Coffee Blunts Mental Stress–Induced Blood Pressure Increase in Habitual but Not in Nonhabitual Coffee Drinkers

Isabella Sudano, Lukas Spieker, Christian Binggeli, Frank Ruschitzka, Thomas F. Lüscher, Georg Noll, Roberto Corti

Abstract—Coffee is widely consumed, especially during mental stress conditions. Cardiovascular impact of coffee remains debated because the underlying mechanisms of action are complex. We reported previously differential cardiovascular stimulation of coffee at rest depending on habitual consumption. The present study was designed to evaluate the effects of coffee on cardiovascular response to mental stress. In 15 healthy volunteers (6 habitual, 9 nonhabitual coffee drinkers), we assessed the effect of mental stress on blood pressure (BP), heart rate (HR), and muscle sympathetic activity (MSA) before and after a triple espresso, intravenous caffeine, and placebo in the same subjects. Under baseline conditions, mental stress significantly increases MSA (+2.5±0.7 volts per minute; +14.1±10.3%), systolic (+11.6±4.1 mm Hg) and diastolic BP (+6.4±2.0 mm Hg), and HR (+9.6±1.8 minutes⁻¹). In nonhabitual coffee drinkers, a triple espresso but not caffeine induced an additional increase in systolic BP (+9±6.3 mm Hg; \( P=0.003 \)) during mental stress, whereas in habitual drinkers, the stress-induced BP increase was blunted (+4±3.9 mm Hg; \( P=\text{NS} \)). As a result, nonhabitual coffee drinkers experienced significantly higher BP during mental stress than habitual drinkers (151±17.9/83±5.6 mm Hg versus 130±7.8/74±6.7 mm Hg; \( P<0.05 \)). Caffeine induced similar effects in habitual and nonhabitual coffee drinkers at rest and during mental stress. The response to the cold pressor test was not influenced by coffee drinking in both groups. In conclusion, in nonhabitual coffee drinkers, coffee enhances the cardiovascular response to mental stress with an additional increase in systolic BP, whereas in habitual drinkers, the response is blunted. Caffeine alone does not exert any potentiating effect, confirming that ingredients other than caffeine are partially responsible for the stimulating effect of coffee on the cardiovascular system. (Hypertension. 2005;46:521-526.)

Key Words: blood pressure monitoring ■ caffeine ■ risk factors ■ baroreflex ■ sympathetic nervous system

Coffee is one of the most popular beverages consumed in large amounts all over the world. Other than for its taste, it is consumed by many as a stimulant. Despite the ubiquitous consumption of coffee and caffeine beverages and their circumstantial intake during stressful situations, little is known about its cardiovascular effects under such conditions.

The sympathetic nervous system plays an important role in regulation of the cardiovascular system. Autonomic nervous system is the primary mediator of the blood pressure (BP) and heart rate (HR) response during mental stress (MS) and cold pressor test (CPT). Vasomotor sympathetic nerve activity to skeletal muscle typically increases in response to MS as well as after exposure to cold. In patients with borderline hypertension, sympathetic nerve reactivity is already enhanced under baseline conditions and in normoten- sive offspring of hypertensive parents during MS. Sympathetic nerve activity can be assessed directly by microneurographic technique by deriving the efferent muscle sympathetic activity (MSA) with an intraneurally placed microelectrode.

Hartley et al demonstrated recently that caffeine induces similar increase in BP at rest and during MS in regular caffeine consumers. In addition, they reported gender-dependent differences in the hemodynamic mechanisms.

We have previously shown that in nonhabitual coffee drinkers, coffee and caffeine led to a comparable increase in MSA and BP, whereas in habitual coffee drinkers, no rise of BP is seen, despite MSA activation after coffee drinking. Moreover, decaffeinated coffee also increases BP and MSA in nonhabitual drinkers, suggesting that ingredients other than caffeine are responsible for cardiovascular activation.

However, the activity of the sympathetic nervous system may not entirely reflect the cardiovascular actions of coffee in physiological conditions. Therefore, it was the aim of the present study to assess the effects of coffee on the cardiovascular response to MS and CPT in humans.

