

# Black Tea Increases Coronary Flow Velocity Reserve in Healthy Male Subjects

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Epidemiologic studies suggest that tea consumption decreases the risk for cardiovascular events. However, there has been no clinical report examining the effects of tea consumption on coronary circulation. The purpose of this study was to evaluate the effects of black tea on coronary flow velocity reserve (CFVR) using transthoracic Doppler echocardiography (TTDE). This was a double-blind crossover study of 10 healthy male volunteers conducted to compare the effects of black tea and caffeine on coronary circulation. The coronary flow velocity of the left anterior descending coronary artery was measured at baseline and at hyperemia during adenosine triphosphate infusion by TTDE to determine CFVR. The CFVR ratio was defined as the ratio of CFVR after bev-

erage consumption to CFVR before beverage consumption. All data were divided into 2 groups according to beverage type: group T (black tea) and group C (caffeine). Two-way analysis of variance showed a significant group effect and interaction in CFVR before and after beverage consumption ( $p = 0.001$ ). CFVR significantly increased after tea consumption in group T ( $4.5 \pm 0.9$  vs  $5.2 \pm 0.9$ ,  $p < 0.0001$ ). The CFVR ratio of group T was larger than that of group C ( $1.18 \pm 0.07$  vs  $1.04 \pm 0.08$ ,  $p = 0.002$ ). Acute black tea consumption improves coronary vessel function, as determined by CFVR. ©2004 by Excerpta Medica, Inc.

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**B**lack tea is known to be rich in flavonoids. Epidemiologic studies have reported a reduced risk for cardiovascular events, such as myocardial infarction, stroke, and cardiac death, in subjects with high flavonoid intake.<sup>1,2</sup> There is also convincing evidence that the dietary intake of antioxidant flavonoids is associated with reduced cardiovascular risk<sup>1-3</sup> and mortality after myocardial infarction.<sup>4</sup> A meta-analysis of tea consumption on the basis of 7 cohort studies demonstrated that the incidence of myocardial infarction decreases by 11% with an increase in tea consumption of 3 cups per day.<sup>5</sup> The potential protective effect of flavonoids has been attributed to antioxidant,<sup>6</sup> antithrombotic,<sup>7</sup> and anti-inflammatory properties.<sup>8</sup> However, there has been no clinical report examining the effects of tea consumption on coronary circulation. Coronary flow reserve measurement has been considered to be a useful physiologic index for coronary circulation.<sup>9</sup> Recent developments in transthoracic Doppler echocardiography (TTDE) enable the estimation of coronary flow velocity reserve (CFVR) noninvasively.<sup>10,11</sup> It is important to investigate the effect of tea consumption on coronary circu-

lation to assess tea consumption in relation to cardiovascular disease. The purpose of this study was to evaluate, using TTDE, the effect of black tea on CFVR in young healthy men.

## METHODS

**Study population:** Ten male volunteers were enrolled in this study. We excluded female subjects, because CFVR is affected by the menstrual cycle.<sup>12</sup> Subjects were healthy medical students and physicians (mean age  $26 \pm 3$  years). All subjects were asymptomatic, normotensive, nondiabetic, and nonsmokers. They had no significant medical histories and no habits of increased tea, caffeine, red wine, or purple grape juice consumption. No subjects had taken any cholesterol-reducing agents or antioxidant vitamin supplements for the preceding 2 months. Each subject gave written informed consent before enrollment.

**Study design:** The study used a double-blind crossover design that compared the effect of black tea (group T) and a caffeine-containing control (group C) on coronary circulation. Volunteers were studied on 2 separate occasions 1 week apart after overnight fasting and abstinence from red wine,<sup>13</sup> purple grape juice,<sup>14</sup> tea, and other known sources of significant amounts of flavonoids for 24 hours before each test session.<sup>15</sup> After baseline CFVR measurements were obtained, volunteers consumed 450 ml of a test beverage in random order (black tea or caffeine-containing control). Two hours after beverage consumption, a second set of measurements were taken. This time point represents the peak blood level of flavonoids after an acute drink of tea.<sup>15</sup> Black tea and caffeine drinks

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Component	Black Tea (mg/package)
Caffeine	128.0
Polyphenols	762.2
Catechins	76.8
Epigallocatechin	20.7
Epigallocatechin gallate	24.6
Epicatechin	14.7
Epicatechin gallate	16.8
Theaflavins	18.6
Theaflavin	6.3
Theaflavin-3-gallate	5.4
Theaflavin-3'-gallate	1.8
Theaflavin-3,3'-digallate	5.1
Other polyphenols	666.8

were formulated to have exactly the same color, taste, and flavor (provided by Unilever Bestfoods North America, Englewood Cliffs, New Jersey). The tea-containing drinks provided 2,100 mg of water-soluble tea extract solids, and the caffeine control contained 120 mg of caffeine (the same amount as delivered by the tea beverages). The contents of the black tea beverage are listed in Table 1.

