Chronic coffee consumption has a detrimental effect on aortic stiffness and wave reflections1,2

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ABSTRACT

Background: The effect of coffee consumption on the cardiovascular system is still an unresolved issue. Aortic stiffness and wave reflections are important prognosticators of cardiovascular disease risk. We have shown that caffeine acutely increases aortic stiffness and wave reflections.

Objective: The objective was to investigate the effect of chronic coffee consumption on aortic stiffness and wave reflections.

Design: This was a cross-sectional study of 228 healthy subjects: 141 men (± SD: 41 ± 8 y old) and 87 women (41 ± 9 y old). Aortic stiffness was evaluated with carotid-femoral pulse wave velocity (PWV). Wave reflections were evaluated with augmentation index (AIx) and augmented pressure (AP) of the aortic pressure waveform with the use of high-fidelity pulse wave analysis. Coffee consumption was ascertained over 1 y with a food-frequency questionnaire.

Results: A linear relation between coffee consumption and PWV, AIx, and AP was observed (P for trend < 0.05). Compared with the nonconsumption group, PWV was on average 13% higher, AIx was 2-fold higher, and AP was 2.4-fold higher (P < 0.01 for all) in the high-consumption group (>450 mL/d). The findings remained significant after control for confounders such as age, sex, smoking habits, body mass index, total and LDL cholesterol, triacylglycerols, blood glucose, mean blood pressure, and heart rate. The linear relation (P for trend < 0.05) observed between coffee consumption and arterial pressures was largely explained when the covariates were entered in the model.

Conclusions: Chronic coffee consumption exerts a detrimental effect on aortic stiffness and wave reflections, which may increase the risk of cardiovascular disease. Am J Clin Nutr 2005;81:1307–12.

KEY WORDS Aorta, caffeine, coffee, stiffness, wave reflections

INTRODUCTION

The results of studies on the effect of coffee intake on cardiovascular disease risk are conflicting and range from a strong, positive association to no association (1, 2). We have shown that there is a J-shaped relation between coffee consumption and the risk of developing acute coronary syndromes (3). The role of caffeine in raising blood pressure is also a controversial issue. Caffeine has a strong, persistent, acute pressor effect (4), but the effect of habitual caffeine intake on blood pressure is less clear (5–7).

Large artery stiffness and wave reflections are important independent prognosticators of cardiovascular disease risk because they determine left ventricular function, coronary blood flow, and mechanical integrity of arteries (8–16). Although we and others previously showed that caffeine (17–21) acutely increases arterial stiffness and wave reflections, the chronic effect of coffee consumption on these indexes has not been defined. The present study was undertaken to investigate whether chronic coffee consumption affects aortic stiffness and wave reflections in healthy subjects.

SUBJECTS AND METHODS

Subjects

The study population consisted of a total of 228 clinically healthy subjects: 141 men (± SD: 41 ± 8 y old) and 87 women (41 ± 9 y old). The subjects were randomly selected from the employees’ records of 2 large industries located in the Athens, Greece, area and represented various socioeconomic categories. Based on a detailed clinical interview and examination, none of the patients had any evidence of cardiovascular disease, hypertension, hypercholesterolemia, diabetes mellitus, or any chronic disease. Furthermore, lipid and fasting blood sugar concentrations were measured in blood samples. Women taking oral contraceptives were excluded from the study.

Current smokers were defined as those who smoked at least one cigarette per day, and former smokers were defined as those who had stopped smoking >1 y before the study began. The remaining participants were defined as nonsmokers. For the multivariate statistical analyses, cigarette smoking was quantified as the number of cigarettes smoked per day, adjusted for a nicotine content of 0.8 mg/cigarette. Body mass index was calculated as weight (in kg) divided by standing height squared (in m). Obesity was defined as a body mass index > 29.9 (in kg/m²).

Physical activity was defined as leisure or occupational time activity of a certain intensity and duration, at least once per week.

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during the past year. The remaining subjects were defined as being physically inactive.

All subjects were studied in the morning after fasting overnight in a quiet, air-conditioned room. After a 15-min rest, arterial blood pressure was measured 3 times on the right arm with a sphygmomanometer. Subsequently, arterial function was measured. The study protocol was approved by our Institutional Research Ethics Committee, and all subjects gave written informed consent.

