Br. J. clin. Pharmac. (1983), **15**, 701–706

ADAPTATION OF BLOOD PRESSURE TO CONTINUOUS HEAVY COFFEE DRINKING IN YOUNG VOLUNTEERS. A DOUBLE-BLIND CROSSOVER STUDY

H.P.T. AMMON[1], P.R. BIECK[2], D. MANDALAZ[3] & E.J. VERSPOHL[1]

[1]Department of Pharmacology, Institute of Pharmaceutical Sciences, Tübingen, [2]Department I of Internal Medicine, Tübingen, F.R.G. & [3]Scientific Computer Centre of Ciba-Geigy, Basel, Switzerland

1 In a double-blind crossover trial, the effect of 4 week daily ingestion of eight cups of regular coffee (corresponding to 504 mg caffeine) *vs* eight cups of decaffeinated coffee was studied. Blood pressure, heart rate and urinary catecholamines were measured in eight healthy, young volunteers.

2 In both groups, regular coffee immediately led to a significant increase in mean blood pressure (+ 3 and + 5 mm Hg respectively). The difference between both groups, however, existed only in the first 3 to 5 days of ingestion of regular coffee. On day 5 after ingestion of regular coffee, and thereafter in weekly intervals, no significant increase in catecholamine excretion was observed.

3 The data suggest that long-term consumption of large amounts of coffee leads to only a small and transient rise in mean blood pressure. This may be due to an adaptation phenomenon.

4 Therefore, continuous heavy coffee ingestion (eight cups/day for 4 weeks) by young persons does not appear to involve a risk of the development of hypertension.

Introduction

Acute administration of caffeine or coffee to healthy subjects has repeatedly been demonstrated to increase systolic blood pressure, the changes being in the range between 5 and 20 mm Hg (Seyffert, 1954; Robertson *et al.*, 1978). Acute administration of caffeine has also been reported to slightly elevate heart rate and increase plasma catecholamine concentration as well as catecholamine excretion (Polonovski *et al.*, 1952; Robertson *et al.*, 1978; Scott & Chen, 1944; Stepp, 1938; White, 1951). In contrast, prospective (Robertson *et al.*, 1979) and retrospective studies (Dawber *et al.*, 1974; Bertrand *et al.*, 1978) have not shown coffee consumption to be associated with an increase in blood pressure.

The aim of the present study was to employ a double-blind crossover trial for investigating whether or not the discrepancy between the results of acute and epidemiological investigations might be explained at least in part by an adaptation phenomenon during continuous heavy daily coffee consumption (eight cups/day for 4 weeks).

Methods

Volunteers

A total of 10 young (20–30 years old) male volunteers (students) was accepted for the study. The MPI system (Maudsley Personality Inventory) was used to exclude subjects with a neurotic tendency and abnormal extraverted behaviour; values were 14.3 ± 5.7 and 26.8 ± 8.5 respectively and were therefore normal and/or lower than the values of Eysenck (1959). The medical history of the volunteers was protocoled. All volunteers were non-smokers, but used to coffee. At the beginning and 1 month after completion of the study a general medical examination including an ECG was performed including laboratory tests and various clinical–chemical measurements (SMA 12, thyroid function). Only volunteers with normal test results and blood pressure of less than 120/80 mm Hg prior to the study were accepted. They were assigned randomly to one of the two treatment groups.

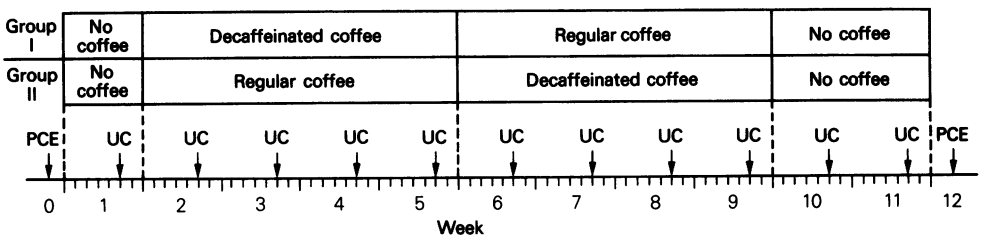
Preparation of coffee

As indicated in Figure 1 (lower part b) eight cups of coffee were drunk each day except during a control period of 1 week. Packed portions containing either 1.8 g of instant regular coffee or 1.8 g of instant decaffeinated coffee were supplied by HAG AG, Bremen, F.R.G. The portion was dissolved in approximately 120 ml of hot water. Instant coffee powder (1.8 g) contained 63 mg caffeine, 1.8 g of decaffeinated coffee powder contained no methylxanthine detectable by high pressure liquid

