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Caffeine and Cerebral Blood Flow

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Summary: Two groups of normal volunteers had regional cerebral blood flow (rCBF) measured, by the ^{133}Xenon inhalation technique, before and 30 minutes after 250 mg or 500 mg caffeine given orally. rCBF was measured in a third group of subjects, twice, at a similar interval under identical laboratory conditions. Subjects who received caffeine showed significant decreases in rCBF while the others showed no rCBF change from the first to the second measurement. However, the two caffeine groups did not differ in degrees of rCBF reduction. There were no regional variations in the post-caffeine decrease in cerebral blood flow. The three groups did not show significant changes in end-tidal carbon dioxide, pulse rate, blood pressure, forehead skin temperature and respiratory rate.

Caffeine is the most widely used psychotropic agent (Gilbert, 1976; Rall, 1980). High levels of coffee consumption have been reported in normals and patients with psychiatric illness (Gilbert, 1976; Winstead, 1976). Excessive use of the drug has been associated with anxiety, restlessness and depression (Furlong, 1975; Lutz, 1978; Hire, 1978; Greden, 1974; Greden *et al*, 1978; Gilliland and Andress, 1981). Caffeine dependence and withdrawal have been described (Gilbert, 1976; Greden *et al*, 1980; Goldstern *et al*, 1969).

In the normal brain, function, metabolism and blood flow are closely interrelated (Ingvar, 1978; Raichle *et al*, 1977). Global and regional alterations in brain activity are associated with parallel changes in cerebral blood flow (CBF) and metabolism (Risberg, 1980; Meyer, 1978). The central nervous system stimulating action of caffeine is well-established (Gilbert, 1976; Rall, 1980). The literature on the effect of caffeine on CBF in animals is inconclusive. Studies conducted on humans indicate a caffeine-related decrease in CBF (Gibbs *et al*, 1935; Shenkin, 1951; Wechsler *et al*, 1950). However, most of these reports were based on small numbers of subjects: CBF was measured with invasive techniques which yield only mean hemispheric values (Kety, 1948).

The present study evaluated the effects of two doses of caffeine on regional cerebral blood flow (rCBF) in normal volunteers. Cerebral blood flow was measured by the ^{133}Xenon inhalation technique which measures the global and regional values of both hemispheres, simultaneously (Obrist *et al*, 1975).

Method

Twenty-four volunteers participated in the study. The principal investigator interviewed all the participants to exclude physical and psychiatric illnesses. All the subjects were regular coffee drinkers. None had taken medications of any kind for a minimum of one month prior to the study. Subjects with histories of alcohol and/or drug abuse were not included in the project. The subjects reported to the laboratory in the morning after having abstained from tobacco, tea and caffeine-containing beverages overnight. They had a standard breakfast of cereal and milk. Hand preference was determined by the Harris Test of Lateral Dominance (Harris, 1974). Cerebral blood flow was measured twice, at an interval of 30 minutes. Nine subjects received 250 mg of caffeine while seven consumed 500 mg of the drug between the two measurements. Caffeine was mixed with lemonade and administered orally immediately after the first CBF run. The remaining eight subjects had two steady-state rCBF measurements under identical laboratory conditions. The subjects were assigned to the three groups in a random fashion. The characteristics of the three groups are given in Table I.

The ^{133}Xenon inhalation technique was used for cerebral blood flow measurement (Obrist *et al*, , 1975; Meyer *et al*, 1978). A mixture of the isotope in air (5–7 mCi/litre) was administered via a sterilized, close-fitting face mask, for one minute. The rate of removal of the isotope from the brain was monitored for 10 minutes by tracing the progressive decline in radioactivity with a system of 16 collimated scintillation detectors mounted on a helmet and applied to the scalp. Blood flow to the regions beneath the scintillation detectors was computed from these clearance curves recorded over the scalp. End-tidal ^{133}Xenon concentration curves were used for two purposes. Air passage artifact was eliminated from the clearance

