

Short- and Long-Term Black Tea Consumption Reverses Endothelial Dysfunction in Patients With Coronary Artery Disease

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Background—Epidemiological studies suggest that tea consumption decreases cardiovascular risk, but the mechanisms of benefit remain undefined. Endothelial dysfunction has been associated with coronary artery disease and increased oxidative stress. Some antioxidants have been shown to reverse endothelial dysfunction, and tea contains antioxidant flavonoids.

Methods and Results—To test the hypothesis that tea consumption will reverse endothelial dysfunction, we randomized 66 patients with proven coronary artery disease to consume black tea and water in a crossover design. Short-term effects were examined 2 hours after consumption of 450 mL tea or water. Long-term effects were examined after consumption of 900 mL tea or water daily for 4 weeks. Vasomotor function of the brachial artery was examined at baseline and after each intervention with vascular ultrasound. Fifty patients completed the protocol and had technically suitable ultrasound measurements. Both short- and long-term tea consumption improved endothelium-dependent flow-mediated dilation of the brachial artery, whereas consumption of water had no effect ($P < 0.001$ by repeated-measures ANOVA). Tea consumption had no effect on endothelium-independent nitroglycerin-induced dilation. An equivalent oral dose of caffeine (200 mg) had no short-term effect on flow-mediated dilation. Plasma flavonoids increased after short- and long-term tea consumption.

Conclusions—Short- and long-term black tea consumption reverses endothelial vasomotor dysfunction in patients with coronary artery disease. This finding may partly explain the association between tea intake and decreased cardiovascular disease events. (*Circulation*. 2001;104:151-156.)

Key Words: antioxidants ■ tea ■ flavonoids ■ endothelium ■ nitric oxide ■ coronary disease

A part from water, tea is the most widely consumed beverage worldwide.¹ Recent epidemiological studies suggest an inverse relationship between tea consumption and cardiovascular disease,²⁻⁵ with one notable exception.⁶ There is also convincing evidence that dietary intake of antioxidant flavonoids from tea and other sources (eg, onions, apples, red wine, and broccoli) is associated with reduced cardiovascular risk.^{2-5,7-9} The benefit of high flavonoid intake may be greater for individuals with established coronary artery disease (CAD),^{2,10} although favorable effects have also been demonstrated in people without evidence of atherosclerosis.^{5,8,9}

One proposed mechanism for the benefit of dietary flavonoids is their antioxidant properties. These polyphenols are effective scavengers of reactive oxygen species¹¹ and can inhibit lipid peroxidation through chelation of transition metal ions¹² or their action as chain-breaking antioxidants.¹³ These properties suggest that flavonoids might prevent LDL oxidation, a key early event in the development of athero-

sclerosis.¹⁴ However, although several flavonoids exert this antioxidant activity in vitro, they do not prevent ex vivo LDL oxidation,^{15,16} and their cumulative concentration in LDL particles with regular tea ingestion is low.¹⁶

Recent experimental evidence also suggests that flavonoids may favorably affect endothelial function.^{17,18} Normal endothelium regulates vasomotor tone, platelet activity, leukocyte adhesion, and vascular smooth muscle proliferation via release of several paracrine factors, including nitric oxide (NO).¹⁹ These endothelial functions are impaired with atherosclerosis and its risk factors.^{14,20} Indeed, endothelial dysfunction may contribute to the pathogenesis of atherosclerosis both in the early stages of lesion formation and late in the disease process when patients develop clinical symptoms.¹⁹ Recent studies have also linked coronary endothelial dysfunction with future cardiovascular disease events.²¹

Endothelial dysfunction in atherosclerosis is associated with increased oxidative stress and may be reversed by

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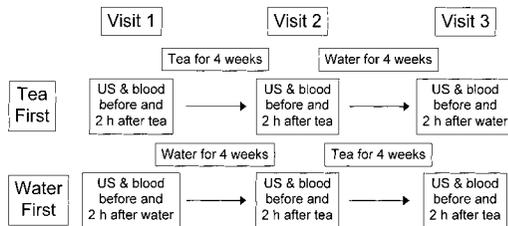


Figure 1. Outline of study design. US indicates brachial artery ultrasound.

antioxidant treatment.¹⁴ To test the hypothesis that tea consumption would improve endothelial function in patients with CAD, we performed a randomized, placebo-controlled, cross-over study of short- and long-term black tea consumption for its effect on brachial artery flow-mediated dilation.