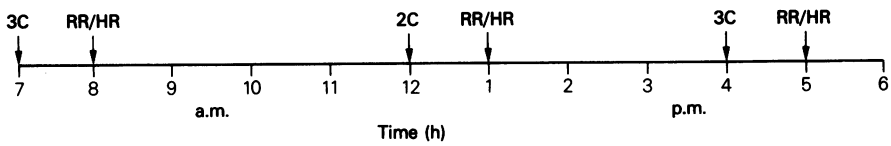
0306–5251 83/0600–7010 $02.00

Figure 1 Protocol of investigation

a Protocol of weekly coffee ingestion of regular and decaffeinated coffee, physical and clinical-chemical examination (PCE) and urine collection for catecholamine determination (UC)



b Protocol of daily coffee ingestion (C = number of cups), determination of blood pressure (RR) and heart rate (HR)



chromatographic analysis. Code numbers for regular or decaffeinated coffee were not disclosed by HAG AG prior to the calculation of the results.

Protocol of coffee ingestion and measurement of blood pressure, heart rate and urinary catecholamines

The present investigation was a double-blind, crossover trial using regular coffee and decaffeinated coffee. Figure 1 shows the protocol of the study. During the investigation, smoking and ingestion of additional caffeine containing beverages were not allowed; daily alcohol consumption of up to half a litre of beer or a quarter litre of wine was permitted and protocoled each day.

Blood pressure and heart rate were measured daily except on Saturday and Sunday (Figure 1). This was the case during coffee consumption periods and during control periods (no coffee consumption) at the beginning and the end of the study. Blood pressure and heart rate were recorded 1 h after coffee consumption when caffeine plasma levels were expected (Robertson *et al.*, 1978) to resemble peak levels, and at equivalent times during the control period (Figure 1). Blood pressure and heart rate were measured manually and simultaneously on the left arm of comfortably sitting patients using a standard arm cuff and an electronic Boso-tron manometer, Bosch, Jungingen, F.R.G. which was tested by the German gauging office. At each time of measurement (08.00 h, 13.00 h and 17.00 h) blood pressure and heart rate were recorded in duplicate two times (5 min and 10 min after arrival and sitting down of the volunteers). Mean values were calculated from the resulting six daily measurements of systolic blood pressure, diastolic blood pressure and heart rate. Mean blood pressure shown in Figure 2 and Table 1 was calculated from 1/3 systolic and 2/3 diastolic blood pressure recordings.

Urine was collected once a week on Friday (fifth day of weekly ingestion period) for 24 h (Figure 1). The urine was acidified with 10 ml 6N HCl immediately after voiding. Urinary catecholamines were determined fluorometrically as described by von Euler & Floding (1955).

Dropouts

The values of one volunteer were not used because he developed a cough. The mean blood pressure of another volunteer was 15.4 mm Hg below the mean value of his group during the control period. Therefore, his values were not included in the statistical evaluation.

Evaluation of data

Daily differences between the two groups were evaluated by Student's *t*-test (see Figures 2 and 3).

For comparison of the overall results of the two 4 week periods and control period (see Table 1) the results were calculated using a method of time series analysis. The 'Autoreg' method of Sas (Sas User's Guide 1979 Edition, Sas Institute Inc., Raleigh, North Carolina 27605, USA) was applied; variables were the means of values (blood pressure and heart

rate) during three different time periods (no coffee consumption, consumption of decaffeinated coffee and ingestion of regular coffee). Comparison of the latter two periods involves a 'two period-change-over design', with two groups of volunteers, individual volunteers, two different treatments and periodical effects.

