

# Blood Pressure Response to Caffeine Shows Incomplete Tolerance After Short-Term Regular Consumption

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**Abstract**—Caffeine acutely raises blood pressure (BP). The clinical significance of this effect depends on whether BP responses persist in persons who consume caffeine on a daily basis. Accordingly, the ability of caffeine to raise BP after 5 days of regular daily intake was tested in a randomized controlled trial. Individual differences in tolerance formation were then examined. Men (n=49) and women (n=48) completed a double-blind, crossover trial conducted over 4 weeks. During each week, subjects abstained for 5 days from dietary caffeine and instead used capsules totaling 0 mg, 300 mg, and 600 mg of caffeine per day in 3 divided doses. On day 6, in the laboratory, they used capsules with either 0 mg or 250 mg of caffeine at 9:00 AM and 1:00 PM. Systolic/diastolic BP increases as a result of 250 mg of caffeine remained significant ( $P < 0.006/0.001$ ) at all levels of previous daily consumption. Individual difference comparisons found that although half the subjects had complete loss of systolic and diastolic BP responses to the challenge doses, the other half showed no loss in BP response, even after using 600 mg of caffeine per day for the previous 5 days ( $F > 7.90$ ,  $P < 0.001$ ). The sexes did not differ in degree of tolerance formation. Daily caffeine consumption failed to eliminate the BP response to repeated challenge doses of caffeine in half of the healthy adults who were tested. Caffeine may therefore cause persistent BP effects in persons who are regular consumers, even when daily intake is at moderately high levels. (*Hypertension*. 2004;43:760-765.)

**Key Words:** caffeine ■ blood pressure ■ men ■ women ■ diet

Caffeine is considered to be the world's most widely consumed pharmacological substance. More than 90% of United States adults report consuming caffeine on a daily basis.<sup>1</sup> The reported intake of caffeine averages 4 mg/kg per day for each adult consumer,<sup>2</sup> an amount equivalent to 2 to 4 cups of brewed coffee. Caffeine enters all tissue compartments,<sup>3</sup> and through its actions at the adenosine receptor,<sup>4</sup> it has widespread effects on the central nervous system and all peripheral tissues. Caffeine's near-universal consumption and its pervasive physiological effects have led to questions about its potential influence on health, particularly cardiovascular disease.

Caffeine's best-known cardiovascular effect is increasing blood pressure (BP),<sup>5,6</sup> and caffeine is found to be the constituent of coffee that causes BP to increase.<sup>6-8</sup> Studies in men show that caffeine increases BP by raising peripheral vascular resistance,<sup>9</sup> an effect consistent with its ability to block vascular adenosine receptors.<sup>10,11</sup> Vascular resistance is also higher in hypertension, and acute caffeine doses produce larger and more long-lasting BP responses in healthy persons at high-risk for future hypertension.<sup>12,13</sup> However, epidemiological studies have not found a consistent relationship between dietary caffeine intake and incidence of hypertension.<sup>14</sup> A reason that is advanced for the lack of such

relationship is that regular caffeine consumption is thought to lead to complete tolerance to its BP effects.<sup>15-17</sup> If true, this would mitigate concerns related to caffeine consumption. However, other work indicates that daily caffeine intake may produce only a partial pharmacological tolerance, with a persistent BP response occurring to repeated daily dosing.<sup>18,19</sup> The relatively small number of controlled clinical studies of caffeine tolerance suggests that formation of tolerance to caffeine's pressor effect is incompletely investigated.

Accordingly, the present study tested whether regular caffeine intake diminishes or abolishes its acute effects on BP in the laboratory. Daily maintenance doses were chosen to mimic a range of consumption commonly found in the US diet, from none (0 mg/d) to moderate (300 mg/d) to high (600 mg/d) intake. Testing then determined the effect of these background intake levels on the BP response to repeated fixed challenge doses (2×250 mg) on a day of laboratory testing. We also examined the range of person-to-person variation in tolerance formation resulting from daily intake of caffeine.

