Hypertension Risk Status and Effect of Caffeine on Blood Pressure

Terry R. Hartley, Bong Hee Sung, Gwendolyn A. Pincomb, Thomas L. Whitsett, Michael F. Wilson, William R. Lovallo

Abstract—We compared the acute effects of caffeine on arterial blood pressure (BP) in 5 hypertension risk groups composed of a total of 182 men. We identified 73 men with optimal BP, 28 with normal BP, 36 with high-normal BP, and 27 with stage 1 hypertension on the basis of resting BP; in addition, we included 18 men with diagnosed hypertension from a hypertension clinic. During caffeine testing, BP was measured after 20 minutes of rest and again at 45 to 60 minutes after the oral administration of caffeine (3.3 mg/kg or a fixed dose of 250 mg for an average dose of 260 mg). Caffeine raised both systolic and diastolic BP (SBP and DBP, respectively; $P<0.0001$ for both) in all groups. However, an ANCOVA revealed that the strongest response to caffeine was observed among diagnosed men, followed by the stage 1 and high-normal groups and then by the normal and optimal groups (SBP $F_{4,175}=5.06$, $P<0.0001$; DBP $F_{4,175}=3.02$, $P<0.02$). Indeed, diagnosed hypertensive men had a pre-to-postdrug change in BP that was $>1.5$ times greater than the optimal group. The potential clinical relevance of caffeine-induced BP changes is seen in the BPs that reached the hypertensive range (SBP $\geq 140$ mm Hg or DBP $\geq 90$ mm Hg) after caffeine. During the predrug baseline, 78% of diagnosed hypertensive men and 4% of stage 1 men were hypertensive, whereas no others were hypertensive. After caffeine ingestion, 19% of the high-normal, 15% of the stage 1, and 89% of the diagnosed hypertensive groups fell into the hypertensive range. All subjects from the optimal and normal groups remained normotensive. We conclude that hypertension risk status should take priority in future research regarding pressor effects of dietary intake of caffeine. (Hypertension. 2000;36:137-141.)

Key Words: caffeine | diet | hypertension, detection and control | blood pressure

Caffeine is the most widely used pharmacologically active substance in the world, with a reported intake of 200 to 300 mg/d in 80% of adults in the United States. Caffeine is consumed in coffee, tea, soft drinks, and, more recently, caffeinated bottled water. The mass appeal of caffeine could have health implications because of its well-documented pressor effect. A recent meta-analysis of controlled clinical trials reported a positive relationship between cups of coffee consumed on a daily basis and elevated systolic blood pressure (SBP), independent of age.

Studies in our laboratory and others have reported that caffeine acutely elevates SBP and diastolic blood pressure (DBP) at rest and during mental and exercise stress. We have shown that this pressor effect is due to the elevation by caffeine of peripheral vascular resistance rather than enhancement of cardiac output. The ability of caffeine to increase vascular resistance raises the question of its effect in hypertension development. A recent ambulatory study of older men and women reported no difference between normotensive abstainers and coffee drinkers in 24-hour BP. However, in hypertensives, ambulatory BP increased in coffee drinkers and decreased in abstainers regardless of medication status.

One way to document the effects of caffeine in hypertension is to examine its pressor effects on persons at different levels of risk for the disease. In separate studies, we have documented greater effects of caffeine in high-risk normotensives, borderline hypertensives, and unmedicated mild hypertensives compared with normotensives with a negative family history and low-normal resting BP levels. However, these results were analyzed and reported separately, making it difficult to compare BP effects quantitatively across risk groups. Therefore, we have taken our collective database, which consists of 182 persons, and classified the subjects according to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) criteria into 5 separate risk groups varying from optimal to diagnosed hypertensive. With these groups, we present a comparison of BP responses to caffeine in the laboratory setting.

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Methods

Overview
Although the studies from which these data were drawn differed in some particulars, all had a common core of methods, including double-blind placebo crossover designs, consistent doses of caffeine (3.3 mg/kg, average 260 mg/person),\(^3\),\(^3.13\),\(^14\) or a fixed dose of 250 mg (W.R. Lovallo, B.H. Sung, T.R. Hartley, T. Thomas, B.S. McKey, T.L. Whitsett, M.F. Wilson, unpublished data, 1999). BPs were measured after 20 minutes of rest and again at 45 to 60 minutes after the oral administration of caffeine.