Results

Blood pressure

Mean blood pressure during the first 7 days of the control period (no coffee) was 97 ± 4 mm Hg in group I and 90 ± 2 mm Hg in group II, which was not statistically different ($P > 0.05$). As shown in the upper part of Figure 2 ingestion of regular coffee led to an immediate change in mean blood pressure of 6 mm Hg ($P < 0.001$ *vs* controls; group II) and by 4 mm Hg ($P < 0.05$ *vs* controls; group I). Significant differences between groups I and II were observed only during the first 3 or 5 days after switching to regular coffee (see hatched area in the upper part of Figure 2).

The overall effect of 4 weeks of treatment with regular coffee on the mean, as well as the systolic and diastolic blood pressure was calculated using the

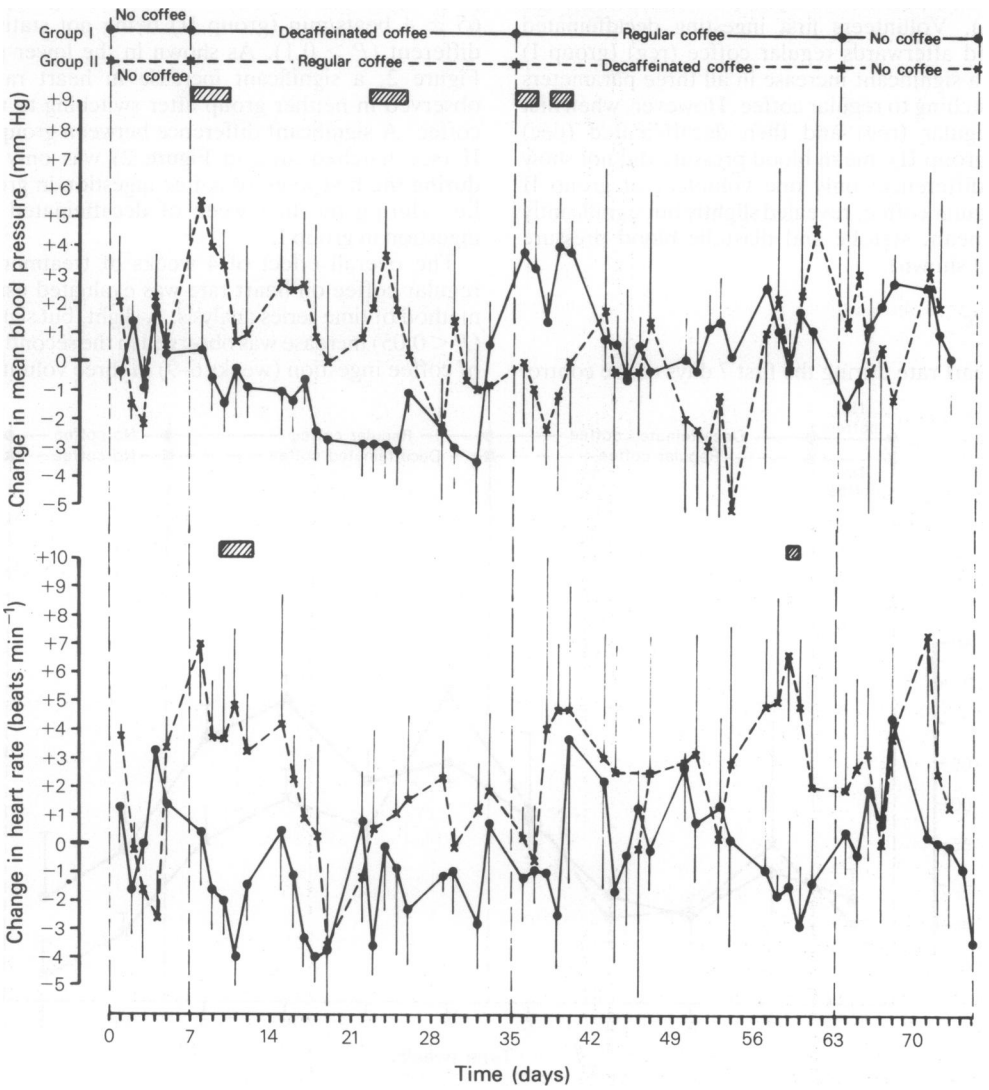


Figure 2 Changes in mean blood pressure and heart rate after heavy drinking of decaffeinated coffee or of regular coffee compared to no coffee. Experimental design as indicated at the top of the figure and in Figure 1. (Mean + s.e. mean). ▨ period of significant difference between both groups.