## Methods

### Subjects

The study population consisted of 97 healthy adults recruited through advertisement from the general populations of Buffalo, NY and

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**TABLE 1. Subject Characteristics by Tolerance Group**

	Tolerance Groups		
	Total Population (n=97)	High (n=48)	Low (n=49)
Sex (M/F)	49/48	21/27	28/21
Age, y	28 (0.6)	28 (0.9)	29 (0.8)
Weight, kg	72 (1.2)	72 (1.6)	72 (1.9)
Height, cm	174 (1.0)	172 (1.5)	176 (1.4)
Body fat, %	20 (0.7)	20 (1.0)	19 (0.9)
Body mass index, kg/m <sup>2</sup>	23.9 (0.3)	24.4 (0.4)	23.4 (0.4)
Parental hypertension, %	13	15	11
Screening blood pressure, mm Hg			
Systolic	112 (1.0)	111 (1.3)	114 (1.4)
Diastolic	66 (0.6)	65 (0.9)	67 (0.9)
Caffeine intake, mg/d	454 (48)	400 (66)	506 (68)
Morning saliva caffeine levels each week, $\mu$ mol/L			
0 mg/d	0.18 (0.1)	0.35 (0.2)	0.03 (0.03)
0 mg/d	0.36 (0.2)	0.67 (0.3)	0.06 (0.04)
300 mg/d	3.56 (0.5)	4.21 (0.09)	2.96 (0.06)
600 mg/d	12.58 (1.7)	15.18 (3.0)	10.14 (1.6)
Morning baseline BP levels in each study week, mm Hg			
Systolic BP			
0 mg/d	113 (0.93)	112 (1.13)	114 (1.47)
0 mg/d	113 (0.92)	112 (1.12)	115 (1.46)
300 mg/d	113 (0.92)	112 (1.23)	114 (1.37)
600 mg/d	113 (0.92)	111 (1.02)	114 (1.40)
Diastolic BP			
0 mg/d	67 (0.70)	66 (0.98)	68 (0.99)
0 mg/d	67 (0.76)	66 (1.12)	68 (1.04)
300 mg/d	66 (0.70)	66 (1.07)	67 (0.91)
600 mg/d	67 (0.74)	67 (1.09)	67 (1.00)

Mean  $\pm$  SEM shown in parentheses.

Caffeine intake reflects usual consumption from all sources based on structured interview. Screening BP is average of 3 readings over 5 minutes after 5 minutes seated. High- and low-tolerance groups were not different in numbers of males and females ( $\chi^2=1.7, P=0.2$ ), percents with a positive parental history of hypertension ( $\chi^2=0.9, P=0.3$ ), or in any other listed variable ( $t<1.85, P>0.08$ ). Caffeine levels from saliva specimens collected at 8:00 am on each test day after 5 days on the indicated daily maintenance dose of caffeine. ANOVA on tolerance group  $\times$  week for C300 and C600 weeks indicated groups did not differ in residual caffeine levels,  $F(1,93)=2.69, P=0.104$ . Morning BPs are resting values before caffeine or placebo in the laboratory. ANOVA for tolerance group  $\times$  week for all 4 weeks showed no BP difference for tolerance groups,  $F(1,95)<1.1, P>0.31$ , or for tolerance groups  $\times$  week,  $F(3,76)<2.0, P>0.13$  for either BP.

Oklahoma City, Okla, as described in Table 1 and randomized as in Figure 1. All volunteers were non-obese and in good health by self-report and routine physical examination. They had normotensive BPs (BP <135/85 mm Hg) at screening, regularly consumed 50 to 700 mg/d of caffeine by structured report, were nonsmokers, and used no medications having cardiovascular or metabolic effects. Parental history of hypertension was obtained by structured interview from 84 of the subjects and confirmed by parent contacts. Women were free from oral contraceptives, not lactating, and were not pregnant, as determined by urine pregnancy test (One Step Pregnancy Test; Inverness Medical, Beachwood Park, North Inverness, Scotland). Half of the volunteers were tested in Buffalo, and half were tested in Oklahoma City. All participants signed a consent form approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and the Veterans Affairs Medical Center in Oklahoma City and SUNY Buffalo, Buffalo, NY, and were paid for participating.

