Haemodynamic and neurohumoral effects of caffeine in elderly patients with symptomatic postprandial hypotension: a double-blind, randomized, placebo-controlled study

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(Received 20 December 1993/7 March 1994 accepted 11 March 1994)

INTRODUCTION

During the past decade, postprandial hypotension has become recognized as a common disorder of blood pressure (BP) regulation in the elderly [1-8] and in patients with autonomic dysfunction [9-12]. Meal-related declines in BP may be asymptomatic or of sufficient magnitude to produce falls and syncope [8, 13, 14]. Postprandial reduction in BP has been reported in 96% of nursing-home residents [8] and has been found to account for 8% of syncopal episodes in this population [13]. In patients with autonomic insufficiency postprandial hypotension is a common cause of profound weakness, dizziness and falls after meals [12].

Unfortunately, there have been very few well-designed studies of potential therapies for this problem, particularly in symptomatic patients who require treatment. Although the somatostatin analogue octreotide prevents the decrease in BP after glucose ingestion in healthy elderly subjects [15, 16] and patients with autonomic failure [17], this approach requires frequent subcutaneous injections, is painful and expensive, and is not well studied in symptomatic elderly patients.

Caffeine is often recommended for the prevention of postprandial hypotension. This treatment is particularly appealing because caffeine is a relatively non-toxic, inexpensive and convenient food constituent that is widely available. Only four previous studies have examined its clinical effect in elderly subjects [18-20] or patients with autonomic failure [21]. However, the generalization of findings from these studies is limited by (i) the inclusion of healthy asymptomatic subjects who would not be candidates for treatment [18, 19], (ii) the use of a glucose drink, rather than a representative mixed meal [20], or (iii) the measurement of BP in a sitting position,

Key words: ageing, autonomic failure, blood pressure, splanchnic circulation, syncope.

Abbreviations: BP, blood pressure; EDV, left ventricular end-diastolic volume; EF, left ventricular ejection fraction; E/I ratio, mean expiratory/inspiratory ratio; HR, heart rate; SV, stroke volume.

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Table 1. Baseline subject characteristics and individual autonomic measurements.

<table>
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<th>VR</th>
<th>Postural changes (supine to standing)</th>
<th>Plasma NA* (pg/ml)</th>
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</tbody>
</table>

*Baseline values measured during the placebo study.
†Patient not able to stand for 3 min.
§Patient not able to sit or stand.
Abbreviations: OH, orthostatic hypotension; PD, Parkinson’s disease; CVD, cerebrovascular disease; PAF, pure autonomic failure; CAD, coronary artery disease; HT, hypertension; SD, Shy-Drager syndrome; UPS, unexplained postprandial syncope; VR, Valsalva ratio; SBP, systolic BP; NA, noradrenaline.

Thus superimposing a postural stress on the experimental conditions [18, 20, 21]. The present study was designed to overcome these limitations and determine the mechanisms of the putative effect of caffeine, by examining the haemodynamic, splanchnic blood pool and neurohumoral responses to caffeine in elderly patients with a history of symptomatic meal-related hypotension. Since caffeine is a pressor agent with potent inhibitory effects on vasodilatory adenosine receptors in the splanchnic circulation [22], we postulated that caffeine administration with a meal would attenuate splanchnic vasodilatation and prevent the development of postprandial hypotension in affected elderly patients.

METHODS

Subjects

Nine elderly subjects (two males and seven females, age range 62–90 years, mean ± SD 76 ± 9 years) were recruited from referrals to the investigators for the evaluation of postprandial syncope, falls, profound weakness or dizziness, associated with 20 mmHg or greater declines in supine or seated systolic BP within 1 h of meal ingestion.

Characteristics of the subjects are summarized in Tables 1 and 2. Only those patients with documented postprandial hypotension that was not solely attributable to drugs, cardiac ischaemia or other meal-related factors, were included in the study. Four subjects had autonomic insufficiency syndromes (one with Shy–Drager syndrome, and three with pure autonomic failure), two had Parkinson’s disease and three had unexplained postprandial syncope. Four subjects were taking fludrocortisone, two were taking hydrochlorothiazide, two were on an angiotensin-converting enzyme inhibitor, two were taking levodopa/carbidopa; one was taking digoxin, one was on pseudoephedrine and one was on ranitidine. Three subjects routinely drank one-half to one cup of caffeinated coffee in the morning, and one subject drank one cup three times a day with meals.

