Vascular Disease

Smoking and Caffeine Have a Synergistic Detrimental Effect on Aortic Stiffness and Wave Reflections

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OBJECTIVES	We investigated the acute and chronic combined effect of cigarette smoking and caffeine intake on aortic stiffness and wave reflections.
BACKGROUND	We have shown that smoking and caffeine separately increase arterial stiffness. Aortic stiffness and wave reflections are important determinants of the efficient performance of the cardiovascular system and prognosticators of cardiovascular risk.
METHODS	The acute effects of smoking (one cigarette), caffeine (200 mg, equivalent to 2 cups of coffee), and smoking plus caffeine were studied in 24 healthy subjects according to a randomized, placebo- and sham procedure-controlled crossover design. The chronic effect of smoking and caffeine was studied in a population study that enrolled 160 healthy subjects.
RESULTS	Acute study: there was a significant interaction between caffeine and smoking with regard to pulse-wave velocity (p < 0.01) and augmentation index (p < 0.05). When smoking followed caffeine intake, pulse-wave velocity and augmentation index increased further by 0.52 m/s and 13.4%, respectively, reaching a total of 0.85 m/s and 17.4%, 0.17 m/s and 9.2% in excess of the mere sum of caffeine effect (0.33 m/s and 4%) alone and smoking effect alone (0.35 m/s and 4.2%). Population study: there was a significant interaction of chronic coffee consumption and smoking regarding pulse-wave velocity (p < 0.05) and augmentation index (p = 0.001).
CONCLUSIONS	The present study shows, for the first time, that when smoking and caffeine intake are combined, they interact and exert a synergistic, unfavorable effect on aortic stiffness and wave reflections on both an acute and chronic basis. (J Am Coll Cardiol 2004;44:1911–7) © 2004 by the American College of Cardiology Foundation

Smoking is the most important modifiable risk factor for coronary artery disease (1). In addition, although it is still an unresolved issue, caffeine consumption may increase cardiovascular risk (2) and may have a prohypertensive effect (3).

Large-artery stiffness and wave reflections are important determinants of left ventricular (LV) function, coronary blood flow, and mechanical integrity of arteries and have been identified as markers of cardiovascular disease and independent prognosticators of cardiovascular risk (4–12). We and others have previously shown that active and passive smoking (13–15) and caffeine (16–19) increase arterial stiffness and wave reflections.

In contemporary lifestyles, smoking is very frequently combined with coffee drinking. Studies have shown that smoking and caffeine have an unfavorable interaction on blood pressure and cardiovascular risk (20–23). This study was undertaken to investigate whether the combination of smoking and caffeine has an additive effect on arterial stiffness and wave reflections resulting from an interaction between the two stimuli.

METHODS

Subjects. The study protocol was approved by our Institutional Research Ethics Committee, and all subjects gave written informed consent.

ACUTE STUDY. The study population consisted of 24 healthy subjects. Aortic stiffness was studied in 14 subjects (7 women, 7 men) age 30 ± 2 years (aortic stiffness group) and wave reflections in 10 subjects (5 women, 5 men) aged 33 ± 3 years (pulse-wave analysis group); all had normal blood pressure and did not have diabetes, hyperlipidemia, or a family history of premature vascular disease. They were clinically healthy and taking neither regular cardiovascular medications nor oral contraceptives. All subjects were current smokers and regular caffeine consumers (>100 mg/day). Subjects abstained from caffeine, ethanol, and nicotine for at least 12 h before each session.

POPULATION STUDY. A total of 202 randomly selected employees of an industry were asked to participate in the study provided they were clinically healthy and had no risk factors for coronary artery disease except for smoking. Women taking oral contraceptives were also excluded. A total of 160 subjects (participation rate 79%) agreed to participate and comprised the final study population. Of

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Abbreviations and Acronyms
HR = heart rate
LV = left ventricular

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these, 97 were chronic smokers and coffee drinkers, 41 were chronic coffee drinkers and nonsmokers, 2 were chronic smokers but not coffee drinkers (data not shown), and 20 were neither coffee consumers nor smokers.