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521
Baseline Characteristics

<table>
<thead>
<tr>
<th>Data</th>
<th>Coffee (H/NH)</th>
<th>Caffeine (H/NH)</th>
<th>Placebo (H/NH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>5 (3 male)/5 (2 male)</td>
<td>5 (3 male)/5 (2 male)</td>
<td>5 (3 male)/5 (3 male)</td>
</tr>
<tr>
<td>Age, years</td>
<td>34±6.1/30±7.3</td>
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<td>BMI (kg/m²)</td>
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<tr>
<td>HR (bpm)</td>
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<td>63±7.0/68±11</td>
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<tr>
<td>SBP (mm Hg)</td>
<td>118±11.2/119±10.7</td>
<td>123±5.2/127±2.7</td>
<td>129±7.1/129±6.9</td>
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<tr>
<td>DBP (mm Hg)</td>
<td>69±5.1/68±4.3</td>
<td>68±5.6/71±6.2</td>
<td>68±5.3/67±5.7</td>
</tr>
<tr>
<td>MSA V/min</td>
<td>10.7±3.2/16±5.4</td>
<td>11±4.5/13±4.7</td>
<td>12±4.7/10±2.9</td>
</tr>
<tr>
<td>MSA bursts/min</td>
<td>42±7.3/44±5.2</td>
<td>43±4.8/48±8.1</td>
<td>44±6.1/42±3.7</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD.

H indicates habitual coffee drinkers; NH, nonhabitual coffee drinkers; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP.

Methods

Study Population

MSA was investigated by microneurography within the peroneal nerve in 15 healthy volunteers (6 habitual and 9 nonhabitual coffee drinkers; 10 male and 5 female) as described previously. Clinical characteristics of our study population are reported in the Table. Smokers and offspring of hypertensive parents were excluded. The ethics committee of the University Hospital Zürich (Switzerland) approved the study, and volunteers gave written informed consent before the study.

Experimental Protocol

Arterial BP, HR, and MSA were recorded continuously during 10-minute baseline, 3-minute MS, and 2-minute CPT before and after administration of caffeine, placebo, and ingestion of a triple espresso (Figure 1). Subjects experienced the interventions on different days, and the order of interventions was randomized.

Habitual coffee drinkers and nonhabitual coffee drinkers (defined as drinking no coffee or any other beverages containing caffeine) were studied after: (1) coffee drinking (triple espresso; n=10; 5 habitual and 5 nonhabitual coffee drinkers); (2) intravenous bolus administration of caffeine (250 mg dissolved in 10 mL NaCl 0.9%; n=11; 5 habitual and 5 nonhabitual coffee drinkers); (3) intravenous administration of placebo (10 mL NaCl 0.9%; n=11; 5 habitual and 6 nonhabitual coffee drinkers).

Subjects were blinded to the intervention (ie, intravenous administration of caffeine versus placebo). All subjects were studied in supine position after coffee abstinence for ≥16 hours under standardized conditions (ie, in the afternoon [2:00 PM] after a light meal and after micturition) to avoid any increase in sympathetic activity through bladder distension.

Caffeine plasma levels were determined at baseline and at 15, 45, and 75 minutes after intravenous caffeine or placebo and (because of slow intestinal absorption) 30, 60, and 90 minutes after oral ingestion of coffee, respectively.

MS and CPT

MS was performed with a highly reproducible and observer-independent mental task; volunteers had to respond as fast as possible to color lights flashing in random order by pressing a push button of the corresponding color. For the CPT, patients were asked to put one hand into ice water (0°C) up to the wrist for 2 minutes. MS and CPT are established stimuli for the sympathetic nervous system. The sequence of these 2 tests was not randomized. Between MS and CPT, a 10-minute rest was required to reach MSA and hemodynamic values comparable to levels before the test.

Drugs and Coffee Preparation

Caffeine sodium benzoate (431 mg) equivalent to 250 mg caffeine was prepared in 10 mL saline solution for intravenous use. Coffee was prepared with an espresso machine (triple espresso; 30 mL). The dosage of coffee was chosen to reach a caffeine plasma concentration equivalent to 250 mg of caffeine administered intravenously. Plasma caffeine levels at rest after administration of caffeine intravenously or after drinking a triple espresso have been reported previously.

Microneurography

Multifiber recordings of MSA were obtained from the peroneal nerve posterior to the fibular head with tungsten microelectrodes (200-μm shaft diameter, 1- to 5-μm uninsulated tip; Medical Instruments; University of Iowa). A reference electrode was inserted subcutaneously 1 to 2 cm from the recording electrode. Electrodes were connected to a preamplifier (gain 1,000) and amplifier (variable gain 10 to 50). Neural activity was fed through a band-pass filter (bandwidth 700 to 2000 Hz) and a resistance-capacitance integrating system.
network (time constant 0.1 seconds) to obtain a mean voltage neurogram with the typical pulse wave–triggered bursts.

