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Original Scientific Paper

The acute effect of green tea consumption on endothelial function in healthy individuals

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Background **Tea consumption is associated with decreased cardiovascular risk. Flow-mediated dilatation (FMD) of the brachial artery is related to coronary endothelial function and it is an independent predictor of cardiovascular risk. Black tea has a beneficial effect on endothelial function; the effect, however, of green tea on brachial artery reactivity has not been defined yet.**

Design and methods **We studied 14 healthy individuals (age 30 ± 3 years) with no cardiovascular risk factors except from smoking (50%) on three separate occasions on which they took: (a) 6 g of green tea, (b) 125 mg of caffeine (the amount contained in 6 g of tea), or (c) hot water. FMD of the brachial artery was measured before each intervention and 30, 90, and 120 min afterward. High-sensitivity C-reactive protein, interleukins 6 (Il-6) and 1b (Il-1b), total plasma antioxidative capacity, and total plasma oxidative status/stress were measured at baseline and at 120 min after each intervention.**

Results **Resting and hyperemic brachial artery diameter did not change either with tea or with caffeine. FMD increased significantly with tea (by 3.69%, peak at 30 min, $P < 0.02$), whereas it did not change significantly with caffeine (increase by 1.72%, peak at 30 min, P = NS). Neither tea nor caffeine had any effect on high-sensitivity C-reactive protein, Il-6, Il-1b, total plasma antioxidative capacity, or total plasma oxidative status/stress.**

Conclusion **Green tea consumption has an acute beneficial effect on endothelial function, assessed with FMD of the brachial artery, in healthy individuals. This may be involved in the beneficial effect of tea on cardiovascular risk. *Eur J Cardiovasc Prev Rehabil* 15:300–305 © 2008 The European Society of Cardiology**

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Keywords: brachial artery, caffeine, endothelial function, tea

Introduction

Although there is no consistency in the studies, habitual tea consumption has been associated with decreased cardiovascular morbidity and mortality [1–8]. This possible beneficial effect is mainly attributed to tea flavonoids, which are polyphenols called catechins. There are two types of tea mainly consumed in the western world: black and green tea. These two types differ in the type of flavonoids and the amount of caffeine they contain. Green tea contains less caffeine than black tea [9]. Most importantly, green tea is rich in monomer catechins, whereas in black tea the oxidization of catechins results in the production of catechins dimers and polymers that are called theaflavins and thearubigins, respectively [9]. This oxidation does not occur in green tea; as a result, green tea flavonoids are more potent antioxidants than those in black tea [10,11], and green tea is considered by many as more protective against cardiovascular disease than black tea [12].

Endothelial dysfunction is a key event in the progression of atherosclerosis and is present in patients with various cardiovascular risk factors [13–15]. Flow-

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mediated dilatation (FMD) of the brachial artery is endothelium-dependent, it correlates well with the endothelial function of coronary arteries [16], and it is an independent predictor of cardiovascular risk [17,18].

Black tea, which is the type that is most widely consumed in the western world and that is most extensively studied, has been associated with improved short-term and long-term endothelial performance [19–22]. On the other hand, green tea has an acute beneficial effect on the endothelial function of resistance arteries [23]. Its effect, however, on the endothelial function of the large arteries, such as the brachial artery, has not been defined yet. This randomized, sham procedure-controlled, crossover (three-arm) study was undertaken to evaluate the acute effect of green tea and its caffeine content on FMD of the brachial artery in healthy individuals. Furthermore, we sought to test the hypothesis that any effect would be associated with changes in inflammatory or oxidative status.

Methods

Study population

The study population consisted of 14 healthy individuals [mean ± standard deviation (SD) age 30 ± 3 years, nine men]. Each of them was studied on three separate occasions.

All patients were nonobese (body mass index $< 27\,kg/m^2$) and they did not have hypertension, diabetes, hyperlipidemia, or a family history of premature vascular disease. Seven patients (50%) were smokers. They were clinically well and taking no regular cardiovascular medications or antioxidant vitamin supplementation. Patients abstained from caffeine and ethanol intake and from smoking for at least 12 h, and from flavonoid-containing food for at least 24 h before each session. Female participants were examined during the follicular phase of the menstrual cycle and none was on oral contraceptives. The study protocol was approved by our Institutional Research Ethics Committee and all patients gave written informed consent.

