# Impact of Acute Caffeine Ingestion on Endothelial Function in Subjects With and Without Coronary Artery Disease

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**Although coffee is a widely used, pharmacologically active beverage, its impact on the cardiovascular system is controversial. To explore the effect of acute caffeine ingestion on brachial artery flow-mediated dilation (FMD) in subjects without coronary artery disease (CAD; controls) and patients with CAD, we prospectively assessed brachial artery FMD in 40 controls and 40 age- and gender-matched patients with documented stable CAD on 2 separate mornings 1 week to 2 weeks apart. After overnight fasting, discontinuation of all medications for ≥12 hours, and absence of caffeine for >48 hours, participants received capsules with caffeine 200 mg or placebo. One hour after drug ingestion, participants underwent brachial artery FMD and nitroglycerin-mediated dilation (NTG) using high-resolution ultrasound. As expected, patients with CAD were more oftein diabetic, hypertensive, obese, dyslipidemic, and smoked more than controls ($p < 0.01$ for all comparisons). Aspirin, Clopidogrel, angiotensin-converting enzyme inhibitors, β blockers, and statins were significantly more common in patients with CAD than in controls ($p < 0.01$ for all comparisons). At baseline, FMD, but not NTG, was significantly lower in patients with CAD compared to controls. Acute caffeine ingestion significantly increased FMD (patients with CAD 5.6 ± 5.0% vs 14.6 ± 5.0%, controls 8.4 ± 2.9% vs 18.6 ± 6.8%, $p < 0.001$ for all comparisons) but not NTG (patients with CAD 13.0 ± 5.2% vs 13.8 ± 6.1%, controls 12.9 ± 3.9% vs 13.9 ± 5.8%, p = NS for all comparisons) and significantly decreased high-sensitivity C-reactive protein (patients with CAD 2.6 ± 1.4 vs 1.4 ± 1.2 mg/L, controls 3.4 ± 3.0 vs 1.2 ± 1.0 mg/L, $p < 0.001$ for all comparisons) in the 2 groups compared to placebo. In conclusion, acute caffeine ingestion significantly improved endothelial function assessed by brachial artery FMD in subjects with and without CAD and was associated with lower plasma markers of inflammation.**  **(Am J Cardiol 2011;107:1255–1261)**

Although coffee is 1 of the most widely used, pharmacologically active beverages, its impact on the cardiovascular system is controversial.[1–9] Although data regarding its effect on endothelial function are limited, several studies have found that coffee consumption is associated with impairment of flow-mediated dilation (FMD) of the brachial artery,[10] aortic stiffness, and wave reflections.[11] Others have maintained that neither caffeinated nor decaffeinated filtered coffee has a detrimental effect on markers of endothelial function,[12] whereas the ATTICA study found that moderate coffee consumption is related to increased plasma concentrations of general inflammation markers.[13] We aimed therefore to explore the effect of acute caffeine ingestion on brachial FMD in subjects without coronary artery disease (CAD) and in patients with stable CAD.

## Methods

In a randomized, double-blind, placebo-controlled, cross-over study, we prospectively assessed brachial artery FMD in 80 consecutive subjects recruited from the endothelial function assessment laboratory of the Leviev Heart Center at the Sheba Medical Center (Tel Hashomer, Israel; 40 volunteers without and 40 age- and gender-matched patients with documented stable CAD) on 2 separate mornings 1 week to 2 weeks apart.

Volunteers without CAD were defined as subjects without a history of chest pain or myocardial infarction, coronary artery bypass grafting surgery, coronary angiography with angioplasty and/or stenting, cerebrovascular accident, or peripheral vascular disease with normal electrocardiogram and echocardiogram on admission. All patients without CAD were referred by primary care physicians or through direct patient request for risk factor evaluation through a primary prevention clinic. No patient was referred because of chest pain. Primary care physicians send patients to the assessment laboratory for CAD assessment (low vs high) to help them decide on

