Caffeine Increases Aortic Stiffness in Hypertensive Patients

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**Background:** Caffeine is the most widely used pharmacologic substance. Aortic stiffness is an important factor for cardiovascular system performance and a prognosticator of cardiovascular risk. We investigated the effect of caffeine on aortic stiffness in treated hypertensive patients.

**Methods:** We studied the effect of caffeine (250 mg) in 12 treated hypertensive patients according to a randomized, placebo-controlled, double-blind, cross-over design during a 3-h period. Aortic stiffness was evaluated by carotid-femoral pulse wave velocity.

**Results:** Systolic blood pressure (BP) and pulse pressure increased significantly throughout the study (by 12.3 and 7.4 mm Hg, \( P = .005 \) and \( P < .01 \), respectively), whereas diastolic BP did not change. Pulse wave velocity increased (by 0.57 m/sec, \( P < .05 \)) denoting an increase in aortic stiffness. This effect of caffeine lasted throughout the study (3 h), peaking at 60 min and decreasing progressively thereafter.

**Conclusions:** These results demonstrate, for the first time, that caffeine exerts an acute unfavorable effect on aortic stiffness in treated hypertensive patients. This finding has important implications for the impact of caffeine consumption on cardiovascular risk in hypertension. Am J Hypertens 2003;16:63–66 © 2003 American Journal of Hypertension, Ltd.

**Key Words:** Aorta, arteries, caffeine, hypertension, stiffness.

Aortic stiffness is an important determinant of cardiovascular system performance, by affecting ventricular function, coronary blood flow, and the mechanical integrity of arteries.1,2 Furthermore, aortic stiffness has been identified as an independent factor of cardiovascular risk.3–5

Caffeine is the most widely used pharmacologic substance; however, its effect on arterial stiffness has not been defined. Furthermore, its role in hypertension is controversial. Caffeine has a strong, persistent, acute pressor effect,6 but the effect of its habitual use on blood pressure (BP) has not been clarified. Nevertheless, accumulating pieces of evidence suggest that systolic (predominantly) and diastolic BP increase in chronic coffee drinkers.7,8

We have previously shown that caffeine increases wave reflection in hypertensive patients9 and it was hypothesized that this effect may be, at least in part, due to an increase in arterial stiffness. The purpose of the present study was to investigate the acute effect of caffeine on aortic stiffness in treated hypertensive subjects.

**Methods**

**Study Population**

The study population consisted of 12 treated patients (aged 60 ± 3 years, 7 men) with mild-to-moderate hypertension, who were considered to be effectively controlled under medication in the past 6 months. The patients were studied while on regular medications (angiotensin converting enzyme inhibitors, calcium channel blockers, \( \beta \)-blockers, diuretics, angiotensin receptor blockers either as monotherapy or in combination) and on each study day for which they had taken their morning dose. One patient had non–insulin-dependent diabetes, two had hyperlipidemia, six had a positive family history for premature vascular disease, and one was a current smoker. All patients were regular caffeine consumers. All patients abstained from caffeine, ethanol, and nicotine for at least 12 h before each session. The study protocol was approved by the St. Vincent’s Hospital Research Ethics Committee and all subjects gave written informed consent.
Study Design
The study was carried out using a randomized, placebo-controlled, double-blind, cross-over design. Each subject was studied in the morning on two separate days, one with caffeine and one with placebo, after an overnight fast. Measurements were obtained in a quiet, air-conditioned room. After a 20-min rest period, baseline measurements were taken while the subjects were lying on a bed. After baseline measurements, the subjects took either 250 mg of caffeine (No-Doz, Key Pharmaceuticals, Rhodes, NSW, Australia, a dose equivalent to 2 to 3 cups of coffee) or placebo, and all measurements were repeated at 30, 60, 120, and 180 min after drug intake.

Evaluation of Aortic Elastic Properties
The pressure pulse generated by ventricular ejection is propagated through the arterial tree at a velocity determined by the elastic and geometric properties of the arterial wall. The pulse travels at a higher velocity in a stiff aorta and vice versa. Pulse wave velocity is a well-established index of arterial elastic properties and a prognosticator of cardiovascular risk.3,4,10 Carotid–femoral pulse wave velocity was calculated from measurements of pulse transit time and the distance traveled between two recording sites (pulse wave velocity = distance [in meters]/transit time [in seconds]) using a validated noninvasive device (Complior, Dupont Medical, Pantin, France) that allows online pulse wave recording and automatic calculation of pulse wave velocity.10 Two different pulse waves were obtained simultaneously at two sites (at the base of the neck for the common carotid and over the right femoral artery) with two transducers. The distance was defined as: (distance from the suprasternic notch to femoral artery) – (distance from carotid artery to the suprasternic notch).

