Coffee—Antihypertensive Drug Interaction: A Hemodynamic and Pharmacokinetic Study With Felodipine

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OBJECTIVES
A period of abstinence from coffee to permit caffeine elimination appears to enable increased blood pressure on subsequent exposure. We hypothesized that this would offset the antihypertensive effect of the dihydropyridine calcium channel blocker felodipine.

METHODS
A randomized, single-dose, crossover study assessed hemodynamic and pharmacokinetic effects following 2 days without coffee and caffeine-containing foods. Consistently brewed black coffee (2 × 300 ml), felodipine maximum recommended dose (10 mg), and coffee plus felodipine were tested in middle-aged normotensive subjects.

RESULTS
Pretreatment plasma caffeine concentrations were unquantifiable. After coffee, blood pressure changes (mm Hg) averaged over study hours 1–4 were increased for brachial systolic (7.6, P < 0.001) and diastolic (4.9, P < 0.001) and aortic systolic (7.4, P < 0.001), pulse (3.0, P < 0.05) and augmentation (1.4, P < 0.05) relative to baseline. After coffee plus felodipine, they were higher for brachial systolic (4.0, P < 0.05) and diastolic (3.9, P < 0.001) and aortic systolic (4.6, P < 0.05) compared to felodipine alone. The pressor effects of coffee and its modulation by felodipine were variable among individuals. Coffee containing caffeine (127 mg) caused maximum pressor effect. Caffeine and felodipine pharmacokinetics were similar for coffee and felodipine given alone or in combination indicating an interaction having a pharmacodynamic basis. Plasma felodipine concentration—diastolic blood pressure reduction relationship shifted with coffee such that doubling the felodipine concentration would eliminate the pressor effect. However, this may increase the risk of adverse drug events particularly during the timeframe without coffee.

CONCLUSION
Intermittent coffee ingestion might complicate hypertension diagnosis and management for many individuals.

Keywords: blood pressure; calcium channel blockers; coffee; drug interactions; felodipine; hypertension; pharmacodynamics; pharmacokinetics.

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Coffee is a globally popular beverage. More than half of the population over the age of 18 years has purchased an estimated $40 billion of coffee each year in the United States alone.1 Coffee can acutely increase blood pressure.2–4 Caffeine alone also caused an acute pressor response, while decaffeinated coffee lacked this effect.2,5 Thus, caffeine appears to be the major active constituent responsible for modifying blood pressure. Following ingestion of coffee, brachial systolic and diastolic blood pressure increased and heart rate modestly decreased likely as a result of enhanced arterial resistance and withdrawal of baroreflex-mediated sympathetic activity, respectively.3–8 Aortic systolic blood pressure was enhanced by the additional mechanism of greater arterial stiffness that caused the pressure pulse wave from left ventricular contraction to return sooner adding more to systolic pressure and reducing further coronary artery perfusion.9–14 Pulse pressure was heightened through an inotropic effect.15

The acute actions of coffee have been proposed as a trigger for adverse cardiovascular events.3 Subsequently, coffee or caffeine consumed less than daily was associated with myocardial infarction and stroke.16–18 Regular daily ingestion had a minimal effect on blood pressure from tolerance development and was not linked with these outcomes.2–4,19 Thus, the duration of time without coffee appears to be an important determinant of circulatory effects. This interval has been reported to be 4–5 times the elimination half-life of caffeine (range: 2–10 hours) which would result in a more than 95% decrease of plasma caffeine concentration.2,3 A recent survey found that 17% percent of 1,355 consumers ingested coffee only 2 or fewer days per week.20 Thus, a large
number of people who routinely ingest coffee or caffeine less than daily may have a regular undesirable pressor response.

Clinical pharmacodynamic interaction investigations between coffee and antihypertensive drugs have been reported in only 2 studies conducted more than 3 decades ago to our knowledge. Coffee-mediated pressor effect was not altered by a thiazide diuretic or beta-blocker (propranolol or metoprolol) in normotensive or hypertensive individuals. In contrast, caffeine-associated elevation of blood pressure was prevented by the dihydropyridine calcium channel blocker, nifedipine. However, nifedipine was administered as an immediate release capsule which caused rapid absorption and marked vasodilatation. Since this formulation was linked with higher cardiovascular morbidity and mortality, it is no longer recommended for clinical use.

Current evidence-based hypertension guidelines provide no advice either for or against coffee consumption during pharmacotherapy. However, a recent meta-analysis showing that the acute effects of caffeine were associated with reduced efficacy of an antihypertensive drug concluded that formal interaction studies are now necessary in order to establish more precise recommendations for combinations of coffee and a specific type of antihypertensive medication.

