Coffee Acutely Increases Sympathetic Nerve Activity and Blood Pressure Independently of Caffeine Content

Role of Habitual Versus Nonhabitual Drinking

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Background—Coffee is the most abundantly consumed stimulant worldwide. However, its cardiovascular safety remains controversial. Possible health hazards have been related to its main ingredient, caffeine. Activation of the sympathetic nervous system by coffee may enhance cardiovascular risk; however, it is unclear whether this effect of coffee is related to caffeine or other substance(s) also contained in decaffeinated coffee.

Methods and Results—In 15 healthy volunteers (6 habitual and 9 nonhabitual coffee drinkers) arterial blood pressure (BP), heart rate, and muscle sympathetic nervous activity (MSA) were continuously recorded before and after drinking a triple espresso or a decaffeinated triple espresso or after intravenous administration of caffeine (250 mg) or placebo (saline) in the same subjects. There was a significant time × condition interaction for the intravenous caffeine and placebo conditions for MSA, with caffeine showing a significant increase in MSA at 60 minutes (53.2±14.1% total activity) and the placebo group showing no effect. A similar significant time effect was found for coffee drinking (54.1±22.5% total activity). Habitual and nonhabitual coffee drinkers demonstrated similar changes in MSA and BP after intravenous caffeine, whereas coffee drinking increased BP in nonhabitual drinkers only, despite comparable increases of MSA and plasma caffeine levels. Nonhabitual coffee drinkers showed similar activation of MSA and BP after caffeine infusion, coffee, or decaffeinated coffee.

Conclusions—Acutely, coffee and caffeine induced comparable increases in MSA and BP in nonhabitual coffee drinkers, whereas habitual coffee drinkers exhibited lack of BP increase despite MSA activation to coffee. Because decaffeinated coffee also increases BP and MSA in nonhabitual drinkers, ingredients other than caffeine must be responsible for cardiovascular activation. **(*Circulation*. 2002;106:2935-2940.)**

Key Words: hypertension ■ nervous system, sympathetic ■ coffee ■ caffeine

Coffee is one of the most popular beverages, consumed in a large amount all over the world. Although its taste is a factor, many consume it for its stimulant properties. Coffee drinking has been associated with increased cardiovascular morbidity and mortality in some[1,2] but not all prospective and epidemiological studies.[3,4] Interestingly, a beneficial effect of coffee was reported recently in the Scottish Heart Health study.[5] Similarly, the role of coffee in the development of hypertension is also controversial, inasmuch as coffee drinking has been linked to both elevated[6] and reduced[7] blood pressure (BP) and has even been shown to have no effect on BP.[8]

The sympathetic nerve system (SNS) plays an important role in the regulation of BP. Indeed, sympathetic overactivity is a well-established pathogenetic mechanism in hypertension.[9–11] SNS reactivity is already enhanced in patients with borderline hypertension[10] as well during mental stress in normotensive offspring of hypertensive parents,[12] which suggests that intermittent activation of the SNS may in the long run lead to persistent increases in BP.

Coffee contains several hundred different substances,[13] but its effects on hemodynamics and on the SNS have been mainly related to caffeine. Indeed, short-term administration of caffeine in non–coffee drinkers increases BP, plasma renin activity, and catecholamines.[14] The direct effects of caffeine and coffee on SNS activity, however, still remain to be determined, particularly because decaffeinated coffee is considered to lack such cardiovascular effects. Thus, the aim of the present study was to assess the effects of caffeine, as well as regular and decaffeinated coffee, on sympathetic nerve activity and hemodynamics in humans in vivo.