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treatment management of patients with risk factors for CAD. All patients underwent a full consultation by a cardiologist who performed primary prevention risk management according to updated National Cholesterol Education Program Adult Treatment Panel III and American Heart Association/American College of Cardiology/European Society of Cardiology guidelines. Patients with stable CAD were defined as those with a >6-month history of myocardial infarction and coronary artery bypass grafting surgery or coronary angiography with angioplasty or stenting >6 months previously. Exclusion criteria included atrial fibrillation, sinus bradycardia (heart rate <50 beats/min) without a pacemaker, sick sinus syndrome, second- or third-degree atrioventricular block, intolerance to nitrates, renal failure with serum creatinine >1.5 mg/dl, New York Heart Association class >II heart failure, history of drug or alcohol abuse, chronic liver disease, or refusal to sign the informed consent form.

After an overnight fast, discontinuation of all medications for ≥12 hours, absence of caffeine ingestion for >48 hours (including coffee, tea, cola, alcohol and flavonoid-containing beverages, and energy supplements), >48-hour cessation of cigarette smoking, and response to a specifically designed dietary questionnaire (for caffeine estimation), participants received capsules containing caffeine 200 mg (80-mg caffeine ingestion = 1 cup of coffee) or placebo administered at 7.00 A.M. with tap water 250 ml. Distribution was in a rotating randomized fashion, such that each subject received caffeine or placebo capsules once throughout the study period. Before (baseline) and 1 hour after study drug ingestion, participants underwent brachial artery FMD and nitroglycerin-mediated dilation (NTG) using high-resolution ultrasound. Electrocardiographic ad echocardiographic assessments and blood tests for serum caffeine levels, lipids, complete blood cell count, electrolytes, fasting glucose, homocysteine, adiponectin, and high-sensitivity C-reactive protein (hs-CRP) were performed.

Blood samples were centrifuged immediately for 15 minutes at 3,000/min. Sera were stored at −20°C and tested at the end of the study. Serum adiponectin levels were assessed using an enzyme-linked immunosorbent assay as described previously.[14] Serum caffeine was assayed by an enzyme-multiplied immunoassay technique (Olympus AU2700, Olympus America, Inc., Center Valley, Pennsylvania).[15] The hospital review board approved the study, and all participants gave written informed consent (http://www.clinicaltrials.gov, identifier NCT00564824).

Caffeine 200 mg and placebo capsules were manufactured by the Sheba Medical Center pharmacy and the therapy sequence for each patient (caffeine at first visit, placebo at second visit, or vice versa) was prepared before study initiation by computer-generated randomization software. Investigators, coordinators, and patients were blinded to the drugs throughout the study. All capsule codes were kept locked at the Sheba Medical Center pharmacy throughout the study period and delivered to the study statistician only at closeout.

Endothelial function in the form of endothelium-dependent brachial artery FMD was measured as previously described[16–22] using a 15- to 6-MHz linear array (15-6L HP) ultrasound system (HP SONOS 7500 cv System, Agilent Technologies, Inc., Andover, Massachusetts). A pneumatic tourniquet (Hokanson, AG101, Bellevue, Washington, DC) placed around the left upper arm proximal to the target artery (upper-arm occlusion) was inflated after the baseline phase to 50 mm Hg above the subject's systolic blood pressure and held for 5 minutes. Diameter and Doppler flow velocity were measured at baseline and immediately after cuff deflation at 20, 40, 60, 90, and 120 seconds.

A second 2-minute baseline scan at rest was recorded to confirm vessel recovery 13 minutes after cuff deflation. Scanning was performed continuously for 5 minutes after administration of a sublingual nitroglycerin tablet (0.4 mg, Nitrostat, Park-Davis, New York, New York).

