Acute Caffeine Intake Influences Central More Than Peripheral Blood Pressure in Young Adults


Background: The aim of this study was to characterize the acute effects of caffeine on peripheral and central blood pressure (BP) in healthy individuals, using validated noninvasive techniques.

Methods: In a randomized double-blind study, 300 mg caffeine or matching placebo was administered orally to 20 healthy adults and hemodynamic responses were observed. Central BP and augmentation index (AIx) were determined by pulse wave analysis; cardiac index (CI) was estimated by transthoracic bioimpedance; and heart rate variability (HRV) given by power spectral analysis of pulse interval. Pressure amplification (peripheral to central pulse pressure ratio) and systemic vascular resistance index were also calculated.

Results: Caffeine administration increased central systolic and diastolic BP by 7 ± 3 (P < .01) and 3 ± 2 mm Hg (P < .05), respectively (mean ± SEM) at 45 min, but had no effect on peripheral BP. Caffeine caused AIx to increase by 7 ± 2 and 0 ± 1%, respectively (P < .05), and pressure amplification to decrease by 1.0 ± 0.1 v 0.2 ± 0.2 (P < .001) placebo at 45 min.

Conclusions: Acute caffeine intake significantly increases central BP and large artery waveform transmission and diminishes pressure amplification in healthy adults. Therefore, the effects of caffeine on BP may be significantly underestimated by measurement of BP at the brachial artery. Am J Hypertens 2003;16:919–924 © 2003 American Journal of Hypertension, Ltd.

Key Words: Pulse pressure, pulse wave analysis, bioimpedance, heart rate variability, power spectral analysis.

Caffeine is the most widely used pharmacologically active substance in the world, and is found in a variety of foods, beverages, and medicinal preparations. Acute caffeine intake has consistently been shown to increase systemic blood pressure (BP), predominantly through effects on systemic vascular resistance. This has been attributed to increased circulating concentrations of catecholamines, but it is also seen in patients who have undergone adrenalectomy. Changes in the concentrations of angiotensin and atrial natriuretic peptide as well as antagonism of vascular adenosine A1 and A2 receptors have also been implicated. By contrast, the effect of chronic caffeine intake on BP is less well characterized, and conflicting data suggest that chronic consumption can increase, decrease, or have no effect on BP. Furthermore, it has been suggested that the acute pressor response to caffeine may be attenuated after several days because of the development of tolerance.

Recently the importance of pulse pressure, rather than systolic or diastolic BP alone, has been emphasized in determining future cardiovascular risk. In health, large artery compliance decreases peak central systolic BP and enhances diastolic BP, thereby lowering central pulse pressure. However, large artery stiffening is associated with a widened pulse pressure and increased central systolic BP, which is augmented by early peripheral waveform reflection. Arterial stiffening is a characteristic finding in the presence of any one of several major cardiovascular risk factors, for example diabetes mellitus or hypercholesterolaemia. There is increasing interest in the potential mechanisms that promote large artery stiffness, because the hemodynamic consequences may contribute to increased cardiovascular risk. Pulse wave analysis (PWA) is an established noninvasive method that allows large artery stiffness to be quantified in vivo. Examination of the radial artery pulse waveform by applanation tonometry allows a corresponding aortic pressure waveform to be constructed using a validated general transfer function. The augmentation index (AIx) quantifies the extent to which central BP is augmented during
systole by pressure waveforms reflected from the peripheries. Increased large arterial stiffness causes more rapid waveform propagation, such that reflected waves summate with central pressure waveforms earlier in the cardiac cycle, augmenting systolic rather than diastolic pressure. Therefore, large arterial stiffening is associated with higher pulse waveform velocity and increased AIx. The AIx can also be influenced by the proximity of the effective reflection point in the peripheral vasculature, which is governed by structural factors, such as arterial branching points, and sites of impedance mismatch. Increased systemic vascular resistance causes more proximal impedance mismatch at interfaces between conduit and resistance vessels, and can increase AIx. Increased systemic vascular resistance is also associated with raised BP, which can increase large arterial stiffening. Therefore, systemic vascular resistance is a potential confounding factor that can influence AIx, independent of changes in large arterial stiffness. Notwithstanding, AIx has been shown to provide a reproducible and reliable measure of large artery stiffness in vivo. A recent study found that caffeinated coffee ingestion caused increased arterial stiffness in healthy subjects, but decaffeinated coffee did not, suggesting that caffeine could have a direct influence on large artery function. A further study in hypertensive patients has shown that acute caffeine administration causes increased AIx and BP, with greater effects on central than peripheral BP.

In addition to increasing circulating catecholamine concentrations, the autonomic nervous system is capable of influencing cardiovascular regulation through adrenergic or vagal neural outflow. Short-term HRV provides a reliable means of assessing the cardiovascular influence of the sympathetic and parasympathetic nervous system by analysis of low frequency (LF) and high frequency (HF) power spectral variability domains, respectively. There is good agreement between the changes in the HRV spectral components and modulation of sympathetic activity elsewhere in the cardiovascular system, measured directly by muscle sympathetic nerve activity over a range of BP. The influence of isometric handgrip exercise, at 30% of maximal voluntary contraction, on HRV can be used as a stimulus of cardiovascular sympathetic activity. Although activation of the sympathetic nervous system has generally been implicated in mediating the pressor response to acute caffeine intake, the potential effect on autonomic activity, represented by HRV spectral domains, is unclear.