Coffee intake assessment

All participants were asked to report their usual frequency of coffee consumption during the past year on a food-frequency questionnaire, which was validated by the Unit of Nutrition, Athens Medical School (22). All reported types of coffee (instant, “Greek” type, filtered, espresso, or cappuccino) were adjusted for 1 cup (150 mL) of coffee and a caffeine concentration of 80 mg. According to the distribution of coffee consumption, we categorized usual coffee consumption as none, low (<200 mL/d), moderate (200–450 mL/d), or high (>450 mL/d). Included in the analysis were the following dummy variables: consumption of decaffeinated coffee, tea, and caffeine-containing drinks (cola types) and chocolate. The duration of coffee consumption (in y) and cessation of coffee intake during the previous year (months of abstinence) were recorded and considered as an interaction term in all analyses. Cup-years were then calculated as the product of cups of coffee consumed times the years of consumption. According to self-reported data, none of the participants took medications (prescribed or over-the-counter) that contained caffeine.

Evaluation of aortic elastic properties and wave reflection

The pulse travels at a higher velocity in a stiff aorta and vice versa. Carotid-femoral pulse wave velocity (PWV), a classic and established index of aortic stiffness (8, 9, 12–14, 18–20, 23, 24), was calculated from measurements of pulse transit time and the distance traveled between 2 recording sites (pulse wave velocity = distance [meters]/transit time [seconds]) with a validated noninvasive device (Complior; Artech Medical, Pantin, France), which allows online pulse wave recording and automatic calculation of pulse wave velocity (25). Two different pulse waves were obtained simultaneously at 2 sites (at the base of the neck for the common carotid and over the right femoral artery) with 2 transducers. The distance was defined as follows: (distance from the suprasternal notch to femoral artery) − (distance from carotid artery to the suprasternal notch).

The pressure waveform recorded at any site of the arterial tree is the sum of the forward traveling waveform, which is the waveform generated by pump ejection, and the backward traveling, which is the “echo” of the incident wave reflected at peripheral sites. The merging point of the incident and the reflected wave can be identified on the pressure waveform as an inflection point (Figure 1), which divides the systole into an early and late systolic phase in most people. Augmentation index (AIx), augmented pressure (AP), and t of the central (aortic) pressure waveform were measured as an index of wave reflection. AP is the pressure added to the incident wave by the returning reflected wave and represents the pressure boost that the left ventricle must cope with and which is caused by wave reflection. AP is defined as the maximum systolic pressure minus the pressure at the inflection point. AIx is defined as the AP divided by the pulse pressure and is expressed as a percentage. AIx is a composite measure of the magnitude of wave reflection and arterial stiffness, which affects the timing of the wave reflection. Larger AIx values indicate increased wave reflection from the periphery, an earlier return of the reflected wave as a result of increased PWV (due to increased arterial stiffness), or both. t is the time from the beginning of the waveform to the inflection point (Figure 1), and it is also an index of arterial stiffness. A pulse wave traveling fast downstream and backward after reflection at the periphery will meet the incident wave at an earlier point of the cardiac cycle; thus, t will be shorter and vice versa. Because AIx and AP are influenced by changes in heart rate (26), this index was included as a covariate in the analysis. AIx was measured by using a validated, commercially available system (Sphygmocor, AtCor Medical, Sydney, Australia), which uses the principle of applanation tonometry and appropriate acquisition and analysis software for noninvasive recording and analysis of the arterial pulse. The technique was previously described in detail (8, 9, 17, 19, 27, 28). In brief, from radial (peripheral) artery recordings, the central (aortic) arterial pressure was derived with the use of a generalized transfer function that has been shown to give an accurate estimate of the central arterial pressure waveform and its characteristics (8, 27, 28). Waveforms of radial pressure were calibrated according to sphygmomanometric systolic and diastolic pressure measured in the brachial artery, because there is practically negligible pressure pulse amplification between the brachial and the radial arteries (8).

Repeatability of arterial function indexes

Our repeatability for determining PWV and AIx according to the Bland-Altman method was previously defined (19). The repeatability coefficient was calculated as defined by the British Standard Institution, ie, according to the following formula:

\[
\text{Repeatability coefficient} = 2 \times \sqrt{\frac{\sum d_i^2}{N}} \quad (I)
\]

where \(N\) is the sample size and \(d_i\) is the difference between the 2 measurements in a pair. The repeatability coefficient values were

FIGURE 1. Representation of pulse waveform analysis. An inflection point in the waveform identifies the merging point of the incident and the reflected wave. AIx, augmentation index; AP, augmented pressure; PP, pulse pressure; \(\Delta t\), time from the beginning of the waveform to the inflection point.
0.575 m/s and 6.06% for PWV and Aix, respectively. Furthermore, the repeatability coefficients were 3.90% and 14.09% for PWV and Aix, respectively.

