Caffeine restriction: effect on mild hypertension //

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Abstract

Objective—To determine the effects on blood pressure of modifying dietary caffeine intake in patients with mild and borderline hypertension by monitoring ambulatory and clinic blood pressure.

Design—Four way, randomised, crossover trial of four consecutive two week dietary regimens: normal diet, caffeine free diet alone, caffeine free diet with decaffeinated instant coffee, caffeine free diet with caffeinated instant coffee (instant coffee phases conducted double blind).

Setting—Hospital hypertension clinic, Scotland.

Patients—52 patients (23 men; aged 26-67 years) with untreated borderline or mild hypertension (diastolic blood pressure 90-105 mm Hg) who normally drank a minimum of three cups of coffee daily.

Main outcome measures—Mean ambulatory blood pressure over 24 hours; mean morning, daytime, and night time ambulatory blood pressure; sitting clinic blood pressure at 1700; plasma caffeine concentration at 1700 on the last day of each regimen.

Results—Mean 24 hour ambulatory blood pressure was not different between regimens. There was no difference in blood pressure variability between regimens. During the caffeine free diet alone morning ambulatory diastolic blood pressure was higher (2.8 mm Hg) than during the caffeine free diet with caffeinated coffee. Mean sitting clinic systolic blood pressure was higher at 1700 (4.7 mm Hg) with a caffeine free diet than with the caffeine free diet with caffeinated coffee ($p < 0.05$). Dietary compliance as assessed by plasma caffeine concentration was excellent. There was no significant correlation between plasma caffeine concentration and blood pressure.

Conclusions—Drinking caffeinated instant coffee over a two week period does not adversely influence blood pressure in patients with borderline or mild hypertension; abstinence is of no benefit.

Introduction

The decision when to treat a patient with borderline or mild hypertension is commonly faced in clinical practice. A sustained diastolic blood pressure of 100 mm Hg or more has been suggested as an indication for starting drug treatment but a diastolic pressure of 90 mm Hg or less has not.¹ Between these two values the decision whether to treat entails measuring blood pressure repeatedly, detecting other risk factors, and assessing the effects of non-pharmacological intervention such as weight reduction, reduction of alcohol intake, regular exercise, increasing potassium intake, and salt restriction.^{2,3} Should caffeine restriction be added to this list?

Coffee or caffeine may raise both systolic and diastolic blood pressure for a few hours after ingestion in subjects who have been abstinent for at least eight hours.⁴⁻⁸ Tolerance to this reported pressor effect develops rapidly.^{9,10} In population studies coffee drinking has been associated with both higher¹¹ and lower^{12,13} blood pressure and with no effect.^{14,15} Randomised

studies of chronic caffeine intake in normal volunteers have shown that a reduction in intake is associated with a fall in blood pressure.^{16,17} Mildly hypertensive patients have been the subjects of only one study, which was small and of insufficient power to be conclusive.¹⁸

We carried out a randomised, crossover study comparing normal diet with a caffeine free diet alone or in conjunction with the ingestion of caffeinated or decaffeinated instant coffee to determine whether caffeine restriction is a useful non-pharmacological treatment in patients with borderline and mild hypertension.

Patients and methods

Fifty two patients who had an untreated sitting diastolic (phase V) blood pressure of between 90 and 105 mm Hg on the second of two screening visits were recruited from those referred to the hypertension clinic of Aberdeen Royal Infirmary. They were selected on the basis of their blood pressure, coffee drinking habits, and willingness to take part in the study. No patient had biochemical, haematological, electrocardiographic, or clinical abnormalities. All patients were coffee drinkers (instant or percolated) and admitted to an intake of a minimum of three cups a day. They all gave written fully informed consent and were aware of the rationale behind the study. The study was approved by the Grampian area ethics committee.

