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Ascorbic Acid Reverses Endothelial Vasomotor Dysfunction in Patients With Coronary Artery Disease

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Abstract

Background In the setting of atherosclerosis, endothelial vasomotor function is abnormal. Increased oxidative stress has been implicated as one potential mechanism for this observation. We therefore hypothesized that an antioxidant, ascorbic acid, would improve endothelium-dependent arterial dilation in patients with coronary artery disease.

Methods and Results Brachial artery endothelium-dependent dilation in response to hyperemia was assessed by high-resolution vascular ultrasound before and 2 hours after oral administration of either 2 g ascorbic acid or placebo in a total of 46 patients with documented coronary artery disease. Plasma ascorbic acid concentration increased 2.5-fold 2 hours after treatment (46 ± 8 to 114 ± 11 $\mu\text{mol/L}$, $P = .001$). In the prospectively defined group of patients with an abnormal baseline response ($< 5\%$ dilation), ascorbic acid produced marked improvement in dilation ($2.0 \pm 0.6\%$ to $9.7 \pm 2.0\%$), whereas placebo had no effect ($1.1 \pm 1.5\%$ to $1.7 \pm 1.5\%$, $P = .003$ for ascorbic acid versus placebo). Ascorbic acid had no effect on hyperemic flow or arterial dilation to sublingual nitroglycerin.

Conclusions Ascorbic acid reverses endothelial vasomotor dysfunction in the brachial circulation of patients with coronary artery disease. These findings suggest that increased oxidative stress contributes to endothelial dysfunction in patients with atherosclerosis and that endothelial dysfunction may respond to antioxidant therapy.

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The integral role of the endothelium in the regulation of vascular tone, platelet activity, and vascular thrombosis is now well established. Control of vasomotor tone is regulated in large part through the release of endothelium-derived relaxing factor (EDRF), which has been identified as nitric oxide (NO),¹ or a closely

related S-nitrosothiol species.^{2 3} Effective release of EDRF in response to shear stress^{4 5 6 7} and other relevant stimuli^{8 9 10} is impaired in patients with either established coronary artery disease or coronary risk factors. There is now convincing evidence that this impairment contributes to the pathogenesis of chronic^{11 12 13} and acute^{14 15} coronary syndromes.

Epidemiological studies indicate an association between increased intake of antioxidant vitamins and reduced risk of coronary disease,^{16 17 18} although the mechanism(s) responsible for these observations are incompletely understood. One possible mechanism is preservation of normal endothelial function by antioxidants, since increased oxidative stress has been related to impaired action of EDRF.^{19 20 21} In particular, increased vascular superoxide production is associated with inactivation of NO²² and loss of endothelium-dependent dilation.^{20 21}

Ascorbic acid, or vitamin C, is the main water-soluble antioxidant in human plasma.²³ It effectively scavenges superoxide and other reactive oxygen species,²⁴ and it plays an important role in the regulation of intracellular redox state through its interaction with glutathione.^{25 26} We therefore hypothesized that ascorbic acid would improve abnormal endothelium-dependent vasomotor function in patients with atherosclerosis. We tested this hypothesis by examining endothelium-dependent, flow-mediated brachial artery dilation before and 2 hours after oral administration of ascorbic acid or placebo in a group of patients with documented coronary artery disease.

Methods

Determination of Ascorbic Acid Pharmacokinetics

We determined plasma concentration of ascorbic acid before and 2 hours after oral administration of 2 g ascorbic acid in six healthy fasting volunteers and again several days later after a 4-g dose. On the basis of this dosing study, we examined the time course of plasma ascorbic acid over a period of 24 hours after a single oral 2-g dose by collecting serial blood samples via an indwelling 20-gauge catheter. Plasma ascorbic acid concentration at each time point was determined by high-performance liquid chromatography with electrochemical detection using established methodology.²³

Patient Population

Patients referred to the cardiology service at Boston University Medical Center Hospital were screened for enrollment, and patients with significant coronary artery disease were eligible for study. In all but two patients studied, the presence of coronary artery disease was confirmed angiographically (at least one coronary stenosis >70%). In the two patients who did not undergo angiography, coronary artery disease was diagnosed by clinical history, ECG changes, and elevation of creatinine kinase MB fraction consistent with myocardial infarction. The extent of coronary artery disease was graded by an established scoring system.²⁷ All patient subjects and normal volunteers gave informed consent, and the study was conducted in accordance with the policies and procedures of the Institutional Review Board of Boston University Medical Center Hospital.