Ultrasound images were recorded on an S-VHS videotape with a SLV-RS7 videocassette recorder (SONY, California). Brachial artery diameter was measured from the anterior to the posterior interface between the media and adventitia ("m line") at a fixed distance. Mean diameter was calculated from 4 cardiac cycles synchronized with R-wave peaks on electrocardiogram. All measurements were calculated at end-diastole to avoid possible errors resulting from variable arterial compliance. Internal diameter was calculated with PC Prosound (University of Southern California, Los Angeles, California) using a Horita data translation image processing board (DT2862-60Hz; Horita, Mission Viejo, California).[17,18] FMD and NTG were expressed as percent change compared to those at the initial scan at rest. FMD was computed from the formula ([maximum diameter minus baseline diameter]/baseline diameter × 100). Percent FMD using maximal brachial artery diameter achieved after cuff deflation was used as an index of endothelium-dependent dilation; percent dilatation obtained 5 minutes after administration of nitroglycerin represented percent NTG. FMD and NTG vasodilatory response measurements were carried out in blind fashion. Intraobserver correlation coefficients for baseline and deflation diameters were 0.99. Absolute errors between measurements were 0 to 0.12 mm (for brachial artery diameter) and 0.02% to 2.98% (for FMD). Determination of endothelial function was performed in accordance with published guidelines.[16]

A power calculation assessment based on the effect of caffeine on endothelial function in healthy subjects[10] was performed before the study. Assuming a standardized difference of 0.72, a p value of 0.05, and a power of 85%, the number per group (healthy subjects and those with CAD) was estimated to be 30. Accounting for a 2-week 5% drop-out rate, we estimated that the total number of enrolled subjects should be 72.[23] Values are expressed as mean ± SD for continuous variables and frequency and percentage for categorical variables. Distributions of continuous variables were assessed using Kolmogorov–Smirnov test. Comparisons between controls and patients with CAD were assessed using independent *t* test for continuous variables and chi-square test for categorical variables. Changes within caffeine and placebo treatments and differences between healthy subjects and those with CAD were calculated by repeated analysis measurements, which produced 3 tests of significance: difference