DESIGN

The study consisted of four regimens of dietary modification, each lasting two weeks. These were (a) a normal diet, (b) a caffeine free diet, (c) a caffeine free diet with caffeinated coffee taken as desired, and (d) a caffeine free diet with decaffeinated coffee taken as desired. The order of regimens was random according to a code drawn up by the pharmacy. During the caffeine free diet regimens patients abstained from all products containing caffeine—that is, coffee other than that provided by us, tea, chocolate, cola-type soft drinks, etc. The instant coffee we used was freeze dried, granulated and either regular (caffeinated) or decaffeinated (Gold Blend, Nestlé). The two types of coffee were packed in identical containers, which were coded by the hospital pharmacy and administered in a double blind fashion. Patients were asked to drink a minimum of three cups of coffee a day during the regimens that included coffee. Coffee jars were weighed on days 1, 13, and 14 to determine the average and final day's coffee consumption. Patients were also asked if they could distinguish between the two types of coffee.

On the 13th day of each treatment phase between 1500 and 1630 a Spacelabs 90207 ambulatory blood pressure monitor (Spacelabs, Redmond, Washington) was fitted to the patients' non-dominant arm and programmed to record blood pressure every 15 minutes between 0600 and 2200 and hourly between 2200 and 0600.¹⁹ An audible warning was given before each measurement during the day. Patients were asked to keep their arm motionless and in the same position when blood pressure was being measured. The study

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was designed to detect a 4 mm Hg change in mean ambulatory blood pressure over 24 hours with 80% power at the 5% level of significance.²⁰

The mean of two blood pressure measurements (Hawksley random zero sphygmomanometer) after patients had been sitting for five minutes was recorded as the clinic blood pressure when patients returned on the final day of each phase.²¹ To assess dietary compliance and to estimate caffeine intake a venous blood sample was drawn for estimation of plasma caffeine concentration as close as possible to 1700 on the final day of the study. This was assayed by high performance liquid chromatography by the method of Lelo *et al.*²²

STATISTICAL ANALYSIS

Analysis of variance was used to detect any overall difference in blood pressure between the four dietary regimens. A two way analysis of variance was carried out on the clinic blood pressure and the mean ambulatory blood pressure over 24 hours to detect any effects due to dietary modification independent of interpatient variability. In addition, three way analysis of variance to test variability between regimens, patients, and time periods and their two way interactions was performed as well as an analysis of carryover order effects.

Data from the monitoring of ambulatory blood pressure over 24 hours were collated according to three time periods: 0600-0959 (morning), 1000-2159 (day-time), and 2200-0559 (night time). These periods were chosen to correspond to first exposure to caffeine after nocturnal abstinence, continuing intermittent exposure, and nocturnal abstinence. Mean systolic and diastolic blood pressures were calculated for each patient during each regimen and time period. Two pairs of missing observations were estimated by iteration with a standard linear model. The three factor interaction was incorporated in the estimation of residual error variance. In a subgroup analyses Scheffé's method of multiple comparisons was used to calculate least significant differences between dietary regimens.²³

Three way analysis of variance was also used to assess the effect of dietary regimens on variability in blood pressure by comparing standard deviations. Diurnal change in variability within the three time periods was also assessed.

Correlation between coffee consumption, plasma

caffeine concentrations, and blood pressure was also calculated.

Results

Fifty patients (27 women; mean age 47 (range 26-63)) completed the study. Two women were withdrawn (one because of pregnancy and the other because she required diuretic treatment for ankle oedema). Seven of the men and two of the women were smokers.

AMBULATORY BLOOD PRESSURE

Table I shows mean systolic and diastolic ambulatory blood pressure for the three time periods and four treatment phases. There were no significant differences between regimens by two way analysis of variance for mean ambulatory blood pressure over 24 hours.

Three way analysis of variance showed the expected significant differences between patients and between time periods, but there were no significant differences between regimens or significant carryover order effects.

Diastolic blood pressure during the caffeine free diet was higher than in the caffeine free diet with caffeinated coffee by 2.8 mm Hg in the 0600-0959 period ($p<0.01$ by Scheffé's method). A similar but non-significant trend was found when the caffeine free diet was compared with the normal diet (table I).

Variability in blood pressure was not significantly different between dietary regimens for either systolic or diastolic blood pressure, but there were differences in the variability of systolic and diastolic blood pressure between time periods. The mean variability in systolic blood pressure was low (SD 3.3 mm Hg) but varied diurnally, being high during the day (5.3 mm Hg), low overnight (1.4 mm Hg), and intermediate in the morning (3.1 mm Hg). The mean variability in diastolic blood pressure was high (11.8 mm Hg) but stable between periods (morning 11.8 mm Hg, daytime 11.9 mm Hg, night time 11.7 mm Hg).