To confirm the presence of postprandial hypotension (defined above), the investigators conducted BP measurements, before and after a meal, for each subject, during a hospitalization for syncope or an office visit. Medications were withheld for at least 12 h before these measurements. All subjects also had autonomic function tests that included heart rate (HR) responses to deep breathing and the Valsalva manoeuvre [23], as well as an echocardiogram and cardiac Doppler study to exclude the presence of valvular heart disease or left ventricular outflow tract obstruction.

The HR response to deep breathing was determined in the supine position by recording the ECG continuously for 3 min while subjects took slow deep breaths at a rate of 5/min in response to verbal
and visual cues from one of the investigators. The ratio of the maximum R–R interval during expiration to the minimum R–R interval during inspiration (E/I ratio) was calculated for each breath. The mean E/I ratio during the second minute was calculated as the average of the five E/I ratios recorded during this minute.

The Valsalva manoeuvre was conducted in the supine position during continuous ECG recording by having subjects blow into a mercury manometer to maintain a pressure of 30mmHg for 10s [23]. Practice sessions were conducted to teach subjects how to exert pressure from their chest. Measurements were taken after a 2 min rest period between trials. The Valsalva ratio was calculated as the ratio of the longest R–R interval after release of the Valsalva to the shortest R–R interval during the procedure. The average ratio of three trials is reported.

The study was approved by the Institutional Review Boards of the Beth Israel Hospital and the Hebrew Rehabilitation Center for Aged. All subjects gave their written informed consent. Two subjects were also included in another study described previously [24].

**Meal study protocol**

The meal study protocol has been described previously [24]. All subjects were studied on two occasions, at least 1 week apart, between 07.30 and 11.00 hours, after an overnight fast from 24.00 hours the day before. If subjects took chronic medications, these were withheld for a minimum of 36 h before the study, except in one patient taking levodopa/carbidopa for Parkinson's disease, who could not have his medication withheld for more than 12 h. All caffeinated beverages were withheld for at least 24 h.

Subjects reported to the Nuclear Medicine Laboratory at 07.30 hours on the day of each study, where a 21-gauge angiocath and heparin lock were placed in one antecubital vein for blood sampling throughout the study. This intravenous catheter was also used to withdraw a 3 ml blood sample during each radioventriculogram to determine the biological clearance of the tracer. A second temporary angiocath was placed in the opposite antecubital vein for collection and reinjection of autologous erythrocytes that were labelled with 740 MBq (20 mCi) of $^{99m}$Tc. This cannula was removed after injection of labelled erythrocytes.

The cuff from a Dynamap automated oscillometric BP device (Critikon, Tampa, FL, U.S.A.) was attached to one arm for BP and HR recordings at 5 min intervals throughout the study. Upper arm and wrist cuffs, and a mercury-in-silastic strain gauge, were attached to the other arm for venous occlusion plethysmographic measurements of forearm blood flow [25]. The same arms were used for all measurements during both studies. Finally, a Holter monitor (Del Mar Avionics, Irvine, CA, U.S.A.) and standard ECG chest leads were attached to monitor cardiac rhythm. After each study, the continuous Holter monitor ECG recordings were used to identify possible arrhythmias associated with caffeine ingestion or with the development of postprandial hypotension.

After injection of $^{99m}$T-labelled erythrocytes and a minimum of 30 min of supine rest, 10 min of basal measurements began. Then subjects sat for 10 min to ingest a liquid 1674kJ meal with a capsule containing either 250 mg of caffeine (No-Doze) or cornstarch placebo. These were dispensed in randomized sequence for the 2 study days by the hospital pharmacist. The capsule ingredients were unknown to the subjects or investigators. The 250 mg dose and the timing of caffeine administration with the meal were based on conventional use, as well as the results of a small pilot study suggesting a beneficial effect of this regimen in four elderly subjects with postprandial hypotension.

After the meal, subjects resumed a supine position for the duration of the study. BP and HR were recorded at 5 min intervals throughout the study. Plasma catecholamine samples were collected as described below, twice before the meal (−5 and 0 min), then at 30, 45, 60 and 90 min after the meal. Forearm blood flow was determined by repeated venous occlusion plethysmography measurements over 3 min periods. Measurements were taken before the meal, then at 15 min intervals beginning 15 min after the meal. Five minute acquisitions for gated cardiac blood pool [26, 27] and 2 min splanchnic blood pool determinations [28] were obtained sequentially before the meal, and at 30 min intervals after the meal. Except for a 10 min period of sitting for meal ingestion, all studies were performed in the supine position, to eliminate the possible effect of orthostatic hypotension. Room temperature remained constant (23 ± 1°C) throughout the study.