All vasoactive medications were withheld for at least 12 hours before study, and all long-acting vasoactive medications were withheld for at least 24 hours. Patients with unstable angina, uncontrolled hypertension, or any other condition that would preclude withholding vasoactive medications and patients taking antioxidant vitamin supplements, estrogen replacement therapy, or allopurinol were excluded from study. All patients were taking aspirin (325 mg/d) at the time of study.

Study Protocol

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Endothelium-dependent, flow-mediated dilation of the brachial artery was determined from two-dimensional ultrasound images according to established and validated methodology.^{28 29 30} Images were obtained with an ATL 10-5 MHz linear array transducer and an ATL Ultramark 9 ultrasound system (Advanced Technology Limited). Imaging was performed with the patient resting supine for at least 5 minutes on an examining table or hospital bed in a quiet setting. For each patient, optimal brachial artery images were obtained between 2 and 10 cm above the antecubital crease. This location was marked, and all subsequent images were obtained at the same location. First, baseline two-dimensional images were obtained. Pulsed-Doppler blood flow velocity was then determined with the signal at a 60° angle to the vessel and the range gate adjusted to 1.0 mm and positioned in the center of the artery. To induce hyperemia, a small-width blood pressure cuff (Electro-Diagnostic Instruments), placed at the most proximal portion of the arm,^{29 30} was next inflated to occlusive pressure (200 mm Hg). Arterial occlusion was maintained for 5 minutes with the ultrasound transducer position carefully maintained. The cuff was then rapidly deflated, and pulsed-Doppler signals were recorded for 15 seconds. Two-dimensional images were obtained 60 seconds after cuff deflation. All images were recorded on super VHS videotape for later analysis.

Patients were then given either 2 g ascorbic acid (1000-mg tablets, Consumer Value Stores) or similar-appearing cellulose-containing placebo tablets. Based on the results of the ascorbic acid dosing study, a repeat brachial ultrasound study was performed 2 hours after treatment. This follow-up study included repeat two-dimensional and pulsed-Doppler measurements before and after reactive hyperemia. After an additional 10-minute rest period (to allow arterial diameter to return to prereactive hyperemia size), two-dimensional images were again obtained at baseline and 3 minutes after sublingual nitroglycerin (0.4 mg). Plasma was obtained before ascorbic acid or placebo administration for later determination of baseline ascorbic acid concentration. To ensure that ascorbic acid does not affect systemic hemodynamics, blood pressure was measured 2 hours after treatment with a standard sphygmomanometer, and heart rate was determined from the pulsed-Doppler recordings.

Brachial Artery Image and Doppler Velocity Profile Analysis

In each patient, a 10- to 20-mm segment of brachial artery was identified for analysis by use of anatomic landmarks. To reproducibly select images at the same point in the cardiac cycle, images at peak systole (maximum dilation) were identified and digitized with a videocassette recorder (Panasonic AG-7344) and a computer (Macintosh Quadra 840 AV) containing a digitizing board (Scion Corp LG-3). For each condition (before and during hyperemia at baseline; before and during hyperemia 2 hours after treatment; and before and after nitroglycerin), three separate images from three different cardiac cycles were digitized. Average segment diameter for each image was determined in a blinded manner with customized image analysis software.²⁹ The three diameter determinations for each condition were analyzed, and the percent changes in diameter in response to hyperemia and nitroglycerin were calculated. An abnormal flow-mediated dilation response was prospectively defined as <5.0%, on the basis of previously published studies.^{6 7 28 29 31}