Study design. ACUTE STUDY. The study was carried out using a randomized placebo- and sham procedure-controlled crossover design. Each subject was studied fasting on four separate days before and after 1) smoking one standard cigarette (1.1 mg nicotine) over 5 min, 2) sham smoking, 3) caffeine intake (200 mg, a dose equivalent to 2 cups of coffee) plus smoking one standard cigarette (1.1 mg nicotine) 60 min after caffeine intake, and 4) placebo (to caffeine) and sham smoking 60 min after placebo intake. Measurements were obtained in a quiet air-conditioned room. Repeated measurements were taken at baseline and at 30 and 60 min after caffeine or placebo and at 5, 10, 20, and 30 min after smoking or sham smoking (Figs. 1 and 2).

POPULATION STUDY. The study assessing the chronic effects of smoking and caffeine was a population study. All subjects were studied in the morning after an overnight fast in a quiet air-conditioned room. Measurements were obtained after a 15-min rest.

Evaluation of aortic elastic properties and wave reflections. The pulse travels at a higher velocity in a stiff aorta and vice versa. Carotid-femoral pulse-wave velocity, an established index of aortic stiffness (4,5,8–10,17–19,24), was calculated from measurements of pulse transit time and the distance traveled between two recording sites (pulse wave velocity = distance [m]/transit time [s]) using a validated noninvasive device (Complior; Artech Medical, Pantin, France) that allows online pulse-wave recording and automatic calculation of pulse-wave velocity (25). 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).

The augmentation index of the central (aortic) pressure waveform was measured as an index of wave reflections. The augmentation index (defined as augmented pressure divided by pulse pressure and expressed as a percentage) is a composite measure of the magnitude of wave reflections and arterial stiffness, which affects timing of wave reflections. Larger values of augmentation index indicate increased wave reflections from the periphery and/or earlier return of the reflected wave as a result of increased pulse-wave velocity (due to increased arterial stiffness) and vice versa. Because the augmentation index is influenced by changes in heart rate (HR), it was also accordingly corrected (26). The
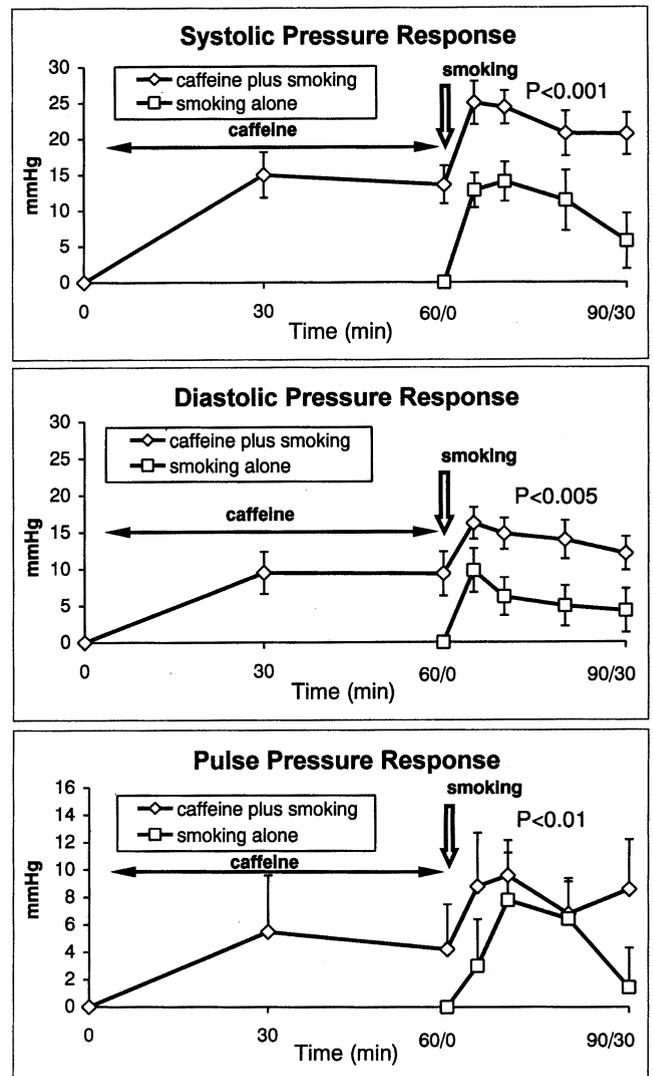