Study design

The studies were carried out using a randomized, single-blind (operator), sham procedure-controlled, crossover design. Patients were studied on three separate days on which they took either: (a) 6 g of green tea (Lipton Tea Company, Crawley, UK) added in 450 ml of boiled water for 5 min, (b) 125 mg of caffeine (the amount contained in 6 g of green tea; see below 'measurement of caffeine contained in tea') diluted into 450 ml of boiled water, or (c) 450 ml of hot water.

Measurements were obtained in a quiet, temperature-controlled room at 23°C, while the patients had fasted for at least 8 h. After a 20-min rest period in the supine position, baseline measurements for the evaluation of endothelial function were taken. Then, the patients were randomized to the different arms of the study and measurements were repeated at 30, 90, and 120 min after baseline measurements. These specific time points were chosen because they represent the time when the peak plasma concentration of caffeine (30 min) and tea flavonoids (90 to 120 min) occurs [24]. Venous blood for measuring high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (Il-6), interleukin-1b (Il-1b), total antioxidative capacity, and total lipid peroxides was drawn at baseline and at 120 min when peak plasma flavonoid concentration is anticipated [24].

Measurement of caffeine contained in tea

The caffeine content in five samples of green tea prepared in an identical manner as in the study sessions was analyzed for caffeine content in the General Chemical State Laboratory, Athens, Greece using high-performance liquid chromatography. The 450 ml (6 g of green tea) beverage contained 128 ± 3 mg of caffeine.

Evaluation of endothelial function

FMD is predominantly dependent on nitric oxide (NO) release by the endothelium and has been used as an estimate of endothelial function. Resting and hyperemic arterial diameters and flows and FMD of the conduit brachial artery were determined by using a high-resolution, linear array ultrasonic transducer of 7.5–10.5 MHz (Hewlett-Packard, Sonos 5500, Andover, Massachusetts, USA). The brachial artery was scanned in the longitudinal plane, above the antecubital fossa. Then, reactive hyperemia was induced by inflating a forearm occlusive cuff at suprasystolic levels for 5 min. Brachial artery was continuously scanned from 30 s before to 90 s after cuff deflation. Hyperemic velocity was assessed by a Doppler signal obtained within the first 15 s after cuff deflation [17]. At least 10 min after the 120 min cuff deflation, endothelium-independent, nitrate-induced dilatation (NID) was measured after delivering a single (0.4 mg) dose of nitroglycerin spray sublingually.

All scans were performed by the same examiner throughout the study. Images were recorded on super-VHS videotape, from which they were digitally acquired and measured offline by the same observer, who was blinded to the image sequence and the randomization assignment. Three cardiac cycles were analyzed and measurements were averaged. Hyperemic artery diameter was measured 50–60 s after cuff release. FMD was calculated as the percentage increase in brachial artery diameter during hyperemia compared with the resting value [17].

Measurement of hs-CRP and interleukins and assessment of plasma antioxidative/oxidative status

The samples were centrifuged within 10 min after collection at 3000 rpm, 4°C for 15 min. Immediately after

centrifugation, the supernatant was stored at −80°C. Serum levels of hs-CRP were measured by immunophelometry (Dade Behring, Marburg, Germany). IL-6 and IL-1b were measured using enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota, USA).

The plasma total antioxidative capacity (TAC) was measured using ImAnOx kit, and the total plasma lipid peroxides were measured using PerOx kit. Both are photometric enzyme-linked immunosorbent assay sandwich tests provided by Immundiagnostik AG, Stubenwald-Allee 8a, D 64625 Bensheim, Germany. Owing to the direct correlation between lipid peroxides and oxygen radicals, it is possible to measure PerOx and characterize total oxidative status/stress (TOS) in biological fluids.