Methods

Volunteers

Boston Medical Center patients with CAD (history of revascularization or ≥ 1 coronary stenosis $>70\%$ on angiography) were eligible. Exclusion criteria included uncontrolled hypertension, heart failure, recent acute coronary syndrome (<3 months), or intake of antioxidant vitamin supplements in doses greater than the recommended daily allowance. The Institutional Review Board approved the study. Volunteers provided written, informed consent.

Study Design

Patients made 3 visits, each 4 weeks apart. Patients fasted overnight and did not smoke for 24 hours. Vasoactive medications were withheld for ≥ 12 hours, and long-acting vasoactive drugs were withheld for ≥ 24 hours. Patients maintained their usual diet but excluded red wine and other tea consumption during the study. Baseline dietary flavonoid intake was estimated by a 1-week food-frequency questionnaire. This included major dietary sources of flavonols (quercetin, kaempferol, and myricetin) and flavanols (the various catechins but not proanthocyanidins), which were quantified through the use of food flavonoid content charts.²²

Patients consumed tea or water first (Figure 1) according to computer-generated randomization numbers. Endothelial function was assessed at 6 time points: (1) baseline; (2) 2 hours after consumption of 450 mL freshly brewed black tea (short-term tea); (3) after consumption of 900 mL (freeze-dried) black tea daily for 4 weeks but none the morning of study (long-term tea); (4) 2 hours later that day after 450 mL freshly brewed tea (short-on-long-term tea); (5) after 900 mL fresh water daily for 4 weeks (long-term water); and (6) 2 hours after 450 mL water (short-term water). Short-term tea effects were examined after 2 hours, coincident with maximal flavonoid bioavailability.^{16,23} For short-term studies, 9.7 g fresh tea leaf (World Blend, provided by Tea Trade Health Research Association, London, England) was brewed in a standard brewer (Bunn-O-Matic Corporation) for 5 minutes with 1 L fresh water. Freeze-dried tea was prepared from the same tea leaf by Lipton, Inc. Tea composition is detailed in Table 1. To increase compliance and mimic usual practice, participants added sugar, lemon, or milk as desired.^{16,23} Compliance was confirmed by direct questioning and counting of empty tea packets. At all 6 time points, blood was collected and vital signs were measured after 10 minutes of semirecumbent rest with an automated monitor,²⁴ and the average of 3 measurements was recorded.

To investigate whether tea effects were related to caffeine, endothelial function and blood pressure were assessed in separate patients before and 2 hours after a 200-mg oral dose of caffeine, which matched the caffeine content of 450 mL brewed tea (Table 1).

TABLE 1. Tea Composition

Component	Brewed Tea, mg/dL	Powdered Tea, mg/dL
Caffeine	42	30
Gallic acid	3.6	6.9
Epigallocatechin	2.0	2.3
Epigallocatechin gallate	3.9	4.8
Epicatechin	1.4	2.2
Epicatechin gallate	6.0	3.6
Total catechins	13.3	12.9
Total theoflavins	6.0	2.5
Tea solids	525	467
Total polyphenols	163	150
Total flavonoids	106	97

Components are in tea after preparation in water for consumption.

