Vitamin E Protects Against Impairment of Endothelium-Mediated Relaxations in Cholesterol-Fed Rabbits


Abstract The vascular effects of dietary vitamin E were investigated in isolated carotid artery preparations from cholesterol-fed New Zealand White rabbits. Rabbits were fed either a control, 1% cholesterol, or 1% cholesterol plus 0.2% vitamin E diet for 4 weeks. In raised-tone preparations, relaxant responses to acetylcholine were enhanced in rabbits fed cholesterol plus vitamin E, reversing the reduction in responses measured in preparations from cholesterol-fed rabbits. Relaxant responses to the calcium ionophore A23187 were significantly enhanced in cholesterol plus vitamin E-fed rabbits compared with those fed cholesterol alone, with no difference between control and cholesterol-fed rabbits. Relaxant responses to sodium nitroprusside were not different between the three dietary groups. Constrictor responses to noradrenaline and serotonin in isolated carotid artery preparations at basal tone were unaltered after cholesterol and cholesterol plus vitamin E diets. The copper-induced oxidation of β-very-low-density lipoprotein (βVLDL) isolated from plasma of rabbits fed a cholesterol plus vitamin E diet was almost completely inhibited compared with the oxidation of βVLDL from rabbits fed cholesterol alone. These results show that vitamin E prevents endothelial dysfunction associated with cholesterol feeding and suggests that vitamin E may be beneficial in preventing functional impairment associated with atherosclerosis. (Arterioscler Thromb. 1994;14:494-499.)

Key Words • rabbit carotid artery • hypercholesterolemia • antioxidants • vitamin E • endothelium

Hypercholesterolemia induces endothelial dysfunction, leading to an impairment of endothelium-mediated relaxant responses. This may be a result of an attenuation in the production, release, or bioactivity of nitric oxide–related endothelium-derived relaxing factor (EDRF). Reactive oxygen species (ROS) are known to be released from monocytes/intimal macrophages, smooth muscle cells, endothelial cells, and LDL during its modification in the arterial wall, and it is possible that they contribute to endothelial dysfunction, since ROS generation is increased in atherosclerotic vessels and there is evidence that ROS inactivate EDRF in vitro.

Vitamin E is the most abundant, naturally occurring, lipid-soluble antioxidant in plasma. It is carried within the low-density lipoprotein (LDL) particle and prevents its oxidation in vitro. Low doses of vitamin E (0.2%) do not have a significant effect on plasma cholesterol levels; therefore, a 1% cholesterol diet containing 0.2% vitamin E could be used to test its action as an antioxidant agent in a model of atherogenesis. In the present study, we have examined the possible role of oxidative processes in the early impairment of endothelium-mediated responses by studying the effects of the antioxidant vitamin E on endothelium-mediated relaxations in the carotid artery of the hypercholesterolemic rabbit.

Methods

Animals and Dietary Protocol

Male New Zealand White rabbits weighing 2.0 to 2.5 kg were obtained at 8 to 10 weeks of age (Rosemead Rabbit Co, Essex, UK). They were assigned to one of three dietary groups: (1) control diet consisting of standard rabbit chow (containing 0.003% vitamin E; Scientific Diet Services, Essex), (2) rabbit chow containing 1% cholesterol, and (3) chow containing 1% cholesterol and 0.2% vitamin E. (A group of rabbits on standard chow supplemented with vitamin E was not included in the study because of the lipophilic nature of vitamin E, meaning that comparable levels of plasma vitamin E could not be attained in the absence of cholesterol feeding.) Rabbits were allowed free access to water. Cholesterol diets were prepared by spraying a solution of cholesterol dissolved in diethyl ether onto the standard chow so as to obtain an even distribution and drying the diet overnight to ensure complete evaporation of the solvent. The control diet was similarly treated with diethyl ether alone. The vitamin E diet was prepared by mixing α-tocopherol directly into diet containing 1% cholesterol. Rabbits were maintained on their respective diets for a period of 4 weeks. Four milliliters of blood was collected from every animal (via the marginal ear vein) before the start of treatment to enable baseline cholesterol and vitamin E concentrations to be established. Animals were killed by a lethal dose of sodium pentobarbitone (60 mg/kg) injected into the marginal ear vein. Blood for the measurement of cholesterol and vitamin E levels and for the isolation of β-very-low-density lipoprotein (βVLDL) was obtained by cardiac puncture and collected in tubes containing citrate solution to a final concentration of 0.38% citrate.