Brachial artery blood flow at rest and during reactive hyperemia was determined by previously described methods.^{28 30} To estimate baseline brachial artery blood flow, pulsed-Doppler signals and internal calibration markings were recorded and digitized, and the flow velocity integral per beat was determined by use of public domain software (NIH Image Version 1.55). Blood flow was estimated as the product of this parameter, vessel cross-sectional area, and heart rate. To calculate percent increase in brachial blood flow during reactive hyperemia, pulsed-Doppler flow signals were taped at baseline and during the first 15 seconds after cuff release. The cardiac cycle with the largest flow velocity integral was selected for calculation of maximal hyperemic flow as above. The relative increase in blood flow during hyperemia was expressed as the percent increase in flow from baseline.

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Reproducibility

The reproducibility and repeatability of the above-described method for assessment of endothelium-dependent, flow-mediated brachial dilation have been extensively validated by previous investigators.^{28 29 30 32} The reproducibility of the diameter determination software used for this study has also been reported previously.²⁹ To examine the reproducibility of our imaging hardware and to assess intraobserver variability, we selected and digitized two ultrasound images from the same study, identified and marked the same vessel segment, and determined segment diameter in a blinded fashion in 72 vessels with an average diameter of 4.62 ± 0.08 mm (mean $\pm$ SEM). The two vessel diameter determinations were compared by linear regression, and we observed a correlation coefficient of .99 with an SEE of 0.1 mm. The average difference between determinations was 0.08 ± 0.006 mm ($1.7 \pm 0.3\%$ of the vessel diameter). These findings compare favorably with previously published methods.^{28 30 32}

Statistical Analysis

All data are presented as mean $\pm$ SEM. The dose response to ascorbic acid was examined with repeated-measures ANOVA and a post hoc Dunn's test. Baseline clinical characteristics, vessel diameter, blood flow, brachial dilator response to nitroglycerin, and blood pressure and heart rate after treatment for the ascorbic acid and placebo groups were compared by the unpaired *t* test or Fisher's exact test as appropriate. Effect of treatment on baseline vessel diameter, extent of brachial dilation, and hyperemic flow were compared by two-way ANOVA with a post hoc Student-Newman-Keuls comparison. Factors affecting brachial dilation were examined by regression analysis. Similar analyses were performed for the group as a whole and for the prospectively defined group of patients with abnormal vasodilator function at baseline. Statistical analysis was performed with SigmaStat software (Jandell Scientific, Inc). Statistical significance was accepted if the null hypothesis was rejected at the $P < .05$ level.