Figure 1. Peripheral systolic, diastolic, and pulse pressure response during the study. Each **line** represents response defined as net caffeine and smoking effect minus placebo and sham smoking effect **(diamonds)** or net smoking effect minus sham smoking effect **(rectangles)** at each time point. The p values on the graphs refer to the interaction between caffeine and smoking. **Error bars** = SEM.

augmentation index was measured by using a validated, commercially available system (SphygmoCor; AtCor Medical, Sydney, Australia) that employs the principle of applanation tonometry and appropriate acquisition and analysis software for noninvasive recording and analysis of the arterial pulse. The technique has been described in detail previously (4,5,16,18,27,28). In brief, from radial 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 (4,27,28). 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 artery (4). The subendocardial viability index was
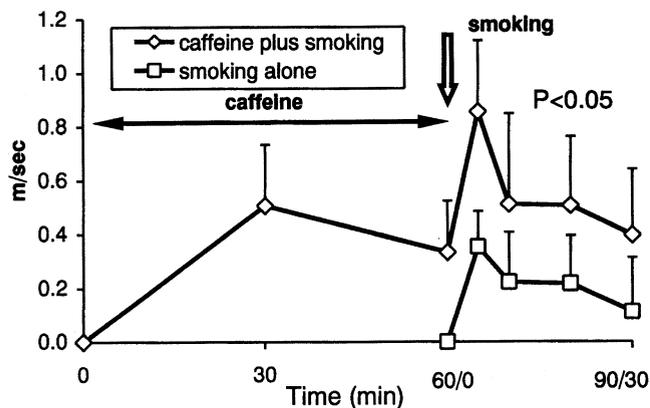
Figure 2. Pulse-wave velocity response during the study. Each **line** represents response, defined as net caffeine and smoking effect minus placebo and sham smoking effect **(diamonds)** or net smoking effect minus sham smoking effect **(rectangles)** at each time point. The p values on the graphs refer to the interaction between caffeine and smoking. **Error bars** = SEM.

calculated as the ratio of the integral of diastolic pressure and time to the integral of systolic pressure and time (29). **Statistical analysis.** Continuous data are expressed as mean values ± SEM, whereas qualitative data are presented as absolute and relative frequencies. Baseline cardiovascular parameters were compared between sessions of the acute study using the Mann-Whitney test. Multi-way analysis of covariance for repeated measurements, testing for equality of variances (homoscedacity), was used to evaluate changes in the investigated parameters as well as the effect of the interaction between caffeine intake and smoking sessions on these parameters. To take into account the potential effect of pressure changes on pulse-wave velocity and of HR changes on subendocardial viability index, we adjusted in multivariate regression models for mean pressure and HR, respectively. The effect of caffeine and smoking on central pressures was compared with their effect on peripheral pressures, by testing the differences on b-coefficients with the use of a *t*-test.

The involvement of the interaction between chronic coffee intake and smoking on the investigated parameters was evaluated using multi-way analysis of covariance after adjusting for age and gender. Based on a statistical power calculation (using East 3, 2003; Cytel Software Corporation, Cambridge, Massachusetts), we found that the number of studied participants (160) was adequate to evaluate >0.5 two-tailed standardized differences of the investigated parameters between groups. In particular, we achieved

statistical power of >0.80 at <0.05 probability level (p value).

Normality tests were applied using the Kolmogorov-Smirnov criterion. The p values <0.05 were considered statistically significant. However, because of multiple comparisons, we used the Bonferroni correction in order to account for the increase in type I error. Data analysis was performed with SPSS software (Version 11.0, SPSS Inc., Chicago, Illinois).

RESULTS

Acute study. There were no differences in all baseline characteristics between the four study sessions in aortic stiffness and pulse-wave analysis groups (Tables 1 and 2).