The purpose of this study was to examine the effects of acute caffeine intake on central BP and large artery stiffness using PWA in a randomized, placebo-controlled, double-blind study. The effects on sympathetic cardiac influence were also studied, using power spectral analysis of pulse interval during rest and sustained isometric handgrip exercise.

Methods

Subjects

Subjects were identified from a community database, held at the Clinical Research Centre of the University of Edinburgh. Men and women aged 18 to 45 years were included. Each subject regularly consumed 350 to 700 mL of coffee per day, containing approximately 180 to 360 mg caffeine. Exclusion criteria were elevated BP (>160/100 mm Hg), a clinical history of diabetes or cardiovascular disease, regular use of any prescribed medication, or use of any over-the-counter medication in the week before examination.

The local research ethics committee approved the study protocol, and written informed consent was obtained from each participant. The study conformed to the principles outlined in the Declaration of Helsinki.

Hemodynamic Measurements

Peripheral BP was recorded in duplicate in the brachial artery of the dominant arm using the validated Omron HEM-705CP oscillometric device (Omron Corp, Tokyo, Japan). Cardiac index was assessed using the noninvasive NCCOM3-R7 transthoracic bioimpedance technique (BioMed, Cheshire, UK). Mean arterial pressure (MAP) was calculated by integration of the arterial pressure waveform using SphygmoCor PWA software (PWH Medical, Sydney, Australia), and systemic vascular resistance index was calculated as MAP divided by CI.

Peripheral pressure waveforms were recorded noninvasively from the radial artery at the wrist of the dominant hand using an applanation tonometer (SPC-301 micromometer, Millar Instruments, Houston, TX), linked to SphygmoCor PWA apparatus. Integral software calculated MAP, based on peripheral systolic and diastolic BP pressure measurements, and the radial artery pressure waveform. SphygmoCor PWA software incorporates a validated transfer function, which allows corresponding aortic pressure waveforms to be constructed. Peripheral and central pressure waveforms are calibrated against MAP by harmonizing areas under both pressure–time curves. After 20 sequential waveforms have been acquired, the system software generates averaged peripheral and central aortic pressure waveforms, and calculates AIx as the difference between the first and second central systolic BP peaks expressed as a percentage of pulse pressure. Pressure amplification was calculated as the ratio of peripheral to central pulse pressure.

Heart Rate Variability

Signals from an electrocardiograph, recorded continuously over 5 min, were delivered to a dedicated computer for offline analysis using Chart software (ADInstruments, Hastings, UK). Artifacts were removed automatically and HRV was determined by fast Fourier transformation of the pulse interval. Variability was expressed as very low...
frequency (< 0.04 Hz), LF (0.04 to 0.149 Hz), and HF (0.15 to 0.4 Hz) domains; the LF:HF ratio was used to represent relative sympatho-vagal cardiac influence.21

**Plasma Caffeine Measurement**

Blood samples were collected in potassium EDTA Monovette tubes (Sarstedt Ltd, Leicester, UK), centrifuged at 1000 g at 4°C for 20 min, and plasma was decanted immediately and stored at −40°C before analysis. Caffeine concentrations were determined by high-pressure liquid chromatography using an Apex ODS C18 5-µm reverse phase column (Jones Chromatography Ltd., Mid Glamorgan, UK), 6% acetonitrile/water mobile phase, and 0.1 mol/L phosphate buffer with a 2 mL/min flow rate, and Hewlett-Packard 1100 series UV detector at a wavelength of 273 nm (Hewlett-Packard, South Queensferry, UK).

**Study Protocol**

A two-way randomized, crossover study was performed in 20 healthy subjects, who had fasted and abstained from caffeine from 10 PM the night before each examination. Studies were performed in the morning in a quiet room maintained at 24° to 26°C. Subjects had chest electrodes applied, and underwent insertion of a 18-standard gauge cannula into a vein in the antecubital fossa of the dominant handgrip exercise were used for HRV analysis. The venous cannula was withdrawn, electrodes were removed, and subjects were free to leave the facility.

**Data Analysis**

Subject numbers were determined from previous experience of the methods involved so as to give at least 80% power to detect a 10% difference in all primary outcome variables (BP, AIX, and LF:HF ratio). The BP and AIX responses to caffeine were compared with placebo by two-way analysis of variance. Baseline, post-treatment, and handgrip measures of LF:HF ratio were compared using paired Student t tests. Statistical significance was accepted at the 5% level throughout.

**Results**

Baseline characteristics of study subjects are shown in Table 1. Plasma concentrations of caffeine are shown at baseline and 1 h after administration of caffeine 300 mg or placebo (Fig. 1). Acute caffeine administration resulted in a significant increase in central (aortic) systolic and diastolic BP as compared with placebo (P < .001 and P < .005, respectively) but had little effect on peripheral (ie, brachial) BP (Table 2). Caffeine caused a greater increase in central systolic BP than peripheral systolic BP (P = .03). The hemodynamic data are presented in Table 2 as absolute values; analyses of the changes from baseline gave similar results. Caffeine caused a significant decrease in heart rate, CI, and pressure amplification compared with placebo, and an increase in systemic vascular resistance index and AIX.

