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A Six-Month Randomized Pilot Study of Black Tea and Cardiovascular Risk Factors

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Abstract

Background—The effects of black tea consumption on cardiovascular risk factors have been inconsistent in previous randomized trials, all of which have been limited to a few weeks duration.

Methods—We conducted a pilot parallel-design randomized controlled trial among 31 adults aged 55 years and older with either diabetes or two other cardiovascular risk factors but no established clinical cardiovascular disease. Participants were randomized to drink three glasses daily of either a standardized black tea preparation or water for six months. Cardiovascular risk factors were measured at the beginning and conclusion of the study.

Results—Three participants dropped out of the study, leaving 14 participants assigned to tea and 14 assigned to water eligible for analyses. We found no statistically significant effects of black tea on cardiovascular biomarkers, including lipids, inflammatory markers, hemoglobin, adhesion molecules, prothrombotic and fibrinolytic parameters, and lipoprotein oxidizability. Assignment to tea did not appreciably influence blood pressure, and heart rate among participants assigned to tea was marginally higher than among control participants at three months (p=0.07) but not six months.

Conclusions—In this randomized trial of black tea intake over six months among older adults with known cardiovascular risk factors, black tea did not appreciably influence any traditional or novel biomarkers of cardiovascular risk. Longer randomized trials are needed to verify the inverse association of tea with risk of cardiovascular disease seen in cohort studies and identify potential candidate mechanisms for such an association.

Tea consumption is highly prevalent worldwide, and has been postulated to have a variety of health benefits, thought chiefly to be related to its complex polyphenolic antioxidants, such as theaflavin and thearubigin in black tea.[1, 2] Indeed, a meta-analysis of 17 observational studies found a 11% lower incidence of myocardial infarction associated with intake of three cups of tea per day compared with abstention from tea.[3]

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Conflict of Interest

We have cited potential conflicts of interest in the manuscript. Funding for this study was received entirely from the AHA and NCCAM. Templar Foods supplied bulk tea at no charge but provided no other support or funding, had no access to data, and had no involvement with drafting of the manuscript, interpretation or analysis of data, or submission of the manuscript. Dr. Vinson has received previous research funding from Lipton and other food manufacturers for research unrelated to this study.

Randomized trials to identify effects of tea on cardiovascular risk factors have yielded mixed results. In the few studies of markers of endothelial function, tea consumption lowered levels of soluble P-selectin but not ICAM-1 or VCAM-1[4] or von Willebrand factor (vWF).[5] Likewise, most human studies have found no effect of short-term tea intake on oxidizability of LDL in ex vivo experiments[6, 7] or on biomarkers of lipid oxidation,[8] although studies that have assessed lipoprotein oxidizability without isolating lipoproteins from hydrophilic antioxidants have suggested otherwise.[9, 10]

The effects of tea on other cardiovascular risk factors have also been mixed. Some studies have shown that tea lowers levels of plasminogen activator inhibitor-1 (PAI-1) in some individuals,[11] while others have not;[4, 12] similar inconsistency exists for fibrinogen.[4, 9, 12] Both animal models and epidemiological studies suggest that tea consumption can lower total cholesterol levels,[9, 13] but feeding studies in humans have not consistently shown such an effect.[6, 14, 15] A few feeding studies have also found no effect of black tea on inflammatory markers.[5, 16] Finally, feeding studies suggest black tea consumption may raise homocysteine levels in some individuals,[17, 18] although observational data suggest the opposite.[19] Virtually all of the randomized feeding trials of tea conducted to date have been limited to four or fewer weeks of follow-up.

To address the inconsistencies in previous studies of tea, and to determine the effects of intermediate-term tea consumption on cardiovascular risk factors, we conducted a six-month, randomized clinical trial of black tea consumption among older adults at increased risk for cardiovascular disease, the longest such trial conducted to our knowledge. This pilot study also sought to determine the feasibility of incorporating magnetic resonance imaging (MRI) into subsequent clinical trials of tea by having participants undergo MRI examinations of the torso six months apart.