Vascular Function Assessment

Endothelium-dependent flow-mediated dilation, endothelium-independent nitroglycerin-mediated vasodilation (0.4 mg), and hyperemic flow of the conduit brachial artery were determined by use of high-resolution vascular ultrasound and an upper-arm occlusive cuff as previously described.^{24–26} To avoid confounding effects, nitroglycerin was administered last at each visit. Nitroglycerin was omitted if systolic blood pressure was <100 mm Hg or if there was a previous adverse reaction. Ultrasound images were digitized online and stored. “Blinded” analysis was performed with commercially available software (Brachial Analyzer, Medical Imaging Applications).

We assessed reproducibility of our analysis system in 20 studies. Intraobserver and interobserver correlation coefficients were 0.99 and 0.99, respectively, for diameter determination and 0.93 and 0.89 for flow-mediated dilation. The average differences between 2 determinations by the same individual were 0.03 ± 0.03 mm for diameter and $0.93 \pm 0.66\%$ for flow-mediated dilation. The average differences between determinations by 2 different individuals were 0.04 ± 0.05 mm for diameter and $1.01 \pm 0.92\%$ for flow-mediated dilation. Reproducibility of flow-mediated dilation over 1 month in our laboratory was documented in 25 volunteers from the present cohort by comparing baseline to the long-term water-phase flow-mediated dilation. The mean \pm SD difference was 1.96 ± 1.16 percentage points.

Biochemical Analyses

Serum total cholesterol, HDL, triglycerides, and glucose were measured by automated analyzer (Hitachi-917). LDL cholesterol was calculated with the Friedewald formula. Plasma catechins (important tea flavonoids)²⁷ and ascorbic acid^{24–26} were measured with high-performance liquid chromatography as previously described. The total antioxidant capacity of plasma was determined with Trolox, an aqueous analog of α -tocopherol, as reference antioxidant. The protein-independent oxygen-radical absorbance capacity of plasma (ORAC) was measured with the method of Cao and colleagues.²⁸ The ferric-reducing ability of plasma (FRAP), a measure of the ability to donate electrons, was measured with the method of Benzie and Strain.²⁹ Results for both are expressed in micromole of Trolox activity per liter of plasma.

Statistical Analysis

Data are mean \pm SD, except in the figures (mean \pm SE). Baseline characteristics were compared with unpaired *t*, χ^2 , or Fisher's exact tests as appropriate. The effects of treatment and treatment order were compared by 2-way repeated-measures ANOVA, with post hoc Student-Newman-Keuls comparison. Univariate clinical and biochemical predictors of flow-mediated dilation were determined by

TABLE 2. Clinical Characteristics

	Water-First Group	Tea-First Group	Data Excluded	Caffeine Group
n	25	25	16	11
Age, y	56±8	54±8	52±18	56±8
Male, %	20 (80)	19 (76)	10 (63)	9 (82)
Diagnosis of high cholesterol, n (%)	18 (72)	20 (80)	15 (94)	10 (91)
Lipid-lowering therapy, n (%)	18 (72)	20 (80)	12 (75)	10 (91)
Total cholesterol, mmol/L	5.0±0.8	4.9±0.9	5.2±1.2	4.9±1.1
Hypertension, n (%)	14 (56)	12 (48)	10 (63)	9 (82)
Family history of premature CAD, n (%)	12 (48)	9 (36)	8 (50)	6 (55)
Smoking history, n (%)	20 (80)	23 (92)	12 (75)	10 (91)
Smoking, pack-y	29±25	31±21	27±28	29±23
Diabetes mellitus, n (%)	6 (24)	4 (16)	2 (13)	2 (18)
Body mass index, kg/m ²	30.9±5.0	28.4±4.3	33.3±7.9*	31.5±7.6

Data are mean±SD when appropriate. High cholesterol was determined by history or serum total cholesterol >5.2 mmol/L; hypertension by history or blood pressure >140/90 mm Hg. Premature CAD means a first-degree relative with CAD at <60 y of age.

* $P=0.04$ for comparison of patients whose data were excluded vs those included.

linear regression. To identify independent predictors of flow-mediated dilation, all clinical variables with univariate $P<0.10$ were entered into a stepwise multivariate regression model. Statistical significance was accepted at $P<0.05$.