**Study Design, Caffeine Dosing, and Compliance**

The study was designed, overseen, and implemented by a committee including the investigators and study coordinators (W.R.L., M.F.W., T.L.W., B.H.S., B.S.M.). The design was a randomized, placebo-controlled, double-blind, crossover trial of caffeine effects on cardiovascular function that lasted 4 weeks. Each study week included 5 days of home self-administration of placebo (P=0 mg/d) or caffeine (C=300 mg/d or 600 mg/d), followed by 1 laboratory test day (3  $\times$  250 mg=750 mg) and 1 crossover day (C=100 mg, 0 mg, and 0 mg to buffer sudden changes in intake between study weeks). Weekly maintenance and laboratory dose combinations are shown in Table 2.

Home maintenance doses were supplied in bottles of identical gelatin capsules (College of Pharmacy, University of Oklahoma, Oklahoma City) containing either lactose or lactose mixed with 100 mg or 200 mg of USP caffeine (Gallipot, St. Paul, Minn). Subjects

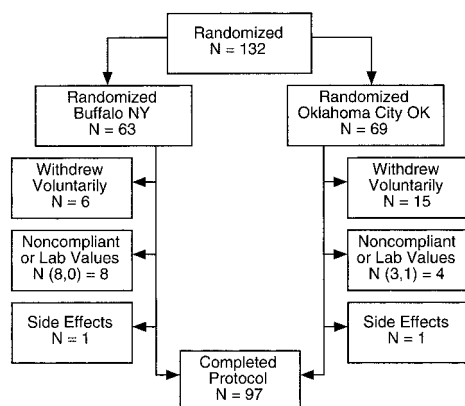


Figure 1. Subject randomization.

were instructed to use one capsule at 8:00 AM, 1:00 PM, and 6:00 PM each day. Test day challenge doses were supplied in capsules containing either lactose or lactose mixed with 250 mg of caffeine administered at 9:00 AM, 1:00 PM, and 6:00 PM.

Compliance was assessed by capsule counts in bottles brought in on laboratory days, by caffeine assay of saliva specimens collected at home each day at 7:00 PM<sup>20</sup> (Salivette; Sarstedt, Germany), and from saliva specimens collected each morning on entering the laboratory. Subjects found to be noncompliant by any of these criteria were eliminated from the study and replaced.

### Laboratory Protocol

The laboratory protocol included saliva specimen, breakfast, instrumentation (60 minutes), a rest period (20 minutes), predrug BP baseline (10 minutes), P or C capsule, postdrug response (60 minutes), mental or exercise stress testing (30 minutes), recovery (1 hour), lunch break (1.5 hours), predrug baseline (30 minutes), capsule, postdrug response (1 hour), and ambulatory BP monitoring (18 hours). This report covers the acute BP responses during the 1-hour periods after the 2×250 mg challenge doses administered at 9:00 AM and 1:00 PM.

BP was measured during screenings and test sessions using a Dinamap 845 oscillometric vital signs monitor (Critikon, Tallahassee, Fla). During the morning and afternoon caffeine challenges, pressures were measured every 3 minutes during the 10 minutes before using a capsule and during minutes 41 to 60 in the next hour to represent the acute response. The data were then averaged to represent the change from baseline during the 41 to 60 minutes after the challenge combined with the morning and afternoon challenges.

Caffeine concentrations in saliva were measured by high-performance liquid chromatography (Waters Corp, Milford, Mass) after precipitation of proteins using a methanol and water mobile phase and ultraviolet detection.<sup>21</sup>

The purpose of the analysis presented here was to evaluate whether daily caffeine consumption would reduce or eliminate acute BP responses after 2 challenge doses in the laboratory after a 5-day structured regimen of caffeine intake at 0 mg/d, 300 mg/d, or 600 mg/d. Results were analyzed by Student *t* test,  $\chi^2$  test, and ANOVA using SAS (SAS System for Windows, ver. 8.2; SAS Institute, Cary,

TABLE 2. Placebo and Caffeine Doses During Study Weeks

Study Week	Maintenance Days	Protocol Days
P-P	0 mg (3×0 mg)	0 mg (3×0 mg)
P-C	0 mg (3×0 mg)	750 mg (3×250 mg)
C300-C	300 mg (3×100 mg)	750 mg (3×250 mg)
C600-C	600 mg (3×200 mg)	750 mg (3×250 mg)

P indicates placebo; C, caffeine; C300-C, 300 mg/d maintenance; C600-C, 600 mg/d maintenance.

Week order was randomized across subjects.