Table 1 Effect of 4 weeks of treatment with regular (reg) and decaffeinated coffee (dec) on blood pressure

Group	Dosage scheme	Mean blood pressure (mm Hg)	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
I	dec	95.5	122.9	81.8
		$P < 0.01$	$P < 0.01$	$P < 0.011$
	reg	98.5	125.7	84.9
II	reg	88.5	No effects	No effects
		NS		
	dec	87.6		

method of time series analysis (see Calculations and Table 1). Volunteers first ingesting decaffeinated (dec) and afterwards regular coffee (reg) (group I) showed a significant increase in all three parameters after switching to regular coffee. However, when first using regular (reg) and then decaffeinated (dec) coffee (group II), mean blood pressure did not show such a difference; only one volunteer of group II using regular coffee, revealed slightly but significantly higher mean, systolic and diastolic blood pressure (data not shown).

Heart rate

Mean heart rate during the first 7 days of the control period (no coffee) was 74 ± 3 beats/min (group I) and 65 ± 4 beats/min (group II) being not statistically different ($P > 0.1$). As shown in the lower part of Figure 2, a significant increase in heart rate was observed in neither group after switching to regular coffee. A significant difference between group I and II (see hatched area in Figure 2) was only found during the first week of coffee ingestion in group II, i.e., during the first week of decaffeinated coffee ingestion in group I.

The overall effect of 4 weeks of treatment with regular coffee on heart rate was evaluated using the method of time series analysis. A slight, but significant ($P < 0.05$) increase was observed in the second period of coffee ingestion (weeks 6–9) in three volunteers in

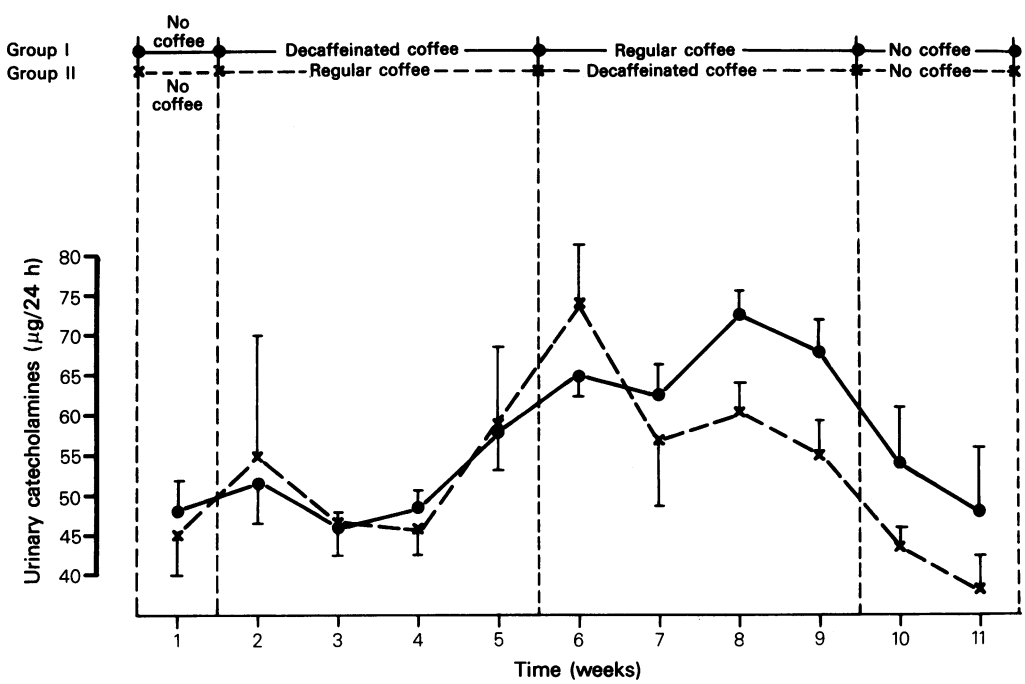


Figure 3 Changes in urinary catecholamine excretion after heavy drinking of decaffeinated coffee or of regular coffee including control periods (no coffee). Experimental design as indicated on top of the figure and in Figure 1. (Mean + s.e. mean).