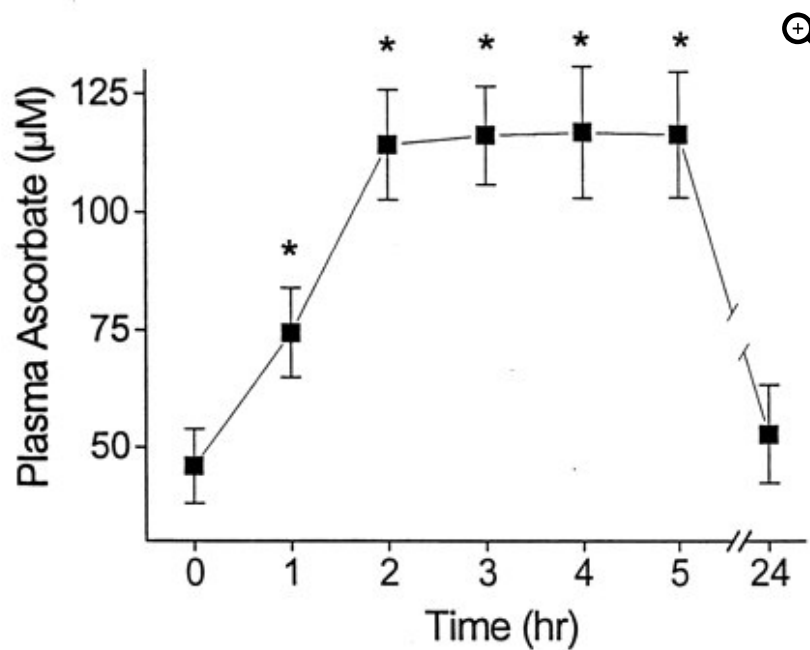
Results

Ascorbic Acid Absorption

Oral ingestion of 2 g ascorbic acid produced a 2.5-fold increase in plasma ascorbic acid concentration (46 ± 8 to 114 ± 11 $\mu\text{mol/L}$, $P = .001$) in the six fasting healthy volunteers. In the same subjects, oral ingestion of 4 g ascorbic acid increased plasma ascorbic acid levels to 197 ± 14 $\mu\text{mol/L}$, a value that exceeded the reported normal range of 30 to 150 $\mu\text{mol/L}$.³³ Since the 2-g dose produced a significant increase in plasma ascorbic acid level within the physiological range, this dose was selected for the study.

Time-dependent determination of plasma levels after ingestion of 2 g ascorbic acid in this same group demonstrated that plasma levels reached a plateau after 2 hours and remained elevated 5 hours after ingestion. By 24 hours after ingestion, plasma levels had returned to baseline (Fig 1⇓). On the basis of these findings, we chose to study patients 2 hours after ascorbate ingestion.

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Figure 1.

Plasma ascorbic acid levels in response to a 2-g oral dose in six healthy volunteers. Plasma was obtained at the indicated times, and ascorbic acid content was determined as described in “Methods.” Data are expressed as mean±SEM. *Significant change from baseline by a post hoc Dunn’s test.

Baseline Characteristics

Fifty patients were enrolled in the study. Technically adequate studies were obtained in 46 patients. Two patients were not able to tolerate blood pressure cuff inflation, and two patients studied were excluded because of poor image quality. The ascorbic acid (n=26) and placebo (n=20) groups were similar with respect to all baseline characteristics analyzed (Table 1↓).

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Table 1.

Baseline Characteristics in Patients According to Treatment Group

	Ascorbic Acid (n=26)	Placebo (n=20)
Age, y (range)	59.4 (40-86)	60.0 (48-85)
Female, %	27	30
Mean cholesterol, mg/dL	192±8	203±14

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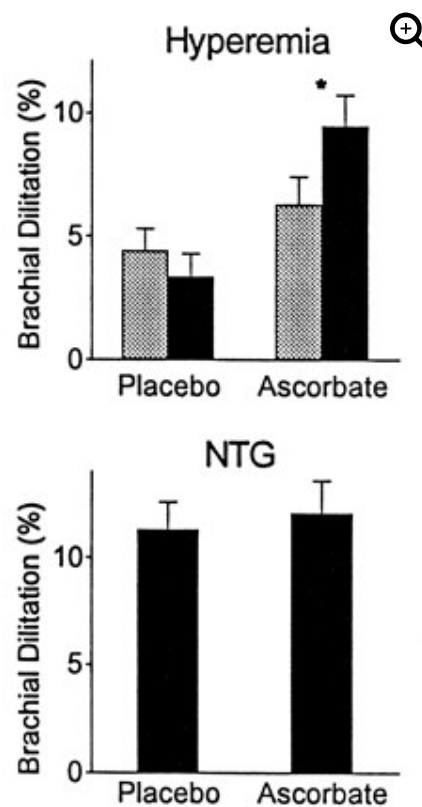
	Ascorbic Acid (n=26)	Placebo (n=20)
Current lipid-lowering medication, %	19	20
Hypertension, %	58	50
Family history premature CAD, %	27	30
History of tobacco use, %	62	80
Current tobacco use, %	35	40
Diabetes mellitus, %	35	25
History of MI, %	54	65
Peripheral vascular disease, %	8	15
Coronary atherosclerosis score	2.6±0.4	2.7±0.2
Plasma ascorbic acid, µmol/L	37±5	30±4

CAD indicates coronary artery disease; MI, myocardial infarction. Clinical characteristics were derived from patients' medical history, and plasma cholesterol and ascorbic acid were determined from a fasting (14-hour) blood sample. The atherosclerosis score was determined as described in text. Values are mean±SEM.