Statistical analysis

On the basis of a statistical power calculation, we found that the number of participants studied was adequate to evaluate >0.5 two-tailed standardized differences of the investigated markers between coffee consumption groups. In particular, we achieved a statistical power >0.80 at a P value < 0.05.

Continuous variables are presented as means ± SD, whereas qualitative variables are presented as absolute and relative frequencies. Associations between coffee consumption groups and sex were tested by use of contingency tables and the calculation of chi-squared tests. Correlations between variables were evaluated by calculating Pearson’s correlation coefficient for the normally distributed variables and Spearman’s correlation coefficients for skewed variables. Comparisons between normally distributed continuous variables and coffee-consuming groups were performed by analysis of variance. Differences in arterial function indexes and arterial pressures between particular subgroups, according to coffee consumption, were tested by using post hoc analysis after correction of the P value for multiple comparisons with the Bonferroni correction.

The univariate generalized regression analysis was applied to evaluate the association between the investigated arterial function indexes (dependent variable) and coffee intake in cup-years, after adjustment for several potential confounders (covariates). The assumptions for linearity and homoscedasticity were tested based on the standardized residuals plots, whereas the assumption of normality for the dependent variable was tested by using the Shapiro-Wilk criterion. First-order interactions between coffee consumption and smoking habits, sex, obesity status, physical activity, and lipid and blood glucose concentrations were tested in all regression models.

All reported P values were based on two-sided tests. SPSS software (version 11.0, 2002; SPSS Inc, Chicago, IL) was used for all of the statistical calculations.

RESULTS

Coffee intake and demographic characteristics

Of the entire group of participants, 31 (14%) reported no coffee consumption, 73 (32%) reported low coffee consumption, 83 (36%) reported moderate coffee consumption, and 41 (18%) reported high coffee consumption. Stratifying our analysis by sex, we observed that the men consumed greater quantities of coffee than did the women (260 ± 140 versus 210 ± 140 mL per day, P = 0.02). The demographic and lifestyle characteristics of the participants are provided in Table 1.

Coffee intake and arterial function indexes and arterial pressures

Values for the investigated variables across various groups of coffee drinking are shown in Table 2. There was a linear relation between coffee consumption and arterial function indexes, as well as with arterial pressures (P for trend < 0.05). Compared with the non-coffee drinkers, the high-consumption group had, on average, 7% higher peripheral systolic pressure values (P < 0.01), 8% higher peripheral diastolic pressure values (P < 0.01), 5% higher peripheral pulse pressure values (P < 0.05), 11% higher mean pressure values (P < 0.01), 10% higher aortic systolic pressure values (P < 0.01), 10% higher aortic diastolic pressure values (P < 0.01), 17% higher aortic pulse pressure values (P < 0.01), 13% higher PWV values (P < 0.01), 2-fold higher Aix values (P < 0.01), 2.4-fold higher AP values (P < 0.01), and 7% lower Δ values (P < 0.01). The difference observed between aortic and peripheral pulse pressure values (ie, 17% compared with 5%), relative to coffee intake, was statistically significant (P < 0.01), which indicated that high coffee consumption has a greater effect on aortic than on peripheral pulse pressure. No other significant differences between aortic and peripheral pressure values were observed.

However, the abovementioned unadjusted associations may be confounded by age, sex, smoking habits, body mass index or height, physical activity, total cholesterol, LDL cholesterol, triacylglycerols, blood glucose concentrations, and heart rate of the

### Table 1

Characteristics of the participants according to coffee consumption

<table>
<thead>
<tr>
<th>Coffee Consumption</th>
<th>&lt; 200 mL/d (n = 73)</th>
<th>200–450 mL/d (n = 83)</th>
<th>&gt; 450 mL/d (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>58</td>
<td>482</td>
<td>672</td>
</tr>
<tr>
<td>Age (y)</td>
<td>34 ± 9*</td>
<td>41 ± 8*</td>
<td>43 ± 8*</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>10</td>
<td>14 ± 15*</td>
<td>17 ± 16*</td>
</tr>
<tr>
<td>Pack-years (%)</td>
<td>1 ± 3</td>
<td>49</td>
<td>55</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>180 ± 34</td>
<td>201 ± 30*</td>
<td>202 ± 47*</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>115 ± 33</td>
<td>134 ± 32</td>
<td>135 ± 32</td>
</tr>
<tr>
<td>Triacylglycerol (mg/dL)</td>
<td>92 ± 34</td>
<td>96 ± 35</td>
<td>97 ± 42</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>85 ± 9</td>
<td>89 ± 12</td>
<td>90 ± 12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 ± 3</td>
<td>25 ± 4</td>
<td>26 ± 3*</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>10</td>
<td>10</td>
<td>19</td>
</tr>
</tbody>
</table>

* P values were derived from ANOVA or chi-square tests; the interactions between coffee consumption group and sex, age, smoking habits, pack-years of smoking, BMI, and obesity status were all statistically significant (P < 0.05).