Statistical analysis

Sample-size calculations were based on data from our unit, which showed that the SD of FMD measurement was 3.5%. Therefore, we estimated that 13 patients would provide 80% power at the 5% level of significance to detect a difference of 3% in FMD in a crossover design study. To provide better confidence we finally decided to include 14 patients.

Numerical data are expressed as the mean ± SD. All variables were tested for homogeneity of variance and normal distribution, before any statistical analysis was applied, and hs-CRP was log-transformed. Baseline parameters between the three sessions were compared using one-way analysis of variance. Changes in hs-CRP, Il-6, Il-1b, TAS, TOS, or NID between tea or caffeine session and sham procedure session were compared using the Student's *t*-test for paired measures. To evaluate the composite effect of tea, or caffeine versus placebo over time on all the other variables, a 4×2 analysis of variance for repeated measures was performed [4 periods (baseline, 30, 90, and 120 min) × 2 interventions (tea or caffeine vs. placebo)]. A *P* value of less than 0.05 was considered statistically significant. Data analysis was performed using the SPSS statistical package for Windows (version 10.0, SPSS Inc., Chicago, Illinois, USA).

Results

Baseline characteristics

There were no differences in all baseline characteristics between tea, caffeine, and placebo sessions (Table 1).

Table 1 Baseline characteristics of the study sessions

	Green tea	Caffeine	Placebo	*P* value
Systolic pressure (mmHg)	107 ± 11	108 ± 12	112 ± 11	0.523
Diastolic pressure (mmHg)	69 ± 9	68 ± 10	70 ± 7	0.847
Resting flow (ml/min)	127 ± 68	128 ± 71	158 ± 96	0.518
Hyperemic flow (ml/min)	730 ± 295	762 ± 369	622 ± 270	0.471
Reactive hyperemia (%)	614 ± 386	593 ± 330	376 ± 240	0.113
Resting diameter (mm)	3.70 ± 0.68	3.71 ± 0.76	3.72 ± 0.69	0.997
Hyperemic diameter (mm)	3.94 ± 0.72	3.97 ± 0.82	3.93 ± 0.73	0.988
FMD (%)	4.38 ± 0.76	4.35 ± 0.79	4.29 ± 0.70	0.528
TAC (μmol/l)	354 ± 37	363 ± 25	344 ± 44	0.384
TOS (μmol/l)	222 ± 141	267 ± 161	261 ± 142	0.685

P value refers to the comparison among the three sessions. Values are mean ± SD. FMD, flow-mediated dilatation; TAC, total antioxidative capacity; TOS, total oxidative status/oxidative stress.

Changes after green tea or caffeine

The effect of tea or caffeine on each variable is better described as changes in the response of each variable, where response is defined as net tea or caffeine minus placebo values at each time point. Accordingly, *P* values refer to changes in the studied variables between the tea or caffeine and the placebo session throughout the whole study.

Effect on blood pressure

Systolic pressure increased both with tea (by 8.2 mmHg, peak at 90 min, $P < 0.05$), and with caffeine (by 7.6 mmHg, peak at 90 min, $P < 0.05$). Diastolic pressure did not increase either with tea or with caffeine.