Results

Baseline Characteristics

We enrolled 66 patients. Eight withdrew, and 8 had ≥ 1 ultrasounds that were technically unsuitable for analysis. These 16 patients were excluded before data analysis, leaving 50 participants. Eleven patients were treated with caffeine tablets. Clinical characteristics are displayed in Table 2. Other than body mass index, there were no differences in baseline characteristics among groups.

Concurrent cardiac medications were aspirin in 50 patients (100%), β -blockers in 45 (90%), calcium channel blockers in 17 (34%), nitrates in 14 (28%), and ACE inhibitors in 8 (16%). Estimated mean dietary flavonoid intake at baseline was 61.1 ± 60.1 mg/d (median, 43.8 mg/d), of which flavanols contributed 42.3 ± 33.4 mg/d and flavanols contributed 18.8 ± 39.4 mg/d. Flavanol intake correlated with baseline total plasma catechin levels ($r=0.37$, $P=0.022$).

Brachial Artery Responses

Baseline brachial artery flow-mediated dilation was comparable in the water- and tea-first groups ($5.2\pm 2.9\%$ versus $6.8\pm 3.7\%$, $P=0.10$). With traditional risk factors and baseline dietary flavonoid intake used as independent variables, the univariate predictors of baseline flow-mediated dilation were flavonoid intake ($r=0.31$, $P=0.026$), diastolic blood pressure ($r=-0.27$, $P=0.056$), and fasting glucose ($r=-0.26$, $P=0.064$). The only independent predictor of baseline flow-mediated dilation was dietary flavonoid intake (adjusted $R^2=0.16$, $P=0.012$).

Both short- and long-term tea consumption improved brachial artery flow-mediated dilation, whereas water had no effect (Figure 2). There was no interaction between beverage order and treatment effects ($P=0.93$). When the results of

patients randomized to tea first and water first were combined, flow-mediated dilation was $6.0\pm 3.4\%$ at baseline, $5.7\pm 3.9\%$ after short-term water, $6.1\pm 4.3\%$ after long-term water, $9.4\pm 3.9\%$ after short-term tea, $9.5\pm 3.6\%$ after long-term tea, and $10.8\pm 4.4\%$ after short-on-long-term tea. Overall, beverage significantly affected flow-mediated dilation ($P<0.001$). By post hoc analysis, flow-mediated dilation was greater after short- and long-term tea consumption compared with baseline and water consumption ($P<0.001$). Furthermore, consumption of short-term tea after 4 weeks of tea (short-on-long term) produced further improvement compared with long-term tea ($P<0.02$).

Tea had no effect on baseline arterial diameter, maximal hyperemia, diastolic blood pressure, or heart rate (Table 3).

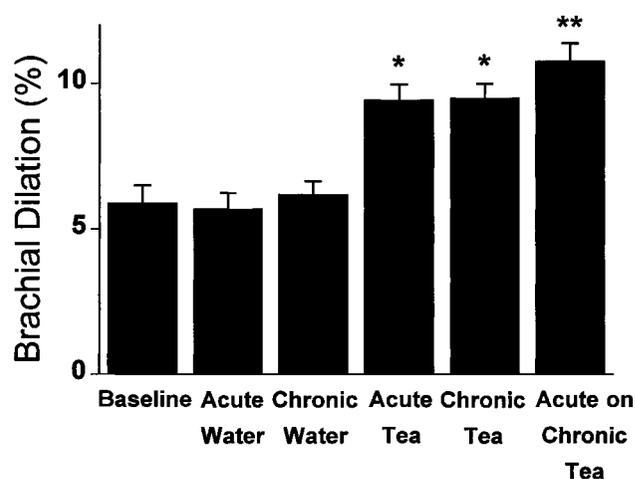


Figure 2. Short- and long-term black tea consumption improves endothelium-dependent, brachial artery flow-mediated dilation. In 50 patients with CAD, beverage consumption significantly affected flow-mediated dilation ($P<0.001$). Post hoc analysis demonstrated that flow-mediated dilation was higher after short- and long-term tea consumption vs baseline and water consumption ($*P<0.001$). Furthermore, short-on-long-term tea ingestion resulted in additional improvement ($**P=0.02$).