TABLE I
Demographic characteristics

	Controls	Caffeine 250 mg	Caffeine 500 mg	
	(*N* = 8)	(*N* = 9)	(*N* = 7)	*P*
Age	31.75 (SD = 7.72)	34.11 (SD = 8.69)	27.14 (SD = 7.58)	NS
Hand preference	8 right	8 right, 1 left	7 right	
Sex	5 men, 3 women	3 men, 6 women	3 men, 4 women	

TABLE II
Comparison of the three groups on the physiological indices recorded during the two rCBF measurements

		Controls		Caffeine 250 mg		Caffeine 500 mg				
	Run	Mean	SD	Mean	SD	Mean	SD	F	df	P
Forehead skin temperature	1	83.98	1.52	82.35	2.01	83.06	3.64	0.97	2/20	NS
Forehead skin temperature	2	83.60	1.77	81.41	3.22	82.06	3.85	0.83	3/22	NS
$PECO_2$	1	35.63	3.93	38.89	2.93	39.57	4.61	2.39	2/21	NS
$PECO_2$	2	35.13	3.23	36.78	3.90	36.43	4.69	2.34	3/23	NS
Pulse rate	1	75.75	12.30	72.33	9.72	65.57	8.59	1.84	2/21	NS
Pulse rate	2	70.75	10.68	68.11	9.38	62.00	9.38	0.08	3/23	NS
Mean blood pressure	1	86.81	6.00	79.66	8.69	79.90	5.83	2.86	2/21	NS
Mean blood pressure	2	86.37	6.12	79.50	9.02	82.09	7.07	0.51	3/23	NS
Respiratory rate	1	11.66	3.67	9.50	2.77	11.00	2.58	0.88	2/21	NS
Respiratory rate	2	12.66	3.96	10.00	3.02	11.28	2.05	0.74	3/23	NS

The mean and standard deviations of the second set of values are unadjusted. However, the significance levels are derived from analysis of covariance.
Skin temperature is given in Fahrenheit. Partial pressure of $PECO_2$ and blood pressure are given in millimetres of mercury.

curves by commencing the curve analysis from the point at which the end-tidal isotope concentration had dropped to 20 per cent of its peak value. The end-tidal levels of the isotope which reflect changes in the arterial concentration were also used for correction of Xenon recirculation to the brain. The slope of the clearance curves at two and a half minutes was used as an index of cerebral blood flow in the present study. This had been shown to be a stable index of grey matter blood flow, with little contamination from extracranial tissues (Meyer *et al*, 1978; Risberg *et al*, 1975). End-tidal levels of carbon dioxide ($PECO_2$), rate of respiration, pulse rate and forehead skin temperature were also recorded during the entire procedure. Blood pressure was taken immediately before the isotope-air mixture was turned on.

rCBF measurements were carried out in a quiet, semi-dark room. The procedure was explained to the subjects in advance and they were allowed sufficient time to acclimatise to the face mask and the laboratory. After the face mask was attached, the isotope-air mixture was not turned on until end-tidal levels of carbon dioxide had stabilized. The patients were instructed to regulate their breathing with the help of a metronome to minimize fluctuations in $PECO_2$ levels during the procedure. One-channel vertex electroencephalographic and electro-oculographic tracings were displayed on an oscilloscope during the procedure to detect onset of drowiness (Foulkes and Vogel, 1965). None of the patients became drowsy during the procedure.