Brachial Responses for All Patients

The brachial artery responses in all patients treated with ascorbic acid and all patients given placebo were analyzed. Ascorbic acid administration resulted in an improvement in endothelium-dependent, flow-mediated dilation, from 6.3±1.1% to 9.5±1.2%, whereas there was no increase in flow-mediated dilation with placebo administration, 4.4±1.1% to 3.4±1.2% (Fig 2 $\downarrow$). By ANOVA, the effect of ascorbic acid treatment on brachial dilation was significantly different from the effect of placebo ($P=.0007$).

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Figure 2.

Brachial artery dilation in response to hyperemia or nitroglycerin (NTG). Patients referred for cardiac catheterization underwent brachial ultrasound imaging according to the protocol described in "Methods." The dilation response to hyperemia (top) was measured before (shaded bars) and after (solid bars) placebo (n=20) or ascorbic acid (n=26) administration. The response to NTG (bottom) was determined after placebo or ascorbic acid as described in "Methods." Data are presented as mean±SEM. *Significant effect of ascorbate treatment compared with placebo, $P=.0007$ by ANOVA.

To examine whether ascorbic acid increased arterial dilation through an effect on the smooth muscle cell response to NO, we compared the responses to nitroglycerin in the ascorbic acid and placebo groups (Fig 2↑). Sublingual nitroglycerin (0.4 mg) produced equivalent brachial artery dilation in the ascorbic acid and placebo groups ($11.3\pm1.3\%$ and $12.1\pm1.5\%$ dilation, respectively, $P=NS$ by ANOVA).

To verify that the observed increase in flow-mediated dilation after ascorbic acid treatment could not be attributed to differences between treatment groups in baseline arterial characteristics, the stimulus for dilation, or an effect of treatment on hemodynamics, we compared baseline vessel diameter, resting blood flow, the hyperemic response, and posttreatment heart rate and blood pressure. As shown in Table 2↓, there were no significant differences in these parameters.

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Table 2.

Brachial Artery Parameters According to Treatment Group

	Ascorbic Acid (n=26)	Placebo (n=20)
Baseline vessel diameter before treatment, mm	4.44±0.10	4.66±0.19
Baseline vessel diameter after treatment, mm	4.38±0.14	4.70±0.14
Baseline blood flow before treatment, mL/min	140±20	193 ±25
Baseline blood flow after treatment, mL/min	156±24	181±21
Hyperemia before treatment, %	671±160	653±86
Hyperemia after treatment, %	552±94	598±60
Mean blood pressure after treatment, mm Hg	92±2	88±3
Heart rate after treatment, beats per minute	71±3	74±4

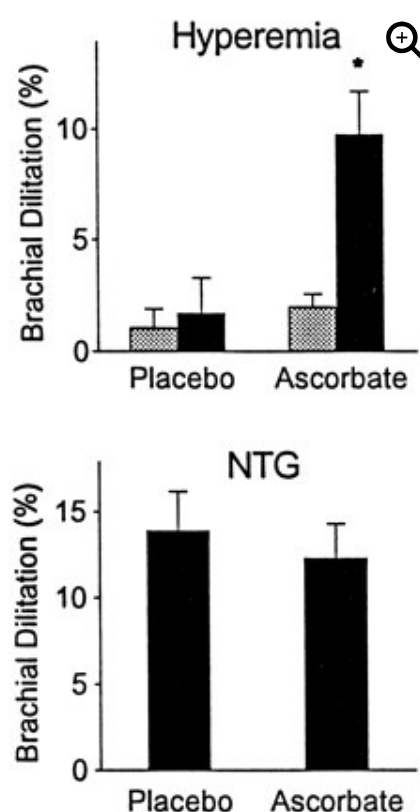
Brachial blood flow was determined as described in "Methods." Hyperemia is expressed as percent increase in flow from baseline. There were no significant differences between the two treatment groups. There were also no significant differences in vessel diameter, flow, and reactive hyperemia before and after ascorbate treatment. Values are mean±SEM.