group I (regular coffee) and four volunteers in group II (decaffeinated coffee) (data not shown).

Urinary catecholamines

A significant effect of regular coffee ingestion on urinary catecholamine excretion was neither observed in group I or in group II (Figure 3). The increase in urinary catecholamines in the second period of coffee consumption compared with the control period in either groups was independent of coffee ingestion (regular and decaffeinated); the method of time series analysis indicated this increase to be a significant periodical effect.

Discussion

Acute administration of coffee stimulates the central and sympathetic nervous system, the latter effect being shown by a rise of serum catecholamines and increased urinary excretion of catecholamines (Robertson *et al.*, 1978, 1979).

When volunteers started the ingestion of regular coffee corresponding to 504 mg caffeine per day subsequent to a caffeine-free period a slight increase in the mean blood pressure was observed. The increase is less compared to the observations made by other authors after acute ingestion of caffeine (Robertson *et al.*, 1978). In the present study, however, this effect on blood pressure disappeared after 3 to 5 days regardless of whether regular coffee was ingested in the first or in the second period. This data is in accordance with that of Robertson *et al.* (1981) using caffeine instead of coffee, and they suggested adaptation to coffee drinking. According to the present results, such adaptation appears as early as 3–5 days after the onset caffeine ingestion. However, the phenomenon of adaptation does not exclude that slight increases in blood pressure may be prolonged in individual cases of coffee intake.

As far as the extent of the blood pressure increase by coffee is concerned, there is some difference between both groups: i.e. the mean blood pressure after switching to regular coffee appears to be slightly more pronounced in group II (upper part of Figure 2). This discrepancy may result from the fact that volunteers of group II were not drinking regular coffee for at least 5 weeks whereas those of group I were abstinent from coffee for only 1 week and therefore were presumably less susceptible to caffeine effects. A similar observation was made by Robertson *et al.* (1981) using 250 mg caffeine in volunteers who had abstained from caffeine intake for either 3 weeks or only 24 h.

The effect of caffeine on blood pressure is generally thought to be mainly due to an increase in cardiac output rather than an increase in the peripheral resistance, since caffeine has been demonstrated to possess vasodilating effects (Eichler, 1975; Sebök, 1950; Somlyo & Somlyo, 1968). In the present study, however, only adaptation of blood pressure to heavy coffee consumption (eight cups/day for 4 weeks) was measured. The increase in the heart rate due to chronic coffee intake was small and not statistically significant, which confirms the results of other authors after acute ingestion of coffee (Fleisch & Wenner, 1954; Colton *et al.*, 1968).

The data of Figure 3 show that the 24 h catecholamine excretion in volunteers receiving regular coffee was not different from those receiving decaffeinated coffee. However, urine was collected on the fifth day of each week. Therefore, no conclusion can be drawn on possible initial changes due to increased sympathetic tone. An increase in plasma catecholamine levels has been reported one day after acute administration of caffeine (Robertson *et al.*, 1978). Our results confirm the data of Robertson *et al.* (1978) who showed that the elevation of urinary catecholamine concentration (adrenaline and noradrenaline) decreased starting from the 2nd day of continued caffeine (250 mg/day) consumption. The baseline range was reached after 4 days (Robertson *et al.*, 1979). This data is comparable to the present data although we used coffee containing 504 mg caffeine/day. Whether or not the elimination of caffeine is influenced by chronic coffee consumption remains to be seen.