**Coronary flow studies:** Echocardiography was performed with the Acuson Sequoia 512 (Siemens AG Medical Solutions, Erlangen, Germany) with a frequency of 7.0 MHz. In color Doppler flow mapping, the velocity range was set in the range of  $\pm 11$  to 23 cm/s. The color gain was adjusted to provide optimal images. The ultrasound beam was transmitted toward the heart to visualize coronary blood flow in the left anterior descending coronary artery (LAD) by color Doppler echocardiography. First, we imaged left ventricle in the long-axis cross section, and the ultrasound beam was inclined laterally. Next, coronary blood flow in the distal portion of the LAD was searched under the guidance of color Doppler flow mapping. With a sample volume (2.5 or 3.0 mm wide) positioned on the color signal in the LAD, Doppler spectral tracings of flow velocity were recorded.

Although we tried to align the ultrasound beam direction to distal LAD flow as parallel as possible, angle correction was needed in each examination because of incident Doppler angle (mean angle  $38^\circ$ , range  $22^\circ$  to  $54^\circ$ ). We first recorded baseline spectral Doppler signals in the distal portion of the LAD over 5 cardiac cycles at end-expiration by TTDE. Intravenous adenosine triphosphate (ATP) was administered ( $140 \mu\text{g}/\text{kg}^{-1} \text{ min}^{-1}$  intravenously) for 2 minutes to record spectral Doppler signals during hyperemic conditions. When the spectral recordings of LAD flow were inadequate to evaluate its velocity, a contrast agent (Levovist, Schering, Berlin, Germany) was used to enhance the Doppler signals. All subjects had continuous heart rate and electrocardiographic monitoring. Blood pressure was recorded at baseline and every minute during ATP infusion.

Each study was analyzed by 2 experienced investigators who were blinded to the other subject data. Measurements were performed off line by tracing the contour of the spectral Doppler signal using the computer incor-

porated in the ultrasound system. Mean diastolic velocities were measured at baseline and peak hyperemic conditions from the Doppler signal recordings. CFVR was defined as the ratio of hyperemic to basal mean diastolic velocity. CFVR measurement was performed before and 2 hours after tea consumption. The CFVR ratio was derived by dividing baseline CFVR by CFVR after beverage consumption.

**Statistical analysis:** Data are presented as mean values  $\pm$  SDs. To compare the effects of ATP administration and treatment, we used 2-way, repeated-measures analysis of variance (ANOVA) for hemodynamic parameters, coronary flow velocity, and CFVR over ATP administration before and after treatment with post hoc Scheffe comparison. Paired *t* tests were used for directed comparisons of beverage intake effects in each group. We used 1-way ANOVA for CFVR ratio to compare the effects of beverage types. Statistical significance was accepted at  $p < 0.05$ .

## RESULTS

Adequate spectral Doppler recordings of diastolic coronary flow in the LAD were obtained in all volunteers (100%) (Figure 1). No participant experienced atrioventricular block, chest pain, flushing, or palpitations during ATP infusion in the TTDE studies. Hemodynamics did not change before and after tea or caffeine intake. Two-way ANOVA showed no significant difference or interaction in terms of heart rate, systolic blood pressure, and diastolic blood pressure between groups T and C during ATP infusion (Table 2).