We investigated the acute interaction between a commonly consumed amount of consistently brewed black coffee and a representative dihydropyridine calcium channel blocker, felodipine, given as the slow-release formulation at maximum recommended dose. Middle-aged normotensive subjects avoided ingestion of coffee and other sources of caffeine for 2 days before testing. Hemodynamics (peripheral and central) and pharmacokinetics (caffeine and felodipine) were assessed.

METHODS

Study population

Thirteen subjects (4 men and 9 women; mean age 52 years (range, 31–65 years); 9 coffee consumers/4 noncoffee consumers) were tested. They were healthy as determined by medical history, physical examination and routine hematologic, and serum chemical testing. No subject had significant medical history, physical examination and routine hemato-

Experimental protocol

An acute 3-way crossover, randomized, open-labelled hemodynamic and pharmacokinetic investigation was conducted. Each study day was separated by an interval of at least 1 week. Subjects avoided coffee, other caffeine-containing foods, grapefruit, Seville orange (marmalades), lime, pom-pomelo, tobacco, alcoholic drinks, medications (prescription or over-the-counter), or natural health products for 48 hours before each study day. Testing was preceded by a 10-hour overnight fast. On each study day, female participants had a urine test prior to administration of any study intervention to confirm that they were not pregnant. Hemodynamics and plasma drug concentrations were determined at baseline and hourly intervals to 8 hours after administration of the treatment. The treatments were as follows: (i) black coffee, (ii) water plus felodipine, and (iii) black coffee plus felodipine. Water at room temperature or black coffee (300 ml) were ingested twice, once at study hour 0 (baseline) and again at hour 1. Black coffee was made from a single source of medium-roasted beans (Columbian Supremo, idrinkcoffee.com, Milton, ON, Canada). The beans were ground to medium coarseness and 3 tablespoons per 300 ml of cold double-distilled water were freshly brewed in a Starbucks Barista Aroma Grand Thermal Coffee Maker. Felodipine was given at the maximum recommended dose as a 10 mg extended-release tablet (Plendil; Astra Pharma, Mississauga, ON, Canada) at study hour 0. A standardized lunch was provided 4 hours after drug dosing (noon) which consisted of a sandwich, ginger ale and ice cream sandwich. Tobacco and other caffeine-containing foods were not permitted during testing.

Hemodynamic measurements

Peripheral (brachial systolic and diastolic blood pressure and heart rate) and central (aortic systolic, pulse, and augmentation blood pressure) measurements were the mean of at least 3 sitting readings after 5 minutes of rest. The respective instruments used were BpTRU Vital Signs Monitor (BpTRU Medical Devices, Coquitlam, BC, Canada) and SphygmoCor CP Pulse Wave Analysis System—Research (AtCor Medical, Itasca, IL).

Assay of felodipine and primary metabolite dehydrofelodipine

Plasma samples were analyzed according a modified previously published method. Sensitivity was increased by extracting plasma (500 µl) with toluene (250 µl) containing the internal standard (H165/04; AB Haesle, Gothenburg, Sweden) by gentle oscillation of the mixture overnight followed by centrifugation and freezing of the aqueous phase at −20 °C before injecting the extract (1 µl) of supernatant toluene phase. The retention times of felodipine, dehydrofelodipine, and internal standard were 20.1, 14.5, and 21.7 minutes, respectively. The coefficients of variation for plasma felodipine and dehydrofelodipine concentrations were 4.7% and 2.9% at 1.0 ng/ml (n = 5). The limit of detection was 0.25 ng/ml for both.

Assay of caffeine

Plasma and coffee samples were quantified for caffeine based on an earlier procedure. The method employed solid phase extraction followed by analysis on a Waters H-class Ultra Performance Liquid Chromatography system coupled to a Waters photodiode array detector. Briefly, plasma (200 µl) was diluted with water (800 µl) and internal standard...
Coffee. Brachial (systolic, diastolic) and aortic (systolic, pulse, augmentation) blood pressures with coffee alone increased above baseline by hour 1 (Figure 1). Heart rate decreased. Since the changes from baseline compared to study hours 1–4 were similar, the average of these 4 measurements was calculated to determine the overall treatment effect during this timeframe (Table 1). Hemodynamic parameters were fundamentally altered following lunch from hours 5 to 8.

Individual responses for brachial (systolic, diastolic) and aortic (systolic) blood pressures 1–4 hours with coffee alone, respectively, ranged from a modest decrease (−3, −3, −3 mm Hg) to a marked increase (17, 10, 17 mm Hg) compared to baseline (Figure 2).