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Baseline Conditions

	Placebo (H/NH)	Caffeine (H/NH)	Coffee (H/NH)	Decaffeinated (NH)
No. of subjects	5/6	6/4	5/5	4
Age, y	35±3/29±3	34±3/30±4	35±3/29±3	30±3
Body mass index, kg/m^2	24.4±1/23.4±1	24.8±1/22.8±1	24.4±1/22.5±1	24.7±1
Heart rate, bpm	64±3/75±6	63±2/66±4	63±4/69±5	74±5
Systolic BP, mm Hg	129±7/128±8	118±5/119±7	124±3/130±3	131±10
Diastolic BP, mm Hg	68±3/69±2	69±2/67±2	69±2/72±3	68±3
MSA, V/min	17±6/9±2	12±2/20±3	15±3/17±6	6±2
MSA, bursts/min	45±4/42±2	48±3/51±2	49±3/49±7	35±5

Data are expressed as mean±SEM. H indicates habitual coffee drinkers; NH, nonhabitual coffee drinkers.

Methods

Subjects

Muscle sympathetic nerve activity (MSA) was investigated by microneurography within the peroneal nerve in 15 healthy volunteers (Table). Smokers and offspring of hypertensive parents (common confounding factors that may affect SNS activity) were excluded.[12] The ethics committee of the University Hospital Zürich (Switzerland) approved the study, and volunteers gave written informed consent before the study.

Experimental Protocol

In 15 healthy volunteers (6 habitual and 9 nonhabitual coffee drinkers) arterial BP, heart rate, and MSA were continuously recorded before and after different interventions (see below) in the same subjects. Habitual coffee drinkers and nonhabitual coffee drinkers (defined as drinking no coffee or any other beverages containing caffeine) were studied after:

(1) intravenous bolus administration of caffeine (250 mg dissolved in 10 mL NaCl 0.9%; n=10, 5 habitual and 5 nonhabitual coffee drinkers);

(2) intravenous administration of placebo (10 mL NaCl 0.9%; n=11, 5 habitual and 6 nonhabitual coffee drinkers);

(3) coffee drinking (triple espresso; n=10, 5 habitual and 5 nonhabitual coffee drinkers); and

(4) drinking of decaffeinated coffee (triple espresso; n=4, nonhabitual coffee drinkers).

Subjects were blinded to the intervention (ie, coffee versus decaffeinated coffee, and intravenous administration of caffeine versus placebo) All subjects were studied in supine position after coffee abstinence for at least 16 hours under standardized conditions—ie, in the afternoon (2:00 PM) after a light meal and after micturition to avoid any increase in SNS activity through bladder distention.[15] The leg was fixed with vacuum cushion, and ECG leads, BP cuff, and respiration strain gauge were attached. An indwelling catheter (DeltaFlo2, 20 gauge, DELTA-MED) was inserted into a cubital vein. After a running-in period and stable hemodynamics for 15 minutes, baseline recordings and blood samplings were obtained.

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.

Microneurography

Microneurography was performed as previously described.[12,16] Multifiber recordings of MSA were obtained during the entire duration of the study 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 network (time constant, 0.1 second) to obtain a mean voltage neurogram with the typical pulse-wave–triggered bursts. The signal was displayed on an oscilloscope, amplified, and connected to a loudspeaker to further identify the characteristic signal and exclude artifacts.[12]

ECG and BP

An ECG was recorded simultaneously throughout the experiment. BP was assessed noninvasively through oscillometric occlusion at the left upper arm (Dinamap, Critikon Inc).

Signal Recording and Signal Processing

MSA and 1-lead surface ECG were continuously recorded with a LabView application, a MIO 16L (National Instruments) A/D conversion board, and a Macintosh computer. The signals were sampled at 500 Hz and stored with 12-bit accuracy.

Signal processing was done with MATLAB (The MathWorks, Inc). MSA was quantified in a computer-assisted evaluation of the frequency and the amplitude of the sympathetic bursts. The results are expressed as bursts per minute (bursts/min) and cumulative sum of the amplitude (ACS) in volts per minute (V/min) for absolute value, as a parameter of the total activity, whereas changes in the SNS activity are expressed as percent of baseline values.