Subjects
Five hypertension risk groups were identified during preliminary screening sessions according to the following JNC VI\(^16\) criteria: (1) optimal, SBP <120 mm Hg and DBP <80 mm Hg; (2) normal, SBP 120 to 129 mm Hg or DBP 80 to 84 mm Hg; (3) high-normal, SBP 130 to 139 mm Hg or DBP 85 to 89 mm Hg; (4) stage 1, SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg; and (5) diagnosed hypertension, recruited from a hypertension clinic.

All subjects were men in otherwise good health on the basis of physical examination and medical history. Among diagnosed hypertensives, 11 men were taking ACE inhibitors (n = 7), \(\beta\)-blockers (n = 2), or hydrochlorothiazide (n = 2). All hypertensive medications were tapered accordingly before the BP screening. Seven men from the clinic were recently diagnosed but not yet medicated.

Protocol
In all experiments, subjects were directed to abstain from caffeine after supper on the evening before coming to the laboratory, which was a period of \(\geq 12\) hours. Because caffeine naïvété could be an issue, we examined any available self-reports of actual time of abstention. Reports were available for 33 in the optimal group, 18 in the normal group, 18 in the high-normal group, and 12 stage 1 men. The average time of abstention was 17.75 hours, and a 1-way ANOVA revealed no group differences \((F_{5,177} = 0.69, P < 0.56)\). Although self-reports were not available from 1 study,\(^13\) the subjects were daily caffeine users and their instructions were identical to those of the other studies, suggesting that the time of abstention was approximately the same. Moreover, the control subjects\(^13\) also had optimal or normal screening BPs and their BP responsiveness to the acute dose of caffeine was no different than that of other optimal or normal groups, suggesting that the duration of caffeine abstention (12 to 18 hours) was not different.

All procedures involved BP cuff placement followed by semisupine rest for 20 minutes, after which baseline BPs were obtained with a Dinamap Vital Signs Monitor (model 1896)\(^3\),\(^14\) (W.R. Lovallo, B.H. Sung, T.R. Hartley, T. Thomas, B.S. McKey, T.L. Whitsett, and M.F. Wilson, unpublished data, 1999) or a Paramed monitor.\(^13\) Baseline BPs were measured after 20 minutes of rest and again at 45 to 60 minutes after the oral administration of caffeine. The pre-to-post drug caffeine BP effects were examined with paired samples \(t\) tests for each group. Predrug baseline BPs were examined with MANOVA with hypertension status as between-subject factors and SBP and DBP as dependent variables. Because group predrug BPs differed significantly, the main analysis of between-subject effects was accomplished with ANCOVA with postbaseline BPs as dependent variables and baseline BPs as covariates. Finally, we used hierarchical multiple regression analyses with change scores (precaffeine and postcaffeine BPs) as dependent variables and risk group, BMI, and age as independent variables.

Caffeine Administration
In 3 of the studies,\(^3\),\(^13\),\(^14\) volunteers consumed unsweetened grapefruit juice mixed with 3.3 mg/kg caffeine (anhydrous, USP; Amend Drug Co) or they drank grapefruit juice alone (placebo). In the fourth study, volunteers took a capsule containing caffeine (250 mg plus lactose) or a placebo capsule (lactose) (W.R. Lovallo, B.H. Sung, T.R. Hartley, T. Thomas, B.S. McKey, T.L. Whitsett, and M.F. Wilson, unpublished data, 1999). The 3.3 mg/kg dose resulted in a mean dose of 260 mg/kg, closely comparable to the fixed 250 mg dose. Prior analyses have shown that small differences of this sort or minor differences in blood concentrations between volunteers did not materially affect the BP responses observed.\(^9\)

Statistical Analysis
Characteristics of the risk groups were compared with the use of 1-way ANOVAs on the following variables: age (years), height (inches), weight (lb), body mass index (BMI) \((\text{BMI} = \text{weight} \times 703/\text{height}^2)\), reported chronic caffeine intake (mg/d), screening BPs, and predrug baseline BPs. Note that predrug baseline BPs are lower overall than screening BPs. We attribute this in part to a difference in posture and in part as a function of resting time.

The pre-to-postdrug caffeine BP effects were examined with paired samples \(t\) tests for each group. Predrug baseline BPs were examined with MANOVA with hypertension status as between-subject factors and SBP and DBP as dependent variables. Because group predrug BPs differed significantly, the main analysis of between-subject effects was accomplished with ANCOVA with postbaseline BPs as dependent variables and baseline BPs as covariates. Finally, we used hierarchical multiple regression analyses with change scores (precaffeine and postcaffeine BPs) as dependent variables and risk group, BMI, and age as independent variables.