Methods

The Tea's Effect on Atherosclerosis (TEA) Pilot Study was a randomized, parallel-design, assessor-blinded clinical trial of black tea consumption among free-living individuals, with measurements conducted at the General Clinical Research Center (GCRC) of Beth Israel Deaconess Medical Center (BIDMC). All patients provided written informed consent, and the BIDMC Committee on Clinical Investigations approved the protocol. The ClinicalTrials.gov identifier for the study is NCT00120107.

Study Participants

Participants were community-dwelling adults aged 55 years and older with either diabetes or two other cardiovascular risk factors (hypertension, current smoking, LDL cholesterol ≥130 mg/dl, HDL cholesterol <40 mg/dl, or family history of premature coronary heart disease). Exclusion criteria included established cardiovascular disease (congestive heart failure, myocardial infarction, coronary, carotid, or peripheral arterial revascularization procedure, stroke, angina, or intermittent claudication), contraindications to MRI (severe claustrophobia, intolerance to previous MRI examinations, pacemaker, intraauricular implants, or intracranial clips), atrial fibrillation (due to requirement for gated MRI images), severe illness expected to cause death or disability within six months, blood pressure ≥180/110 mmHg, serum creatinine >2.5 mg/dl or dialysis, history of hyponatremia, use of vitamin supplements greater than the recommended daily allowance, inability to speak English, and lack of a working telephone.

Study Materials

Dehydrated soluble black tea powder (Templar Food Products, Inc., New Providence, NJ) was provided to participants in unit-dose containers. Each container included 2.0 gm of powder,

and three containers (representing a single day supply) were bagged together. The catechin content of the tea, measured in duplicate on six separate containers, was 106 +/− 7 mg/serving (i.e., 318 mg/day) of catechin equivalents using a standard colorimetric assay.[20]

Study Protocol

Interested participants were screened for eligibility and then randomized using random permuted blocks of sizes two and four using a SAS macro specifically developed for this purpose. Randomization assignments were placed into opaque, sealed, sequentially-numbered envelopes in a locked, off-site location.

Participants randomized to tea were asked to consume three servings daily. No restrictions were made on addition of milk or sweeteners, reconstitution with hot or cold water, or time of day of consumption, as in previous positive trials.[21] Control subjects were asked to consume three glasses of water daily to control for fluid intake.[22] The only dietary restrictions were consumption of non-study tea (green, oolong, or black). Participants were also asked to keep their intake of red wine and multivitamins consistent during the trial.

Participants attended the GCRC for a screening/entry visit, followed by visits at two weeks, three months, and six months. At each visit, nurses measured vital signs, ascertained changes in medication, and queried possible side effects. Dieticians collected 3-day dietary records at the second and final visits. At the initial and final visits, participants were asked to fast for at least eight hours beforehand and underwent phlebotomy, with immediate storage of samples at −80 °C. All assays were performed by technicians blinded to treatment assignment.

Measurements

All measurements were performed by technicians or investigators blinded to treatment assignment. Interleukin-6 (IL-6), tissue necrosis factor alpha (TNFα), VCAM-1, and ICAM-1 were analyzed by immunoassays (R & D Systems, Minneapolis, MN). C-reactive protein (CRP) was measured with a high-sensitivity chemiluminescent assay (Diagnostic Products, Los Angeles, CA). Tissue plasminogen activator (tPA) antigen and vWF were measured by enzyme-linked immunosorbent assays (Diagnostica Stago, Parsippany, NJ). Albumin, glucose, and lipids were analyzed on a Roche autoanalyzer using Roche reagents (F. Hoffmann-La Roche, Basel, Switzerland). Homocysteine was measured on an Abbott (Abbott Park, IL) AxSYM using Abbott reagents. Complete blood counts were performed on the Bayer (Bayer Diagnostics, Tarrytown, NY) Advia 120 using Bayer reagents. Factor VIII was assessed on the bioMerieux (bioMérieux SA, Marcy l'Etoile, France) MDA180, using reagents from Precision Biologics. Fibrinogen was analyzed by the Clauss method on the MDA180, with bioMerieux reagents.