Pharmacological Procedures

Preparation of Tissue for Pharmacology

Both left and right carotid arteries were excised and divided into a total of six rings, each approximately 7 mm long.
Vascular rings were mounted horizontally under isometric conditions in 10-mL organ baths according to the method of Bevan and Osher. The tissues were bathed in Krebs’ solution of the following composition (mmol/L): NaCl 133, KCl 4.7, NaH₂PO₄ 1.35, NaHCO₃ 16.3, MgSO₄ 0.61, glucose 7.8, and CaCl₂ 2.52. The Krebs’ solution was bubbled with 95% O₂/5% CO₂ and maintained at a constant temperature of 37°C.

Preparations were allowed to equilibrate for at least 1 hour under a predetermined optimal resting tension of approximately 2.0 g. Responses of the circular smooth muscle were recorded by use of a Grass FT03C transducer and displayed on an ink-writing oscillograph (Grass model 79).

Pharmacological Protocol

Noradrenaline (0.01 to 300 μmol/L) and serotonin (0.01 to 30 μmol/L) were added cumulatively to the bath so that contractile concentration-response curves could be constructed. To study relaxation, vessel tone was raised by the addition of a concentration of noradrenaline that produced approximately 60% to 70% of the maximum contractile response in each vessel (10 μmol/L). Acetycholine (0.1 to 100 μmol/L), the calcium ionophore A23187 (0.1 to 30 μmol/L), and sodium nitroprusside (0.1 to 300 μmol/L) did not cause desensitization and were therefore added cumulatively to the bath.

At least 20 minutes was allowed between consecutive dose-response curves, during which time the Krebs’ solution was changed every 5 minutes. All vascular rings were tested with noradrenaline, serotonin, and acetycholine, with three rings being randomly selected to be tested with the calcium ionophore A23187 and the remaining three with sodium nitroprusside.

Biochemical Procedures

Isolation of βVLDL

Blood collected by cardiac puncture from cholesterol- and cholesterol+vitamin E-fed rabbits at the time they were killed was centrifuged to obtain plasma. The plasma obtained from individual rabbits within each of the two groups was pooled separately. βVLDL (density < 1.006) was obtained from the plasma by ultracentrifugation for 20 hours at 50,000 rpm at 4°C in a Ti 70 rotor (Beckman Instruments Inc, Fullerton, Calif). The βVLDL layer was recovered and recentrifuged at density 1.006 for 20 hours at 50,000 rpm at 4°C. The supernatant (βVLDL) was collected and used for oxidation studies. Protein content was determined by the Lowry method, using bovine serum albumin as the standard, so that equivalent amounts of βVLDL could be used in the oxidation studies.

Oxidative Modification of βVLDL

βVLDL was incubated at a concentration of 100 μg protein/mL in 5 μmol/L copper sulfate solution for various time intervals (0 to 6 hours) at 37°C. Ten microliters of 5 mmol/L butylated hydroxytoluene was added to each tube at the end of the set incubation times to halt the oxidation reaction.

Determination of Lipid Peroxidation

Lipid peroxidation was determined by measuring the thiobarbituric acid–reactive substances (TBARS) in the medium. One and one half milliliters 20% trichloroacetic acid (TCA) and 0.5 mL 0.67% thiobarbituric acid were added to 300 μL of each sample, using 0.2, 0.5, and 1.0 nmol/L malondialdehyde (MDA) as a standard. After boiling for 60 minutes, MDA-like compounds in each sample were extracted into 2 mL butanol, and the fluorescence was measured with a Perkin-Elmer fluorometer with excitation at 515 nm and emission at 533 nm.
average value per animal was taken. In the figure legends, n
refers to the number of animals from which vessels were used.