TABLE 3. Brachial Artery and Hemodynamic Parameters

	Baseline	Short-Term Water	Long-Term Water	Short-Term Tea	Long-Term Tea	Short-on-Long-Term Tea
Systolic blood pressure, mm Hg	137±17	139±21	137±17	141±19*	136±19	141±20*
Diastolic blood pressure, mm Hg	78±7	78±8	77±8	80±7	77±9	80±9
Heart rate, bpm	65±10	63±10	63±11	63±10	64±10	62±10
Resting arterial diameter, mm	4.6±0.7	4.6±0.7	4.6±0.7	4.6±0.7	4.6±0.7	4.6±0.7
Hyperemic arterial diameter, mm	4.8±0.7	4.8±0.7	4.8±0.7	5.0±0.7†	5.0±0.7†	5.0±0.7†
Hyperemic flow, % increase	619±283	609±272	629±360	701±333	600±279	693±282

Data are mean±SD. Short-term tea and short-on-long-term tea increased systolic blood pressure 2 hours after consumption ($P=0.015$; * $P<0.05$ by Student-Newman-Keuls post hoc comparison). Short-term tea, long-term tea, and short-on-long-term tea increased the hyperemic arterial diameter ($P<0.001$; † $P<0.001$ by Student-Newman-Keuls post hoc comparison). There were no significant differences in the other parameters based on treatment or time.

Short-term tea ingestion increased systolic blood pressure by ≈ 5 mm Hg ($P=0.015$); however, this effect was not evident after long-term tea consumption. Neither short-term nor short-on-long-term tea consumption affected nitroglycerin-induced endothelium-independent vasodilation ($n=44$, $P=0.85$; Figure 3).

Baseline flow-mediated dilation was comparable in the caffeine and tea groups ($7.8\pm 5.2\%$ versus $6.0\pm 3.4\%$, respectively; $P=0.16$). Flow-mediated dilation remained similar 2 hours after caffeine treatment ($7.8\pm 5.2\%$ versus $7.7\pm 4.3\%$, $P=0.86$), suggesting that the short-term effects of tea are not attributable to caffeine. Caffeine treatment tended to increase systolic blood pressure to an extent similar to that of tea, from 142 ± 24 to 148 ± 21 mm Hg ($P=0.153$). Diastolic blood pressure (78 ± 10 versus 80 ± 5 mm Hg, $P=0.38$) and heart rate (60 ± 7 versus 59 ± 6 bpm, $P=0.39$) were unaffected by caffeine.

Biochemical Parameters

Long-term water or tea consumption had no effect on fasting lipid, glucose, or ascorbic acid levels (Table 4). However, short- and long-term tea consumption increased total plasma catechins. Total plasma catechin concentrations were 25.5 ± 17.1 ng/mL at baseline, 21.5 ± 12.6 ng/mL after short-term water, 25.1 ± 13.0 ng/mL after long-term water, 32.8 ± 22.4 ng/mL after short-term tea, 34.6 ± 20.1 ng/mL after long-term tea, and 33.7 ± 17.2 ng/mL after short-on-

long-term tea ($n=39$, $P<0.001$). By post hoc analysis, total plasma catechins were greater after short-term, long-term, and short-on-long-term tea consumption compared with baseline and water consumption ($P<0.05$). Long-term tea consumption also tended to increase total antioxidant capacity of plasma measured as ORAC or FRAP ($P=0.09$), although only 21 patients had complete data (Table 4).