Changes after the active intervention sessions (caffeine, smoking, caffeine plus smoking) compared with those of control procedures (placebo and/or sham smoking) are better described and displayed as "response," defined as net active intervention effect minus control procedure effect at each time point (Figs. 1, 2, and 3). Results on peripheral pressures are described analytically for the aortic stiffness group; results were similar for the pulse-wave analysis group. Results on central pressures refer to the pulse-wave analysis group.

There was a significant interaction between caffeine and smoking with regard to peripheral systolic, diastolic, pulse, and mean pressure (p < 0.01 for mean pressure) (Fig. 1). There was a significant interaction between caffeine and smoking with regard to central systolic, diastolic, and pulse pressure (p < 0.005, p < 0.001, and p < 0.001, respectively). When smoking followed caffeine intake, central systolic, diastolic, and pulse pressures increased further by 7.5, 4.4, and 3.1 mm Hg, respectively, reaching a peak increase of 16.4, 11.7, and 4.7 mm Hg, respectively. The effect of smoking and caffeine on central and peripheral pressures was similar.

There was a significant interaction (p < 0.05) between caffeine and smoking regarding ejection duration. When smoking followed caffeine intake, ejection duration decreased further by 16.2 ms, reaching a total decrease of −16.6 ms, 11.7 ms less than the mere sum of caffeine effect (−0.4 ms) alone and smoking effect alone (−4.5 ms).

There was a significant interaction (p < 0.01) between caffeine and smoking regarding pulse-wave velocity, indicating a synergistic effect of the two interventions leading to a significant deterioration in aortic stiffness. The interaction

Table 1. Baseline Characteristics of the Study Sessions in the Aortic Stiffness Group

	Caffeine Plus Smoking	Control to Caffeine Plus Smoking	Smoking	Sham Smoking	p Value
Heart rate (beats/min)	62.7 ± 2.6	65.0 ± 2.6	62.8 ± 2.0	63.2 ± 2.7	NS
SP (mm Hg)	103.1 ± 3.0	109.5 ± 4.5	106.9 ± 3.5	105.9 ± 3.4	NS
DP (mm Hg)	66.3 ± 2.3	70.1 ± 3.3	65.2 ± 2.2	65.4 ± 2.5	NS
PP (mm Hg)	36.9 ± 3.0	39.4 ± 2.8	41.6 ± 3.5	40.6 ± 2.5	NS
PWV (m/s)	5.76 ± 0.37	5.73 ± 0.27	5.43 ± 0.19	5.34 ± 0.16	NS

DP = diastolic pressure; NS = not significant; PP = pulse pressure; PWV = pulse wave velocity; SP = systolic pressure.

Table 2. Baseline Characteristics of the Study Sessions in the Pulse-Wave Analysis Group

	Caffeine Plus Smoking	Control to Caffeine Plus Smoking	Smoking	Sham Smoking	p Value
Heart rate (beats/min)	75.7 ± 2.3	78.8 ± 2.2	74.9 ± 2.3	75.9 ± 1.7	NS
Peripheral SP (mm Hg)	120.4 ± 2.5	118.4 ± 2.4	119.4 ± 2.9	122.3 ± 2.5	NS
Peripheral DP (mm Hg)	70.3 ± 1.4	70.2 ± 2.4	69.0 ± 2.5	68.2 ± 1.4	NS
Peripheral PP (mm Hg)	50.2 ± 1.9	48.1 ± 1.9	51.2 ± 2.3	53.3 ± 1.3	NS
Peripheral MP (mm Hg)	87.5 ± 2.4	86.5 ± 1.4	85.7 ± 1.8	86.8 ± 2.2	NS
Central SP (mm Hg)	104.4 ± 2.2	102.3 ± 2.3	103.8 ± 2.3	104.8 ± 2.1	NS
Central DP (mm Hg)	71.5 ± 2.5	71.5 ± 1.3	69.3 ± 1.5	70.3 ± 2.5	NS
Central PP (mm Hg)	32.9 ± 1.9	30.8 ± 1.8	34.5 ± 1.6	34.5 ± 1.5	NS
Central MP (mm Hg)	87.5 ± 2.4	86.5 ± 1.4	85.7 ± 1.8	86.8 ± 2.2	NS
AIx (%)	10.1 ± 3.5	8.2 ± 4.0	13.7 ± 2.6	11.2 ± 3.14	NS
AP (mm Hg)	3.8 ± 1.6	2.7 ± 1.7	4.8 ± 1.0	4.3 ± 1.3	NS
SVI (%)	147.2 ± 3.4	149.1 ± 2.9	150.3 ± 3.9	147.6 ± 3.1	NS