NC) and SPSS (SPSS for Windows, rel. 10.1.0; SPSS, Inc, Chicago, Ill). Potential violation of the sphericity assumption in univariate repeated measures ANOVA was avoided using a multivariate solution for repeated measures factors. For pairwise comparisons, family-wise error rate was controlled across tests at the 0.05 level using Holm sequential Bonferroni procedure. In preliminary analyses, men and women did not differ in their BP responses to challenge doses; therefore, data are presented only for the combined sample.

## Results

### Partial Tolerance Effects

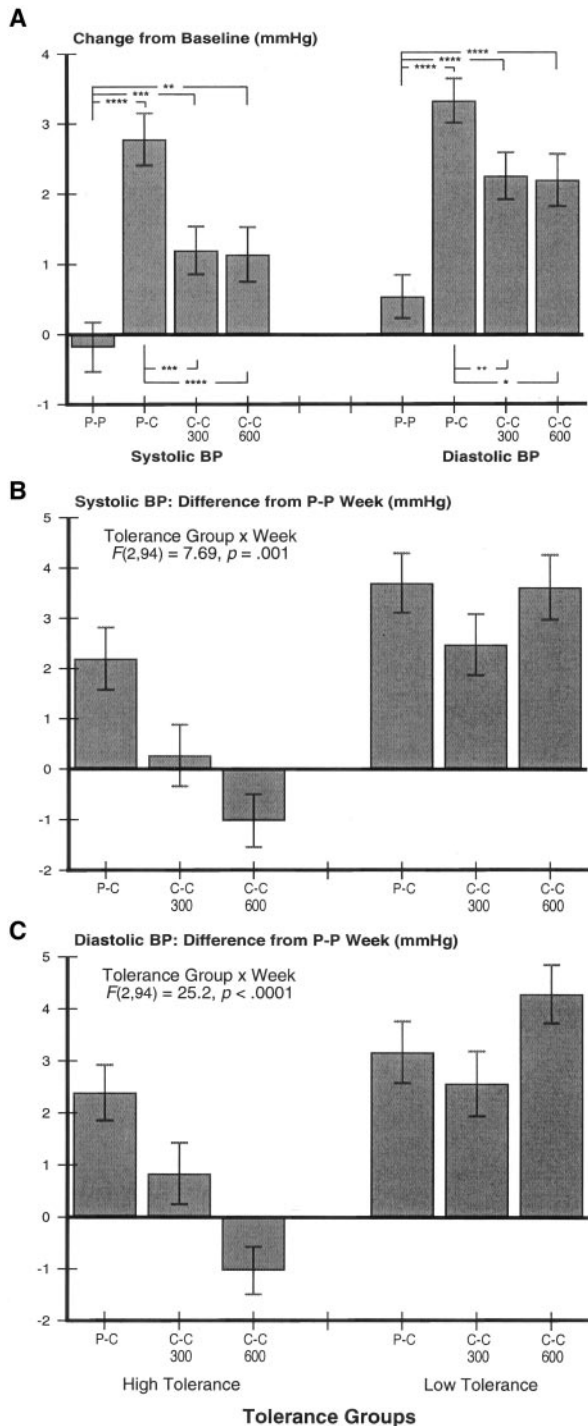
The largest BP response to caffeine was expected to occur during the P-C week in response to the 2×250-mg challenge doses administered after 5 days of P maintenance (0 mg/d). If tolerance developed with regular intake, then the BP response to C challenge in the laboratory was expected to diminish as daily caffeine intake increased to C300 and C600 maintenance levels. Figure 2A shows the BP changes in the total study population after P or C challenge after each of the 5-day maintenance periods during each of the 4 study weeks. Systolic and diastolic BP responses both varied significantly across weeks, [Wilks  $\lambda=0.67$ ,  $F(3, 94)=15.41$ ,  $P<0.0001$  for systolic BP; Wilks  $\lambda=0.66$ ,  $F(3, 94)=15.96$ ,  $P<0.0001$  for diastolic BP]. As expected, BP changes from predrug to postdrug were minimal during the P-P week, which constituted a resting control condition. The largest changes occurred during the P-C week when no tolerance was expected and in which successive 250-mg doses were consumed in the laboratory after 5 days of 0 mg/d intake.