We assessed lipoprotein oxidation using an affinity-column to isolate lipoproteins without removing adherent polyphenols.[9] We measured lag time in response to 25 μM cupric ion standardized to protein concentration; longer lag time indicates greater resistance to oxidation.

As a planned measure of adherence, urine samples were tested for 4-O-methylgallic acid at baseline and at the three- and six-month visits by high-performance liquid chromatography as described.[23] However, freeze-thaw related sample degradation limited these to a subsample of participants.

Participants underwent electrocardiogram-gated T2-weighted spin-echo MRI examination of the abdomen at the two-week and six-month visits using a previously published protocol.[24] A single board-certified radiologist (NO) reviewed all scans in a tandem manner at the completion of the study.

Statistical Analyses

We assessed the effect of tea intake as the arithmetic difference between 6-month and baseline values for participants in each of the treatment arms, using t-tests for normally distributed values and Wilcoxon rank sum tests where skewed. Single extreme outlying values for baseline CRP and ICAM-1 were deleted, but their inclusion did not materially affect any of our results. Results using t-tests with logarithmic transformation of skewed values (rather than rank sum tests) were not materially different. For blood pressure and heart rate, which were measured serially, mixed models with compound symmetry were used, with model terms of time, intervention assignment, and their interaction (the primary estimate of the effect of tea through time). In all cases, participants were analyzed on an intention-to-treat basis. SAS v9.0 (Cary, NC) was used for all analyses.

Results

Figure 1 shows the CONSORT flow of participants in the TEA Pilot Study. A total of three participants did not complete the trial, including two who left the study within two weeks of entry for non-study related reasons (change in job and surgery for pre-existing back pain). A third participant assigned to tea developed bacterial peritonitis from unrecognized non-alcoholic fatty liver disease. Characteristics of the 28 participants who completed the study are shown in Table 1. Median baseline tea consumption was 1 cup per week among those assigned to tea and 2 cups per week among those assigned to water, and only 2 subjects reported no tea consumption in the previous year. Caffeine consumption estimated from dietary records at the two-week and final visits was similar in the two groups (two-week: 143 vs. 116 mg per day, p=0.56; final: 128 vs. 165 mg per day, p=0.39).

Table 2 shows the primary results of tea intake on endothelial, inflammatory, metabolic, and hematological factors. We did not find significant differences between participants assigned to tea or to water. There was also no statistically significant difference in lipoprotein oxidizability as measured by oxidation lag time.

Figure 2 illustrates the change in vital signs over time during the trial. We found no significant effects of assignment to tea on heart rate or systolic blood pressure, although heart rate tended to be higher at the 3 month visit in both groups; the difference in heart rate at that visit between the two groups was of borderline significance (p=0.07). Mean diastolic blood pressure was also uninfluenced by assignment to tea (p=0.76). Mean weight gain was 0.05 ±0.4 kilograms among participants assigned to tea, compared with 0.5 ±0.8 kilograms among participants assigned to water (difference 0.45 ±0.9 kg; p=0.85).

Among 22 participants with satisfactory samples, mean 4-O-methylgallic acid levels were 13.0 ±8.8 μmol/L in the tea group and 0.3 ±0.1 μmol/L in the water group (p=0.29). Of the 11 participants in each treatment group, six in the tea group and one in the water group had mean levels of at least 1.0 μmol/L (p=0.06). Two participants assigned to water reported consuming any tea during the six months of follow-up.