AIx = augmentation index; AP = augmented pressure; MP = mean pressure; SVI = subendocardial viability index; other abbreviations as in Table 1.

remained significant ($p < 0.005$) after correction for changes in mean pressure. When smoking followed caffeine intake, pulse wave velocity reached a total increase of 0.85 m/s, 0.17 m/s in excess of the mere sum of caffeine effect

Figure 3. The augmentation index (corrected for changes in heart rate) and subendocardial viability index (SVI) response during the study. Each **line** represents response defined as net caffeine and smoking effect minus placebo and sham smoking effect **(diamonds)** or net smoking effect minus sham smoking effect **(rectangles)** at each time point. The p values on the graphs refer to the interaction between caffeine and smoking. **Error bars =** SEM.

(0.33 m/s) alone and smoking effect alone (0.35 m/s) (Fig. 2, diamonds).

There was a significant interaction ($p < 0.05$) between caffeine and smoking with regard to augmentation index corrected for changes in HR, indicating a synergistic effect of the two interventions leading to a significant increase in wave reflections. When smoking followed caffeine intake, the augmentation index increased to 17.4%, 9.2% in excess of the mere sum of caffeine effect (4%) alone and smoking effect alone (4.2%) (Fig. 3, diamonds). Likewise, there was a significant interaction ($p < 0.001$) regarding augmented pressure adjusted for HR (peak increase by 5.6 mm Hg at 5 min of smoking following caffeine). Despite a trend, the interaction was not significant regarding the augmentation index uncorrected for changes in HR.

There was a significant interaction ($p < 0.001$) between caffeine and smoking regarding subendocardial viability index, indicating a synergistic effect of the two interventions (Fig. 3). The interaction remained significant ($p < 0.001$) after correction for changes in HR. There was no effect of gender on any of the significant interactions.

Population study. Characteristics and values of variables of subjects who participated in the observational study are shown in Table 3. Because the age of the participants differed significantly in the groups of the study, all the analyses carried out were age-adjusted. The p values in Table 3 refer to the interaction between smoking and coffee.

Coffee consumers/nonsmokers, as well as coffee consumers/smokers, had increased pulse wave velocity levels compared with non-coffee consumers/nonsmokers ($p < 0.05$ for both). Furthermore, a significant interaction was observed between chronic smoking and coffee consumption on pulse-wave velocity ($p < 0.05$), indicating a synergistic effect of the two habits. The interaction was still significant ($p < 0.05$) after correction for mean pressure.

Coffee consumers/nonsmokers, as well as coffee consumers/smokers, had an increased augmentation index and augmented pressure levels compared with non-coffee con-
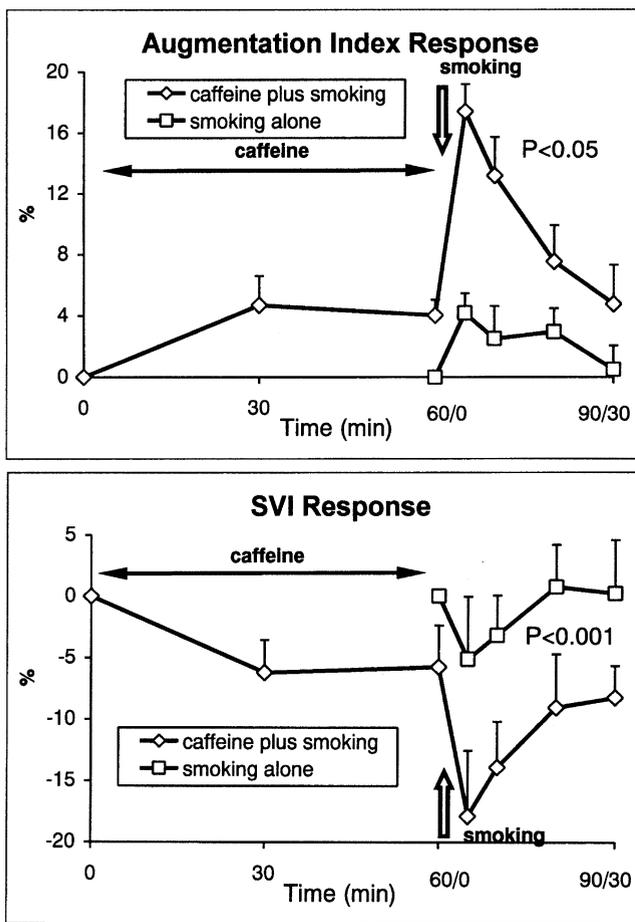
Table 3. Characteristics of the Study Population