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). The dosage of coffee was chosen to reach a caffeine plasma concentration equivalent to 250 mg of caffeine administered intravenously, in accordance with pilot experiments that showed that after 60 minutes the caffeine plasma concentration reached with a triple espresso—prepared with the automatic espresso machine—was equal to caffeine plasma concentration 45 minutes after intravenous administration of 250 mg caffeine. Decaffeinated coffee of the same brand was prepared with an espresso machine in the same way as the triple espresso.

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 registered data at baseline, 30 minutes, and 60 minutes was used in the statistical analysis. The 5-minutes averages occurred at least 10 minutes after each blood drawing. Results are reported as mean±SEM. The analyses began with an overall 3×2 repeated-measures ANOVA followed by tests of the effect of time within each condition. Significant within-condition time effects were than followed up with tests of specific trends (eg, linear, quadratic). The effect of coffee on habitual drinkers was assessed by comparing the 60-minute change in the physiological parameter's value to zero (baseline) with a 1-sample *t* test. Similar comparisons were made for

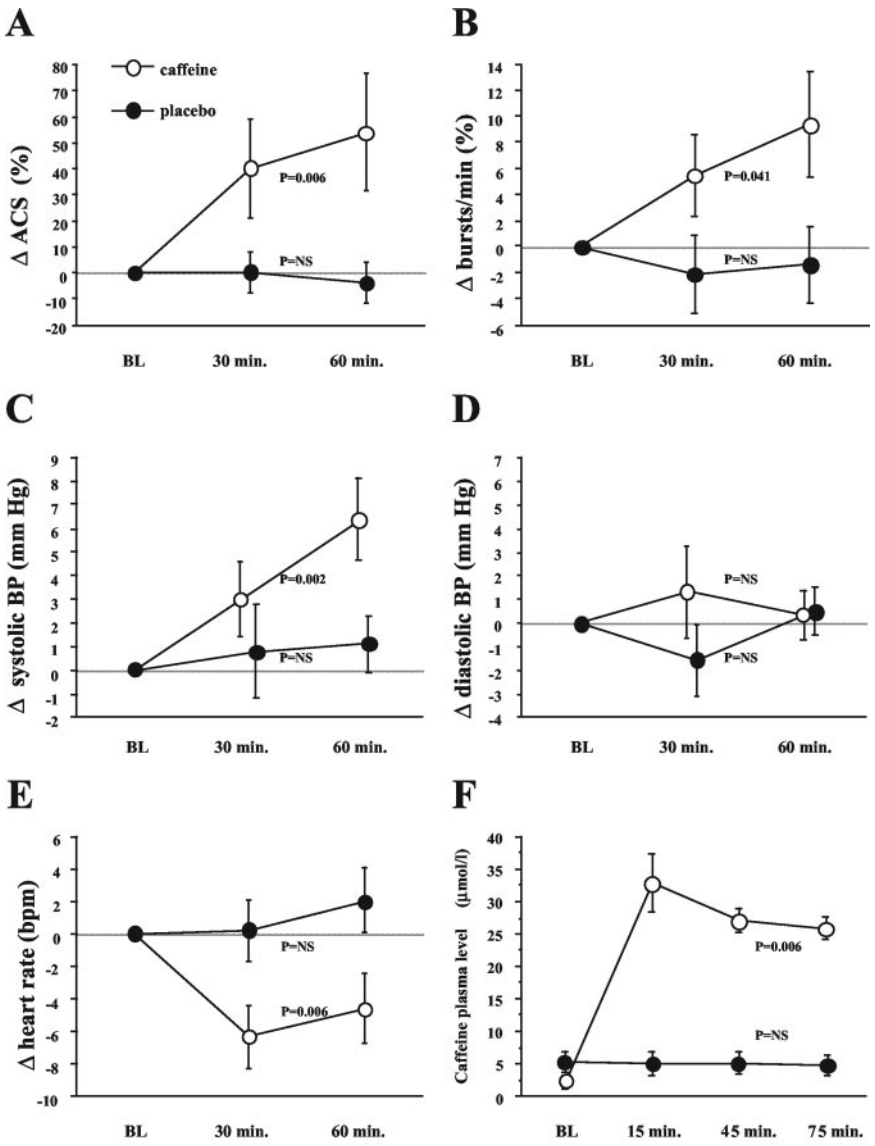

Figure 1. The effect of caffeine (open circles) on sympathetic nerve activity (A, B) and hemodynamic (systolic, C; diastolic BP, D; and heart rate, E) is compared with placebo (black circles). Course of caffeine plasma level is displayed (F). Statistical significance (probability value) for time by condition interaction is reported. T bars indicate standard error. Changes in the sympathetic nerve activity are expressed as percent of the baseline value. ACS indicates the cumulative sum of the amplitude in volts per minute, as a parameter of the total sympathetic nerve activity.

nonhabitual drinkers. A value of $P<0.05$ was considered statistically significant.

Results

