Acute Effect of Caffeine on Arterial Stiffness and Aortic Pressure Waveform

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Abstract—Caffeine acutely increases blood pressure and peripheral vascular resistance, in part because of sympathetic stimulation. Its effects on large artery properties are largely unknown. In a double-blind crossover study, 7 healthy subjects 26±2.6 years of age (mean±SEM) were studied for 90 minutes while in the supine position on 2 occasions separated by a week in random order after ingestion of 250 mL caffeinated (150 mg) and decaffeinated (<2 mg) coffee. Compared with baseline, arterial stiffness measured by carotid femoral pulse wave velocity increased progressively from 7.2±0.41 to 8.0±0.6 m/s (P<0.05) at 90 minutes after caffeine intake, an effect that may be independent of changes in blood pressure. In addition, arterial wave reflection, measured by applanation tonometry from the aortic pressure waveform, also increased from −5.7±7.6% to 5.28%±5.6 (P<0.01). No such changes were seen with decaffeinated coffee intake. Although the integral of the brachial systolic and diastolic blood pressure values over the 90 minutes was larger (P<0.05) after caffeinated than decaffeinated coffee intake, the effect on aortic systolic and diastolic blood pressures was more pronounced (P<0.05) than on the brachial artery. These results show a significant effect of caffeine intake on arterial tone and function and suggest that caffeine acutely increases arterial stiffness. (Hypertension. 2001; 38:227-231.)

Key Words: caffeine ■ arterial stiffness ■ aortic pressure waveform ■ blood pressure ■ pulse wave velocity ■ augmentation index

There is conflicting evidence on the effect of caffeine on systemic hemodynamics.1–3 In short-term studies, it has been shown to increase blood pressure and peripheral vascular resistance, but tolerance rapidly develops.4 The pressor effect of caffeine is predominantly due to its action on the resistance vessels rather than an increase in cardiac output.5 Although the increases in sympathetic nervous system activity, serum adrenaline, and renin have been causally linked, the acute pressor effect is also seen in adrenalectomized patients.6 Vasoactive hormones such as aldosterone, vasopressin, and arterial natriuretic peptide, however, are not increased by caffeine.4,7 Caffeine is a nonselective antagonist of adenosine at both A1 and A2 receptors. Adenosine A1 receptor stimulation inhibits the release of norepinephrine at the sympathetic smooth muscle junction, whereas A2 receptors have a direct vasodilatory effect.8,9

There is a growing appreciation of the role of the aorta in the pathogenesis of raised blood pressure, particularly systolic.10–12 The aorta and large arteries serve a major function in the cardiovascular system as a conduit and buffering organ. The large arteries buffer the pressure changes resulting from intermittent ventricular ejection of blood into the aorta. By absorbing a proportion of the energy of ventricular ejection in systole and releasing it in diastole, they maintain coronary blood flow and avoid an increase in left ventricular afterload. Blood flow to the periphery is thus smoothed. Pressure waves are reflected back from the periphery of the circulation and summate with the forward-going wave to produce the characteristic aortic pressure waveform. When the timing of such ventricular-vascular coupling is optimal, the reflected waves return during diastole and do not affect aortic systolic pressure, but they will enhance coronary blood flow.10 On the other hand, with vascular stiffening, pulse wave velocity (PWV) and the amplitude of the reflected waves both increase, so the reflected wave arrives earlier in systole rather than in diastole and thereby augments central systolic pressure. This early wave reflection elevates systolic and pulse pressures and may decrease coronary perfusion.10 Increased large artery stiffness is associated with a number of cardiovascular risk factors, including age, smoking, hypertension, diabetes, hypercholesterolemia, and atherosclerosis.12 Increased stiffness may precede the onset of clinically overt atheromatous disease.13

The technique of pulse wave analysis can be used to assess aortic blood pressures noninvasively.14 Radial artery pressure waveform is recorded noninvasively by applanation tonometry,15 and when a validated integral transfer function is applied,16 the aortic pressure waveform can be derived. In
particular, aortic pressures can be measured, and the augmentation index (A1%), a measure of arterial wave reflection in the aorta, calculated. A high A1% is closely related to aortic stiffness.17

The elastic properties of large arteries can be assessed noninvasively by determination of the velocity of the pulse wave along the respective arterial segment as PWV. For the aorta, measurement of carotid-femoral PWV provides a useful index of vascular stiffness. Although the concept of arterial stiffness is not new and arterial stiffness contributes to the development of hypertension, particularly systolic hypertension in the elderly,18 there is increasing evidence that aortic PWV is an independent risk factor for cardiovascular and all-cause mortality in hypertension19,20 and in renal disease.21

Caffeine is one of the most widely consumed vasoactive substances, with 80% of adults in the United States having a daily intake of 200 to 300 mg.22 A recent meta-analysis suggests that long-term coffee consumption may increase systolic blood pressure.3 The acute effects of caffeine on large artery properties, however, are not described. Because early wave reflection and PWV, measures of arterial stiffness, are associated with an increase in systolic blood pressure, we examined the effect of caffeine on these properties of large arteries.