	Coffee Drinking and Smoking	Coffee Drinking and Nonsmoking	Non-coffee Drinking and Nonsmoking	p Value
Number of participants	97	41	20	—
Pack-yrs of smoking	22.2 ± 1.7	—	—	—
Coffee cup-yrs	60.8 ± 3.8	40.3 ± 5.5	—	—
Male gender (%)	68	49	50	NS
Age, yrs (range)	43.3 ± 0.7 (26–60)	42.5 ± 1.2 (28–56)	33.8 ± 2.2 (18–57)	0.001
Height (cm)	172 ± 1	170 ± 2	174 ± 2	NS
BMI (kg/m^2)	26.1 ± 0.4	26.3 ± 0.6	23.9 ± 0.6	NS
Heart rate (beats/min)	68.2 ± 1.0	69.1 ± 1.2	66.5 ± 2.0	NS
Peripheral SP (mm Hg)	117.8 ± 1.6	119.0 ± 2.5	114.4 ± 3.9	NS
Peripheral DP (mm Hg)	72.1 ± 1.2	71.4 ± 1.9	69.0 ± 2.0	0.05
Peripheral PP (mm Hg)	45.9 ± 0.7	47.6 ± 1.4	45.4 ± 2.6	NS
Peripheral MP (mm Hg)	88.9 ± 1.3	88.8 ± 2.0	83.8 ± 2.6	0.05
Central SP (mm Hg)	107.3 ± 1.5	107.7 ± 2.4	100.0 ± 3.3	0.05
Central DP (mm Hg)	73.3 ± 1.2	72.7 ± 1.9	70.0 ± 2.0	0.05
Central PP (mm Hg)	34.0 ± 0.6	35.0 ± 1.3	30.1 ± 1.6	0.07
Central MP (mm Hg)	88.9 ± 1.3	88.8 ± 2.0	83.8 ± 2.6	0.05
AIx (%)	22.7 ± 1.1	21.7 ± 2.1	11.0 ± 2.6	0.001
AP (mm Hg)	8.14 ± 0.50	8.08 ± 0.90	3.48 ± 0.91	0.001
SVI (%)	145.0 ± 2.2	140.8 ± 3.1	156.1 ± 6.7	0.005
PWV (m/s)	6.36 ± 0.11	6.31 ± 0.18	5.80 ± 0.23	0.05

All probability values are also age-adjusted and corrected for multiple comparisons using the Bonferroni correction.
BMI = body mass index. Other abbreviations as in Tables 1 and 2.

sumers/nonsmokers ($p < 0.005$ and $p < 0.001$, respectively, for groups for both variables) after correction for HR and height. In addition, a significant interaction was observed between chronic smoking and coffee consumption on the augmentation index and augmented pressure ($p = 0.001$ and $p < 0.005$, respectively) after correction for height and HR.

Coffee consumers/nonsmokers, as well as coffee consumers/smokers, had lower subendocardial viability index levels compared with non-coffee consumers/nonsmokers ($p < 0.005$ and $p < 0.05$, respectively) after correction for HR. Furthermore, a significant interaction was observed between chronic smoking and coffee consumption on the subendocardial viability index ($p = 0.001$) after correction for HR.