ECG and BP
An ECG was recorded simultaneously throughout the experiment. BP was assessed noninvasively through oscilometric occlusion at the left upper arm (Dinamap; Critikon Inc) every 2 minutes, and it was also measured continuously with a Finapress device (Finapress 2300; Ohmeda) during 10-minute baseline, 3-minute MS, and 2-minute CPT. The analysis of BP, HR, and MSA was done by an investigator blinded to the experiment and to the subject’s data.

Signal Recording and Signal Processing
MSA and 1-lead surface ECG were recorded continuously with a LabView application, an MIO 16L (National Instruments) analog-to-digital conversion board, and a Macintosh computer. The signals were sampled at 500 Hz and stored with 12-bit accuracy.

Usually, MSA is evaluated manually by experienced observers. For computer-assisted analysis of MSA, we used software written in Matlab (The Mathworks) developed in our laboratory. First, the MSA signal is low-pass filtered. Detection criteria for bursts are amplitude, slope, and time of occurrence in the RR interval. The correlation between computer and an experienced observer is good (r=0.92) as shown in 10 healthy volunteers at rest and during cold pressor testing. The computer program is slightly more sensitive to small bursts, probably because of filtering increasing the signal-to-noise ratio.

MSA was quantified in a computer-assisted evaluation of the frequency and the amplitude of the sympathetic bursts. The results are expressed as cumulative sum of the amplitude in volts per minute (V/min) and percent increase in respect to baseline. As already described for BP and HR, MSA was also analyzed by an investigator not aware of the interventions.

Data and Statistical Analysis
Data were entered and analyzed with SYSTAT version 10.0 (SPSS, Inc.). For each subject, a 5-minute average of continuously acquired data at baseline, 60 minutes after caffeine and placebo, or 90 minutes after oral coffee was used. For analyzing MS and CPT, continuously acquired data were averaged for every minute of the tests. Results are reported as mean±SD. Data were analyzed with repeated-measures ANOVA. The effect of interventions was evaluated by comparing the values before and after MS and CPT with a t test. A value of P<0.05 was considered statistically significant.

Results
At baseline, resting BP, HR, and MSA did not differ between habitual and nonhabitual coffee drinkers. Despite ≥16 hours of coffee abstinence, caffeine plasma levels were significantly higher in habitual coffee drinkers (5.7±1.3 μmol/L) than in nonhabitual coffee drinkers (1.9±1.6 μmol/L).

Response to MS and Cold Pressor Testing
Under baseline conditions, a uniform hemodynamic and sympathetic response to stress tests was seen. MS (Figure 2) led to an increase in HR (+9.6±1.9 minutes⁻¹; P=0.0003), systolic BP (+11.6±3.9 mm Hg; P=0.0009), and diastolic BP (+6.4±1.9 mm Hg; P=0.0065). Mean MSA resulted to be increased by MS (+2.5±0.7 V/min; +14.1±10.3%; P=0.009; Figure 3). Similarly, CPT (Figure 4) induced a significant increase in HR (+4.7±2.6 minutes⁻¹; P=0.0005), systolic (+23.5±3.8 mm Hg, P<0.0001) and diastolic BP (+13.2±3.7 mm Hg; P<0.0001), as well as MSA (+8.3±2.7 V/min; +115.8±41.7%; P<0.0001). No difference between habitual and nonhabitual coffee drinkers was seen at baseline conditions during MS or CPT. Intravenous placebo administration did not influence the cardiovascular response to MS or CPT, confirming the reproducibility of the tests.

Effects of Coffee Drinking
Drinking a triple espresso led to differential cardiovascular effects at rest and during MS in habitual and nonhabitual coffee drinkers, respectively. In fact, as reported previously, at rest, coffee induced a significant increase of systolic (+13.5±3.6 mm Hg; P=0.0011) and diastolic (+7.7±3.5 mm Hg; P=0.012) BP and MSA (cumulative sum of the amplitude +5.1±2.3 V/min; +52±32%; P=0.04) in nonhabitual drinkers, whereas in habitual coffee drinkers, BP did not change despite a similar increase in MSA. After drinking a triple espresso, MS led to different responses in nonhabitual and habitual coffee drinkers. In nonhabitual coffee drinkers, an additional significant increase in HR (+11±2.3 minutes⁻¹,
rest and after drinking coffee, no additional increase was detected during MS in both groups.