**Significantly different from no coffee consumption (Bonferroni correction): 2 P < 0.05, 4 P < 0.01.

* ± SD (all such values).
participants. Therefore, we applied multiple linear regression analysis for each of the investigated variables to control for the aforementioned potential confounders. Furthermore, PWV, AIx, AP, and Δt were also corrected for mean pressure. AIx and AP were controlled for mean pressure. AIx and AP coefficients (and their SEs), are shown in Table 3. Coffee consumption (cup-years) was the main independent variable, whereas measures of aortic stiffness and wave reflections were considered dependent variables. PWV and Δt were significantly associated with coffee consumption, even after control for various confounders, which indicated an increase in aortic stiffness with increasing coffee intake. AIx and AP were also significantly associated with coffee consumption, which indicated an increase in wave reflections with increasing coffee intake. However, the observed unadjusted associations between peripheral and central pressures and coffee intake were largely explained when covariates, such as age, sex, smoking habits, body mass index, physical activity, blood lipids, and glucose were entered in the model.

**DISCUSSION**

The present study showed that chronic coffee consumption has a detrimental effect on aortic stiffness and wave reflections in healthy subjects. Importantly, this association remained significant even after various confounders were controlled for. This finding extends previous investigations from our laboratory and those of others, which showed an acute unfavorable effect of caffeine intake on arterial function (17–21).

**Clinical implications**

These findings have important clinical implications. Despite the extensive consumption of coffee worldwide, determination of its true effect on human health remains a challenge for the

### TABLE 3

**β-Coefficients (± SE) for the dependent variables from the 4 different regression models that evaluated the association between coffee consumption (independent variable) and arterial function indexes (dependent variables)**

<table>
<thead>
<tr>
<th></th>
<th>PWV (m/s)</th>
<th>AP (mm Hg)</th>
<th>AIx (%)</th>
<th>Δt (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee consumption (cup-years)</td>
<td>0.0029 ± 0.003²</td>
<td>0.0211 ± 0.003²</td>
<td>0.0356 ± 0.019²</td>
<td>−0.039 ± 0.023²</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.052 ± 0.013²</td>
<td>1.08 ± 0.01²</td>
<td>0.23 ± 0.01²</td>
<td>−0.61 ± 0.02²</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>0.42 ± 0.227³</td>
<td>−2.14 ± 0.23⁴</td>
<td>−4.6 ± 0.13⁵</td>
<td>10.5 ± 0.1²</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.020 ± 0.080</td>
<td>0.012 ± 0.05</td>
<td>−0.035 ± 0.03</td>
<td>0.01 ± 0.02</td>
</tr>
<tr>
<td>Smoking habits (pack-years)</td>
<td>0.008 ± 0.09³</td>
<td>0.23 ± 0.07³</td>
<td>0.058 ± 0.02³</td>
<td>−0.072 ± 0.03</td>
</tr>
<tr>
<td>Physical activity (%)</td>
<td>−0.102 ± 0.08</td>
<td>−0.012 ± 0.05</td>
<td>−0.144 ± 0.01</td>
<td>−0.012 ± 0.02</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>0.018 ± 0.08²</td>
<td>0.399 ± 0.087²</td>
<td>0.11 ± 0.1³</td>
<td>−0.24 ± 0.09²</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>−0.004 ± 0.08</td>
<td>−0.66 ± 0.06⁴</td>
<td>−0.14 ± 0.02²</td>
<td>−0.19 ± 0.02</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>0.003 ± 0.02</td>
<td>0.007 ± 0.07</td>
<td>−0.008 ± 0.02</td>
<td>−0.18 ± 0.03</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>−0.001 ± 0.01</td>
<td>−0.007 ± 0.07²</td>
<td>−1.56 ± 0.02²</td>
<td>−0.003 ± 0.01</td>
</tr>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>−0.003 ± 0.01</td>
<td>−0.005 ± 0.02</td>
<td>−0.001 ± 0.02</td>
<td>−0.002 ± 0.03</td>
</tr>
<tr>
<td>Adjusted R² (%)</td>
<td>33</td>
<td>52</td>
<td>51</td>
<td>15</td>
</tr>
</tbody>
</table>