Significant interactions between chronic smoking and coffee consumption were also observed regarding peripheral diastolic pressure ($p < 0.05$), peripheral and central mean pressure ($p < 0.05$), central systolic pressure ($p < 0.05$), and central diastolic pressure ($p < 0.05$), whereas central pulse pressure showed a marginal trend ($p = 0.07$). There was no effect of gender on any of these interactions.

DISCUSSION

Smoking and caffeine separately deteriorate aortic stiffness and wave reflections (13–19). The present study is the first, to the best of our knowledge, to show that when smoking and caffeine consumption are combined they have both an acute and chronic detrimental effect on arterial stiffness and wave reflections, which, most importantly, is synergistic. Another interesting interpretation of the results of our study is that neither stimulus "exhausts" the capacity of the vessel's elastic properties to deteriorate, but there is room for further deterioration when a harmful intervention (not only those of the present study) is added.

These findings have important clinical implications. Aortic stiffness and wave reflections have a causative role in the pathogenesis of systolic hypertension. Furthermore, aortic stiffness and wave reflections and their pathophysiologic manifestations, such as increased systolic pressure, increased pulse pressure (especially central pulse pressure), and reduced diastolic pressure, have been identified as markers of cardiovascular disease and independent predictors of risk (8–12,30–33). A stiff aorta and enhanced wave reflections increase LV load and myocardial oxygen demands and impair ventricular function. Concurrently, they compromise coronary blood flow and predispose to ischemia, especially in the presence of coronary insufficiency. Furthermore, by increasing pulse pressure, they increase pulsatile stretch of the arteries, leading to mechanical fatigue of their elastic components (4–7). On the other hand, arterial stiffness, wave reflections, and central pressures emerge as appealing specific targets of treatment (34).

Accordingly, our study provides an explanatory mechanism for the results of previous investigations in which combined cigarette smoking and coffee consumption were shown to have an acute unfavorable synergistic effect on blood pressure (20,22). Furthermore, case-control studies have shown that habitual cigarette and coffee consumption increase systolic blood pressure (21) and the risk of acute myocardial infarction (23).

The underlying mechanism at the basic level responsible for the interactive effect of the two interventions is unclear at this stage. A plausible mechanism could be through antagonism of adenosine and/or release of catecholamines (35–38).

Whether the increase in aortic stiffness is a blood pressure-dependent or an independent effect is a significant issue. Undoubtedly, aortic stiffening is partly due to the increase in blood pressure (passive effect). However, using appropriate high-fidelity methodology we have shown previously that smoking has a direct, pressure-independent effect on the aortic wall (13,14). Furthermore, the fact that interaction between caffeine and smoking remained significant after adjustment for changes in mean pressure indicates the contribution of an active effect on the intrinsic properties of the aorta. This is also corroborated by the fact that the increase in the aortic stiffness when smoking was added to caffeine was proportionally larger than the respective increase in blood pressure. Nevertheless, the importance and the clinical implications of our findings are valid irrespective of the mechanism involved.

Wave reflection indices may be influenced by changes in HR and by height and subendocardial viability index by changes in HR. Therefore, the effects of smoking and caffeine on these parameters were corrected either according to previously reported quantifications of their covariation (26) (augmentation index and HR, acute study) or with adjustments in multivariate regression models.

Our study refers to young, apparently healthy adults, and results might not be directly extendable to other population groups.

In conclusion, our study provides novel information regarding the effect of the combination of smoking and caffeine intake on aortic stiffness and wave reflections. In particular, when these two stimuli are combined, they interact and exert an acute detrimental effect on arterial stiffness, which, most importantly, is not just additive but synergistic. Aortic stiffness and wave reflections are prognosticators of cardiovascular risk by being important determinants of LV function, coronary perfusion (especially in the presence of coronary insufficiency), and arterial wall integrity. Consequently, given the frequent combination of smoking and caffeine intake, these effects on arterial function may have important implications for human health.

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