Administration of ascorbic acid did not alter extent of reactive hyperemia, which was the stimulus for brachial artery dilation (Table 2↑). Baseline (before cuff inflation) brachial artery diameter and blood flow also were similar before and 2 hours after ascorbic acid administration (Table 2↑). These findings suggest that ascorbic acid improved effective release of EDRF from conduit vessels in response to increased flow but did not measurably affect basal EDRF release or the largely endothelium-independent dilation of resistance vessels that produces reactive hyperemia.

Patients With Abnormal Baseline Flow-Mediated Dilation

Thirteen patients (50%) in the ascorbate group and 10 patients (50%) in the placebo group met the prospectively defined definition of abnormal baseline vasodilator responses to hyperemia (<5%). As shown in Fig 3↓, ascorbic acid administration in these patients with vasomotor dysfunction produced a marked improvement in endothelium-dependent, flow-mediated dilation, from 2.0±0.6% to 9.7±2.0%. There was no significant change in flow-mediated dilation with placebo administration, 1.1±0.9% to 1.7±1.5%. By ANOVA, the effect of ascorbic acid treatment on brachial dilation was significantly different from the effect of placebo ($P=.003$).

By ANOVA
the effect of ascorbic acid treatment on brachial dilation was significantly different from the effect of placebo ($P=.003$).
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Figure 3.

Brachial artery dilation in response to hyperemia or nitroglycerin (NTG) in patients with an abnormal baseline flow-mediated dilation. Patients were studied as in Fig 2†, and data from patients with an abnormal baseline response (<5% dilation) are presented. The dilation response to hyperemia (top) was measured before (shaded bars) and after (solid bars) placebo (n=10) or ascorbic acid (n=13) administration. The response to NTG (bottom) was determined after placebo or ascorbic acid as described in “Methods.” Data are presented as mean±SEM. *Significant effect of ascorbate treatment compared with placebo, $P=.003$ by ANOVA.

Smooth muscle cell response to NO, as assessed by arterial dilation to nitroglycerin, was similar in the ascorbate and placebo groups ($12.3\pm2.0\%$ and $13.9\pm2.3\%$, respectively, $P=NS$ by ANOVA) (Fig 3†). Baseline vessel size, blood flow, hyperemic response, and posttreatment heart rate and blood pressure in the two groups were also similar (data not shown, $P=NS$). The effect of treatment on baseline diameter, baseline flow, and extent of hyperemia also was similar for the ascorbic acid and placebo groups ($P=NS$).

Correlates of Improved Endothelium-Dependent Dilation

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To determine whether ascorbic acid deficiency itself is an important mechanism of endothelial dysfunction in the setting of atherosclerosis, baseline ascorbic acid levels were determined in a total of 28 subjects. Plasma ascorbic acid concentration did not correlate with the extent of baseline brachial dilation ($r=-.18$, $P=NS$). There was also no correlation between baseline ascorbic acid level and improvement in arterial dilation in the patients receiving ascorbic acid ($r=.27$; $P=NS$). In the patients who received ascorbic acid, the extent of improvement after treatment correlated inversely with the pretreatment dilator response ($r=-.61$, $P=.001$),

confirming our observation that patients with an impaired response at baseline demonstrated improvement with ascorbic acid treatment. Other baseline characteristics, including sex, baseline vessel diameter and flow, and extent of hyperemia, did not correlate with extent of dilation during hyperemia or the extent of improvement with ascorbic acid treatment.