There were few side effects attributable to tea noted during the trial. A single participant assigned to tea developed chest pain; this was attributed to esophageal reflux from adding large quantities of fresh lemon, and he completed the trial without further symptoms. A second participant noted tooth staining that dental evaluation attributed to concurrent use of stannous fluoride. Other adverse events included a new diagnosis of prostate cancer and a single hospitalization for influenza among participants assigned to tea, and a brief psychiatric hospitalization following cessation of antidepressant use in a participant assigned to water.

All 28 participants completed technically satisfactory MRI examinations. No efficacy analyses of MRI scan findings were planned or performed, but the scans revealed incidental findings in a large proportion of cases. These included seven cases of renal cysts, one hepatic cyst, one splenic cyst, and two cases of cholelithiasis. Two participants were referred for further work-up, including one with generalized lymphadenopathy (found to be chronic lymphocytic leukemia) and one with nonspecific left adrenal gland enlargement. Of the 28 participants, 12 (43%) had at least one incidental finding.

Discussion

In this six-month randomized trial of black tea consumption among adults at higher cardiovascular risk, we found no significant effects of black tea on any biomarkers of advanced cardiovascular risk.

Several possible explanations for our findings should be considered. First, black tea may truly have no important effects on the outcomes we studied, at least over a sustained period of time. Indeed, clinical trials have generally not supported strong effects of black tea on most biomarkers.[4–6, 12, 15, 18, 25, 26] If this explanation is correct, then the observed associations of tea with lower risk of cardiovascular disease in cohort studies may either reflect uncontrolled confounding or effects of black tea on other plausible pathways. For example, we did not measure flow-mediated vasodilatation or any other functional measure of vascular function; several clinical trials have shown benefits of tea on such functional parameters.[14, 21, 27, 28]

Second, the dose of black tea may have been insufficient to produce meaningful effects on these biomarkers. While the dose of three cups/day that we used corresponds well to the levels of intake found to be associated with lower risk in observational studies,[3] it is smaller than the doses typically used in those clinical trials that have found benefits of black tea consumption on biomarkers.[4, 11] Moreover, because the dose was somewhat smaller than in previous trials, any lack of adherence may have biased our results toward the null findings we observed. Although we undertook extensive efforts to promote adherence, including providing prepackaged containers of a readily solubilized powder and frequent contact with participants, the exact magnitude of adherence is difficult to ascertain in the absence of a long-term biomarker uniformly specific for tea exposure; 4-O-methylgallic acid does not fit this criterion.[29, 30]

Third, the black tea preparation we chose may not share the benefits of others previously tested, although we have no strong reason to suspect this. We chose a commercially available, representative black tea with ample polyphenol content. While substantial attention has been given to green tea, all forms of tea contain antioxidant polyphenols, and the positive findings in observational studies from the U.S. and Europe clearly reflect the predominately black tea consumption in these populations.

Fourth, the inherent variability in many of these markers – and particularly those related to inflammation and endothelial function – may have obscured any true, modest effect of tea, especially in a population of older adults with cardiovascular risk factors. We intentionally selected this higher risk group based on observational studies,[31–33] which have generally supported stronger beneficial effects among higher risk individuals, but it may have introduced additional variability that would overshadow modest effects of tea in a small study such as this. Trials of this duration in younger, healthier subjects will be an important future step.

Fifth, our study was of limited size, and although powered to detect differences similar to those seen in other trials of dietary supplements,[34] the confidence limits around our estimates indicate that differences of a potentially important magnitude, at least at the population level,

could have been missed. Meta-analyses of small trials like ours may pose the best opportunity to clarify effects of tea with precision.

Although we did not find large benefits of tea, our study provides some reassurance about the safety of long-term tea intake in a clinical trial setting. Despite the inhibitory effect of tea on iron absorption,[35] we did not find major changes in hemoglobin levels through the trial, consistent with recent reviews that identified this interaction as being chiefly relevant for individuals with borderline iron status.[36, 37] Although some trials have found that tea consumption acutely raises blood pressure[14], we found no such effect over 6-months of follow-up, and a recent meta-analysis of five supplementation studies of four-week duration found no significant effect of tea on blood pressure.[38] Heart rate tended to rise somewhat more among the tea group than the water group at 3 months, but it also fell more steeply at 6 months in the tea group.