The present data obtained from young volunteers does not support the notion that heavy coffee ingestion (eight cups/day for 4 weeks) involves a risk of developing hypertension. The relevance of such findings to older or hypertensive persons remains an object of further investigation.

Conclusions

The present double-blind crossover study in young healthy volunteers indicates that heavy coffee ingestion (eight cups/day = 504 mg caffeine per day, over 4 weeks) only slightly raises blood pressure, for no longer than 3–5 days. Thereafter, blood pressure differences are not observed between consumers of regular and decaffeinated coffee—probably due to an adaptation phenomenon. Therefore, long-term consumption of large amounts of coffee by young persons does not appear to be a risk factor in the development of hypertension.

This work was supported by a grant from HAG AG, Bremen, FRG.

References

BERTRAND, C.A., POMPER, I., HILLMAN, G., DUFFY, J.C. & MICHELL, I. (1978). No relation between coffee and blood pressure. *New Engl. J. Med.*, **299**, 315–316.

COLTON, T., GOSSELIN, R.E. & SMITH, R.P. (1968). The tolerance of coffee drinkers to caffeine. *Clin. Pharmac. Ther.*, **9**, 31–39.

DAWBER, T.R., KANNEL, W.B. & GORDON, T. (1974). Coffee and cardiovascular disease: observations from the Framingham study. *New Engl. J. Med.*, **291**, 871–874.

EICHLER, O. (1975). *Kaffee und Coffein*, pp 65–320. Berlin, Heidelberg, New York: Springer-Verlag.

EYSENCK, H.J. (1959). *Das 'Maudsley Personality Inventory' (MPI)*, Dr C.J. Hogrefe, Göttingen, FRG: Verlag für Psychologie.

FLEISCH, A. & WENNER, V. (1954). Les effets physiologiques du café et des extraits de café. *Schweiz med. Wochenschr.*, **84**, 223–226.

POLONOVSKI, M., DONZELOT, E., BRISKAS, S. & DOLIOPOULOS, T. (1952). The comparative effects of coffee and instant extracts of coffee on normal persons and on cardiacs. *Cardiologia*, **21**, 809–816.

ROBERTSON, D., FRÖLICH, J.C., CARR, R.K., WATSON, J.T., HOLLIFIELD, J.W., SHAND, D.G. & OATES, J.R. (1978). Effects of caffeine on plasma renin activity, catecholamines and blood pressure. *New Engl. J. Med.*, **298**, 181–186.

ROBERTSON, D., GARLAND, A.J., ROBERTSON, R.M., NIES, A.S., SHAND, D.G. & OATES, J.A. (1979). Comparative assessment of stimuli that release neuronal and adrenomedullary catecholamines in man. *Circulation*, **59**, 637–643.

ROBERTSON, D., WADE, D., WORKMAN, R. & WOOSLEY, R.L. (1981). Tolerance to the humoral and hemodynamic effects of caffeine in man. *J. clin. Invest.*, **67**, 1111–1117.

SCOTT, C.C. & CHEN, K.K. (1944). Comparison of the action of l-ethyl theobromine and caffeine in animals and man. *J. Pharmac. exp. Ther.*, **82**, 89–97.

SEBÖK, I. (1950). Koffeinwirkung bei Hypertonikern. *Dtsch med. Wochenschr.*, **33/34**, 1067–1070.

SEYFFERT, H.M. (1954). Physiologische und psychologische Wirkungen von Kaffee und Coffein. *Arzneimittel-Forsch.*, **4**, 207–209.

SOMLYO, A.V. & SOMLYO, A.P. (1968). Electromechanical and pharmacomechanical coupling in vascular smooth muscle. *J. Pharmac. exp. Ther.*, **159**, 129–145.

STEPP, W. (1938). Kaffee und Coffein als Gift und als Heilmittel. *Arch. exp. Path. Pharmak.*, **190**, 256–270.

Von EULER, U.S. & FLODING, I. (1955). Measurement of catecholamines. *Acta physiol. Scand.*, **33**, (Suppl.) 57.

WHITE, P.D. (1951). *Heart disease*. 4th ed., p 871. New York: MacMillan.

(Received July 26, 1982, accepted March 7, 1983)