Discussion

This placebo-controlled, blinded study demonstrated that oral administration of 2 g ascorbic acid, a water-soluble antioxidant, reverses endothelial vasomotor dysfunction in patients with coronary artery disease. The improvement in vasodilation after ascorbic acid was not due to an increase in the stimulus for dilation (reactive hyperemia), a change in baseline vessel tone, or a change in the ability of the artery to dilate to an exogenous source of NO (nitroglycerin). Taken together, these findings suggest that ascorbic acid restores effective endothelial release and/or action of EDRF in the brachial artery of patients with coronary atherosclerosis.

Ascorbic Acid and Potential Effects on EDRF Action

Ascorbic acid is an extremely effective antioxidant, and it has been demonstrated to have potent antioxidant actions in human plasma.²³ Among its antioxidant properties, ascorbic acid has been shown to be an efficient scavenger of many reactive oxygen species, including superoxide anion.³³ This ability provides one possible explanation for the observed beneficial effects of ascorbic acid on endothelial function. Superoxide anion has the capacity to react rapidly with NO and limit the biological activity of EDRF.²² Excess vascular superoxide production has been demonstrated in disease states associated with endothelial dysfunction, including hypercholesterolemia^{20 21} and diabetes.³⁴ In animal models of hypercholesterolemia, other interventions that reduce superoxide production or scavenge superoxide are associated with improved endothelium-dependent dilation.^{20 21} Interestingly, Lehr and colleagues³⁵ recently demonstrated parallel effects of ascorbic acid and superoxide dismutase on leukocyte adhesion to endothelium in vivo under conditions of increased oxidative stress, further supporting the hypothesis that ascorbic acid may influence vascular function through an effect on superoxide metabolism.

Ascorbic acid also plays a central role in the regulation of intracellular redox state.^{25 26} Under conditions of increased oxidative stress, glutathione, an important intracellular thiol species, is oxidized to glutathione disulfide.^{25 26} Ascorbic acid spares glutathione from oxidation and may thus preserve intracellular reduced glutathione concentration.^{25 26} Prevention of glutathione oxidation by ascorbic acid could improve EDRF action in the short term by a number of mechanisms. Depletion of reduced thiol leads to decreased synthesis of NO in cultured endothelial cells^{36 37} and isolated enzyme preparations,^{38 39} possibly through an effect on the activity of NO synthase and/or the availability of essential cofactors for the enzyme, including FAD, tetrahydrobiopterin, and NADPH. Further, a number of investigators have suggested that EDRF is an S-nitrosothiol species^{3 40} and that formation of such species leads to stabilization of NO.^{40 41 42 43} Increased availability of reduced thiol species has been shown to potentiate the effects of EDRF on platelet activity² and on shear stress-mediated EDRF release.⁴⁴ Thus, increasing intracellular ascorbic acid concentration could increase the availability of reduced thiol and thereby improve EDRF action through increased synthesis of NO and/or stabilization of NO.

Several other possible explanations of how ascorbic acid administration may reverse endothelial vasomotor dysfunction warrant consideration. Humans are incapable of synthesizing ascorbic acid and obtain adequate amounts of ascorbic acid only by dietary means. Several large epidemiological studies have suggested that dietary intake of ascorbic acid and plasma ascorbic acid concentration are inversely associated with the risk of ischemic heart disease.^{16 45 46} In the present study, only patients with coronary atherosclerosis were

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examined, and this group had ascorbic acid levels in the low-normal range. There was no relation, however, between baseline ascorbic acid concentration and baseline endothelial function or extent of improvement with treatment. Correction of an absolute ascorbic acid deficiency per se is unlikely to explain the reversal of endothelial dysfunction.

Ascorbic acid effectively prevents the oxidation of LDL,⁴⁷ a process that has been implicated in atherogenesis.⁴⁸ In animal models, protection of LDL against oxidation with chronic antioxidant treatment is also associated with improved EDRF action.^{19 21 49} In this study, however, vasodilation was observed to increase over a period of only 2 hours. It is unlikely that this improved dilation over such a brief period of time is due to reduced formation of oxidized LDL or any effect on the composition or extent of atherosclerotic lesions.