Statistical Analysis
Data are expressed as the mean ± SEM. P values less than .05 were considered statistically significant. Characteristics and resting cardiovascular parameters were compared between the caffeine and placebo sessions using the paired t test. Repeated-measures analysis of variance (averaged F) was used to detect statistically significant changes over time in variables performing three different analyses 1) within the caffeine and 2) within the placebo session separately, and 3) between the caffeine and the placebo session compositely (= 2 drugs [caffeine versus placebo] × 5 periods [baseline, 30, 60, 120, 180, min postdrug]); the latter is referred to as drug interaction in the Results section. Data analysis was performed with SPSS software, version 9.0 (Chicago, IL).

Results
There were no differences in all baseline characteristics between the two sessions.

Changes After Caffeine or Placebo Intake
Heart rate decreased both in the caffeine and the placebo session (by 4.6 and 2.5 beats/min; P = .001 and P < .005, respectively); however, the drug interaction was not significant between the two sessions. Systolic BP increased in the caffeine session (P < .001), whereas it remained unchanged in the placebo session. Furthermore, the drug interaction was significant between the two sessions (P = .005; Fig. 1). Diastolic BP increased in the caffeine session but not in the placebo session.
(P < .05), whereas it remained unchanged in the placebo session; however, the drug interaction between the two sessions was not significant (Fig. 1). Pulse pressure increased in the caffeine session (P < .001). In contrast, it remained unchanged in the placebo session. Moreover, the drug interaction was significant between the two sessions (P < .01; Fig. 1).

Pulse wave velocity increased significantly in the caffeine session (P < .005), whereas it remained unchanged in the placebo session. The drug interaction was significant between the two sessions (P < .05) and the response (net caffeine minus placebo values at each time point) exhibited an initial increase at 30 min, reached a peak at 60 min, and decreased progressively thereafter, without, however, returning to baseline values at 3 h (Fig. 1).

Discussion

Our study shows for the first time that caffeine consumption increases acutely aortic stiffness in treated hypertensive patients. This effect lasts for at least 3 h, reaching a peak at 60 min, and decreasing progressively thereafter without, however, returning to baseline values. We have previously shown that caffeine increases wave reflection in hypertensive patients9 and aortic stiffness in healthy subjects.11 Moreover, similar findings have been reported in a study with a limited number of young subjects.12

This unfavorable effect of caffeine on aortic stiffness may have an important clinical impact due to its wide applicability (80% or more of adults in Western societies are caffeine consumers), its considerable duration (at least 3 h), and, most important, due to the significance of aortic function. Aortic stiffness has been identified as an independent predictor of cardiovascular risk.3–5 A stiff aorta increases left ventricular load and myocardial oxygen demands and impairs ventricular function. Concurrently, it compromises coronary blood flow and predisposes to ischemia. Furthermore, by increasing pulse pressure, it increases pulsatile stretch of the arteries, leading to mechanical fatigue of their elastic components.1,2 Our findings have particular significance for hypertensive patients in whom aortic stiffness is already increased compared to healthy subjects.3,13

Although still a not completely resolved issue, evidence supports that habitual caffeine intake increases systolic (predominantly) and diastolic BP chronically, and especially in older adults.7,8 Increased stiffness of large arteries plays an important role in the pathogenesis of hypertension, particularly isolated systolic hypertension in the elderly. Thus, increased arterial stiffness may be a mechanism involved in the prohypertensive effect of chronic caffeine intake.

The patients were intentionally studied while on medication. Therefore, the results of our study imply that antihypertensive therapy does not provide a complete protection from the effects of caffeine on arterial stiffness. In this context, it should be noted that hypertensive patients exhibit a stronger response to caffeine than normotensive subjects.7,14

Tolerance develops to caffeine with repeated exposure; thus, it may be questioned whether this acute effect on aortic stiffness is applicable to chronic caffeine consumers. However, it should be stressed that the response of a habitual coffee drinker to caffeine is not uniform throughout the day with the effect being inversely related to the plasma caffeine levels at the time the substance is ingested.15 Our protocol was designed to mimic the typical consumption pattern (abstinence ≥12 h, study in the morning). Overnight abstinence leads to practically complete clearance of caffeine from the body and thus the consumer is rendered sensitive to arterial stiffening for a prolonged period the next morning when, typically, the first exposure to caffeine takes place.15

The methodology used in the present study does not allow for clarification of the mechanism involved in changes in aortic stiffness. However, apart from the increase in BP (passive effect), an active effect of the drug on the intrinsic properties of the aorta may contribute. Caffeine causes vasoconstriction due to antagonism of endogenous adenosine or due to increased circulating catecholamines. However, studies with specially designed methodology5,13 are needed to clarify the nature of the effect of caffeine. Nevertheless, the clinical implications of the effect of caffeine on aortic elastic properties stand irrespective of the mechanism.

Caffeine may be the strongest but it is not the only substance in coffee and, therefore, the results may not be completely extendable to coffee consumption. On the other hand, caffeine is contained in tea, soft drinks, “energy” drinks, and caffeinated bottled water and, therefore, our results relate to those beverages as well.

The results of the present study demonstrate, for the first time, that caffeine has an acute unfavorable effect on aortic stiffness in treated hypertensive patients. This effect may be involved in the pathogenesis of hypertension and may have important implications for cardiovascular risk in hypertensive patients.

References