Table 1
Patient characteristics

| Variable | Controls (n = 40) | Patients With CAD (n = 40) | p Value |
|---|---|---|---|
| Age (years) | 53 ± 6 | 53 ± 8 | 0.846 |
| Men | 33 (83%) | 33 (83%) | 0.981 |
| Smokers | 2 (5%) | 8 (20%) | 0.043 |
| Diabetes mellitus | 0 | 11 (28%) | <0.001 |
| Hypertension | 1 (3%) | 21 (53%) | <0.001 |
| Body mass index >25 kg/m$^2$ | 4 (10%) | 32 (80%) | <0.001 |
| Hypercholesterolemia (>200 mg/dl) | 2 (5%) | 40 (100%) | <0.001 |
| Family history of coronary artery disease | 10 (25%) | 19 (48%) | 0.030 |
| Concomitant medications | | | |
| Aspirin | 1 (3%) | 40 (100%) | <0.001 |
| Clopidogrel | 0 | 10 (25%) | 0.001 |
| $\beta$ Blockers | 1 (3%) | 28 (70%) | <0.001 |
| Calcium channel blockers | 0 | 2 (5%) | 0.246 |
| Angiotensin-converting enzyme inhibitors | 0 | 24 (60%) | <0.001 |
| Diuretics | 0 | 4 (10%) | 0.057 |
| Statins | 2 (5%) | 38 (95%) | <0.001 |
| Vitamins | 2 (5%) | 4 (10%) | 0.338 |
| Physical examination | | | |
| Heart rate at rest (beats/min) | 69 ± 13 | 65 ± 11 | 0.211 |
| Systolic blood pressure (mm Hg) | 127 ± 17 | 128 ± 17 | 0.912 |
| Diastolic blood pressure (mm Hg) | 78 ± 10 | 78 ± 10 | 0.818 |
| Weight (kg) | 76 ± 18 | 85 ± 14 | 0.141 |
| Height (m) | 1.70 ± 0.10 | 1.76 ± 0.09 | 0.024 |
| Waist circumference (cm) | 92 ± 15 | 98 ± 15 | 0.143 |
| Body mass index (kg/m$^2$) | 26 ± 5 | 28 ± 4 | 0.418 |
| Blood tests | | | |
| White blood cell count (number/$\mu$l) | 6,260 ± 1,825 | 7,176 ± 1,519 | 0.018 |
| Hemoglobin (g/dl) | 13.8 ± 2.4 | 14.1 ± 1.1 | 0.531 |
| Platelet count (number/$\mu$l) | 219,780 ± 48,902 | 209,230 ± 49,958 | 0.346 |
| Potassium (mEq/L) | 4.2 ± 0.5 | 4.3 ± 0.3 | 0.245 |
| Chloride (mEq/L) | 105 ± 2 | 105 ± 2 | 0.918 |
| Sodium (mEq/L) | 139 ± 2 | 139 ± 2 | 0.821 |
| Creatinine (mg/dl) | 0.95 ± 0.15 | 1.01 ± 0.13 | 0.074 |
| Urea (mg/dl) | 30 ± 8 | 34 ± 6 | 0.006 |
| Glucose (mg/dl)* | 89 ± 13 | 95 ± 19 | 0.130 |
| Total cholesterol (mg/dl) | 188 ± 32 | 137 ± 22 | <0.001 |
| Low-density lipoprotein cholesterol (mg/dl) | 114 ± 24 | 84 ± 17 | <0.001 |
| Triglycerides (mg/dl) | 107 ± 50 | 123 ± 57 | 0.207 |
| High-density lipoprotein cholesterol (mg/dl) | 51 ± 14 | 38 ± 7 | <0.001 |
| Homocysteine ($\mu$mol/L) | 12 ± 7 | 14 ± 7 | 0.354 |
| High-sensitivity C-reactive protein (mg/L) | 3.4 ± 3.0 | 2.6 ± 1.4 | 0.345 |
| Adiponectin ($\mu$mol/L) | 11.0 ± 6.5 | 7.4 ± 4.2 | 0.428 |
| Left ventricular ejection fraction (%) | 60 ± 5 | 46 ± 11 | <0.001 |
| Endothelial function | | | |
| Baseline brachial artery diameter (mm) | 5.1 ± 1.2 | 5.8 ± 0.8 | <0.01 |
| Percent flow-mediated dilation† | 8.4 ± 2.9 | 5.6 ± 5.0 | <0.001 |
| Percent nitroglycerin-mediated dilation‡ | 12.9 ± 3.9 | 13.0 ± 5.2 | 0.535 |

Values are presented as mean ± SD or absolute number.
* Blood glucose levels were measured after a 12-hour fast.
† Percent brachial artery diameter added by endothelium-dependent vasodilation after cuff deflation.
‡ Percent brachial artery diameter added by smooth muscle-dependent vasodilation after nitroglycerin administration.

in treatment changes between groups (interaction between treatment and group), total changes between treatments, and differences between groups in general. Correlations between serum caffeine levels and other continuous variables were assessed using Pearson or Spearman correlation test. Multivariate regression analysis was performed to predict percent FMD by independent variables. All statistical calculations were performed using SPSS 17.0 (SPSS, Inc., Chicago, Illinois). A p value <0.05 represented statistical significance.

## Results

The cohort consisted of 80 consecutive subjects, of whom 40 had stable CAD and 40 were without established cardiovascular disease (controls). Table 1 presents baseline