Pairwise comparisons were conducted to address whether caffeine challenge still produced significant responses during C300 and C600 maintenance weeks. In Figure 2A, the top set of comparisons shows that relative to the P-P control week, the systolic/diastolic BP responses were significantly larger during the P-C ( $P<0.001/0.001$ ), C300 ( $P<0.002/0.001$ ), and C600 ( $P<0.006/0.001$ ) weeks. The results indicate that the BP response to caffeine was preserved even after subjects consumed 300 mg/d and 600 mg/d for the 5 preceding days.

Additional pairwise comparisons were performed to determine the degree of loss of BP response accompanying the partial tolerance that developed during the C300 and C600 maintenance weeks, as compared with the P-C week. In Figure 2A, the bottom comparisons indicate a reduction in the BP response to caffeine challenge, indicating that the systolic/diastolic BP response was smaller during the C300 ( $P<0.002/0.006$ ) and C600 ( $P<0.001/0.008$ ) weeks than during the P-C week, in keeping with a partial tolerance effect.

### Individual Differences in Tolerance

The partial, but not complete, tolerance that developed after regular caffeine intake in the full sample suggested that tolerance formation differed from person to person. Accordingly, we formed high- and low-tolerance groups by a median split during the C600 week, when tolerance would be expected to be at its greatest. The averaged diastolic BP responses to the 9:00 AM and 1:00 PM doses during the C600 week, relative to the same ones during the P-P week, had a median elevation of 2.39 mm Hg. High-tolerance persons would be expected to show sharp reductions in BP response



**Figure 2.** A, Mean ( $\pm$ SEM) BP change at 40 to 60 minutes after placebo (P) or caffeine (C) challenge at 9:00 AM and again at 1:00 PM in the laboratory on a test day after 5 days of 0 mg/d caffeine in the diet (P) compared with 300 mg/d (C300) or 600 mg/d (C600) caffeine in the diet. Significance values are based on Bonferroni corrected multivariate contrasts. Systolic (B) and diastolic (C) BP responses to caffeine in subgroups that showed high- vs low-tolerance to caffeine challenge in the laboratory as function of 5 days of consuming 0 mg/d, 300 mg/d, or 600 mg/d of caffeine intake at home. Tolerance group  $\times$  week ANOVAs on systolic/diastolic BP responses had significant interactions ( $P < 0.001/0.0001$ ), in which the high-tolerance group showed a steady decrease in BP responses to caffeine challenge vs the low-tolerance group that showed no reduction in BP response to caffeine, regardless of level of intake. \* $P < 0.01$ , \*\* $P < 0.007$ , \*\*\* $P < 0.003$ , \*\*\*\* $P < 0.001$ .

to caffeine challenge from P-C to C300 and C600 weeks relative to the change during the P-P week. Low-tolerance persons would be expected to show correspondingly smaller reductions in BP response. We then addressed whether these groups would differ in their pattern of tolerance across the P-C, C300, and C600 weeks.

Figure 2B and 2C shows systolic and diastolic BP responses for the resulting high- and low-tolerance groups. ANOVAs revealed significant tolerance group  $\times$  week interactions for systolic [ $F(2, 94) = 7.68$ ;  $P = 0.001$ ] and diastolic [ $F(2, 94) = 25.2$ ;  $P < 0.0001$ ] BP responses to caffeine challenge. Analyses for linear trends showed a significant trend across weeks for the high-tolerance group in systolic and diastolic BP ( $P < 0.001$ ). In contrast, the low-tolerance group had no significant trend across weeks for systolic BP responses ( $P > 0.05$ ) and small linear ( $P = 0.038$ ) and quadratic trends ( $P = 0.02$ ) in diastolic BP responses. These indicate that the high-tolerance group had a decreasing BP response to caffeine challenge with higher levels of daily intake. The BP response to caffeine challenge did not diminish with higher-maintenance doses in the low-tolerance group. These results provide evidence that for some persons, the acute BP responses to caffeine are not substantially diminished by regular intake of 300 mg or 600 mg of caffeine per day.