Effect on flow-mediated dilatation

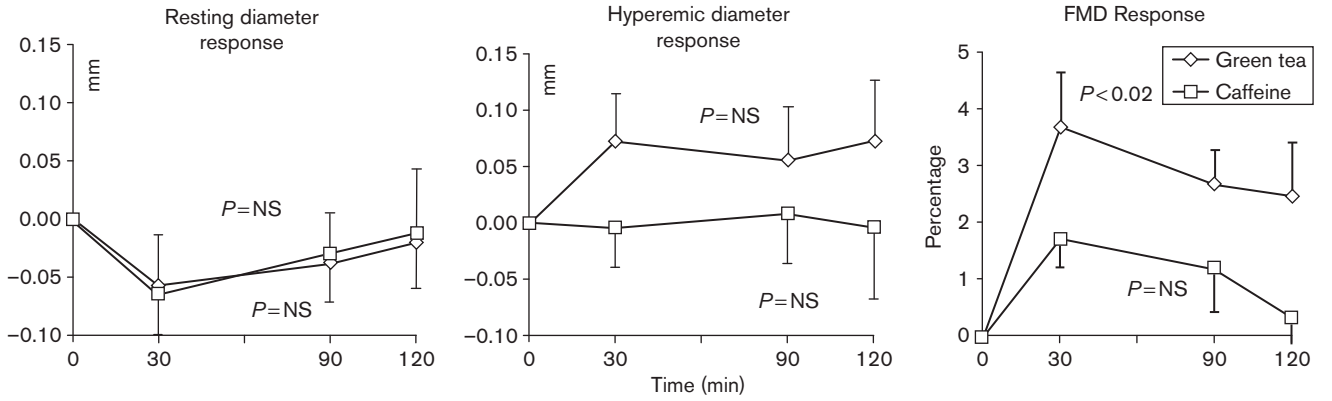
Resting and hyperemic brachial artery diameter did not change significantly either with green tea or with caffeine (Fig. 1). FMD of the brachial artery increased significantly with green tea (by 3.69%, peak at 30 min, $P < 0.02$), whereas it did not change significantly with caffeine (Fig. 1). Endothelium-independent NID did not change either with green tea or caffeine compared with placebo (20.4 ± 7.5 vs. 18.8 ± 6.7 vs. 16.9 ± 7.2% for green tea, caffeine, and placebo sessions, respectively, P = NS for both comparisons). Resting brachial artery flow showed a trend to increase with green tea (by 45.5 ml/min at 120 min, $P = 0.07$) and remained practically unchanged with caffeine (increase by 24.6 ml/min at 90 min, P = NS). Neither green tea nor caffeine produced a significant change in hyperemic brachial artery flow, or in the percentage of reactive hyperemia compared with placebo (data not shown).

When the effect of green tea was compared with that of caffeine, no differences were observed in any of the studied parameters.

Effect on hs-CRP, interleukins, and plasma antioxidative/oxidative status

Green tea and caffeine had no effect on hs-CRP (decrease by 0.01 ± 0.11 and increase by 0.02 ± 0.11 mg/l, respectively, P = NS for both), on Il-6 (increase by 0.01 ± 0.34 and decrease by 0.26 ± 0.85 pg/ml, respectively, P = NS for both), or on Il-1b (increase by 0.89 ± 3.37 and decrease by 0.66 ± 4.37 pg/ml, respectively, P = NS for both). Green tea and caffeine did not

Fig. 1



Changes in response to resting and hyperemic diameter of the brachial artery and to flow-mediated dilatation. Response is defined as net green tea (or net caffeine) minus control values at each time point in the green tea (or caffeine) and control session during the study (mean ± SEM). *P* values derived from analysis of variance refer to the composite effect of green tea (or of caffeine) versus control.

either have any effect on total antioxidative capacity (TAC; increase by 5.6 ± 39.6 and by 2.3 ± 21.5 μmol/l, respectively, *P* = NS for both) or on total oxidative status/oxidative stress (TOS; increase by 28.0 ± 77.6 and by 26.6 ± 70.7 μmol/l, respectively, *P* = NS for both).

Discussion

This is the first study, to the best of our knowledge, to show that green tea consumption results in an acute increase in FMD of the brachial artery. Our results are inline with previous studies that have examined other types of tea or the effect of green tea on other vascular beds. It has been demonstrated that black tea has an acute and a chronic beneficial effect on endothelial function [19–22]. Furthermore, it has recently been shown that green tea reverses endothelial dysfunction in smokers, as this was assessed in the arterial bed of the forehand [23].

The beneficial effect of green tea on endothelial function may be attributed to its high flavonoid content. As has been shown, epigallocatechin gallate, a major catechin in tea, acutely improves endothelial function in humans with coronary artery disease [25]. Green tea is supposed to be more protective against cardiovascular diseases than black tea [12]. In this context, we have recently shown that green tea has no adverse effect on aortic stiffness, whereas black tea increases aortic stiffness acutely [26]. The beneficial effect of other flavonoid-rich foods and beverages, such as red wine and red grapes, and dark chocolate, on endothelial function has also been demonstrated in various studies [27,28].