Results
Caffeine raised both SBP and DBP \((P < 0.0001)\) in all groups, and effect sizes were large \((d = 0.92)\), with the exception of pre-to-post SBP and DBP in the optimal group, which had medium effect sizes \((d = 0.72\) and 0.77), respectively (Figure 1). However, ANCOVA revealed that the largest BP response occurred in diagnosed hypertensive men, followed by stage I and high-normal groups and then by optimal and normal groups \((\text{SBP}, F_{4,175} = 5.06, P < 0.001; \text{DBP}, F_{4,175} = 3.02, P < 0.02)\). Indeed, diagnosed hypertensive men had SBP and DBP responses \(> 1.5\) times greater than the optimal group, indicating differential sensitivity to caffeine in those with hypertension.

Table 1 displays demographic characteristics of the risk groups. Groups were similar in height and reported caffeine intake. The diagnosed hypertensive men were older and heavier and had a correspondingly greater BMI. Screening DBPs were different among all groups ascending from the optimal group to the diagnosed hypertensive group. Screening SBPs followed a similar pattern except that the stage I and diagnosed hypertensive groups were the same. During testing, predrug baseline SBP and DBP values differed among the groups, with the exception of high-normal and stage I group men, for whom the values were statistically identical. Note that the predrug baseline BPs were lower overall than
the screening BPs. During screening, subjects rested in a seated position for 5 minutes before and during BP readings. During the study proper, all readings were taken after 20 minutes of rest while the subject was semisupine.

Because age and BMI may affect BP independent of any caffeine effects, group BP response to caffeine was tested after control for these factors with a multiple regression analysis. The best predictor of SBP responsivity was hypertension status \((r=0.24, P<0.001)\). Likewise, hypertension status was the best predictor of DBP responsivity \((r=0.23, P<0.002)\). Effect sizes for both measures were large \((d=0.95)\). Other single variables, including BMI and age, failed to produce a significant increment in the explained proportion of BP response beyond hypertension status alone.

The potential clinical relevance of the BP response to caffeine was examined in each group by tabulating BPs that reached the hypertensive range \((SBP \geq 140 \text{ mm Hg}, \text{DBP} \geq 90 \text{ mm Hg}, \text{or both})\). Because no optimal or normal subjects reached the hypertensive range, we collapsed them into 1 group for purposes of this particular analysis. As shown in Figure 2 and Table 2, the number of persons with BPs in the stage I and stage II hypertension range after caffeine increased across risk groups. We examined these hypertensive responses with a multiple regression analysis. Hypertension status again was the single best predictor of a hypertensive response to caffeine \((r=0.64, P<0.0001)\); however, age \((r=0.40, P<0.0001)\) added to the increment in the explained proportion of hypertensive response. The effect size was medium \((d=0.55)\).

### Discussion

To our knowledge, this is the first quantitative examination of the pressor effects of caffeine across hypertension risk groups. The present study demonstrates that caffeine affects persons to a progressively greater degree according to their BP classification. It further demonstrates that the higher the risk classification, the more likely are BPs in the hypertensive range 45 to 60 minutes after consumption of a dietary dose of caffeine and while resting.

Although the present study does not directly address issues about tolerance to the pressor effects of caffeine, the results are not altogether unrelated. Most recent long-term studies have shown an independent positive association of caffeine consumption and higher BP, indicating that tolerance to caffeine is not complete.\(^2\) Several short-term studies have also provided evidence that tolerance is not complete.\(^17\) Moreover, the present study illustrates consistent, large BP responses to caffeine in habitual users given a morning dose equivalent to 2 to 3 cups of coffee after a brief overnight abstinence, an abstinence that reasonably mimics typical use patterns. Clearly, any degree of tolerance in these long-term users did not negate acute BP responses to caffeine.

The present study shows that chronic elevations in BP associated with a greater risk for hypertension are accompanied by increasingly large BP responses to acute doses of caffeine. These findings suggest that caffeine may exert greater BP effects in those with a greater risk of hypertension. Table 2 indicates a progressive increase across risk groups in the percentage of men with high-normal or stage I and diagnosed hypertensive BPs after caffeine.