The cardiovascular effect of CPT, which represents a maximal physiological peripheral stimulus of the sympathetic nervous system, was not influenced by the administration of coffee or caffeine (Figure 4).

**Effect of Caffeine**

Caffeine administration equally increased BP and MSA at rest in habitual as well as in nonhabitual coffee drinkers. Interestingly, after caffeine administration, no difference in the cardiovascular effect during MS and CPT was seen between habitual and nonhabitual coffee drinkers.

**Discussion**

This study demonstrates for the first time that coffee blunts the cardiovascular response to MS in habitual but not in nonhabitual drinkers. In fact, the stress-induced response of systolic BP was preserved after drinking a triple espresso in nonhabitual drinkers, whereas it was blunted in habitual coffee drinkers. Caffeine alone did not exert any potentiating effect in habitual and nonhabitual coffee drinkers, confirming that ingredients other than caffeine are responsible for the stimulating effect of coffee on the cardiovascular system.

Interestingly, although habitual and nonhabitual drinkers showed a similar increase in sympathetic nerve activation at rest and after drinking coffee, no additional increase was detected during MS in both groups.

The effect of coffee is very selective and limited to the centrally induced stress because the pressor effect of a peripheral activation of the sympathetic nervous system by CPT was not influenced by coffee administration. The different responses to the 2 stressors confirm qualitative differences between MS and CPT. Sympathetic activation during MS is initiated from the cerebral cortex, eliciting a mixed pattern of $\alpha$-adrenergic and $\beta$-adrenergic cardiovascular reactions, whereas cold exposure of the extremities activates afferent nerves linked to cutaneous cold receptors that enter the hypothalamus directly, predominantly involving $\alpha$-adrenergic neurotransmission.

It was reported previously that ingestion of a large volume (500 mL) of tap water could induce sympathetic activation, probably as a response to stomach distension, whereas
ingestion of smaller volumes (200 to 300 mL) did not lead to sympathetic activation.\textsuperscript{18} The small volume of coffee (30 mL) used in our study is therefore not expected to induce a significant activation of the sympathetic nervous system.

The available evidence suggests that coffee induces some kind of tolerance to MS in habitual coffee drinkers. The phenomenon of “tolerance” to repetitive stress tasks can be excluded as a confounding factor because the response to MS was preserved after placebo administration. Because the lack of a BP increase during MS in habitual coffee drinkers was associated with preserved MSA and HR, a possible explanation of the underlying mechanism could involve alterations in cardiac stroke volume. More likely even, a possible interaction of coffee with peripheral neurotransmission or vascular adrenergic receptors should also been taken into account. For instance, adenosine receptors modulate peripheral sympathetic neurotransmission, and they could be a possible target for coffee with different receptor upregulation and downregulation in light and heavy drinkers, respectively. In fact, differential regulation of the cardiac and peripheral sympathetic nerve activity has been demonstrated.\textsuperscript{19,20} These findings may help to explain why many people drink coffee before or during stressful tasks. Nevertheless, because of the limited number of observations, it is not possible to generalize our results to a large population. In conclusion, in nonhabitual coffee drinkers, coffee enhances the cardiovascular response to physiological stress with additional increase in systolic BP, whereas in habitual coffee drinkers, the response to MS is blunted. Thus, drinking coffee leads to a stronger cardiovascular response to MS in nonhabitual coffee drinkers. Caffeine alone does not exert any potentiating effect, confirming that ingredients other than caffeine are responsible for the stimulating effect of coffee on the cardiovascular system.

**Perspectives**

Other substances than caffeine seem to be responsible for the effect on BP of coffee at rest and during stress. Many substances have been isolated in coffee; several hundreds are responsible for the aroma or other characteristics of coffee, and most of them have potential cardiovascular effects (for example potassium, magnesium, chlorogenic acid, just to name a few). Moreover, the mechanisms underlying the BP increase induced by MS are not yet completely understood. We already showed previously that in habitual coffee drinkers, the BP increase induced by coffee was reduced compared with nonhabitual coffee drinkers and that caffeine had comparable effects in both groups. Therefore, coffee may also contain substances able to reduce the MS-induced BP increase. More studies are needed to identify the mechanisms and the substances responsible for the differential cardiovascular effects of coffee.

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