Coffee plus felodipine. Brachial (systolic, diastolic) and aortic (systolic) blood pressures 1–4 hours with coffee plus felodipine were elevated compared to those with felodipine alone. Brachial blood pressures 5–8 hours were also higher.

Individual pressure differences were variable. At the lowest range, 1 individual had brachial (systolic, diastolic) and aortic (systolic) 1- to 4-hour pressure readings, respectively, decreased by −13, −2, and −15 mm Hg with coffee plus felodipine compared to felodipine alone, respectively. This individual also had a nonpressor effect with coffee alone (−3, −3, −3 mm Hg) and nearly double the plasma felodipine concentration with the combination (AUC<sub>0-4</sub> 5.6 vs. 3.4 ng h/ml).

At the highest range, another individual had blood pressures correspondingly increased by 23, 10, 27 mm Hg with coffee plus felodipine compared to felodipine alone. This subject additionally had a minor pressor effect with coffee alone (2, 3, 5 mm Hg) and a markedly lower plasma felodipine concentration with the combination (AUC<sub>n-4</sub> 1.2 vs. 6.2 ng h/ml).

Pharmacokinetic analyses

The area under the plasma drug concentration-time profile (AUC) was calculated from 0 to 8 hours by the linear trapezoidal method. Plasma peak drug concentrations (C<sub>max</sub>) and the time to reach C<sub>max</sub> (t<sub>max</sub>) were obtained directly from the experimental data. The terminal elimination rate constant (ke) was determined by log-linear regression of the final data points (at least 3). The apparent elimination half-life of the log-linear phase (t<sub>1/2</sub>) was calculated as 0.693/ke.

Data analyses

Analysis of variance for repeated measures was used for initial comparisons among the groups. For those analyses with P <0.05, Bonferroni test for multiple comparisons was subsequently conducted between selected pairs of treatments. Linear regression analysis was used to assess relationships between study parameters. Results are presented as the mean ± SEM or 95% confidence interval.

RESULTS

Hemodynamic effects

Coffee. Brachial (systolic, diastolic) and aortic (systolic, pulse, augmentation) blood pressures with coffee alone increased above baseline by hour 1 (Figure 1). Heart rate decreased. Since the changes from baseline compared to study hours 1–4 were similar, the average of these 4 measurements was calculated to determine the overall treatment effect during this timeframe (Table 1). Hemodynamic parameters were fundamentally altered following lunch from hours 5 to 8.

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Pharmacokinetics and pharmacodynamics

Caffeine. All plasma concentrations of caffeine just before testing were unquantifiable (<0.2 µg/ml) on the 3 study days in all but 1 subject (0.3 and 0.6 µg/ml).

The pharmacokinetics and dose of caffeine were not different between coffee alone and coffee plus felodipine (Table 2). The first cup of coffee alone produced a plasma caffeine concentration at hour 1 that was associated with higher blood pressure (Figure 3). Although the second cup directly thereafter almost doubled plasma caffeine concentrations between hours 2 and 4 compared to hour 1, no further increase in blood pressure was observed. Plasma caffeine concentrations between hours 5 and 8 remained elevated above that at hour 1.

Felodipine. The pharmacokinetics of felodipine and its single primary inactive metabolite, dehydrofelodipine, were not different between felodipine alone and coffee plus felodipine (Table 3).

Higher plasma felodipine concentration was associated with greater reduction in diastolic blood pressure among individuals (Figure 4). These relationships differed between treatments such that more than doubling of the felodipine concentration would be required with coffee to produce an equivalent reduction of blood pressure.

DISCUSSION

Caffeine had a mean half-life approximating 9 hours in this investigation. This explains its overall unquantifiable baseline plasma concentration on study days following no coffee and other caffeine-containing foodstuffs for 2 days. Consumption of coffee caused clear hemodynamic changes that were manifest during 1–4 hours of the study. However, the food at lunch caused additional actions making...
Coffee Interaction With Felodipine

**Figure 1.** Sitting brachial and aortic hemodynamic time profiles with coffee, coffee plus felodipine, and felodipine. Data are expressed as the mean ± SEM.