The meal was a 1674kJ (400 kcal) drink (Carnation Instant Breakfast in lactose-free whole milk) containing 40% carbohydrate, 45% fat, 15% protein, 12 mmol of sodium and no caffeine. Its composition was that of a mixed meal, similar to meals that were shown to produce hypotension in these subjects. It was served at a temperature of 22°C to avoid potential temperature effects on BP [29] and was ingested within 10 min.

**Radionuclide ventriculogram**

The left ventricular ejection fraction (EF) was calculated with a fixed region of interest method. The area and longest axis of the region of interest was used to calculate absolute left ventricular end-diastolic volume (EV). From these measurements we calculated stroke volume (SV) as EDV × EF, and cardiac output as SV × HR.
Splanchnic blood volume determination

Relative changes in radionuclide activity from a region of interest overlying the bowel were used as an index of changes in splanchnic blood volume [28]. Compared with Doppler measurements of superior mesenteric artery blood flow, which have been used previously [12], this method has the advantage of assessing splanchnic blood pooling, which is more directly related to the pathophysiology of postprandial hypotension. A $^{57}$Co marker was attached to the lower abdomen to aid in repositioning the patient and to align the images during analysis. Two sequential 2 min images of the abdomen were obtained during the baseline period to establish that equilibrium had been adequately achieved. Images were obtained at 15, 30, 60 and 90 min after the meal. Images were obtained in the anterior position to decrease the contribution from excreted activity. An attempt was made to exclude the urinary system from the region of interest when it could be identified. The counts were corrected for background, biological clearance and physical decay. Changes in splanchnic blood volume are reported as a percentage of the baseline activity. The intraindividual variability of the radionuclide technique has been reported to be 1–3% [28].

Catecholamine and caffeine assays

Blood for catecholamine and caffeine determinations was collected from the antecubital intravenous catheter, without the use of a tourniquet, in vacutainer tubes containing EGTA and reduced glutathione. The tubes were placed immediately on ice. Plasma was separated by refrigerated centrifugation then fast frozen in dry ice and acetone, and stored at $-70^\circ$C until assayed. Plasma noradrenaline and adrenaline concentrations were determined by the single-isotope radioenzymatic assay described by Peuler and Johnson [30]. The assay has a sensitivity of 20 pg/ml of plasma. The within-run coefficient of variation is less than 7.5%. Since the interassay variability is 10–15%, all of each subject's samples were assayed at one time.

Caffeine was measured by a commercial toxicology laboratory (METPATH) using h.p.l.c.

Data analysis

Basal values for physiological variables (mean arterial BP, systolic BP, diastolic BP, HR, plasma catecholamines) that were measured more than once during the 10 min baseline period before the meal were calculated by averaging all pre-meal measurements. For all other variables the single pre-meal measurement was used as the baseline value. Fifteen minutes after the start of the meal, mean values for BP and HR were calculated at 15 min intervals. Each mean value is the average of three measurement 5 min apart, before, during and after each time point of interest. Mean arterial BP was calculated as the sum of the diastolic BP and one-third of the pulse pressure. Forearm vascular resistance was calculated as mean arterial BP divided by the forearm blood flow, and systemic vascular resistance was calculated as mean arterial BP divided by cardiac output (in litres/min). Splanchnic blood volume was normalized to 1.00 before the meal, then calculated as a percentage of the basal value at the time each image was taken.

Within-group changes over time for each variable were evaluated by repeated measures analysis of variance. Changes for each variable over time were compared between the caffeine and placebo phases of the study using a two-factor (treatment and time) repeated measures analysis of variance. Data summaries and analyses were performed using the SAS (v6.06.01) system on a MicroVAX computer. An alpha level of 0.05 was used as the criterion for determining statistical significance. Data are presented as means ± SEM, unless indicated otherwise.

RESULTS

Haemodynamic and plasma noradrenaline responses to meal ingestion with and without caffeine are shown in Figs. 1 and 2. Baseline value for these variables during the placebo phase are shown in Table 2. Baseline measurements did not differ significantly between the placebo and caffeine phases of the study.

Mean arterial BP declined significantly after the meal under both conditions ($P=0.006$, analysis of variance), falling a maximum of 19 ± 6 mmHg by 30 min in the placebo phase, and 31 ± 7 mmHg after 250 mg of caffeine (Fig. 1a). The BP decline persisted until the end of the study at 90 min. There was no significant difference in the postprandial decline in systolic, diastolic or mean arterial BP between placebo and caffeine.