Sustained isometric handgrip exercise caused a significant rise in the LF:HF ratio of power spectral HRV domains in the placebo arm of the study (P < .05). Administration of caffeine tended to lower the LF:HF ratio under resting conditions, and attenuated the rise in LF:HF ratio during isometric handgrip exercise (Fig. 2).
Table 2. Effect of caffeine or placebo administration on hemodynamic variables

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<td>80 ± 2</td>
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<td><strong>AIx (%)</strong></td>
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<td>8.0 ± 0.3</td>
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<td>10.1 ± 0.6</td>
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<td>9.6 ± 0.6</td>
<td>10.1 ± 0.6</td>
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* P < .05; † P = .01; ‡ P < .001.

Discussion

In this study, acute administration of 300 mg caffeine had a significant impact on cardiovascular function in healthy adults accustomed to regular caffeine ingestion. As expected, significantly higher plasma concentrations were attained 1 h after administration of caffeine than placebo, consistent with reported values from a previous study.  

Maximal hemodynamic responses occurred 45 min after caffeine administration, which coincides with the expected peak plasma concentrations based on previous reports and suggests a concentration-dependent relationship. High-pressure amplification and low AIx at baseline were consistent with the healthy young study population. Caffeine caused an acute pressor response, which predominantly affected central BP. The acute increase in AIx significantly underestimated the effects of caffeine on central BP. This could account at least in part for a lack of consistency between reports describing the effects of chronic caffeine intake on BP, in studies or cases in which only peripheral BP had been examined. Furthermore, previous studies that failed to show an acute pressor response to caffeine, in the context of regular caffeine intake, may have been limited by the use of peripheral BP assessment.

The present hemodynamic observations are consistent
with the effects of 250 mg caffeine in treated hypertensive patients, which increased AIx and increased central systolic BP more prominently than peripheral BP, and are similar to the effects of acute coffee ingestion on large artery stiffness previously observed in healthy subjects. The present findings provide direct evidence that caffeine accounts for the effects of caffeinated coffee intake on large artery compliance.

The interval between last caffeine intake and clinical examination was approximately 10 to 14 h, and allowed sufficient clearance, as confirmed by measurement of baseline plasma concentrations (Fig. 1). The current study group was accustomed to regular moderate coffee consumption, and studies were performed in the morning after an overnight fast. This is consistent with a normal everyday situation and is unlikely to cause significant withdrawal effects that could be encountered after longer periods of caffeine abstinence. The present hemodynamic findings indicate that regular coffee intake does not cause complete tolerance to the effects of caffeine on central BP, consistent with previous reports.

Heart Rate Variability

The trend toward a lower LF:HF ratio as well as the blunted LF:HF response to isometric handgrip exercise suggest that caffeine exerts a predominant parasympathetic rather than sympathetic cardiac influence. A recent study compared the effects of coffee or decaffeinated coffee intake or intravenous caffeine administration on muscle sympathetic nerve activity in healthy subjects, and found that caffeinated and decaffeinated coffee increased peripheral sympathetic activity and BP to a similar extent, suggesting that factors unrelated to caffeine may be responsible. Furthermore, caffeine enhanced parasympathetic cardiac influence resulting in lowered resting heart rate. These data are consistent with the present findings and suggest that heart rate slowing may be a baroreceptor-mediated response to increased BP. A previous study has shown that acute caffeine intake increases parasympathetic influence on spectral HRV domains in healthy volunteers. Caffeine appears to mediate increased central BP through effects on large artery stiffness and peripheral vascular resistance associated with a secondary increase in cardiac vagal tone and reduction in resting heart rate.

Study Limitations

Modification of resting heart rate has been shown to influence AIx in older patients with permanent pacemakers, such that a heart rate reduction of 5 beats/min causes a 4% increase in AIx. Furthermore, it is possible that increases in MAP and systemic vascular resistance index could further contribute to the observed increase in AIx, although these changes were comparatively small. Extrapolating these data to the current population, the observed maximal change in mean heart rate and MAP could account only for up to one half of the observed changes in AIx. The changes in potential confounding factors could account for part, but not all, of the observed increase in AIx, and therefore do not sufficiently explain the present findings.

A further potential limitation is that the study population was young and healthy. The effects of raising central BP may be of greater importance in individuals with higher cardiovascular risk including those with diabetes mellitus, hypertension, or advanced age; and the findings require confirmation in these groups.

In summary, the influence of regular caffeine intake on cardiovascular risk remains controversial, predominantly because of its association with other confounding factors. However, the observed effects on central BP are likely to have a significant clinical impact if sustained. Further work is required to clarify the potential mechanisms through which caffeine influences central BP and large artery function. In addition, the effects of chronic caffeine intake on central BP merit further investigation.

Acknowledgment

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References