We acknowledge several limitations to the present study. This is not a study of the long-term effects of caffeine; rather, the data are based on multiple BP readings taken 45 to 60 minutes after caffeine ingestion. In addition, under some circumstances, the acute effects of a pharmacologically active substance may be opposite in direction to longer-term actions. Indeed, the entire area of the relationship of caffeine use to BP is controversial. Although evidence we cited showed long-term pressor effects (trials ranged from 14 to 79 days)\(^2\) and incomplete tolerance to the effects of caffeine,\(^17\) the epidemiological evidence does not consistently support a relationship of caffeine to the usual sequelae of higher BP, such as stroke, myocardial infarction, or total mortality. However, other investigators have commented on potential causes for inconsistencies in these studies, including differences in research design, inadequate control of confounders, population differences, and problems associated with the measurement of chronic caffeine consumption (see James\(^17\)).

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### Table 1: Subject Characteristics and Predrug Baseline BPs for Hypertension Status Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Optimal BP (n=73)</th>
<th>Normal BP (n=28)</th>
<th>High Normal BP (n=36)</th>
<th>Stage I (n=27)</th>
<th>Hypertension (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>29±1</td>
<td>26±1</td>
<td>26±1</td>
<td>27±1</td>
<td>39±1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Height, in</td>
<td>71±1</td>
<td>70±1</td>
<td>71±1</td>
<td>71±1</td>
<td>71±1</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, lb</td>
<td>175±2</td>
<td>174±3</td>
<td>178±4</td>
<td>183±4</td>
<td>205±7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index, weight×703/(height)(^2)</td>
<td>24±1</td>
<td>23±1</td>
<td>25±1</td>
<td>24±1</td>
<td>28±2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Caffeine consumption, mg/d</td>
<td>241±32</td>
<td>225±36</td>
<td>233±39</td>
<td>166±21</td>
<td>232±52</td>
<td>NS</td>
</tr>
<tr>
<td>Screening SBP, mm Hg</td>
<td>111±1</td>
<td>123±1</td>
<td>132±1</td>
<td>138±2</td>
<td>138±3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Screening DBP, mm Hg</td>
<td>67±1</td>
<td>73±1</td>
<td>77±1</td>
<td>85±2</td>
<td>94±3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Predrug baseline SBP, mm Hg</td>
<td>110±1</td>
<td>114±1</td>
<td>122±1</td>
<td>122±2</td>
<td>138±2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Predrug baseline DBP, mm Hg</td>
<td>62±1</td>
<td>66±1</td>
<td>70±1</td>
<td>70±2</td>
<td>91±2</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM. P values refer to significance of F test with between-group ANOVA. Screening BPs were measured with subjects sitting upright; predrug baseline BPs were measured with subjects in a semisupine position and after a 20-minute rest period.
Another possible limitation to our study concerns the diagnosed hypertensive group. These men may have exhibited exaggerated responses in part because they were withdrawn from medication. However, other research has shown that acutely administered caffeine raises BP in the presence of β-blockade and in hypertensives taking diuretics. It is likely, then, that the responses of the diagnosed hypertensives would be similar with or without medication.

Findings from the present study support the need for further research concerning the accuracy of diagnosis for hypertension. For example, JNC VI guidelines call for patients to refrain from smoking or ingesting caffeine during the 30 minutes preceding BP measurement. All 5 groups in our study showed BP elevations from 45 to 60 minutes after caffeine ingestion and while resting, indicating that possible confounds in measurement could occur for at least double the suggested 30-minute abstinence from caffeine. In addition, further controlled studies are called for to examine whether the differential acute effects we have seen across groups manifest chronically even in small elevations of BP, which could shift upward the risk distribution for cardiovascular disease. It has been calculated that a 2 to 3 mm Hg reduction in those with a high-normal BP should result in a 25% to 50% decrease in the incidence of hypertension.

In summary, the present findings show progressively larger BP responses to caffeine in persons with increasing risk of hypertension. Future research should focus on those with elevated BP and both treated and untreated hypertensives. Because the discrepancy in BP between the genders narrows in later life, priority should also be given to postmenopausal women in regard to dietary caffeine use.

**Acknowledgments**

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**TABLE 2. Percentage of Subjects by Risk Group Who Exhibited BP in the Hypertension Range Before and After Caffeine**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Before Caffeine</th>
<th>After Caffeine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage I</td>
<td>Stage II</td>
</tr>
<tr>
<td>Optimal/normal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>High normal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stage I</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Diagnosed hypertension</td>
<td>61</td>
<td>17</td>
</tr>
</tbody>
</table>

Values are taken from the test day with subjects in a semisupine position. Before-caffeine BPs were taken after 20 minutes of rest, and after-caffeine BPs were taken from 45 to 60 minutes after caffeine consumption. Because no men with optimal or normal values reached the hypertensive range, we combined them into 1 group.
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References
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