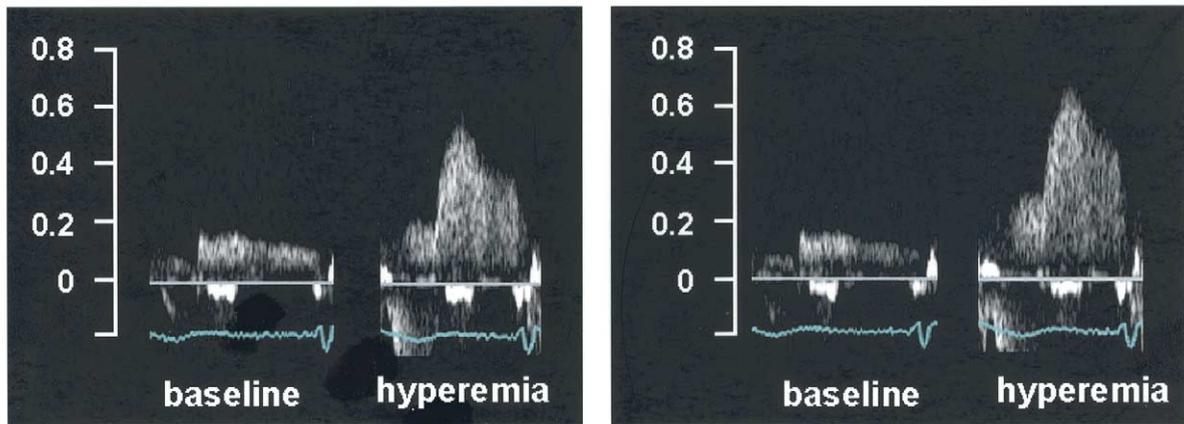
**Coronary flow responses:** Mean diastolic velocities at baseline were comparable in 2 groups before and after black tea and caffeine intake (Table 2). There was no significant difference in CFVR at baseline in the 2 groups. However, 2-way ANOVA showed a significant group effect and interaction in CFVR before and after beverage consumption ( $p = 0.01$ ). CFVR significantly increased after black tea consumption ( $4.5 \pm 0.9$  vs  $5.2 \pm 0.9$ ,  $p < 0.0001$ ) (Tables 2 and 3). One-factor ANOVA showed a significant group effect in CFVR ratio ( $p = 0.002$ ). The CFVR ratio in group T was greater than that in group C ( $1.18 \pm 0.07$  vs  $1.04 \pm 0.08$ ,  $p = 0.002$ ) (Tables 2 and 3, and Figure 2).

Interobserver and intraobserver variabilities for the measurement of Doppler velocity recordings were 4.9% and 4.0%, respectively.

## DISCUSSION

This study demonstrated that the consumption of black tea increases CFVR in young healthy men acutely. The results of this study suggest that black tea consumption has a beneficial effect on coronary circulation.

Using TTDE, we assessed CFVR, which has previously been used as a surrogate for coronary flow reserve.<sup>10,11</sup> Abnormalities in the microcirculation of the heart are associated with the well-known risk factors for cardiovascular disease, hypercholesterolemia, diabetes, and hypertension, and these abnormal-



**FIGURE 1.** Example case of coronary flow velocity recordings before black tea consumption (*left*) and after black tea consumption (*right*). Coronary flow velocity at baseline did not change after black tea consumption, but coronary flow velocity during hyperemia increased after black tea consumption.

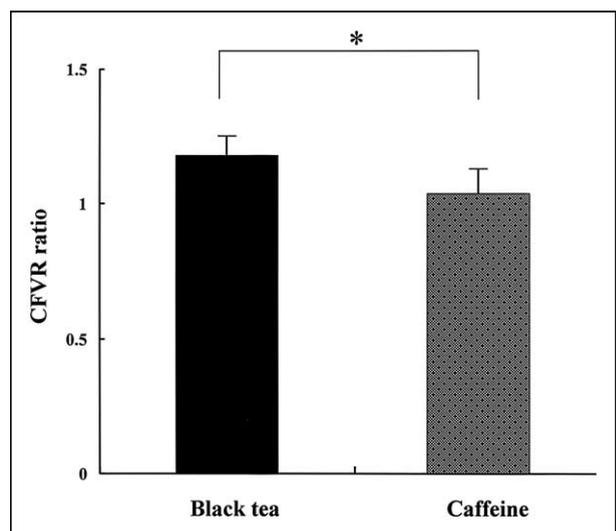
**TABLE 2** Hemodynamics and Coronary Flow Velocity Measurements

		Black Tea		Caffeine	
		Before	After	Before	After
Heart rate (beats/min)	Baseline	61 ± 8	60 ± 9	62 ± 7	61 ± 8
	ATP infusion	62 ± 9	61 ± 8	61 ± 8	61 ± 9
Systolic blood pressure (mm Hg)	Baseline	109 ± 11	110 ± 11	111 ± 10	109 ± 9
	ATP infusion	106 ± 10	109 ± 10	110 ± 11	109 ± 10
Diastolic blood pressure (mm Hg)	Baseline	69 ± 8	69 ± 9	67 ± 8	68 ± 8
	ATP infusion	65 ± 8	65 ± 8	66 ± 9	66 ± 7
Mean diastolic velocity (cm/s)	Baseline	19 ± 4	18 ± 4	17 ± 3	17 ± 3
	ATP infusion	84 ± 24	95 ± 25*	78 ± 10	81 ± 11
CFVR		4.5 ± 0.9	5.2 ± 0.9*	4.7 ± 0.7	4.9 ± 0.8
CFVR ratio		1.18 ± 0.07 <sup>†</sup>		1.04 ± 0.08	

\*p < 0.01 for the comparison with the value before consumption.  
<sup>†</sup>p < 0.05 for the comparison with the value after caffeine consumption.