Baseline Data

At baseline resting BP, heart rate and MSA did not differ between the study groups (Table). BP averaged 126±3/69±1 mm Hg; heart rate, 68±2 bpm; and MSA, 44.7±1.8 bursts/min and 13.5±1.6 V/min.

In spite of coffee abstinence of at least 16 hours' duration, caffeine was still detectable in habitual coffee drinkers (5.5±1.3 μmol/L), and that level was significantly higher than in nonhabitual drinkers (1.9±1.6 μmol/L, $P=0.04$).

Intravenous Administration of Caffeine

Intravenous administration of caffeine (Figure 1) significantly increased circulating caffeine levels (Figure 1F). The pattern of increase had both significant linear ($F_{1,9}=50.8$, $P<0.001$) and quadratic ($F_{1,9}=56.2$, $P<0.001$) components. This increase was accompanied by a marked increase in sympathetic nerve activity (Figure 1A). A significant time by condition interaction was also obtained for total sympathetic nerve activity ($F_{2,10}=5.5$, $P=0.04$). In fact, total sympathetic nerve activity (ACS) increased in the caffeine condition by 40.3±19% at 30 minutes and by 54.1±22.5% at 60 minutes, a significant linear trend ($F_{1,6}=17.8$, $P=0.006$). In the placebo condition, there was no significant effect of time ($F_{2,16}<1$). For the remaining physiological parameters, the overall 3×2 ANOVA did not yield significant time × group interactions, although most of these tests were marginally significant. However, we view these results as reflecting our low level of statistical power to detect these ordinal interactions. Thus, we also tested the effect of time and its trend components separately for the caffeine and placebo conditions. With the exception of diastolic BP ($F_{2,16}<1$) we found a significant effect of time in the caffeine condition for burst count per minutes ($F_{2,12}=4.2$, $P=0.041$), systolic BP ($F_{2,18}=8.7$, $P=0.002$), and heart rate ($F_{2,16}=5.9$, $P=0.012$). All of these changes reflect a linear increase or decrease, with the exception of heart rate, where we also obtain a significant