Both HR (Fig. 1b) and cardiac output (Fig. 1c) increased significantly after each meal ($P<0.009$), and to a similar extent after placebo and caffeine. The maximum response occurred between 30 and 45 min. Splanchnic blood volume (Fig. 1d) increased significantly by 30 min, and remained elevated over the duration of the study. Splanchnic blood volume increased by a maximum of 18 ± 5% ($P<0.0001$) 30 min after placebo, and 36 ± 9% ($P<0.0001$) at the same time after caffeine (between-group effect: $P=0.14$). Systemic vascular resistance (Fig. 2a) decreased significantly by 7 ± 2 units ($P<0.0001$) and 12 ± 2 units ($P<0.0001$) with placebo and caffeine, respectively, by 30 min after each meal (between group effect: $P=0.37$). EDV (Fig. 2b), SV (data not shown) and forearm vascular resistance (Fig. 2c) remained unchanged.

Plasma noradrenaline (Fig. 2d) showed a tendency to increase after both meals, but this did
not reach statistical significance \((P=0.07)\). Plasma adrenaline data (not shown) were available for five subjects and showed no significant change after either meal. There was no difference in either catecholamine response between placebo and caffeine.

The mean plasma caffeine level after the caffeine treatment phase is shown in Fig. 3. Plasma caffeine concentration reached \(3.2 \pm 0.9 \text{mg/l}\) by 60 min after the meal. There was no detectable caffeine at this time point during the placebo phase.

Table 3 shows individual BP, HR and plasma adrenaline responses 60 min after the meal for the placebo and caffeine phases of the study. Although intraindividual responses were quite variable, there was no consistent effect of caffeine on any haemodynamic or neurohumoral variable. All subjects remained asymptomatic while lying supine, without the development of tachyarrhythmias during each study. The lack of response to caffeine was uniform among all subjects and was unrelated to caffeine level or a history of coffee consumption.

**DISCUSSION**

The results of this randomized, double-blind, placebo-controlled study suggest that a single oral 250 mg dose of caffeine given with a meal does not prevent the development of postprandial hypotension in elderly patients with symptomatic meal-related BP declines. Furthermore, caffeine administration did not attenuate the increase in splanchnic blood pooling or decrease in systemic vascular resistance that was associated with postprandial hypotension in our subjects. Despite an increase in HR and cardiac output after the meal, these subjects were unable to maintain sufficient vascular resistance to prevent the development of postprandial hypotension.
Only two previous randomized studies have examined the effect of caffeine on postprandial BP in elderly patients with symptomatic postprandial hypotension [20, 21]. In the placebo arm of their study of 20 frail elderly patients (mean age 84 ± 5 years) with multiple illnesses and medications, Heseltine et al. [20] found four patients with symptoms of lethargy, tiredness and light-headedness, associated with a large postprandial fall in systolic BP to below 100 mmHg. The postprandial decline in BP was slightly attenuated and symptoms were relieved in all four subjects after administration of 100 mg of caffeine. The absence of symptoms may have been due to the stimulating effects of caffeine on the central nervous system [22]. Also, several methodological differences from our study deserve note. Subjects were tested at 12.00 hours, they were sitting in a chair and they consumed a 1674 kJ glucose drink, followed by caffeinated or decaffeinated coffee. Therefore, it is not clear whether the BP decline observed in these subjects was due to pure glucose ingestion and/or orthostatic hypotension, or whether the positive effect of caffeine was due to its ingestion as coffee. Furthermore, caffeine did not attenuate the fall in standing BP.

Onrot et al. [21] studied the effect of 250 mg of caffeine, given 30 min before a mixed meal, on postprandial BP in six middle-aged and elderly patients with autonomic failure. Caffeine increased BP before the meal and attenuated the postprandial decline in BP. However, these subjects also were studied in the seated position. Furthermore, the caffeine trial was not blinded, nor compared with a placebo control. Therefore, the total of ten symptomatic patients examined in these two studies to date, have not clearly defined a role for caffeine in the treatment of symptomatic postprandial hypotension.
Two other studies of healthy elderly subjects demonstrated a pressor effect of caffeine which helped maintain BP at a higher level after a meal [18, 19]. In one of these studies [18], there was a similar postprandial decline in BP after caffeine and placebo, but with caffeine pretreatment, baseline BP was higher. Furthermore, the subjects of these studies would not be candidates for treatment.