CLINIC BLOOD PRESSURE

Table II shows the mean clinic blood pressures at 1700. There were no differences between regimens in diastolic blood pressure. By Scheffé's technique for multiple comparisons the most extreme of the six possible paired comparisons of systolic blood pressure showed that the caffeine free diet was associated with a small (4.7 mm Hg) but significant increase ($p<0.05$) in systolic blood pressure compared with the caffeine free

TABLE I—Ambulatory systolic and diastolic blood pressures (mm Hg) by time period and dietary regimen in 50 patients. Values are means (95% confidence intervals)

Caffeine free diet					
Time (h)	Normal diet	Alone	With decaffeinated coffee	With caffeinated coffee	Mean (time period)
Systolic blood pressure					
0600-0959	133.4 (130.5 to 136.3)	135.7 (132.8 to 138.6)	134.5 (131.6 to 137.4)	132.2 (129.3 to 135.1)	134.0 (133.3 to 134.6)
1000-2159	143.1 (140.2 to 146.0)	142.7 (139.8 to 145.6)	142.8 (139.9 to 145.7)	142.0 (139.1 to 144.9)	142.7 (142.0 to 143.3)
2200-0559	125.4 (122.5 to 128.3)	124.5 (121.6 to 127.4)	124.5 (121.6 to 127.4)	125.9 (123.0 to 128.8)	125.1 (124.4 to 125.7)
Mean (regimen)	134.0 (133.0 to 135.0)	134.3 (133.3 to 135.3)	133.9 (132.9 to 134.9)	133.4 (132.4 to 134.4)	
Diastolic blood pressure					
0600-0959	86.7 (85.0 to 88.5)	89.2 (87.4 to 90.9)*	88.2 (86.5 to 89.9)	86.4 (84.6 to 88.1)	87.6 (87.2 to 88.0)
1000-2159	94.0 (92.3 to 95.7)	93.5 (91.8 to 95.3)	93.9 (92.1 to 95.6)	93.6 (91.8 to 95.3)	93.7 (93.4 to 94.1)
2200-0559	78.2 (76.5 to 79.9)	77.4 (75.7 to 79.1)	77.0 (75.3 to 78.7)	78.6 (76.9 to 80.3)	77.8 (77.4 to 78.2)
Mean (regimen)	86.3 (85.7 to 86.9)	86.7 (86.1 to 87.3)	86.4 (85.8 to 87.0)	86.2 (85.6 to 86.8)	

* $p<0.01$ When compared with caffeinated coffee regimen.

TABLE II—Clinic systolic and diastolic blood pressures by dietary regimen in 50 patients. Values are means (95% confidence intervals)

	Normal diet	Caffeine free diet		
		Alone	With decaffeinated coffee	With caffeinated coffee
Blood pressure:				
Systolic	141.9 (136.9 to 145.8)	144.5 (140.0 to 149.0)*	141.5 (137.3 to 145.7)	139.7 (135.6 to 143.8)
Diastolic	92.2 (89.3 to 95.0)	93.2 (91.1 to 95.3)	91.7 (89.4 to 94.0)	91.5 (89.0 to 94.0)

* $p<0.05$ When compared with caffeinated coffee regimen.

diet with caffeinated instant coffee. A similar but smaller and non-significant trend was seen in diastolic blood pressure.

COFFEE CONSUMPTION

Table III shows the mean amounts of coffee consumed in the double blind phases of the study.

TABLE III—Mean (SD) coffee consumption and plasma caffeine concentrations by dietary regimen in 50 patients

Regimen	Coffee consumption (g)		Plasma caffeine (mg/l)
	14 Day	24 h*	
Normal diet			4.86 (3.57)
Caffeine free diet:			
Alone			Undetectable
With caffeinated coffee	107.3 (49.5)	10.4 (5.7)	4.91 (2.60)
With decaffeinated coffee	109.0 (52.0)	9.5 (6.2)	0.60 (0.61)

*Five and 13 observations missing for the caffeinated and decaffeinated coffee regimens respectively.