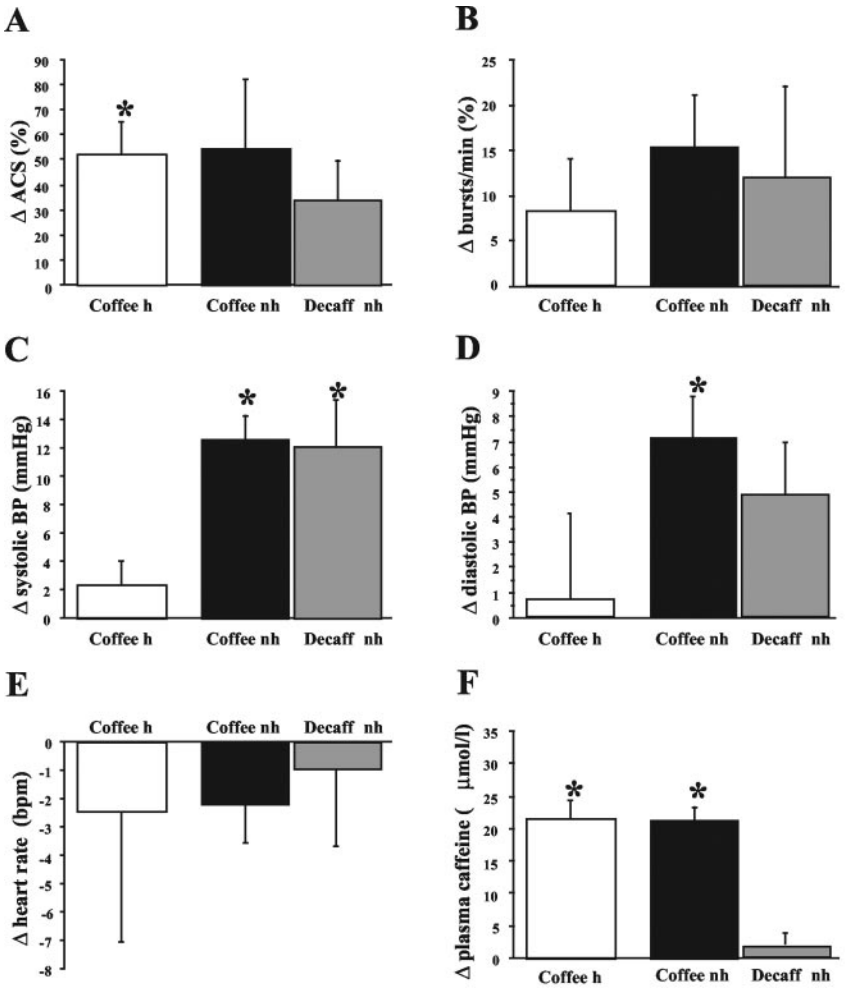

Figure 2. Bar graph indicating the effect of coffee drinking in habitual (white bars) and nonhabitual (black bars) coffee drinkers, as well as the effect of decaffeinated coffee in nonhabitual drinkers (gray bars), achieved 60 minutes after consumption. Changes in the sympathetic nerve activity (A, B) are expressed as percent of the baseline value. ACS indicates the cumulative sum of the amplitude in volts per minute, as a parameter of the total activity. Hemodynamic changes, expressed as systolic (C), diastolic BP (D) and heart rate (E), are given as absolute values. Plasma caffeine concentrations at 60 minutes are also indicated (F). Asterisks indicate significant changes compared with the baseline value for that condition. Δ indicates change.

quadratic trend ($F_{1,8}$=8.5, P=0.02). This quadratic trend is consistent with the immediate effect of caffeine on heart rate. There were no significant changes in the physiological parameters for the placebo condition.

The increase in burst count averaged 5.5±3% and 9.4±4% at 30 and 60 minutes. Systolic BP increased by 3±1.6 mm Hg and 6.4±1.7 mm Hg after 30 and 60 minutes, respectively Figure 1B), and heart rate significantly decreased (by −7.1±2 bpm at 30 minutes and −4.6±2 bpm at 60 minutes) after intravenous administration of caffeine.

Furthermore, no difference in the course of BP, heart rate, or MSA was seen between habitual and nonhabitual coffee drinkers after receiving the same intravenous dose of caffeine.

Coffee Drinking

Sixty minutes after drinking a triple espresso, plasma caffeine concentrations reached the peak (23.6±2.3 μmol/L) and were comparable to those achieved 45 minutes after intravenous caffeine (27.0±1.8). Importantly, habitual and nonhabitual coffee drinkers showed identical increases in plasma caffeine concentration (Figure 2F).

We first analyzed the overall effect of coffee drinking without regard to the subjects' status as habitual or nonhabitual coffee drinkers. Sympathetic nerve activity showed a sustained increase after coffee drinking. Total activity increased by 29.3±9.6% and 53.2±14.1% at 30 and 60 minutes. The percent increase in bursts per minute was 7.2±4% and 11.8±4%, respectively. The magnitude of changes in MSA seen 60 minutes after coffee drinking was comparable to that after intravenous administration of caffeine.