In summary, we found no consistent effects of six months of black tea intake on biomarkers of cardiovascular risk in this study. Our results do not preclude an important effect of tea intake on risk of cardiovascular disease, but they do suggest that alternate mechanisms are apt to be most important, and that long-term randomized trials of tea intake are needed to determine its true effects on cardiovascular risk with certainty.

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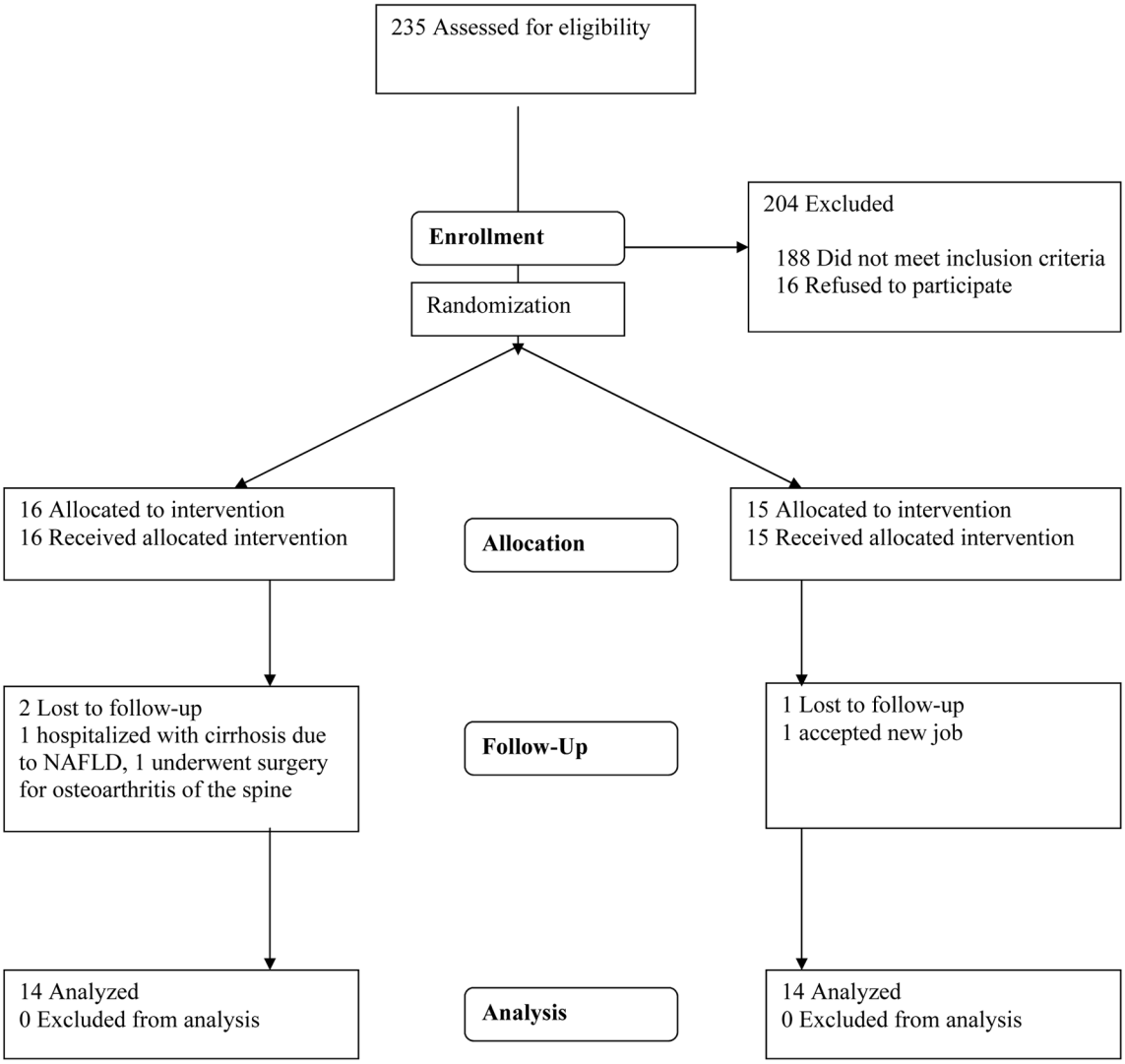