**TABLE 3** CFVR Measurement

Subject	Black Tea			Caffeine		
	Before	After	Ratio	Before	After	Ratio
1	3.81	4.88	1.28	3.85	4.71	1.22
2	5.83	6.60	1.13	5.53	6.12	1.11
3	3.08	3.37	1.09	3.35	3.17	0.95
4	4.41	5.10	1.16	5.18	4.78	0.92
5	4.71	5.38	1.14	5.29	5.24	0.99
6	3.91	5.14	1.31	4.50	5.09	1.13
7	5.19	5.86	1.13	5.32	5.35	1.01
8	3.84	4.62	1.20	4.13	4.25	1.03
9	5.61	6.41	1.14	5.32	5.22	0.98
10	4.12	4.94	1.20	4.59	4.66	1.01



**FIGURE 2.** Brackets indicate SD. By post hoc analysis, the CFVR ratio of group T was significantly greater than that of group C (\*p < 0.01).

ities are reflected by coronary flow reserve capacity.<sup>16–18</sup> In these studies, coronary flow reserve was measured by positron emission tomography, Doppler catheter or guidewire, and transesophageal Doppler echocardiography. Compared with the other methods, TTDE as used in the present study is completely noninvasive and relatively inexpensive to perform. Furthermore, this technique provides CFVR measurement with a high success rate using a high-frequency

transducer and a reduced velocity range in color Doppler echocardiography. Using this noninvasive technique, we previously assessed the effects of red

wine,<sup>13</sup> passive smoking,<sup>19</sup> and the menstrual cycle<sup>12</sup> on microcirculation. Thus, this noninvasive technique was ideal for the evaluation of serial changes in CFVR in the present study's subjects.

**Effect of black tea consumption on coronary circulation:** In the present study, tea and caffeine consumption had no effect on baseline coronary flow velocity. However, tea consumption increased coronary flow velocity during ATP administration and thus increased CFVR. In contrast, caffeine intake did not affect CFVR. These findings suggest that some component of tea, but not caffeine, improves CFVR without altering coronary circulation at rest.

Duffy et al<sup>15</sup> reported that short-term and long-term black tea consumption reverses endothelial dysfunction in patients with coronary artery disease. Endothelial dysfunction with atherosclerosis is associated with increased oxidative stress and may be reversed by antioxidant treatment. Thus, tea flavonoids may act on the endothelium of peripheral arteries to improve its function. Coronary flow reserve assessed during ATP-induced hyperemia relates to the endothelium-dependent and endothelium-independent vasodilatation of coronary arteries.<sup>20,21</sup> Our result suggests that black tea flavonoids may improve coronary endothelial function, similar to findings in the study of Duffy et al<sup>15</sup> demonstrating the beneficial effect of tea on peripheral endothelial function.<sup>22</sup>

The precise mechanism by which black tea increases CFVR was not determined. However, there is experimental evidence that purified antioxidant flavonoids improve endothelium-derived nitric oxide bioactivity by enhanced nitric oxide synthesis.<sup>23</sup> Thus, improvement in coronary endothelial function by tea flavonoids may be a possible mechanism for increased CFVR after tea consumption.

**Study limitations:** There are several limitations to the present study. First, we measured coronary flow velocity change in the epicardial coronary artery, not coronary flow volume change, to determine CFVR. However, CFVR can be used for the assessment of coronary flow reserve because coronary flow velocity change correlates well with coronary flow volume change during drug-induced hyperemia.<sup>24</sup> Thus, CFVR in the LAD should reflect the status of coronary microcirculation. Second, we enrolled only 10 young male healthy volunteers in this study. To clarify the relation between tea and coronary circulation, further studies in larger populations with various clinical characteristics are needed. A study in patients with coronary artery disease is especially warranted. It is necessary to assess the long-term effect on CFVR in future studies as well. Finally, several investigators have demonstrated that the response to ATP is attenuated by pharmacologic actions of caffeine.<sup>25,26</sup> In the present study, black tea and caffeine consumption had no effect on hemodynamics and baseline coronary flow. We did not measure serum caffeine concentration before and after beverage consumption. However, the black tea-containing drink we used in the present study contained the same amount of caffeine as the caffeine-containing drink. The black tea-containing

drink increased coronary flow velocity during ATP administration compared with the caffeine-containing drink. These findings suggest that some component of black tea improves CFVR, even under the interference of the ATP effect by caffeine and other xanthenes contained in black tea.

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