The beneficial effect of green tea on endothelial function could be mediated through various mechanisms. It has been shown *ex vivo* that green tea flavonoids inhibit angiotensin-converting enzyme activity [29], although higher molecular weight flavonoids are more effective in inhibiting angiotensin-converting enzyme activity than monomers found in green tea. It has also been found that green tea increases NO production by endothelial cells [29]. There is experimental evidence that purified antioxidant flavonoids improve endothelium-derived NO bioactivity, an effect mediated by enhanced NO synthesis rather than by decreased superoxide-mediated NO breakdown [30]. Furthermore, tea polyphenols stimulate Akt-mediated endothelial-derived NO synthase activity [31].

According to our results, the changes in endothelial function were not associated with changes in inflammatory or oxidative status assessed by hs-CRP, Il-6, Il-1b, TAC, and TOS at 120 min after consumption. Although measures of antioxidant status have shown to change within 2 h of tea consumption [32–34], our results are inline with studies that have found that the beneficial effect of tea on endothelial function is not accompanied by a change in inflammatory or oxidative status [35–38]. We, however, cannot exclude the possibility that changes could have occurred earlier than 120 min [32–34], which was the time point of our blood sampling.

Although not supported by findings regarding the specific inflammatory markers we measured in our study, green tea may exert its beneficial effects through anti-inflammatory pathways [39]. Short-term, that is, 6 weeks, tea consumption reduced hs-CRP in one study [40]. As has been shown, inflammation has a detrimental effect on vascular function [41,42] and a reduction in inflammatory status with green tea could induce an improvement in endothelial function.

Although we and others have previously shown that caffeine consumption impairs vascular performance by

increasing arterial stiffness and wave reflections acutely and on a chronic basis [43–47], the effect of caffeine on endothelial function has not been clarified yet. In this study, we found no overall effect of caffeine on endothelial function. The lack of an effect of caffeine on endothelial function is inline with Duffy *et al.* [19], who showed that caffeine had no effect on FMD of the brachial artery 2 h after consumption. Varying results have also been reported in other studies regarding the effect of coffee/caffeine on endothelial function; caffeinated coffee was shown to adversely affect endothelial function of the brachial artery [48]; on the contrary, oral caffeine was associated with improved endothelial function of the resistance arteries [49].

Green tea consumption resulted in an acute increase in systolic blood pressure. This finding is in accord with earlier studies from our and other laboratories that have examined the pressor effect of black and green tea [26,50], The chronic effect of tea consumption on blood pressure, however, is probably neutral [51]. The changes in FMD observed in our study are not likely because of changes in blood pressure. Indeed, studies have shown that the effect of an intervention on FMD is either unrelated to changes in blood pressure [52,53] or is inversely related (a decrease in blood pressure is associated with an increase in FMD) [54].

Clinical implications

These findings have important clinical implications. Tea consumption has been associated with reduced cardiovascular morbidity and mortality, although this association was not found in all studies [1–8]. Lesser green tea is consumed in the western world than black tea; however, it could be more beneficial, as black tea flavonoids are oxidized during the fermentation process [9]. Endothelial function is of paramount importance for the proper function of the cardiovascular system, and its dysfunction is a key event in the progression of atherosclerosis [13–18]. The beneficial effect of green tea on cardiovascular risk could partly be explained by the improvement of endothelial dysfunction.

Study limitations

Our study population consisted of young healthy individuals with no cardiovascular risk factors except from smoking (50% of the participants). Thus, our results may not be applicable to population groups with different characteristics, such as the elderly.

The lack of difference in FMD between tea and caffeine could be attributed to the fact that caffeine produced a small, yet nonsignificant, change that was in the same direction as that of tea.

A possible differential effect of green and black tea cannot be inferred from the results of our study. Further studies, specially designed, could offer valuable information toward this end.

Finally, owing to the acute nature of the study, no conclusions can be made for the long-term effect of green tea consumption on endothelial function.

Conclusion

In conclusion, green tea has an acute beneficial effect on endothelial function in healthy individuals. This could contribute to the possible beneficial effect of green tea on cardiovascular risk.

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Conflict of interest: none.

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