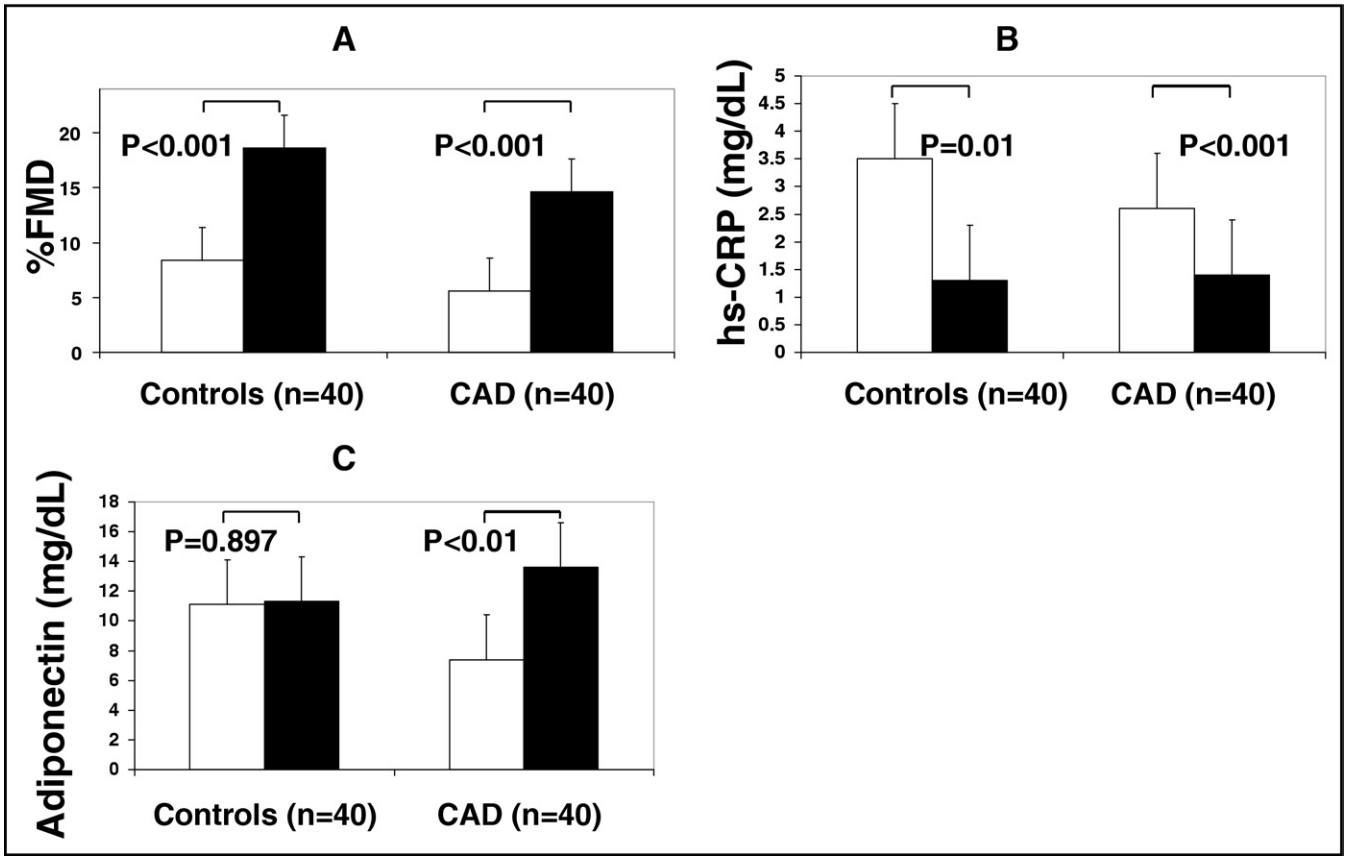


Figure 1. Bar graphs show effect of acute caffeine *(closed bars)* compared to placebo *(open bars)* ingestion on *(A)* percent flow-mediated dilation, *(B)* high-sensitivity C-reactive protein, and *(C)* adiponectin in subjects without coronary artery disease (controls, n = 40) and those with coronary artery disease (n = 40). Data are expressed as mean ± SD.