### Variables Related to Tolerance Formation

We examined variables that might potentially distinguish high- from low-tolerance groups. Table 1, columns 2 and 3, compare tolerance groups on anthropometric and other variables. Males and females were similarly represented in both tolerance groups ( $\chi^2 = 1.85$ ,  $P > 0.05$ ), and the men and women in each tolerance group had similar BP responses ( $P = 0.883$ ). Parental history of hypertension was also similar in the 2 tolerance groups ( $\chi^2 = 1.29$ ,  $P > 0.50$ ). The tolerance groups did not differ by age, weight, height, body mass index, percent body fat, weekly caffeine consumption, or BP at screening (all  $t < 1.85$ ,  $P > 0.08$ ).

We next examined data associated with caffeine metabolism. Although this study did not assess pharmacokinetics, caffeine measurements were made in saliva specimens collected on arrival in the laboratory during each week's test day, as shown in Table 1. During the C600 week, the level of daily intake and the dosing schedules were such that subjects showed a residual caffeine level the next morning in the laboratory. If the high- and low-tolerance groups differed in their rates of caffeine elimination, the morning levels during the C600 week would be expected to show higher residual values in the slower metabolizing group. Low- and high-tolerance groups did not differ in morning saliva caffeine concentrations during any week ( $P > 0.05$ ), indicating that by this measure they were not eliminating caffeine from their systems at different rates. In line with this reasoning, the predrug resting BP values for the tolerance groups were not significantly different across weeks or between groups, also suggesting that residual caffeine values and associated BP changes did not play a role in the tolerance differences.

### Discussion

This study examined whether short-term daily caffeine intake at low or high doses caused tolerance to develop to its BP



effects. The low daily dose was similar to average US adult consumption equivalent to  $\approx 3$  cups of coffee per day. The high dose represented  $\approx 6$  cups of coffee per day, matching high levels of dietary intake. Daily caffeine consumption for 5 days reduced, but did not abolish, the BP response to 2 successive 250-mg challenge doses in the laboratory. This result may have implications for how we view the effects of caffeine intake in the population. The subjects were all regular consumers of caffeine who were placed in a 5-day crossover trial at 3 maintenance doses (0, 300, and 600 mg/d). These regular consumers still had BP increases to caffeine used the day after an overnight fast from caffeine. Notably, the degree of tolerance varied considerably from person to person. Half the subjects were completely tolerant to caffeine after consuming 300 and 600 mg/d for 5 days. The other half had little or no reduction in BP response to caffeine, regardless of their level of daily consumption. If these findings are reasonable to extrapolate to the population, then they would indicate that for half of all caffeine consumers, the BP response remains intact with each morning's intake of caffeine, and that this effect persists for a period of hours during the day. These results raise several points concerning caffeine's possible effects on long-term BP regulation.

Caffeine's ability to raise BP is well established.<sup>5,6</sup> This pressor effect is greater in persons at high-risk for hypertension<sup>13</sup> and is prolonged in those with diagnosed hypertension.<sup>22</sup> Although the BP effects of caffeine are minor in persons at lowest risk for the disorder (negative parental history and BP <120/80),<sup>23</sup> its effects are greater in those with positive parental histories and prehypertensive pressures (BP=120/80 to 139/89 mm Hg) as designated by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).<sup>24</sup> The goal of early hypertension treatment is to modify diet and lifestyle in this prehypertensive stage. Dietary recommendations in JNC VI<sup>23</sup> cited tolerance to caffeine as evidence that its use has no bearing on hypertension prevention or treatment. JNC 7 makes no comment.<sup>24</sup> The question of caffeine tolerance and its completeness in the population or in given individuals is therefore a central issue in considering its long-term effects.

Several sources of evidence suggest incomplete tolerance to the BP effects of caffeine in habitual consumers: (1) Acute dosing in regular users shows consistent BP responses to caffeine after overnight abstinence,<sup>9,25-27</sup> even with repeated dosing.<sup>28-30</sup> Higher BP was seen during orthostatic challenge when volunteers consumed 6 cups of coffee per day for 8 weeks versus none.<sup>31</sup> Both findings are consistent with a continued effect of acute caffeine in regular users. (2) Residual plasma caffeine levels affect the results of adenosine perfusion scans. Patients having plasma caffeine levels ranging from 0.1 to 8.8 mg/L (consistent with drinking up to 5 cups of coffee before entering the clinic) showed reduced responses to adenosine infusion and fewer anginal symptoms with higher levels of intake,<sup>32</sup> again consistent with persistent caffeine effects in regular users. (3) A meta-analysis of controlled trials concluded that the effects of caffeine on BP persist with regular use.<sup>33</sup> Casual BPs measured in population screenings are higher in persons reporting regular caffeine use than in nonusers<sup>34</sup> and/or in those with higher current