Statistical analysis of results within the three groups was
performed with one-way ANOVA, applying the Bonferroni
method when ANOVA indicated a significant difference
between the groups. A probability of P<.05 was considered
significant. Statistical analysis of results was performed on a
Dell 316SX PC using GraphPAD INSTAT software. For the
measurement of lipid peroxidation by TBARS, duplicate de-
terminations were carried out and the average values ex-
pressed in terms of MDA equivalents (nmol MDA equivalents
per milliliter of sample).

Results

Body and Vessel Segment Weights

There was no significant difference in either body
weights or the wet weight of vessel segments between
the three different groups of rabbits (Table).

Serum Cholesterol and Vitamin E

The average baseline serum cholesterol level at the
start of the dietary regimen was 1.9±0.1 mmol/L. Serum
cholesterol levels were significantly greater at the time
of death in the cholesterol-fed rabbits, whether or not
they received vitamin E supplementation (Table).

Mean average baseline serum vitamin E levels were
2.3±0.8 µg/mL. After 4 weeks of a cholesterol diet
enriched with vitamin E, vitamin E levels rose signifi-
cantly, to 76.8±10.4 µg/mL (P<.001).

Pharmacology

Acetylcholine, A23187, and sodium nitroprusside
produced dose-dependent relaxant responses in all
raised-tone preparations of the rabbit carotid artery
tested. Relaxant responses to acetylcholine in prepara-
tions from cholesterol-fed rabbits were significantly
reduced compared with rabbits fed the control diet at
0.3, 1.0, and 3.0 µmol/L acetylcholine (Fig 1). Relaxant
responses measured in preparations from cholesterol
plus vitamin E-fed rabbits were significantly greater
than in those from cholesterol-fed rabbits at all concen-
trations of acetylcholine tested. There was no difference
between responses in preparations from control and
cholesterol plus vitamin E-fed rabbits. Relaxant re-
sponses to the calcium ionophore A23187 were signifi-
cantly greater in preparations from cholesterol plus
vitamin E-fed rabbits compared with cholesterol-fed
rabbits at 3.0, 10, and 30 µmol/L (Fig 2). Preparations
from control versus cholesterol-fed rabbits and also
from control versus cholesterol plus vitamin E-fed
rabbits did not vary in their response to A23187.

Relaxant responses to sodium nitroprusside measured
in preparations from the three groups were not different
over the concentration range tested (Fig 3).

Both noradrenaline (0.01 to 300 µmol/L) and serotonin
(0.01 to 30 µmol/L) produced a dose-dependent
contractile response in all carotid artery preparations
tested at resting tone. There was no significant differ-
ence between responses to noradrenaline and those to
serotonin in artery segments obtained from rabbits fed
any of the three dietary regimens (Figs 4 and 5).

Copper Oxidation of βVLDL

The copper-induced oxidation of βVLDL from rab-
bits fed the cholesterol plus vitamin E diet was inhibited
compared with the ability of βVLDL isolated from the
plasma of rabbits fed a cholesterol-enriched diet alone
(Fig 6).