Table 2
Effect of caffeine on endothelial function and factors of inflammation

| | Controls (n = 40) | | | Patients With CAD (n = 40) | | | p Value | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo | Caffeine | p Value | Placebo | Caffeine | p Value | Interaction | Group | Caffeine |
| Percent flow-mediated dilation* | 8.4 ± 2.9 | 18.6 ± 6.8 | <0.001 | 5.6 ± 5.0 | 14.6 ± 5.0 | <0.001 | 0.625 | 0.007 | <0.001 |
| Percent nitroglycerin-mediated dilation† | 12.9 ± 3.9 | 13.9 ± 5.8 | 0.768 | 13.0 ± 5.2 | 13.8 ± 6.1 | 0.867 | 0.458 | 0.426 | 0.623 |
| High-sensitivity C-reactive protein (mg/dl) | 3.4 ± 3.0 | 1.2 ± 1.0 | 0.012 | 2.6 ± 1.4 | 1.4 ± 0.009 | 0.009 | 0.197 | 0.393 | <0.001 |
| Adiponectin (mg/dl) | 11.0 ± 4.5 | 11.3 ± 7.5 | 0.897 | 7.4 ± 4.2 | 13.6 ± 5.9 | 0.001 | 0.035 | 0.614 | 0.021 |

Values are presented as mean ± SD.
* Percent brachial artery diameter added by endothelium-dependent vasodilation after cuff deflation.
† Percent brachial artery diameter added by smooth muscle-dependent vasodilation after nitroglycerin administration.

characteristics and clinical features of the entire study population. As expected, all CAD risk factors were more common in patients with CAD. In addition, aspirin, clopidogrel, $\beta$ blockers, angiotensin-converting-enzyme inhibitors, and statin administration were more common in patients with CAD whose left ventricular ejection fraction was significantly lower compared to controls.

As previously demonstrated,[21] baseline brachial artery diameter was larger in the CAD group (Table 1), whereas FMD was significantly greater and NTG was similar in subjects without CAD compared to patients with CAD. No adverse effects were noted during brachial artery testing of the 2 groups.

Although acute caffeine ingestion significantly improved FMD in patients with CAD and those without CAD, improvement was significantly greater in subjects without CAD compared to those with CAD (Figure 1, Table 2). Acute caffeine ingestion, however, did not significantly change NTG in the 2 study groups. Although acute caffeine ingestion significantly decreased hs-CRP in subjects without and those with CAD, its impact on control subjects without CAD was significantly higher compared to patients

Table 3
Effect of caffeine on biochemical variables, blood count, heart rate, blood pressure, and brachial diameter

| | Controls (n = 40) | | | Patients With CAD (n = 40) | | |
|---|---|---|---|---|---|---|
| | Placebo | Caffeine | p Value | Placebo | Caffeine | p Value |
| Fasting glucose (mg/dl) | 89 ± 13 | 90 ± 13 | 0.541 | 99 ± 25 | 98 ± 20 | 0.683 |
| Potassium (mEq/L) | 4.3 ± 0.3 | 4.1 ± 0.6 | 0.103 | 4.4 ± 0.3 | 4.3 ± 0.3 | 0.569 |
| Creatinine (mg/dl) | 0.9 ± 0.2 | 0.9 ± 0.2 | 0.536 | 1.0 ± 0.2 | 1.0 ± 0.1 | 0.446 |
| Urea (mg/dl) | 28.6 ± 8.5 | 29.6 ± 9.2 | 0.191 | 34.4 ± 6.9 | 32.8 ± 6.1 | 0.511 |
| Caffeine ($\mu$g/ml) | 0.6 ± 0.8 | 4.6 ± 1.5 | <0.001 | 0.5 ± 0.7 | 4.5 ± 1.0 | <0.001 |
| Total cholesterol (mg/dl) | 180 ± 29 | 180 ± 33 | 0.313 | 137 ± 27 | 135 ± 23 | 0.565 |
| Low-density lipoprotein cholesterol (mg/dl) | 107 ± 25 | 107 ± 24 | 0.467 | 84 ± 20 | 83 ± 18 | 0.592 |
| Triglycerides (mg/dl) | 105 ± 46 | 103 ± 49 | 0.641 | 119 ± 58 | 119 ± 46 | 0.971 |
| High-density lipoprotein cholesterol (mg/dl) | 50 ± 13 | 50 ± 14 | 0.247 | 38 ± 8 | 37 ± 7 | 0.367 |
| Hemoglobin (g/dl) | 14.0 ± 1.1 | 13.9 ± 2.5 | 0.881 | 13.8 ± 0.8 | 14.2 ± 1.0 | 0.211 |
| Platelet count ($\times 10^3$) | 203.6 ± 39.3 | 203.6 ± 46.2 | 0.845 | 208.0 ± 50.2 | 208.3 ± 48.0 | 0.932 |
| White blood cell count ($\times 10^3$) | 6.3 ± 1.4 | 6.3 ± 1.8 | 0.711 | 7.2 ± 2.0 | 7.2 ± 1.6 | 0.891 |
| Heart rate (beats/min) | 67 ± 11 | 66 ± 13 | 0.515 | 65 ± 11 | 65 ± 12 | 0.881 |
| Systolic blood pressure (mm Hg) | 130 ± 20 | 126 ± 15 | 0.344 | 127 ± 20 | 131 ± 19 | 0.048 |
| Diastolic blood pressure (mm Hg) | 77 ± 11 | 77 ± 8 | 0.854 | 74 ± 12 | 78 ± 12 | 0.024 |
| Brachial artery diameter (mm) | 5.3 ± 0.9 | 5.0 ± 1.2 | 0.142 | 5.8 ± 0.7 | 5.7 ± 0.8 | 0.172 |