Methods

Subjects
Seven healthy volunteers (4 female) 26-6 years of age (mean±SD) abstained from smoking and drinking alcohol- or caffeine-containing beverages in the 12 hours before the study, which had the institution’s ethics committee approval.

Subjects received 250 mL freshly brewed caffeinated or decaffeinated coffee in a randomized, double-blind, crossover protocol on 2 separate days ≥1 week apart. The caffeine content of the 250 mL coffee determined by high-pressure liquid chromatography23 was 150±5 and <2 mg for caffeinated and decaffeinated coffee, respectively. The hemodynamic measurements were performed in a quiet room at 20°C to 23°C. Subjects were supine throughout the study. After a stable baseline measurement was obtained, hemodynamic measurements were performed in a quiet room at 20°C to 23°C. Subjects were supine throughout the study. After a stable baseline measurement was obtained, hemodynamic measurements were made in the left arm at baseline and 30, 60 and 90 minutes after ingestion of coffee.

Blood Pressure Measurements
Brachial blood pressure and heart rate were measured with an automated digital oscillometric blood pressure monitor (Omron model HEM 705-CP), and a mean of 3 readings was taken.

Deviation of the Aortic Pressure Waveform
Immediately thereafter, the radial artery pulse was recorded by applanation tonometry with a high-fidelity micromanometer (BPAS-1, PWV Medical). The central arterial waveform was derived from radial tonometry by use of a previously validated transfer factor within the software package (Sphynxocor) as previously described.24 The A1% was calculated from the derived aortic pressure waveform as the height of the late systolic peak divided by pulse pressure. The validity of the derived A1% has been confirmed by simultaneous direct central aortic measurements and is highly reproducible in both healthy and diseased populations.25,26

PWV Measurements
Carotid-femoral PWV (m/s) was determined by using the foot-to-foot method with the Complior device from simultaneous recordings by 2 pressure-sensitive transducers and measuring the time delay of successive records from the foot of each wave divided by the measured surface distance between the transducers. Because the direction of blood flow in the carotid artery is opposite that in the aorta, there is a small margin of error, which is considered insignificant.27 Furthermore, repeated measurement in the same subjects over time considers only the change in PWV. The validity of the Complior has been established.28

Statistical Analysis
The baseline values for both study days were analyzed by 1-way ANOVA. The effect of coffee on time-dependent patterns of evolution of blood pressure, PWV, and A1% was tested for treatment and period effects by repeated-measures ANOVA. Because blood pressure influences arterial hemodynamic parameters, we made a complementary analysis on these variables from baseline over time, adjusting for changes in blood pressure at the time they were measured. Comparison of the area under the blood pressure–time curve corrected to the baseline reading by the trapezoidal rule was made by the Wilcoxon rank-sum test. Correlations were examined by least-squares regression analysis. The results are presented as mean±SEM (n=0.05).

An expanded Methods section can be found in an online data supplement at http://www.hypertensionaha.org.

Results

There was no significant difference in the baseline hemodynamic values for both study days.

Acute Effects of Caffeine on Blood Pressure and Heart Rate

The changes in brachial systolic and diastolic blood pressures over the 90 minutes after intake of both caffeinated and decaffeinated coffee are shown in Figure 1. There was a significant increase in brachial diastolic blood pressure but not in brachial systolic blood pressure over 90 minutes. However, the integrated change in blood pressure, represented by the area under the systolic and diastolic blood pressure–time curve, was greater after intake of caffeinated than decaffeinated coffee (P<0.05). Aortic systolic and diastolic blood pressures increased significantly with time after caffeinated but not decaffeinated coffee ingestion (P<0.05). Moreover, the effect of caffeine was more pronounced on aortic blood pressure than brachial systolic pressures (P<0.05) as shown by a larger increase in the area under the blood pressure–time curve for aortic than brachial blood pressure (Figure 1). There was no significant change in heart rate after intake of either caffeinated or decaffeinated coffee.

Acute Effects of Caffeine on PWV
After caffeinated coffee intake, PWV increased progressively from 7.2±0.4 to 8.0±0.6 m/s at the end of 90 minutes (P<0.05). No change was seen with decaffeinated coffee (Figure 2). No correlation was found between a change in PWV and the increase in blood pressure. The increase in PWV, however, remained significant after adjustment for the changes in blood pressure at 30 minutes for systolic blood pressure only (P=0.02 for systolic, P=0.06 for diastolic) and at 60 minutes (P<0.05) for both systolic and diastolic pressures but not at 90 minutes.

Acute Effects of Caffeine on Arterial Wave Reflection
The A1% increased from −5.1%±7.6 to 5.28%±5.6 after caffeine intake over 90 minutes (P<0.01). There was no
significant effect of decaffeinated coffee intake on AI% (Figure 2). The increase in AI% showed a trend to significance after adjustment for blood pressure at 60 minutes ($P=0.056$ for systolic, $P=0.07$ for diastolic) only. There was no correlation between the increase in AI% and the increase in blood pressure.