A triple espresso increased—at 30 and 60 minutes, respectively—systolic BP by 5±1.5 mm Hg and 7.5±2 mm Hg and diastolic BP by 6±1 mm Hg and 4±2 mm Hg. Accordingly, heart rate decreased by 4±1.5 bpm at 30 minutes and 2±2 bpm at 60 minutes.

Effects of Coffee Drinking According to Habitual Coffee Consumption

In nonhabitual coffee drinkers, systolic BP increased markedly after coffee consumption (12.6±1.6 mm Hg at 60 minutes, t_4=7.8, P=0.001, Figure 2C). In contrast, in habitual coffee drinkers, no significant change was observed (2.3±1.6 mm Hg at 60 minutes, t_4=1.4, P=0.227).

Elevation of diastolic BP was also more pronounced in nonhabitual drinkers (Figure 2D). At 60 minutes, diastolic BP was increased by 7.1±1.6 mm Hg (t_4=4.4, P=0.012), and for habitual drinkers, the change was not significant (0.7±3.4 mm Hg, t_4<1).

Even though there was a significant and linear time interaction for coffee in both the habitual and the nonhabitual group, we found a significant increase compared with baseline for the habitual coffee drinkers ($t_3=3.2$, $P=0.025$) but not for nonhabitual coffee drinkers ($t_3=1.9$, $P=0.147$). For heart rate (Figure 2E) or bursts per minute (Figure 2B), there were no significant changes for either habitual or nonhabitual coffee drinkers.

Decaffeinated Coffee

In nonhabitual coffee drinkers, decaffeinated coffee did not increase plasma caffeine levels ($t_3=2.54$, $P=0.084$, Figure 2F). More interestingly, despite the absence of caffeine, systolic BP increased by 5.5±2.5 mm Hg at 30 minutes and by 12±3 mm Hg at 60 minutes ($t_3=3.8$, $P=0.033$, Figure 2C). Total sympathetic activity showed only a marginally significant increase at 60 minutes (22.1±12.3%, $t_3=2.1$, $P=0.128$, Figure 2A) compared with baseline. However, when we considered the complete trend across time by adding the data from 30 minutes, we found an overall effect for time on total sympathetic activity ($f_{2,6}=6.8$, $P=0.029$), which was primarily a significant linear trend ($f_{1,3}=21.2$, $P=0.019$). Diastolic BP (Figure 2D), heart rate, (Figure 2E) and number of bursts per minute (Figure 2B) did not show any changes after decaffeinated coffee.

Discussion

Our data suggest that coffee and caffeine similarly increase MSA and BP in nonhabitual coffee drinkers, whereas habitual coffee drinkers show no BP response in spite of MSA activation. Moreover, decaffeinated coffee and caffeine resulted in a similar time by condition interaction for total sympathetic nerve activity, suggesting that substances other than caffeine may be responsible for the stimulating effect of coffee on the cardiovascular system. The fact that, in nonhabitual coffee drinkers, coffee and decaffeinated coffee similarly increased MSA and BP is intriguing and supports the hypothesis that substances other than caffeine are responsible for the cardiovascular effect of drinking coffee.

The present study demonstrates for the first time that caffeine activates the SNS, increases systolic and diastolic BP, and decreases heart rate, although coffee drinking caused an increase in SNS activity with concomitant elevation of BP in nonhabitual coffee drinkers only. Furthermore and surprisingly, nonhabitual coffee drinkers also exhibited similar cardiovascular responses after decaffeinated coffee.