Values are presented as mean ± SD.

Table 4
Association of serum caffeine and other variables in study cohort

| | Controls (n = 40) | | Patients With CAD (n = 40) | |
|---|---|---|---|---|
| | r* | p Value | r* | p Value |
| Fasting glucose | −0.372 | 0.022 | 0.230 | 0.887 |
| Adiponectin | 0.579 | <0.001 | 0.146 | 0.374 |
| Total cholesterol | 0.344 | 0.032 | 0.357 | 0.025 |
| High-density lipoprotein cholesterol | 0.420 | 0.008 | 0.076 | 0.645 |
| High sensitivity C-reactive protein | 0.138 | 0.403 | 0.316 | 0.047 |
| Triglycerides | −0.044 | 0.790 | 0.339 | 0.035 |
| Low-density lipoprotein cholesterol | 0.213 | 0.192 | 0.358 | 0.025 |
| Baseline brachial artery diameter | −0.215 | 0.189 | −0.449 | 0.004 |

* Pearson correlation.

with CAD (Figure 1, Table 2). Baseline serum adiponectin was higher, although not statistically significant, in controls compared to patients with CAD (Figure 1, Table 1). Adiponectin, however, although increased by acute caffeine ingestion in the 2 study groups, reached statistical significance only in patients with CAD compared to controls (Figure 1, Table 2).

As expected, acute caffeine (200 mg) ingestion significantly increased serum caffeine levels by nearly 4 $\mu$g/ml in the 2 study groups, although it did not change heart rate at rest in either group (Table 3). Furthermore, caffeine did not change systolic or diastolic blood pressure in controls, although it significantly increased blood pressure in patients with CAD (Table 3).

In univariate analysis fasting serum glucose, adiponectin, total cholesterol, and high-density lipoprotein cholesterol were correlated with serum caffeine levels in controls, whereas total cholesterol, low-density lipoprotein cholesterol, hs-CRP, triglycerides, and baseline brachial artery diameter were correlated to serum caffeine in patients with CAD (Table 4). In multivariate analysis serum caffeine levels were found to be independent predictors for percent FMD after controlling for age, gender, CAD, baseline brachial artery diameter, and hyperlipidemia.

## Discussion

The present study demonstrates for the first time that ingestion of a capsule with caffeine 200 mg improved brachial endothelial function in subjects without CAD (controls) and patients with CAD. Furthermore, the increase of serum caffeine levels by almost 4 $\mu$g/ml in the 2 study groups was associated with a decrease of inflammatory markers such as hs-CRP and an increase in serum adiponectin, an adipocyte-derived plasma protein that plays a role in the development of diabetes mellitus and metabolic syndrome, has antidiabetic and antiatherogenic properties,[24] and is associated with atherosclerotic burden and coronary plaque vulnerability.[14,25]

Our results are in accord with those of Umemura et al[26] who demonstrated that acute caffeine ingestion (300 mg) augments endothelium-dependent vasodilation in healthy young men through an increase in nitric oxide production.