Results

The three groups were compared on pulse rate, blood pressure, forehead skin temperature, $PECO_2$, rate of respiration, and rCBF by analysis of variance,

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TABLE III

Comparison between the three groups on right hemispheric rCBF (ISI_2)

		Controls		Caffeine 250 mg		Caffeine 500 mg				
Variable	Run	Mean	SD	Mean	SD	Mean	SD	F	df	P
Right hemisphere	1	55.99	11.64	57.38	12.18	71.91	6.65	4.33	2/16	0.03
	2	58.28	12.55	44.90	7.08	46.40	4.28	9.04	3/15	0.004
Pre-frontal	1	60.10	12.00	61.10	13.60	75.74	12.85	3.40	2/20	0.05
	2	65.42	12.88	48.15	6.84	51.22	6.68	12.31	3/19	0.001
Superior frontal	1	53.48	13.05	57.80	15.67	67.41	8.43	2.24	2/20	0.13
	2	56.53	13.98	45.18	7.93	46.53	3.43	11.49	3/21	0.001
Frontal	1	54.90	11.73	57.28	11.53	70.04	11.30	3.67	2/21	0.04
	2	58.18	14.67	46.41	8.47	46.17	4.92	9.24	3/23	0.001
Parietal	1	52.52	9.67	54.48	12.58	68.91	8.44	4.66	2/20	0.02
	2	54.15	11.43	43.48	6.84	44.55	2.93	11.46	3/21	0.001
Superior-temporal	1	55.88	9.79	57.61	14.68	67.55	11.02	1.87	2/20	0.17
	2	58.68	13.97	45.51	7.04	45.67	4.10	6.23	3/20	0.009
Temporal-parietal	1	54.62	12.02	57.86	12.84	71.25	7.39	3.88	2/18	0.04
	2	55.52	10.16	45.43	8.38	45.16	4.86	11.39	3/20	0.001
Occipital	1	53.73	14.20	55.56	14.79	65.68	7.78	1.82	2/21	0.18
	2	53.15	11.04	44.21	7.41	44.20	4.38	14.20	3/23	0.001
Temporal	1	57.10	9.13	56.51	10.57	72.35	10.17	5.93	2/20	0.009
	2	57.13	12.92	46.05	8.30	46.65	4.40	8.26	3/22	0.003

ISI_2 is the slope of the Xenon clearance curve at 2½ minutes.
The means and standard deviations of the second set of values given are unadjusted. The F ratios and significance levels are derived from analysis of covariance. The rCBF values given are not $PECO_2$ corrected. In all cases where drug effects were significant, posteriori contrasts (Duncan's Multiple Range Test) showed normals were significantly different from both caffeine groups.

TABLE IV

Comparison between the three groups on left hemispheric rCBF (ISI_2)

		Controls		Caffeine 250 mg		Caffeine 500 mg				
Variable	Run	Mean	SD	Mean	SD	Mean	Sd	F	df	P
Left hemisphere	1	54.48	9.34	53.90	11.28	70.84	6.19	6.69	2/17	0.007
	2	60.67	10.52	44.18	7.36	46.32	3.29	7.61	3/14	0.008
Pre-frontal	1	60.95	9.14	61.28	14.00	73.80	7.89	3.42	2/19	0.05
	2	66.75	10.60	50.11	9.15	52.88	3.87	13.28	3/19	0.001
Superior frontal	1	52.71	8.65	54.57	13.15	66.70	12.12	3.20	2/21	0.06
	2	56.86	12.47	44.23	7.87	45.77	4.81	11.74	3/23	0.001
Frontal	1	53.67	9.70	57.25	15.30	68.20	10.63	2.76	2/21	0.09
	2	56.13	10.87	44.84	7.65	45.24	4.44	10.34	3/23	0.001
Parietal	1	51.05	7.74	52.62	11.06	62.78	7.13	3.69	2/21	0.04
	2	54.92	13.10	42.27	7.14	42.72	3.94	8.41	3/20	0.003
Superior-temporal	1	54.15	8.73	56.85	13.17	65.42	7.41	2.38	2/21	0.11
	2	57.95	13.71	45.45	8.39	48.22	5.15	7.86	3/21	0.004
Temporal-parietal	1	52.41	10.02	55.22	11.60	72.31	9.75	6.81	2/20	0.005
	2	54.48	11.46	45.50	9.44	43.66	4.31	9.78	3/21	0.001
Occipital	1	52.83	11.00	55.51	14.31	64.91	10.00	2.39	2/21	0.11
	2	55.71	9.40	45.21	6.95	44.28	4.05	12.84	3/21	0.001
Temporal	1	54.70	10.13	55.83	9.17	72.62	13.41	5.97	2/19	0.009
	2	59.18	13.80	43.70	7.05	47.65	3.69	8.66	3/19	0.003