Histology

Silver nitrate stained the endothelial cell membrane
and confirmed the presence of a normal intimal endo-
thelial monolayer (Fig 7). Oil red O staining revealed no

![Graph 1](http://atvb.ahajournals.org/.../fig1.png)

**Fig 1.** Graph of isolated transverse ring preparations of the
rabbit carotid artery with tone raised by noradrenaline (10
µmol/L). Cumulative concentration-response curves to acetyl-
choline (ACh) (0.1 to 100 µmol/L) in preparations taken from
rabbits fed control (c, n=8), 1% cholesterol (a, n=10), and 1%
cholesterol plus 0.2% vitamin E (b, n=8) diets for 4 weeks. Data
points are means, with SEM shown by vertical bars. Statistical
analysis between the three groups was carried out by the
Bonferroni method, in which analysis of variance indicated a
significant difference between groups. *Significant difference of
P<.001 compared with group 1.
or minimal (<5%) intimal lipid deposition in vessels from both cholesterol only- and cholesterol plus vitamin E-fed animals. Vessel segments from animals on the control diet also showed no oil red O staining. Light and electron microscopy revealed that the appearance of the carotid arteries from the cholesterol-fed animals was essentially normal. At this time, the endothelium was intact, and no subendothelial foam cells could be detected. Occasional adherent leukocytes were observed by scanning electron microscopy in cholesterol-fed and cholesterol plus vitamin E–treated animals.

Discussion

Hypercholesterolemia Impairs Endothelial Cell Signal Transduction

Several studies have shown that hypercholesterolemia induces macrovascular endothelial dysfunction.22–24 Our data confirm that receptor-mediated, endothelium-dependent responses are rapidly impaired in the carotid artery of the cholesterol-fed rabbit and precede the development of overt atherosclerotic lesions.

Endothelium-dependent vasodilatation is mediated by EDRF, which has been identified as nitric oxide or a closely related molecule. There are a number of possible sites at which hypercholesterolemia may interfere with receptor-mediated responses. In a recent review, Flavahan25 presented the evidence supporting the view that hypercholesterolemia affects a G protein–dep-
dent pathway. Other authors have proposed effects on
the availability of the EDRF precursor L-arginine,26 the
stability of nitric oxide,5 or the activity of smooth muscle
cell guanylate cyclase.27
We found that although hypercholesterolemia caused
impaired responses to acetylcholine, responses to the
calcium ionophore A23187 and sodium nitroprusside
were unaffected. This suggests that at this time point,
hypercholesterolemia has led to a defect in the musca
rinic receptor/G protein-coupling mechanism proximal
to the level of intracellular calcium release.

Vitamin E Protects Endothelium From
Cholesterol-Induced Injury
The generation of ROS is enhanced in atherosclerotic
arteries.7,8 These free radical species can inactivate
EDRF9,10 or lead to oxidative modification of lipopro-
teins such as LDL and βVLDL.28,31 Some of the by-
products of lipoprotein oxidation, including hydroper-
oxides, reactive aldehydes, and lysophosphatidyl
choline, also have direct cytotoxic effects.
Vitamin E is a potent chain-breaking antioxidant that
inhibits lipoprotein oxidation and scavenges ROS. We
found that dietary supplements of vitamin E preserved
the vasodilator responses to acetylcholine in cholestero-
l-fed rabbits. In these animals, the responses to
A23187 were also significantly enhanced above control
values, although the responses to sodium nitroprusside
were unaltered. These data suggest that vitamin E may
enhance EDRF generation or preserve its bioactivity,
perhaps by preventing its destruction by ROS such as
superoxides. In addition, vitamin E would inhibit the in
vivo oxidation of βVLDL (since the in vitro oxidation of
βVLDL from vitamin E–fed, hypercholesterolemic rab-
bits was inhibited), thus preventing an inhibition of
endothelium-mediated responses resulting from the
presence of oxidized βVLDL.
In support of our findings, Mügge et al32 have shown
that treatment of atherosclerotic rabbits with polyethyl-
ene glycolated superoxide dismutase for 1 week resulted
in enhanced responses to acetylcholine and A23187 but
not sodium nitroprusside. Since this enhancement was
not observed in control rabbits, it was concluded that
the endothelial dysfunction was likely to have been
cause at least in part by the increased generation of
ROS. There have been several other treatments in
animals fed a cholesterol–rich diet that have been shown
to improve endothelium–dependent relaxations. These
include the calcium antagonist PN200110 and dipyr-
damole.33,34 In both cases, however, treatment also led
to a reduction in the formation of arterial lesions, which
would have contributed to the improvement of func-
tional responsiveness of the endothelium.
In conclusion, this study suggests that dietary vitamin
E has a protective role on the endothelium signaling