1. AIx, augmentation index; AP, augmented pressure; PWV, pulse wave velocity; Δt, time from the beginning of the aortic waveform to the inflection point.
2. P < 0.05 (Student’s t test).
3. P < 0.01 (Student’s t test).
medical community. Although still an unresolved issue, chronic coffee consumption may increase cardiovascular disease risk (1, 3). On the other hand, aortic stiffness and wave reflections and their pathophysiologic manifestations, ie, increased systolic pressure, increased pulse pressure (and especially central pulse pressure), and reduced diastolic pressure, have been identified as independent predictors of cardiovascular disease risk (12–15, 29–32). A stiff aorta and enhanced wave reflections increase left ventricular load and myocardial oxygen demands and impair ventricular function. Concurrently, they compromise coronary blood flow and predispose to ischemia. Furthermore, by increasing pulse pressure, they increase pulsatile stretch of the arteries leading to mechanical fatigue of their elastic components (8–11). Accordingly, our study provides an explanatory mechanism for the results of previous investigations that showed an increase in cardiovascular disease risk with chronic coffee consumption. It is interesting to note that both aortic stiffness (13) and heavy coffee consumption (3, 33) increase the risk of acute coronary events, which indicate that impaired arterial function may be one of the mechanisms involved in the effect of heavy coffee consumption on the risk of acute coronary events.

In keeping with the results of acute studies (17, 19–21), the increase in pulse pressure with chronic coffee consumption was larger in the aorta than in the periphery. This has important implications because central pressures are the ones that are physiologically significant. The systolic pressure in the ascending aorta is the pressure that the left ventricle has to confront. Furthermore, the distending pressure in the central arteries is very important, because these elastic arteries (aorta and carotid) are those that are predominantly affected and that degenerate with aging and in hypertension, in contrast with the less-affected muscular peripheral arteries, such as the brachial and radial arteries (8, 34). Importantly, central and not brachial pulse pressure is a predictor of mortality in patients with end-stage renal disease (31) and is a determinant of intima-media thickness in the carotid arteries (35) and of ascending aorta diameter in patients with Marfan syndrome (36).

Mechanisms

Whether the increase in aortic stiffness is a blood-pressure–dependent or independent effect is a significant issue. Aortic stiffness may increase passively as a result of an increase in blood pressure or actively because of a modification in the intrinsic elastic properties of the vessel. However, the fact that the association remained significant after adjustment for changes in mean pressure indicates an active effect on the intrinsic properties of the aorta. Nevertheless, the importance and the clinical implications of our findings are valid irrespective of the mechanism involved.

The basic underlying mechanism could be related to the antagonism of adenosine, the release of catecholamines, or both (37, 38). Promotion of inflammation by coffee consumption could also account for the increase in aortic stiffness and wave reflections. Indeed, we have shown that chronic coffee consumption is associated with inflammatory markers (39) and that aortic stiffness is associated with acute (C Vlachopoulos et al, unpublished observations, 2005) and chronic inflammation (40). However, an association between coffee consumption and the main determinants of aortic wall elasticity, ie, elastin and collagen, cannot be substantiated at this stage, and this issue deserves further investigation.

Specific comments and limitations

Our study was conducted in apparently healthy subjects; therefore, our results may not be directly extendable to other population groups. Coffee drinking was evaluated on the basis of the subjects’ self-reports. Thus, the real amount of coffee consumed may have been over- or underestimates. This was a cross-sectional study that did not address issues of causality; however, it provides evidence for the association between habitual coffee intake and arterial stiffness and forms the basis for further investigation. The precise consumption of food accompaniments, such as cream, was not recorded and thus was not included in the analysis. However, cream is not regularly added to coffee in Greece; when it is added, the quantities are small enough that they would not be expected to affect the investigated variables.

Conclusion

In conclusion, our study provides evidence that chronic coffee consumption unfavorably affects arterial stiffness and wave reflections and suggests that studies that investigate arterial function should control for coffee intake. Given the widespread consumption of coffee throughout the world, together with the major influence of aortic stiffness and wave reflections on cardiovascular function and cardiovascular disease risk, our findings have important implications for human health.

We thank Betsy Theodoropoulou and Kyriaki Velizelou for their help recruiting the subjects and organizing the data collection.

CV conceived the original idea of the study, designed the study, interpreted the results, and wrote the manuscript. DP designed the study, performed the data analysis, interpreted the results, and wrote the manuscript. NI conducted the study and drafted the manuscript. ID conducted the study and drafted the manuscript. CS interpreted the results and drafted the manuscript. There was no potential conflict of interest.

REFERENCES


