechanisms of the increased basal tone and the supersensitive constrictor response to ACh in spasm coronary arteries. The present study shows that the production of TBARS in the coronary circulation during ACh infusion was significantly higher in patients with coronary spastic angina than in control patients, irrespective of the presence or absence of myocardial ischemia due to coronary spasm. Furthermore, Miwa et al. (19) recently showed that plasma levels of vitamin E, a natural antioxidant, were decreased in patients with coronary spastic angina. These data suggest that oxidative stress may be increased in patients with coronary spastic angina. Therefore, it is possible that the increase in oxidative stress and oxygen-derived free radicals may cause endothelial dysfunction or inactivate endothelium-derived nitric oxide, leading to the hypercontractile response to ACh in spasm coronary arteries of patients with coronary spastic angina.

Possible sources of increase in oxidative stress. Several lines of clinical studies from our (7,15) and other (11,20) laboratories indicate that oxidative stress is increased in cigarette smokers, resulting in the impairment of nitric oxide–mediated endothelium-dependent vasodilation in vivo in humans. Furthermore, cigarette smoking is known to be highly prevalent in patients with coronary spastic angina (21). Therefore, oxidative stress associated with cigarette smoking may be one of the free radical sources in patients with coronary spastic angina and cigarette smoking. However, cigarette smoking cannot completely explain the abnormal vasomotor reactivity of spasm coronary arteries because the present study showed that the vitamin C infusion was also effective in the subgroup of patients with coronary spastic angina and nonsmoking. The myocardial ischemia/reperfusion, which is known to generate oxygen-derived free radicals in coronary endothelium and myocardium (22,23), is repeated by coronary spasm and is one of the characteristic features in patients with coronary spastic angina. Therefore, it could be another source of oxidative stress in spasm coronary arteries.

TBARS production. It should be noted that the production of TBARS in the coronary circulation during ACh infusion was increased in control patients as well as patients with coronary spastic angina. Intracoronary infusion of ACh is known to increase coronary blood flow (24,25). Laurindo et al. (26) previously reported that the increase in blood flow triggers endothelial free radical generation; such generation of oxygen-derived free radicals may partly explain the increase in TBARS in the coronary circulation during ACh infusion, even in control coronary arteries. In patients with coronary spastic angina, the preexisting oxidative stress due to smoking, repeated myocardial ischemia/reperfusion or other causes may increase the susceptibility of lipid peroxidation in plasma lipoproteins and vascular cell membranes to oxygen-derived free radicals produced in the circulation during the ACh-induced increase in blood flow because the preexisting oxidative stress could have consumed the antioxidants in plasma and the intracellular antioxidant defenses of vascular cells in the spasm coronary arteries. This may partly contribute to the higher production of TBARS in the coronary circulation in spasm coronary arteries than in control coronary arteries during ACh infusion, even at the subthreshold concentrations that did not induce coronary spasm. The endothelial generation of oxygen-derived free radicals by the increase in blood flow during ACh infusion, which possibly also occurs in the epicardial coronary arteries, may play a critical role in the abnormal vasomotor reactivity of the spasm coronary arteries in response to ACh because the infusion of vitamin C alone had no effect on the baseline diameter of the spasm coronary arteries.

Study limitations. There are few reports showing direct evidence of the long-term therapeutic value of the vitamin C administration in patients with coronary artery disease. It also remains to be determined whether vitamin C treatment could prevent anginal attack in patients with coronary spastic angina. Many assays are available for measuring lipid peroxidation, but no single assay accurately reflects free radical generation. TBARS measurement is also susceptible to artifacts caused by
variations in sample lipid content and iron contamination of reagents. In the present study, we prevented autooxidation of the samples by addition of butylated hydroxytoluene to the samples.

Conclusions. The present results indicate that vitamin C improves the abnormal vasomotor reactivity in response to ACh in epicardial coronary arteries of patients with coronary spastic angina. Oxidative stress or oxygen-derived free radicals may at least in part play a role in the abnormal vasomotor reactivity in spasm coronary arteries.

References