blood levels of caffeine.<sup>35</sup> (4) Caffeine withdrawal can lower BP acutely<sup>18</sup> and over a period of weeks,<sup>36,37</sup> suggesting sustained pressure elevations, even in regular users. (5) The former evidence is indirect, perhaps circumstantial; however, 2 studies examined tolerance more directly. Denaro<sup>17,38</sup> compared placebo, low (4.2 mg/kg), or high (12 mg/kg) doses of caffeine administered for 5 days in a randomized crossover design. Although some subjects showed complete tolerance, others had a persistent BP response, even at the high dose. In a crossover design, James<sup>18</sup> found that laboratory and ambulatory BPs were still elevated by acute caffeine doses (200 mg $\times$ 3 daily) after 1 week of daily intake.

In the present study, the high- and low-tolerance groups did not appear to differ in caffeine metabolism. The groups had similar residual morning caffeine concentrations after overnight abstinence, and they had comparable caffeine levels in saliva after dosing in the laboratory. Other factors, such as adenosine receptor density or dynamics may account for the effects we observed. Although these evaluations were beyond the scope of the present study, pharmacokinetic and pharmacodynamic modeling suggests that acute caffeine tolerance develops and diminishes quickly, as with overnight abstinence, and with substantial individual differences.<sup>38</sup> Future studies using a tolerance design similar to the present one should incorporate pharmacokinetic modeling and analyses of adenosine receptor function. Although the subjects were kept for only 5 days at each maintenance dose, they were all regular consumers of caffeine, suggesting that this short-term maintenance may generalize to longer periods of intake. Longer maintenance periods should be tested in future studies to establish the relevance of present results to longer periods of caffeine intake in the diet. In light of our earlier finding that caffeine has a stronger pressor effect on persons at high-risk for hypertension, the interaction of caffeine tolerance formation should be tested in groups selected to be at high-risk for hypertension based on family history and mildly elevated BP. No persons in the present study met both of these hypertension risk criteria.

### Considerations for Caffeine Use in Hypertension

Reported caffeine use has not been associated with the development or progression of hypertension in epidemiological studies; therefore, a role for caffeine in the development of hypertension is presently unproven. Habitual caffeine effects on long-term BP regulation may not appear evident with standard epidemiologic study designs for several reasons. Lack of attention to specific high-risk groups may fail to identify those for whom caffeine may contribute to disease. Caffeine intake reports may be unreliable or taken too infrequently. It may be difficult to obtain a representative caffeine-free control group when consumption is near universal in the population. Finally, potential individual differences in tolerance formation may attenuate effects among the population as a whole.

Although the BP increase seen with caffeine in the present study is not large, hypertension risk and the consequences of hypertension are graded continuously with each increment in BP. In large samples, given clinical outcomes can be ascribed to small elevations in BP.<sup>39</sup> An increase in BP of as little as 2 mm Hg can have a

disproportionate effect on cardiovascular disease outcomes in subpopulations at high-risk by other criteria.<sup>39,40</sup>

**Perspectives**

The present study found significant sustained BP responses to repeated acute dosing in half of the subjects. In view of greater BP responses in persons at risk for hypertension,<sup>12,13</sup> future epidemiologic studies may profitably focus on caffeine intake, with specific reference to subgroups stratified according to established hypertension risk factors. In addition, clinical trials of hypertension treatment could systematically place patients on caffeine restriction to examine progression of BP over time and its effects on need for medication adjustment.

Caffeine intake for 5 days appears to reduce, but not to abolish, the BP response to repeated acute doses administered in the laboratory. Although complete tolerance develops in some subjects with regular caffeine intake, others show no development of tolerance at usual dietary doses of caffeine consumption. This range of tolerance variation suggests strategies for focusing on specific subgroups in evaluating the long-term effects of caffeine with specific reference to BP regulation in persons at high-risk for hypertension.

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