Discussion

This study demonstrates that short- and long-term consumption of black tea improves brachial artery flow-mediated dilation in patients with CAD. This improvement was associated with increased total plasma catechins. Tea consumption had no effect on baseline diameter, extent of reactive hyperemia, or nitroglycerin-induced vasodilation, suggesting that tea acted to improve endothelial vasomotor function rather than acting to alter resting vascular tone, increase the stimulus for dilation, or improve vascular smooth muscle function. Baseline flow-mediated dilation in the present population was comparable to that in prior studies of patients with CAD and blunted compared with that of healthy control subjects.^{24–26,30} Flow-mediated dilation with short-on-long-term tea consumption was comparable to that of healthy volunteers in our laboratory ($11.2\pm 5.7\%$).²⁴ These findings suggest that tea consumption reverses endothelial vasomotor dysfunction in patients with CAD and are comparable to our recent findings with the antioxidant ascorbic acid.²⁶

No previous study has examined the effects of tea on vascular function. However, our findings concur with experimental studies^{17,18} and with 2 smaller clinical studies that examined the effects of grape-derived flavonoids.^{31,32} Stein and colleagues³¹ demonstrated that purple grape juice consumption for 14 days improved brachial artery flow-mediated dilation and decreased LDL oxidizability in 15 patients with CAD. That study was limited by lack of a control group. In contrast to the present study, nitroglycerin-induced vasodilation was also improved, and lipid and insulin levels changed with treatment. Possible reasons for these apparently discrepant results include differences in flavonoid composition of grapes versus tea, the additional carbohydrate load, and differences in study populations. In a recent randomized, crossover study, Agewall et al³² demonstrated improved brachial artery flow-mediated dilation <1 hour after ingestion of dealcoholized red wine but not after red wine with

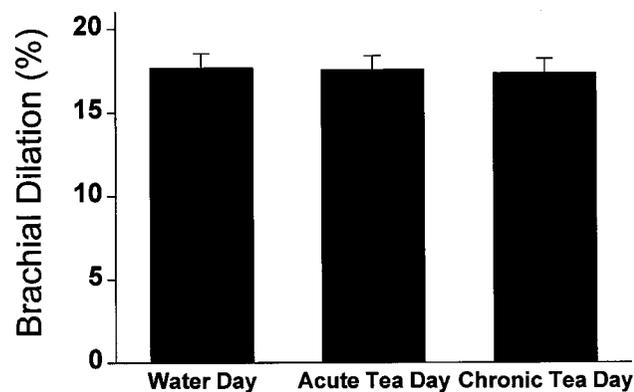


Figure 3. Black tea consumption had no effect on endothelium-independent, brachial artery vasodilation to nitroglycerin in 44 patients with CAD ($P=0.85$).

TABLE 4. Biochemical Parameters

	Baseline	Long-Term Water	Long-Term Tea
Total cholesterol, mmol/L	4.9±0.8	4.9±0.9	4.8±0.7
LDL, mmol/L	2.9±0.7	2.7±0.7	2.7±0.8
HDL, mmol/L	1.2±0.3	1.2±0.4	1.2±0.4
Triglycerides, mmol/L	2.0±1.0	2.0±1.1	2.1±1.6
Glucose, mmol/L	6.6±2.1	6.9±2.8	6.8±2.3
ORAC, μ mol Trolox activity (n=21)	1017±288	961±283	1133±400*
FRAP, μ mol Trolox activity (n=21)	621±167	631±199	693±171*
Ascorbic acid, μ mol/L (n=45)	53.1±30.1	54.2±36.1	55.8±32.6

Data (mean±SD) are from fasting blood taken on arrival each day and are available for all patients unless indicated. ORAC is a measure of protein-independent antioxidant activity in plasma; FRAP is a measure of the ability to donate electrons.

* $P=0.09$.

alcohol in 12 healthy volunteers. That study did not examine nitroglycerin responses and lacked a placebo group, but it supports our finding that short-term tea flavonoid intake improves endothelial function.