Figure 1.
CONSORT flowchart of participants in the TEA Pilot Study.

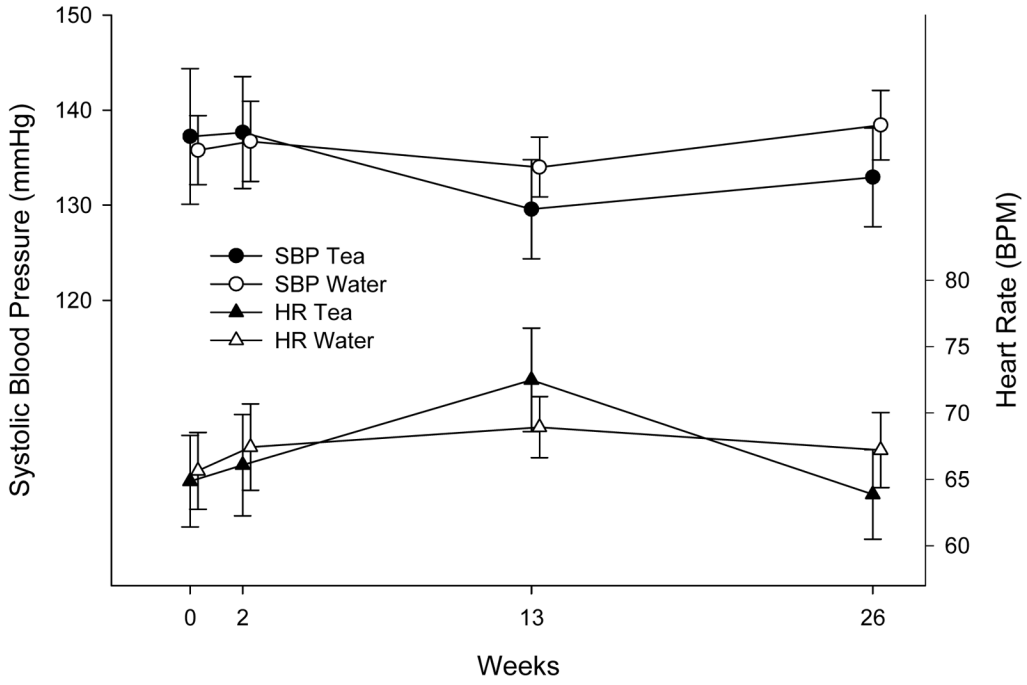

Figure 2.
Systolic blood pressure and heart rate according to tea or water assignment. Means with standard errors are shown.

Table 1

Baseline characteristics of TEA Pilot Study participants.

	Tea (n=14)	Water (n=14)	P-value
Age (years)	66.6 ±8.0	64.9 ±7.0	0.55
Body-Mass Index (kg/m^2)	27.7 ±4.5	30.5 ±4.5	0.11
Female	9 (64%)	9 (64%)	1.0
White	14 (100%)	12 (86%)	0.48
Married	9 (64%)	6 (43%)	0.45
Education			
High School or Less	6 (43%)	4 (29%)	0.63
College	4 (29%)	7 (50%)	
Graduate School	4 (29%)	3 (21%)	
Current Smoker	2 (14%)	0 (0%)	0.48
Diabetes	3 (21%)	1 (7%)	0.60
Hypertension	11 (79%)	13 (93%)	0.60
Hypercholesterolemia	12 (86%)	13 (93%)	1.0
Statin Use	11 (79%)	8 (57%)	0.42

P-values derived from Fisher exact tests.