**Discussion**

This study demonstrates an acute effect of coffee on aortic waveform, blood pressure, and vascular stiffness. We believe this can be attributed to caffeine because the effect was not seen with decaffeinated coffee. These results not only suggest the possibility that this action of coffee may contribute to its "hypertensive effect" but also emphasize the importance of controlling caffeine intake in studies on vascular stiffness.

Although we have shown an acute effect on arterial stiffness, it is interesting to note that a recent meta-analysis suggests that caffeine intake is incomplete. During long-term ingestion of coffee, systolic but not diastolic blood pressure is elevated. Chronic arterial stiffness is associated particularly with increased systolic rather than diastolic pressure. The deterioration of the elastic properties of the aorta in this study as shown by increased PWV and arterial wave reflection may be one of the mechanisms underlying the pressor effects of caffeine that hitherto have been overlooked. Although it is not possible to definitely conclude that this effect is independent of the effect of caffeine on blood pressure because the number of subjects studied is relatively small, we did not find any correlation between the increase in blood pressure and these variables. In addition, after adjustment for changes in blood pressure, the effect of caffeine on PWV and possibly AI% still remained significant. Furthermore, the greater increase in aortic than in brachial blood pressure, as reflected by a comparison of the area under time-pressure curves, suggests an effect additional to peripheral sympathetic vasoconstriction. Increased PWV and arterial wave reflection are the probable explanation for this finding. These results also suggest an underestimation of the pressor effects of caffeine when the effects on aortic pressure are not specifically measured. The increased PWV is considered to reflect an increase in aortic stiffness, whereas the effect on AI% or arterial wave reflection may be due in part
to both increased PWV and increased vascular smooth muscle tone of the peripheral muscular arteries.

We also noted a pressor effect on peripheral blood pressure, the magnitude of which is smaller than that seen in some other studies. This can be attributed largely to the dose (150 mg) administered. We chose this dose because it represents the usual social intake of caffeine better than the 250-mg dose used in other studies, which is more equivalent to the total daily dose. Although the number of subjects is relatively small, the study was randomized and double blind. Furthermore, the results are internally consistent because the surrogate markers of vascular stiffness were measured simultaneously by 2 independent methods, applanation tonometry and PWV.

The published data relating to intake of coffee and caffeine on blood pressure in humans were recently reviewed from MEDLINE and Current Contents databases searched from 1966 to April 1999. Short-term intake of coffee increases blood pressure, and the pressor response is strongest in hypertensive subjects. Repeated administration of caffeine showed a persistent pressor effect in some studies, whereas in others, long-term caffeine ingestion did not increase blood pressure. Epidemiological studies have also produced contradictory findings regarding the association between blood pressure and coffee consumption. However, during regular use, tolerance to the cardiovascular responses develops in some people; therefore, no systematic elevation of blood pressure in long-term and in population studies can be shown. Overall, they concluded that regular coffee ingestion may be harmful to some hypertension-prone subjects, and a more recent meta-analysis shows a significant chronic effect on systolic pressure alone.

Different sensitivity, an issue of particular importance, has recently been specifically addressed. The acute effect of caffeine on arterial blood pressure was compared in 5 male hypertension risk groups: groups with optimal blood pressure, normal blood pressure, high to normal blood pressure, stage 1 hypertension, and treated hypertension. Caffeine (250 mg) raised both systolic and diastolic blood pressures, but the strongest response to caffeine was observed among diagnosed men, followed by the stage 1 and high to normal groups and then by the normal and optimal groups. Diagnosed hypertensive men had a predrug to postdrug change in blood pressure that was 150% greater than in the optimal group. The acute blood pressure elevation with caffeine is also enhanced in borderline hypertension. Caffeine also seems to have an additive pressor effect with stress in male medical students with a family history of hypertension and high to normal blood pressure. Both systolic and diastolic blood pressures were affected. In contrast, in the long-term studies, the effect of caffeine seems to be predominantly systolic. In normotensive middle-aged men who were habitual coffee drinkers, switching to decaffeinated coffee also led to a significant reduction in mean systolic but not diastolic ambulatory blood pressure. In this context, it should be noted that the effects of chronic vascular stiffness manifest predominantly as changes in systolic pressure.

The cardiovascular effects of caffeine are mediated largely through blockade of both A1 and A2 adenosine receptors. Inhibition of phosphodiesterases is also seen, but only in pharmacological doses. That caffeine may have vascular effects is also suggested in a recent study in which it attenuated the increase in forearm blood flow after exercise. In that study, caffeine also induced an increase in angiotensin II. The main novel finding in our study is that caffeine acutely stiffens the aorta and impedes the function of the peripheral muscular arteries, which may be an additional vascular mechanism for the hypertensive effect of caffeine. On the other hand, there may be some tolerance to this effect of caffeine, an issue that requires a longitudinal study.

Epidemiological data now show that PWV is an independent risk factor for total and cardiovascular mortality. Recently, measurement of PWV in hypertensive patients and in those at risk of cardiovascular disease has been recommended. In addition, arterial wave reflection is commonly assessed in vascular studies. Therefore, our findings are also important in view of the ubiquitous intake of caffeine, and studies conducted on vascular stiffness should control for its intake.

References


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