![Fig 6. Graph of copper-induced oxidation of pooled β-very-low-density lipoprotein isolated from cholesterol- (●) and cholesterol plus vitamin E-fed rabbits (●) at incubation times of 15 and 30 minutes and 1, 2, 4, and 6 hours. TBARS were determined as described in the "Methods" section and are expressed as malondialdehyde (MDA) equivalents. TBARS indicates thiobarbituric acid–reactive substances.](http://atvb.ahajournals.org/)

![Fig 7. Histological section of endothelium from a cholesterol-fed rabbit stained with 0.25% silver nitrate showing an intact vascular endothelium. Original magnification ×400.](http://atvb.ahajournals.org/)
isms, which are compromised after cholesterol
Vitamin E appears to exert its protective effects
sites in the signal transduction pathway, one
the release of intracellular calcium, the
the level of EDRF generation or bioactivity.

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or assistance in measuring serum cholesterol levels.

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responses in isolated aortas of control and hypercholesterolemic
At its October 1990 meeting the Scientific Publishing Committee explored the use and prevalence of Système International (SI) units for reporting measures of clinical and laboratory data. The committee since has sanctioned the use of SI units in the American Heart Association (AHA) journals.

The SI, an update of the metric system, is the outcome of a century of effort to provide a common system of measurement between nations and among the sciences. To promote its use, which can reduce the present confusion about measurements, the World Health Assembly in 1977 recommended the use of SI units in medicine.

The SI base units are the meter, kilogram, second, ampere, kelvin, and candela, and mole, respectively representing length, mass, time, electric current, temperature, luminous intensity, and amount of substance. By multiplying a base unit by itself, or by combining two or more basic units by multiplication or division, many units can be formed, known as SI-derived units. Examples of derived units are the square meter, cubic meter, mole per cubic meter, pascal (Pa), and joule (J).

Exceptions to the rule for SI unit conversion as currently applied to biomedical sciences include blood pressure, oxygen pressure, and enzyme activity. Retained as presently used are temperature, the pH scale, and the use of liter for volume. Table 1 illustrates the measurements excluded from SI unit conversion.

In the AHA journals, an average article contains few items that need conversion. Often the same conversion is made over and over in a manuscript and takes little extra effort. It is our belief that, in return for a small effort, the AHA can take a large step, along with many other international and domestic journals, toward perpetuating a common system for reporting medical and scientific measurements. The SI unit is to be used in text, followed by the presently used measurement in parentheses.

The accompanying conversion table (Table 2) lists the measurements most commonly used in the AHA journals and their corresponding SI units. A review of this table may serve as an introduction to the forthcoming transition to SI units.

### TABLE 1. Measurements Currently Not Converted to Système International (SI) Units in Biomedical Applications

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<td>Oxygen pressure</td>
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<td>Enzyme activity</td>
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<td>H⁺ concentration</td>
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<td>Temperature</td>
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<td>Volume</td>
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### TABLE 2. Examples of Measurement Conversions to Système International (SI) Units for American Heart Association Journals*

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<th>Current Unit</th>
<th>Conversion Factor</th>
<th>SI Unit</th>
<th>Normal Laboratory Values†</th>
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<td>atm</td>
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<td>/mm³</td>
<td>0.001</td>
<td>10⁹/L</td>
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*For a brief discussion of the development and use of SI units, see World Health Organization: The SI for the Health Professions, Geneva, Switzerland: World Health Organization, 1982. For a convenient list of commonly used laboratory measurement conversions to SI units, see "SI unit implementation—the next step" (editorial) in JAMA (1988;260:73-76).
†For illustration only; normal values may vary by laboratory.
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