Prospective and epidemiological studies yielded controversial results on the cardiovascular effects of coffee drinking. In fact, coffee drinking has been linked to both elevated[6] and reduced[7] BP and even to no effect on BP.[8] The inconsistencies in the reported studies can partially be attributed to methodological defects and failure to control confounding variables, including baseline BP, smoking habits, sex differences, dietary and alcohol intake, stress, and obesity, as well as inaccurate determination of daily coffee and caffeine intake.[17,18] It is likely that different distribution of coffee habitus within these studies may, in accordance with our observations, account for some of the inconsistencies of the studies analyzing the hypertensive potential of coffee. In this context, studies showing acute increase in BP were conducted in nonhabitual drinkers or in habitual drinkers after a prolonged abstinence only.

In particular, the differential acute effects of caffeine and coffee on SNS have previously not been assessed in humans in vivo. The present study is the first that demonstrates an activation of the SNS by caffeine and coffee as well as decaffeinated coffee. The pressor effect of caffeine and coffee seen in nonhabitual coffee drinkers must be related to a central or possibly peripheral SNS activation. The fact that BP increased while heart rate decreased or remained unchanged suggests a differential stimulation of peripheral and cardiac sympathetic nerve activity by caffeine and coffee. Indeed, it is likely that the increase in BP induced a baroreceptor-mediated inhibition of cardiac sympathetic activity because it is seen after infusion of a vasopressor substance.[19,20] Pressor effect of drinking water has been described[21] in subjects who were encouraged to drink a large volume (≈500 mL) as quickly as possible and was linked (even though not directly measured) to activation of the SNS. This effect may be in part due to bladder distention, known to activate SNS.[15] Considering the small volume of espresso drunk in our study (≈30 mL), this is less likely to happen.

So far, the cardiovascular stimulatory effects of coffee have been linked to sympathetic nerve activation by caffeine. Indeed, also in our study, intravenously applied caffeine did induce this expected response. However, we here provide evidence that in nonhabitual coffee drinkers, the cardiovascular activation by coffee is independent of caffeine content. In fact, decaffeinated coffee led to an increase in MSA and BP similar to that caused by caffeine-containing espresso, suggesting that substance(s) other than caffeine mediate sympathetic activation and the BP increase after coffee drinking. This interpretation is supported by other findings: The ingestion of a triple espresso did not cause any increase in BP in habitual coffee drinkers, probably because of induced tolerance. However, the differences in the BP changes between habitual and nonhabitual coffee drinkers were not related to a loss in sympathetic nerve activation by caffeine. To the contrary, intravenous caffeine evoked similar changes in sympathetic activity in both groups. Thus, tolerance to coffee also does not appear to be related to caffeine. A placebo effect in nonhabitual coffee drinkers cannot be excluded with certainty; however, the pattern changes over time, with a slow, progressive increase in BP and MSA, in line with the increase in circulating caffeine levels, which suggests a true pharmacological effect.

According to our results, the impact of habitual versus nonhabitual coffee drinking is so important that appropriate stratification of patients seems essential in analyzing any data in this field. In fact, most of the studies on the acute effect of caffeine or coffee reporting a pressor effect were performed in nonhabitual coffee drinkers[14] or after a prolonged abstinence.[22] The acute effect of coffee drinking in habitual coffee drinkers has never been documented, whereas epidemiological studies are mostly based on habitual coffee drinkers. Recently published epidemiological studies failed to demonstrate a clear association between increasing levels of coffee

consumption and risk of cardiovascular morbidity or mortality,[3] and even a beneficial effect has been postulated.[5]

It is quite possible that the potential adverse effects previously adjudicated to coffee could be significantly less apparent when consumed regularly. Indeed, on the basis of our results—and epidemiological studies[8]—it is likely that in normotensive individuals without a genetic background for hypertension, coffee drinking cannot be considered a risk factor for hypertension. Whether offspring of hypertensive parents react differently to coffee or caffeine—as they do to mental stress[12]—remains to be investigated. Certainly, in habitual coffee drinkers, coffee restriction does not seem to be medically necessary. Identification of the ingredient(s) of coffee other than caffeine responsible for cardiovascular activation could lead to new forms of coffee truly lacking undesirable stimulants.

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