Our present findings, however, are discordant with those reported by Papamichael et al[10] who recently found that a cup of coffee (caffeine 80 mg) led to a decrease of brachial FMD, lasting for ≥1 hour after intake, compared to a decaffeinated beverage (caffeine <2 mg) in 17 healthy young adults. This discrepancy could be explained by the fact that a cup of coffee contains various ingredients other

than caffeine such as polyphenols, antioxidants, etc., that could act differently on peripheral vasculature. Furthermore, we used a 2.5-fold increase of caffeine (200 vs 80 mg) administered in purified capsules to prevent influence from other ingredients.

Other studies[4–7] have also demonstrated that caffeine may possibly have an acute unfavorable effect on arterial elastic properties in healthy subjects, assuming that increased arterial stiffness is associated with endothelial dysfunction.[27] Although a previous in vitro study[28] has suggested that caffeine increases CRP production by cytokines in 2 human hepatoma cell lines (Hep 3B and NPLC/PRF/5), our study is the first to demonstrate that acute caffeine ingestion decreases hs-CRP in subjects without CAD and patients with CAD. To the best of our knowledge, our study also shows for the first time that acute caffeine ingestion does not only increase but is also associated with adiponectin and with acute favorable effects on human FMD.

Our study results are in accord with those of Kempf et al[29] who observed a decrease in markers of subclinical inflammation including interleukin-18 but no change in systemic CRP or interleukin-6 after 2 months of coffee consumption (4 cups/day in first month followed by 8 cups/day in second month) in 47 healthy subjects <65 years old. Our present work demonstrated acute effects of caffeine on hs-CRP, although Kempf et al[29] measured chronic changes. Furthermore, Kempf et al found a positive association between serum caffeine concentration and plasma adiponectin in healthy subjects.

In a review article, Papaioannou et al[30] reported that, in addition to its pressor effects, acute caffeine ingestion provokes arterial stiffness, wave reflections, and central aortic systolic blood pressure, factors that are often overlooked. Mechanisms underlying the effects of caffeine ingestion and their role in cardiovascular risk are not always clear. However, in the present study, caffeine ingestion did not change heart rate at rest in controls or patients with CAD but significantly increased blood pressure in patients with CAD.

This study has some weaknesses: (1) its short 1-hour span (effects were measured 1 hour after a single oral dose of caffeine/placebo) because longer periods of caffeine consumption could have had stronger effects; (2) endothelial function was assessed using a single technique without taking into account endothelial activation markers (endothelin, reactive oxygen species such as superoxide anions, Regulated on Activation, Normal T Expressed and Secreted, Recombinant Human soluble CD40 Ligand, and interleukin-10) and oxidative stress status, which could have provided a more comprehensive understanding of endothelium function; (3) a tolerance factor may have occurred, causing effects of long-term therapy to differ from those of acute administration; (4) a causal relation could not be established based on present data; (5) despite being withheld for >12 hours, interference of concomitant vasoactive medications cannot be excluded; (6) some control patients may have had subclinical CAD (thus actually strengthening the overall findings regarding a difference between the 2 groups); (7) there were few women participants; (8) a relatively large dose of caffeine (200 g or 2.5 cups of coffee) may not be generally accepted typical consumption; and (9) FMD was measured only 2 times, before and 1 hour after caffeine ingestion, whereas 4 measurements (baseline, 30 minutes, 1 hour, and 2 hours) would have better described the FMD changes after caffeine ingestion. In light of these limitations, long-term studies are warranted to investigate the effect of long-term caffeine intake on FMD and its impact on future cardiovascular risk. Our present study does not resolve the controversy as to whether long-term coffee and/or caffeine intake improve or adversely affect vascular reactivity. Only a large-scale cross-over study comparing the effects of coffee (boiled and filtered, caffeinated and decaffeinated) and caffeine on vascular reactivity may solve this issue.

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