Patients were consistent in the average amount consumed in each phase ($r=0.89$), although there was a greater than fivefold difference in consumption between the 50 patients. The missing observations for the 24 hour period were due to patients forgetting to bring their coffee jars for weighing on day 13.

PLASMA CAFFEINE CONCENTRATION

Table III shows plasma caffeine concentration at 1700. Dietary compliance was excellent. During the caffeine free diet alone regimen only two samples had detectable caffeine concentrations (1.32 and 0.45 mg/l).

Plasma caffeine concentration correlated with mean caffeine consumption measured on day 14 ($r=0.38$, $p<0.01$) and with consumption on the final day caffeine ($r=0.43$, $p<0.01$).

There was no correlation between plasma caffeine concentration and clinic blood pressure, mean ambulatory blood pressure, or mean daytime ambulatory systolic or diastolic blood pressures. A subgroup analysis of patients with high (>6.0 mg/l), medium (2.7-6.0 mg/l), and low (<2.7 mg/l) plasma caffeine concentrations also failed to detect any significant correlation with blood pressure.

Patients were unable to accurately discriminate between caffeinated and decaffeinated coffee, 32 being incorrect in their assessment.

Discussion

The results of this study show that restriction of dietary caffeine or a change to decaffeinated coffee is not a clinically useful therapeutic manoeuvre for patients presenting with borderline or mild hypertension.

Although individual readings taken by an ambulatory blood pressure monitor are more variable than standard sphygmomanometer readings, the greatly increased number of measurements taken allows for overall greater precision. This increases the statistical power of crossover studies, measures diurnal effects, and permits the detection of subtle differences between treatments.²⁴

A subgroup analysis of the ambulatory blood pressure data detected a marginally higher diastolic blood pressure with the caffeine free diet alone compared with the caffeinated coffee regimen, but only in the morning. We do not wish to overemphasise this single observation. The decaffeinated coffee regimen might be expected to be similar to the caffeine free regimen and the normal diet regimen to be similar to the caffeinated coffee regimen, but though such trends were found, there were no other significant differences. In any case, such a small difference in

blood pressure (less than 3 mm Hg) is unlikely to be clinically significant.

We also found that clinic systolic blood pressure was higher with the caffeine free diet alone than with the caffeinated coffee regimen, but we found no similar trend with the decaffeinated coffee and normal diet regimens. Had clinic blood pressure readings been the sole end point in this study we might have concluded that a caffeine free diet increases blood pressure or that long term caffeine intake lowers blood pressure. The ambulatory monitoring data do not support this as no consistent rise in blood pressure was seen during the daytime period. A transient rise in systolic blood pressure may have occurred in the late afternoon; it may not have been detected because of the increased variance in systolic blood pressure measurement during this time. Finally, the clinic pressure may have been different by chance alone.

Patients were asked to drink three or more cups of coffee a day during the appropriate phases. Table III shows a wide range of consumption patterns. Caffeine displays a large interindividual variation in pharmacokinetics.²⁵ Nevertheless, Lelo *et al* found that a good measure of exposure to caffeine could be obtained from a single plasma sample drawn at 1700²²; in samples drawn at this time we found a significant correlation between plasma caffeine concentration and caffeine consumption over the previous 24 hours. We also found plasma caffeine concentrations similar to those reported by Lelo *et al*.

These results cannot be extrapolated to patients with more severe hypertension or to drinkers of percolated, filtered, or brewed coffee. Ingesting caffeinated instant coffee for longer than two weeks might conceivably have different effects, but we doubt that a dramatic increase in blood pressure would occur. If caffeine were to raise blood pressure when taken long term regular consumers would be expected to have an increased cardiovascular risk. A recent study by Grobbee *et al* prospectively followed a cohort of 45 589 men and found no association of cardiovascular disease with caffeinated coffee.²⁶ Decaffeinated coffee carried a small and marginally significant increased risk of coronary heart disease.

In conclusion, we found no evidence that caffeine restriction or a change to decaffeinated coffee is beneficial in reducing blood pressure in the non-pharmacological management of patients with borderline or mild hypertension.

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Eradicating *Helicobacter pylori* and symptoms of non-ulcer dyspepsia

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Abstract

Objective—To examine the effect of eradication of *Helicobacter pylori* on symptoms of non-ulcer dyspepsia.