**Table 1.** Differences in brachial and aortic hemodynamic measurements

<table>
<thead>
<tr>
<th>Hemodynamic Measurement</th>
<th>Period (1–4h)</th>
<th>Period (5–8h)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Coffee vs. baseline</td>
<td>Coffee + felodipine vs. felodipine</td>
</tr>
<tr>
<td>Brachial</td>
<td></td>
<td></td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>7.6 (4.9, 10.3)***</td>
<td>4.0 (0.8, 7.2)*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>4.9 (3.4, 6.3)***</td>
<td>3.9 (2.0, 5.9)***</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>−4.5 (−5.6, −3.4)***</td>
<td>−1.0 (−2.8, 0.8)</td>
</tr>
<tr>
<td>Aortic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>7.4 (4.7, 10.2)***</td>
<td>4.6 (0.9, 8.3)*</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>3.0 (1.1, 4.8)*</td>
<td>1.1 (−1.2, 3.4)</td>
</tr>
<tr>
<td>Augmentation (mm Hg)</td>
<td>1.4 (0.5, 2.3)*</td>
<td>0.9 (−0.6, 2.3)</td>
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Mean (95% CI) *P < 0.05, **P < 0.01, ***P < 0.001. Abbreviation: CI, confidence interval.

The interpretation of the effect of coffee complicated during 5–8 hours.

Coffee elevated brachial (systolic, diastolic) and aortic (systolic, pulse pressure) blood pressure consistent with previous findings. It also enhanced the aortic augmentation pressure from greater arterial stiffness. However, this accounted for only 20% of the rise in aortic (systolic) blood pressure indicating that this mechanism was a minor component. Variability was high among subjects. The effect was of sufficient magnitude that consumption of coffee prior to a...
Hemodynamics were altered soon after coffee ingestion and sustained for several hours. Importantly, we now report that hemodynamics were not further altered following the second serving of coffee despite an almost doubling in plasma caffeine concentration. This suggests that there is a threshold in terms of the effect of caffeine consumption on hemodynamics. Thus, the first serving of coffee containing caffeine was associated with acute maximum hemodynamic changes. The 300 ml volume of coffee used in this study routinely contains 120–240 mg of caffeine. A lower dose of caffeine, which can be found in other food-stuffs, might have a similar outcome but this information is not available to our knowledge. Such data would offer better knowledge of the overall potential for caffeine to cause routine medical examination might result in the diagnosis of hypertension in certain individuals.

Table 2. Caffeine pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Caffeine</th>
<th>Coffee</th>
<th>Coffee + felodipine</th>
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<tbody>
<tr>
<td>AUC$_{0-8}$ (µg h/ml)</td>
<td>29.3±2.3</td>
<td>29.8±2.4</td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-inf}$ (µg h/ml)</td>
<td>71.7±8.5</td>
<td>71.8±11.5</td>
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</tr>
<tr>
<td>C$_{max}$ (µg/ml)</td>
<td>5.0±0.3</td>
<td>5.3±0.4</td>
<td></td>
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<tr>
<td>t$_{max}$ (h)</td>
<td>2.5±0.3</td>
<td>2.4±0.2</td>
<td></td>
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<tr>
<td>t/2 (h)</td>
<td>8.7±0.9</td>
<td>8.3±1.0</td>
<td></td>
</tr>
<tr>
<td>Dose (mg/600ml)</td>
<td>253.6±12.9</td>
<td>274.0±10.2</td>
<td></td>
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</table>

Abbreviation: AUC, area under the plasma drug concentration-time profile; C$_{max}$, plasma peak drug concentrations; t$_{max}$, time to reach C$_{max}$; t/2, half-life of the log-linear phase.

Table 3. Felodipine and dehydrofelodipine pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Felodipine</th>
<th>Coffee + felodipine</th>
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</thead>
<tbody>
<tr>
<td>AUC$_{0-8}$ (ng h/ml)</td>
<td>8.66±0.70</td>
<td>10.57±0.86</td>
</tr>
<tr>
<td>C$_{max}$ (ng/ml)</td>
<td>1.65±0.14</td>
<td>2.10±0.20</td>
</tr>
<tr>
<td>t$_{max}$ (h)</td>
<td>3.7±0.5</td>
<td>3.4±0.4</td>
</tr>
<tr>
<td>Dehydrofelodipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-8}$ (ng h/ml)</td>
<td>13.34±1.65</td>
<td>15.02±1.22</td>
</tr>
<tr>
<td>C$_{max}$ (ng/ml)</td>
<td>3.01±0.39</td>
<td>3.79±0.35</td>
</tr>
<tr>
<td>t$_{max}$ (h)</td>
<td>2.3±0.3</td>
<td>3.0±0.4</td>
</tr>
<tr>
<td>Dehydrofelodipine/felodipine</td>
<td>1.54±0.12</td>
<td>1.46±0.10</td>
</tr>
</tbody>
</table>

Abbreviation: AUC, area under the plasma drug concentration-time profile; C$_{max}$, plasma peak drug concentrations; t$_{max}$, time to reach C$_{max}$.
adverse pressor effects and misdiagnosis of patients with hypertension.