ISI_2 is the slope of the Xenon clearance curve at 2½ minutes.
The means and standard deviations of the second set of values given are unadjusted. The F ratios and significance levels are derived from analysis of covariance. The rCBF values given are not $PECO_2$ corrected. (see Table III for posteriori contrasts).

using the information obtained during the first CBF run. Next, the three groups were compared on the second set of values by analysis of covariance, with the first set of values as the covariate (Tables II, III and IV). There were statistically significant reductions of blood flow for both caffeine groups, but no change in the controls. The three groups did not show significant differences on the second set of values for pulse, respiration, forehead skin temperature, blood pressure and $PECO_2$. The analysis was repeated with the first and second rCBF values corrected for the differences in $PECO_2$ (Olesen *et al*, 1971). The same results were obtained. Next, the rCBF data was examined to find out whether there were regional differences in the cerebral blood flow response to caffeine. The differences of the regional values from the corresponding hemispheric mean values were expressed as percentages of the mean. The three groups were compared on these percentile values. No significant differences emerged between the three groups on the first, or second cerebral blood flow values.

Discussion

The present study confirms previous reports of reduced cerebral blood flow following the administration of caffeine (Gibbs *et al*, 1935; Shenkin, 1951). In addition, the results reported here indicate that the cerebral blood flow reduction does not show regional differences. Maximum CBF changes were obtained with 250 mg of caffeine; further increments in dose did not produce more CBF reductions.

Most central nervous stimulants increase cerebral blood flow and metabolism (Carlsson *et al*, 1975; Berntman *et al*, 1976; Berntman *et al*, 1978). However, caffeine a well known stimulant, was found to reduce cerebral capillary perfusion. At present, the mechanism responsible for this phenomenon is not clear. Activation is dependent upon the balance between facilitatory and inhibitory brain mechanisms (Grey, 1982). Increases in activation can be brought about by suppression of the inhibitory pathways. For example, benzodiazepines and barbiturates, which reduce cerebral blood flow and metabolism, are known to induce dishibition and behavioural activation in predisposed people (lassen, 1959; Cotev and Shalit, 1975; Rockoff *et al*, 1980). The reduction in cerebral blood flow seen following caffeine administration might be related to the suppression of the inhibitory pathways. It is also possible that caffeine has a direct vasoconstrictive action on the cerebral blood vessels, unrelated to its effects on arousal (Wechsler *et al*, 1950). However, the reason why brain capillaries should have a different response to this drug than capillaries elsewhere is uncertain (Rall, 1980).

Regional blood flow is one of the factors which determine patterns of distribution of drugs in the body. Brain blood flow is thus an important determinant of the effectiveness of psychotropic drugs, especially those with rapid onset of action (Mayer *et al*, 1980). Decrease in CBF is very likely to limit the delivery of the drug to the brain and reduce its potency. Caffeine has been shown to antagonize drugs like barbiturates and benzodiazepines (Dureman, 1962; Forrest *et al*, 1972; Molde, 1975; Proctor and Greden, 1982). It is also known to exacerbate symptoms in hospitalized psychiatric patients (Goldstern *et al*, 1969). CNS stimulation and hepatic microsomal induction due to the drug are generally believed to be responsible for these phenomena (Proctor and Greden, 1982; Mitoma *et al*, 1968). CBF reduction associated with caffeine, and the consequent decrease in drug delivery to the brain seem to be important factors in the antagonism between caffeine and other psychotropic agents.

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