An interesting finding of the present study is the significant relation between dietary flavonoid intake and baseline endothelial function. Estimated daily flavonoid intake was comparable to that of some population studies,^{2,3,9,10} albeit at the upper end of the observed range for flavonols,³ which may limit generalization of the observed correlation. Our cohort's relatively high flavonoid intake is partly explained by inclusion of flavanol plus flavonol intake, because previous studies did not quantify dietary flavanol.^{2,3,9,10} Flavanols are particularly important if tea or red wine is regularly consumed,^{16,22} and flavanols represented one third of our cohort's baseline dietary flavonoids. These dietary questionnaire results lend further support to our conclusion that dietary flavonoids importantly affect vascular function.

The precise mechanism by which tea improves endothelial function was not determined. However, our findings do provide some insights. Tea consumption did not influence traditional atherosclerotic risk factors, consistent with previous randomized studies.¹⁵ Indeed, endothelial function improved after short-term tea despite modestly increasing systolic blood pressure. This increase in blood pressure was not observed after long-term tea consumption and is likely due to caffeine, because oral caffeine had a similar effect.

Several lines of evidence suggest that the observed benefit relates to antioxidant flavonoids in tea. First, baseline dietary flavonoids correlated with flow-mediated dilation, as noted above. Second, tea consumption increased plasma catechins, consistent with prior data.¹⁶ Like other phenolic compounds, flavonoids can accumulate in tissues with long-term consumption³³ and might favorably affect tissue redox status. Third, short-term tea consumption can increase plasma antioxidant activity in vivo in healthy volunteers,²³ findings that are consistent with our data. However, tea flavonoids do not appear to affect ex vivo LDL oxidizability.^{15,16} Finally, there is experimental evidence that purified antioxidant flavonoids improve endothelium-derived NO bioactivity.^{17,18} Interestingly, this effect may be mediated by enhanced NO synthesis

rather than by decreased superoxide-mediated NO breakdown,¹⁸ similar to our recent findings with ascorbic acid.³⁴

Regarding potential limitations, one issue is the relevance of peripheral artery endothelial function for coronary events, although prior studies have shown a close relation between vasomotor responses in these 2 vascular beds.³⁰ A second limitation is the use of water as placebo, preventing us from blinding volunteers to treatment. Unfortunately, prior experience indicates that it is not possible to produce a placebo beverage that convincingly tastes like tea but lacks tea flavonoids (personal communication, Douglas Balentine, Lipton, Inc, April 1998). Third, this study used caffeinated tea. Although caffeine alone had no short-term effect, we cannot exclude the possibility that caffeine influenced our long-term results. Importantly, studies of other caffeinated beverages have failed to demonstrate health benefits similar to those of tea.⁵ Fourth, it is conceivable that concurrent medications could have confounded our results, although the crossover design minimizes this concern. Fifth, it is noted that the 16 excluded volunteers were significantly more overweight than those included in the study, possibly reflecting the difficulty in imaging the brachial artery in these patients. Finally, although the benefit of tea was sustained for 4 weeks, the longer-term effects remain unknown.

The present study has important clinical implications. There is growing evidence that endothelial dysfunction is important for the pathogenesis and clinical expression of cardiovascular disease.^{19,21} Furthermore, recent studies support the concept that reversing endothelial dysfunction may partly explain the beneficial effects of other interventions proven to reduce cardiovascular risk, such as lipid lowering, ACE inhibitors, and exercise.³⁵ The present study represents a relatively large and well-controlled study demonstrating a beneficial effect of short- and long-term black tea consumption on endothelial function. Thus, it provides a plausible biological mechanism in humans to explain the inverse relation between black tea consumption and cardiovascular disease.²⁻⁵ The findings fit well with the growing appreciation that diet and lifestyle modifications are important approaches to the prevention and treatment of atherosclerotic vascular disease. Further prospective, randomized studies of tea consumption appear warranted.

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