The pharmacological actions of caffeine include blockade of vasodilatory adenosine receptors and phosphodiesterase inhibition [22]. The latter probably occurs at higher levels than are normally achieved with the usual doses of caffeine [21, 31]. The cardiovascular effects of caffeine are variable, but generally include an increase in respiratory rate, cardiac output, vascular resistance and BP in caffeine-naive healthy young subjects [22]. Healthy elderly subjects have been reported to have greater increases in BP after 250 mg of oral caffeine than young subjects [32]. Variable plasma renin and catecholamine responses to caffeine have been reported [22, 31–33]. Our catecholamine findings are consistent with those of several investigators [18, 21, 32], who found no effect of 250 mg of caffeine on plasma noradrenaline or adrenaline levels in elderly or dysautonomic subjects.

Previous investigators have suggested that caffeine has a vasoconstrictor effect on the splanchnic circulation [19, 21]; however, to our knowledge, this has not been studied in humans. We used radionuclide blood-pool scintigraphy [28] to measure splanchnic blood volume and could not demonstrate an inhibitory effect of caffeine on postprandial splanchnic blood pooling. In fact, there was a tendency toward greater blood pooling after caffeine than placebo.

The absence of a pressor effect of caffeine on postprandial BP in our study is difficult to explain. This may be due in part to the relatively low plasma levels of caffeine by 60 min after the meal in our subjects. The time it takes for caffeine to reach peak plasma levels after its administration is highly variable, averaging 50–60 min in healthy young subjects [34]. In our subjects, plasma caffeine levels were also quite variable, and did not increase until after the onset of hypotension. Absorption of caffeine may have been delayed, thus delivering the drug to adenosine receptors after they were already occupied or activated. As a result, caffeine may not be able to reverse adenosine-mediated splanchnic vasodilatation and hypotension after it is initiated. The previous positive results of Heseltine et al. [19, 20] using coffee suggest that caffeine may be more readily bioavailable in liquid, rather than capsule form. Alternatively, it may be more effective if given before a meal [21].

Another potential explanation for the lack of a pressor effect is prior daily exposure of four subjects to small amounts of caffeine. It is well known that chronic caffeine intake of 300 mg/day (three cups of brewed coffee), or greater, results in tolerance to its cardiovascular effects [32]. However, only one of our subjects ingested a sufficient quantity of caffeinated beverages to approximate this amount, and all subjects had undetectable caffeine levels at baseline. Furthermore, subjects with no prior caffeine exposure also had no response. It is noteworthy that in three previous studies reporting a pressor effect of caffeine in elderly subjects, the subjects were accustomed to mean daily intakes ranging from 200 to 700 mg/day [18–20].

There are several potential limitations to the current study. The sample size was small, but the uniform lack of response to caffeine among our subjects makes it unlikely that our findings are due to a Type II error. Several subjects took medications that may have influenced postprandial BP responses. However, medications were held for as long as it was safe to do so, and for the same amount of time in both the caffeine and placebo phases of the study. If a drug like caffeine is to be useful clinically, it needs to be effective regardless of other medications that a patient may be taking. Finally, our study does not assess whether caffeine is effective in the sitting position, whether a different dose, preparation or time of administration is more effective, or whether its effect might be enhanced by combined therapy with other vasoconstrictor agents.

ACKNOWLEDGMENTS

We are grateful to Drs Adam Burrows, Sheila Ryan and Palmi Jonsson for technical assistance during the meal studies. We also thank Dr Roy Freeman for his assistance in identifying subjects, Dr Carol Waksmonski for performing screening echocardiograms, Dr Alice Shapiro and her dietary staff at the Beth Israel Hospital Clinical Research Center for preparing the experimental meals, and
Table 3. Individual BP, HR and noradrenaline changes at 60 min after the meal with placebo or caffeine. Abbreviations: SBP, systolic BP; MABP, mean arterial BP; NA, noradrenaline.

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Jamie Noonan and the Pharmacy staff at the Hebrew Rehabilitation Center for Aged for dispensing the caffeine. This work was supported by a Teaching Nursing Home Award (no. AG04390) and Claude Pepper Geriatric Research and Training Center Grant (no. AG08812) from the National Institute on Aging, and a General Clinical Research Center Grant to Beth Israel Hospital (RR01032) from the National Institutes of Health. L. A. L. holds the Irving and Edyth S. Usen and Family Chair in Geriatric Medicine at the Hebrew Rehabilitation Center for Aged. R. W. M. M. J. is a recipient of a grant from the Van Helten Foundation, Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands.

REFERENCES