Ascorbic acid has also been shown to increase prostacyclin synthesis in cultured human endothelial cells,⁵⁰ and one experimental study suggests that ascorbic acid may enhance prostacyclin synthesis in hypercholesterolemia.⁵¹ However, since all patients were taking aspirin at the time of study, it is unlikely that ascorbic acid increased vasodilation entirely through an effect on prostaglandin synthesis.

One previous study used ascorbic acid in an investigation of the effects of antioxidants on endothelium-dependent dilation and failed to demonstrate a beneficial effect.⁵² In that study, Gilligan and colleagues treated hypercholesterolemic patients without evidence of coronary artery disease with a combination of ascorbic acid (1 g/d), vitamin E (800 IU/d), and β -carotene (30 mg/d) for 1 month. Using venous occlusion plethysmography, they observed no improvement in endothelial vasodilator function in forearm resistance vessels in response to intra-arterial acetylcholine. The patient populations and type and duration of antioxidant treatment were quite different between that study and the present study. Furthermore, the prior study examined receptor-dependent EDRF release in the microvasculature, whereas the present study examined non-receptor-dependent EDRF release in a conduit artery. These important differences in study methodology most likely account for the apparently discordant results.

Ascorbic acid, vitamin E, and β -carotene may all favorably influence cardiovascular risk, but there are several important differences between these naturally occurring antioxidants. Ascorbic acid is water-soluble and is present in most body fluids; vitamin E and β -carotene are both lipid-soluble, and the concentrations of these compounds in plasma and specific cellular compartments differ. The primary antioxidant mechanisms of these antioxidants also are distinct. As discussed above, among the important antioxidant properties of ascorbic acid are its abilities to scavenge superoxide anion and to preserve intracellular reduced glutathione concentration. The primary antioxidant effects of vitamin E relate to its ability to scavenge lipid peroxyl radicals and thus inhibit lipid peroxidation in LDL and cell membranes. The antioxidant actions of carotenoids result, in part, from their ability to quench singlet oxygen and to scavenge peroxyl radicals.³³ Under conditions of increased oxidative stress, EDRF action may be impaired by a number of mechanisms and may therefore be differentially affected by different antioxidants, depending on their location and reactivity.⁵³ Thus, the beneficial effects of ascorbic acid on endothelial vasodilator function observed in this study cannot necessarily be extrapolated to other antioxidants.

Applicability of Brachial Artery Findings to the Coronary Circulation

Since the present study examined the effects of ascorbic acid on the brachial artery, inferences about the possible effects of ascorbate on the coronary circulation must be made with caution. However, several lines of evidence suggest that examination of the brachial circulation is relevant to coronary atherosclerosis. Although the brachial artery does not develop obstructive atherosclerotic lesions, it can develop nonobstructive atherosclerotic changes. Known systemic risk factors for coronary events, including hypercholesterolemia, hypertension, diabetes mellitus, and tobacco use, have been shown to adversely affect endothelial vasomotor

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function in the brachial artery.^{6 7 28} Abnormal endothelium-dependent brachial responses have been shown to correlate with the presence of coronary artery disease.³² Further, one preliminary study demonstrated a strong correlation between endothelial function/dysfunction in conduit brachial and coronary arteries of the same patients.⁵⁴ Finally, flow-mediated EDRF release may be a particularly relevant response for study, because loss of flow-mediated dilation has been implicated in the pathophysiology of abnormal coronary reactivity in the setting of clinically relevant stimuli such as exercise and mental stress.^{11 12}

In summary, this study demonstrates that oral administration of the antioxidant ascorbic acid in a physiological dose reverses endothelial vasomotor dysfunction in the brachial artery of patients with coronary artery disease. This finding suggests that increased oxidative stress may be an important mechanism for impaired endothelial function in this setting. Improved vasomotor function of the endothelium could explain, in part, the association between increased intake of antioxidant vitamins and reduced risk of ischemic heart disease and provide further rationale for ongoing trials of antioxidant therapy for primary and secondary prevention of cardiovascular disease.

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Footnotes

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