The interaction between coffee and felodipine provided the key aspects of this investigation. Since caffeine and felodipine had similar pharmacokinetics when given alone or combined, it indicated that the hemodynamic changes had primarily a pharmacodynamic basis. One potential explanation is that caffeine-mediated vasoconstriction modified the vasodilatory effect of felodipine on arterial vessel resistance vasodilatation. Pressor actions of coffee were not abolished during both 1- to 4-hour study periods even by felodipine at the maximum recommended 10 mg dose.

The difference in blood pressure between coffee plus felodipine and felodipine alone was variable among individuals. At the lowest range, 1 subject had lower blood pressure with the combination. This individual also had no pressor effect with coffee alone and increased felodipine AUC with the combination. At the highest range, another subject had a pressor effect with coffee alone and increased felodipine AUC with the combination. This individual also had no pressor effect while the other half showed little reduction. These 2 groups did not differ in caffeine dose, gender, pretreatment blood pressures, or saliva caffeine concentration. Another study of similar design but differing by extending blood pressure monitoring to 24 hours had the same essential outcomes. Thus, high scientific quality data suggested that some daily coffee consumers might also have an interaction like that observed in this investigation. On the other hand, coffee contains additional vasoactive substances (chlorogenic acid, hydroxyhydroquinone, cafestol, kahweol) that might modify the interaction and would require testing.

A possible shortcoming of this study might be variability in the normal routine of coffee consumption of subjects before the start of the study. The pressor effect may be less for those with daily compared to infrequent ingestion. Yet, this response to coffee appears to return after avoidance for 4–5 elimination half-lives of caffeine. Thus, subjects in this study were without caffeine-containing foods for 2 days before testing, had a mean caffeine elimination half-life less than 9 hours (range: 4–15 hours) and recorded an overall unquantifiable pretreatment plasma caffeine concentration on study days. Although the main active metabolite paraxanthine was not measured, the timeframe of 2 days was adequate for its removal as well. On the other hand, a longer period may be required for some individuals to return completely to baseline responsiveness. In this case, this suggests that the data in this study might underestimate the full magnitude of differences between treatments.

Since a time control arm of the study involving water alone was not included, it might be argued that the effects of felodipine and coffee on blood pressure were not adequately shown. Yet, identical baseline values and consistent direction and magnitude of change with felodipine and coffee to that reported previously supported this approach.

In summary, 2 days abstaining from coffee was sufficient to eliminate caffeine from the systemic circulation. Coffee containing caffeine (127 mg) caused maximum pressor effect by 1 hour after intake, which was sustained for several hours and potentially clinically important in some individuals. Coffee plus felodipine 10 mg (maximum recommended dose) elevated blood pressure above felodipine alone through a pharmacodynamic interaction. This suggests that coffee consumption acutely blocks the beneficial antihypertensive effect of felodipine. Our study indicates that an increase of healthcare provider might increase the dose of felodipine or another dihydropyridine calcium channel blocker having equivalent blood pressure-lowering efficacy. Given the transient effect of caffeine, there might be greater risk of adverse drug effects especially during the period without coffee for the occasional consumer. Hypotension, shock, or acute kidney injury from excessive dose of dihydropyridine calcium channel blockers may occur in older patients.

Tolerance to the pressor effect of coffee and caffeine is known to occur with repeated administration. However, more recent reports indicated that this process is unpredictable. For example, 1 randomized, double-blind crossover study assessed caffeine at low (100 mg) or high (200 mg) dose 3 times daily (equivalent to 3 or 6 cups of coffee per day) or placebo for 5 days in healthy adult men (n = 49) and women (n = 48). Half of the subjects displayed complete loss of pressor effect while the other half showed little reduction. These 2 groups did not differ in caffeine dose, gender, pretreatment blood pressures, or saliva caffeine concentration.

Figure 4. Plasma felodipine concentration correlation with change in brachial diastolic BP from baseline for felodipine and coffee plus felodipine. Data are presented for each individual over the 1- to 4-hour study period (n = 52 per treatment). The increase in plasma felodipine concentration to produce an equivalent reduction in BP with concomitant coffee ingestion is depicted by the horizontal arrow. Abbreviation: BP, blood pressure.
more than double the dose of felodipine would be required to abolish the pressor effect of coffee, but this approach has the possibility to augment the risk of adverse drug events. Based on our data, occasional coffee consumption may adversely impact the management of hypertensive patients treated with dihydropyridine calcium channel blockers.

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DISCLOSURE

The authors declared no conflict of interest.

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