Design—Four week prospective study.

Setting—One hospital outpatient and endoscopy department.

Patients—90 adults with persistent symptoms typical of non-ulcer dyspepsia but no clinical or endoscopic evidence of other peptic, biliary, pancreatic, or malignant disease; all had histological and microbiological evidence of infection with *H pylori*. 83 patients completed the treatment regimen.

Intervention—Colloidal bismuth subcitrate 120 mg four times a day for four weeks (27 patients); metronidazole 400 mg and amoxycillin 500 mg each three times a day for one week (27); and bismuth subcitrate 120 mg four times a day for four weeks, metronidazole 400 mg three times a day for one week, plus amoxycillin 500 mg three times a day for the first week (29).

Main outcome measures—Change in symptom scores determined with questionnaire; histological evidence of gastritis and microbiological evidence of presence of *H pylori* in biopsy specimens.

Results—Overall, *H pylori* was eradicated in 41 (49%) patients. Although gastritis scores improved significantly in only patients in whom *H pylori* had been eradicated (from 1.56 to 0.61, $p < 0.01$ v from 1.83 to 1.07, $p = 0.52$) mean symptom scores after treatment were similar in patients in whom *H pylori* had or had not been eradicated (3.0 v 2.3, NS). Similarly the mean symptom score improved whether or not gastritis improved (2.8 v 3.1 respectively, $p = 0.72$). The observations were similar for treatment groups analysed individually.

Conclusion—Antral infection with the organism does not seem to have an important aetiological role in non-ulcer dyspepsia short term.

Introduction

The discovery of *Helicobacter pylori* and its close association with chronic active gastritis^{1,2} and peptic ulcer disease^{3,4} had led to speculation that it may have a role in causing symptoms of non-ulcer dyspepsia. In Europe non-ulcer dyspepsia accounts for almost a third of all gastroenterological referrals⁵ and up to a quarter of all general practice consultations.⁶ The definition of the non-ulcer dyspepsia syndrome varies widely, making comparison of studies of non-ulcer dyspepsia difficult. In 1988 an international working party defined

non-ulcer dyspepsia as "upper abdominal or epigastric pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to be referable to the upper gastrointestinal tract, and lasting for more than four weeks, unrelated to exercise and for which no focal lesion or systemic disease can be found responsible."⁷ Clearly, patients with the syndrome constitute a heterogeneous group for whom no effective treatment is available at present. The higher prevalence of *H pylori* in patients with non-ulcer dyspepsia compared with age matched blood donors supports the theory that *H pylori* has an important role in the aetiology of non-ulcer dyspepsia.⁸ *H pylori*, however, is also common in the asymptomatic population,⁹ and its prevalence varies with age and ethnic group.¹⁰ Therefore, in an attempt to show whether *H pylori* plays an important part in the pathogenesis of non-ulcer dyspepsia we carried out a prospective study to examine the effect of eradication of *H pylori* on symptoms and histological appearance of the gastric antrum in patients with non-ulcer dyspepsia in whom *H pylori* was cultured.

Patients and methods

All patients referred to our endoscopy department over six months for investigation of persistent symptoms consistent with non-ulcer dyspepsia were considered suitable for the study. The study was approved by the medical ethics committee of the Meath and Adelaide Hospitals, and informed consent was obtained from all patients. Only patients with histological and microbiological evidence of infection with *H pylori* and with persistent symptoms of at least two months' duration were included in the study. Patients with evidence of active or previous peptic ulcer disease, gall bladder disease, oesophagitis, malignancy, or previous abdominal surgery were excluded, as were patients receiving non-steroidal anti-inflammatory agents or those who had taken antibiotics up to four weeks before the start of the study. Pregnant women were also excluded. All patients were examined by endoscopy at entry and again at four weeks after completion of treatment to check for eradication of *H pylori*. Endoscopy was performed with an Olympus Q10 gastroscope and on each occasion two biopsy specimens were taken from the gastric antrum for histological and microbiological examinations. In total, 90 patients were enrolled during the study period, and each was sequentially allocated one of three treatment regimens: (a) colloidal bismuth subcitrate 120 mg four times a day for four weeks; (b) metronidazole 400 mg and amoxycillin 500 mg each three times a day for one

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