Table 2

Baseline levels and changes over 6-month follow-up in cardiovascular biomarkers among TEA Pilot Study participants.

	Tea (n=14)			Water (n=14)			
	Baseline	**6-months**	**Difference**	**Baseline**	**6-months**	**Difference**	**P-value**
HDL-C (mg/dl)	62 ±3	62 ±2	−0.5 ±2.0	64 ±4	64 ±5	+0.1 ±3.4	0.87
Triglycerides (mg/dl)	148 ±24	116 ±13	−32 ±19	160 ±46	125 ±20	−35 ±28	0.65
LDL-C (mg/dl)	111 ±12	98 ±9	−13 ±10	116 ±8	119 ±9	+2 ±5	0.32
Glucose (mg/dl)	92 ±4	99 ±6	+7 ±4	102 ±14	103 ±9	+1 ±6	0.91
WBC (K/μl)	6.3 ±0.4	5.8 ±0.3	−0.5 ±0.2	7.3 ±0.4	7.0 ±0.4	−0.2 ±0.4	0.25
Hemoglobin (g/dl)	13.5 ±0.3	13.4 ±0.3	−0.1 ±0.3	13.5 ±0.3	13.5 ±0.3	+0.1 ±0.2	0.59
Albumin (g/dl)	4.31 ±0.08	4.36 ±0.06	+0.05 ±0.07	4.26 ±0.07	4.41 ±0.06	+0.15 ±0.06	0.29
Homocysteine (μmol/L)	8.4 ±0.4	8.7 ±0.4	+0.3 ±0.2	9.9 ±0.5	9.7 ±0.6	−0.1 ±0.5	0.31
Fibrinogen (mg/dl)	330 ±19	319 ±25	−11 ±23	379 ±27	391 ±22	+12 ±29	0.52
Factor VIII (%)	134 ±10	135 ±9	+3 ±7	161 ±13	152 ±10	−9 ±9	0.31
CRP (mg/dl)	0.13 ±0.03	0.14 ±0.03	+0.01 ±0.02	0.79 ±0.27	0.67 ±0.16	−0.12 ±0.28	0.50
IL-6 (pg/ml)	1.6 ±0.2	1.5 ±0.1	−0.2 ±0.3	2.0 ±0.3	2.2 ±0.3	+0.2 ±0.4	0.35
TNF-α (pg/ml)	1.9 ±0.2	2.3 ±0.2	+0.4 ±0.2	2.0 ±0.3	2.4 ±0.3	+0.5 ±0.2	0.86
sICAM (ng/ml)	238 ±13	235 ±16	−3 ±11	276 ±19	268 ±16	−8 ±8	0.72
sVCAM (ng/ml)	703 ±58	819 ±96	+116 ±57	719 ±58	764 ±68	+53 ±26	0.42
vWF (%)	140 ±13	136 ±9	−4 ±7	158 ±14	165 ±15	+7 ±7	0.28
tPA-antigen (ng/ml)	8.9 ±0.6	8.1 ±1.0	−0.8 ±0.7	10.5 ±1.1	10.1 ±0.9	−0.4 ±0.7	0.69
PAI-1-activity (U/ml)	15 ±5	24 ±5	+9 ±5	18 ±4	23 ±7	+5 ±4	0.60
Lag time (seconds)	76 ±11	85 ±11	+9 ±19	96 ±8	80 ±7	−16 ±10	0.31

P-values derived from t-tests or Wilcoxon rank sum tests comparing baseline-to-6-month differences among participants assigned to tea versus water.

Single outlying values deleted for baseline CRP and sICAM.