CAFFEINE is present in a wide variety of beverages, food substances and over-the-counter drugs.\(^1\)\(^2\) Large numbers of people of all age groups consume this substance in some form or other. Approximately twenty to thirty percent of the general population have been found to ingest more than 500–600 mg of the drug daily.\(^3\)\(^4\) Caffeine-containing beverages and foods are served in most hospitals, and patients with a wide variety of diseases consume it.

Cerebral vasosconstrictive effects of caffeine are well established.\(^6\)\(^9\) Several investigators have reported on the reduction in cerebral blood flow (CBF) induced by intravenous administration of the drug. These reports do not, however, address the more clinically relevant issue of the effects of small oral doses of the drug (comparable to the quantities in which it is usually consumed in daily life) on cerebral circulation. Similarly, no information is available on the duration of the change in cerebral circulation thus induced. In a recent study, we found significant reductions in CBF 30 minutes after oral administrations of 250 and 500 mgs of caffeine.\(^10\) The two doses did not result in significantly different intensity of associated CBF reduction. The present project was designed to evaluate duration of caffeine induced cerebral vasoconstriction and to extend the results of the above mentioned open trial by using a double-blind, placebo controlled design.

Method

Volunteer subjects were recruited through local advertising. They were carefully screened for physical and mental disorders. Those who gave a history of consuming more than three cups of coffee, tea or cola per day or any caffeine containing drug were excluded. Similarly, subjects with a history of alcohol and substance abuse were also excluded. Participants were required to remain medication free (prescription and over-the-counter) for a minimum of two weeks prior to the study. Subjects were instructed to abstain from all caffeine containing substances for at least two hours before the experiment.

First, a venous blood sample was obtained for the determination of hemoglobin values. This was required for the computation of the CBF values (see below). Regional cerebral blood flow was measured three times in each subject under identical laboratory conditions. Immediately after the first CBF measurement, subjects received either 250 mg of caffeine or a placebo with lemonade under double-blind conditions. Caffeine ingestion was found to be associated with significant reductions in cerebral perfusion thirty and ninety minutes later. The placebo group showed no differences between the three sets of cerebral blood flow values.

**SUMMARY** While the caffeine induced cerebral vasoconstriction is well documented, the effects of oral ingestion of the drug in a dose range comparable to the quantities in which it is usually consumed and the intensity and duration of the associated reduction in cerebral circulation are unknown. Cerebral blood flow was measured via the \(^{133}\)Xenon inhalation technique before and thirty and ninety minutes after the oral administration of 250 mg of caffeine or a placebo, under double-blind conditions. Caffeine ingestion was found to be associated with significant reductions in cerebral perfusion thirty and ninety minutes later. The placebo group showed no differences between the three sets of cerebral blood flow values.

**Caffeine Induced Changes in Cerebral Circulation**

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measurements were repeated twice more, thirty minutes and ninety minutes after the administration of the drug/placebo. Relevant demographic data concerning the drug and placebo groups is given in table 1.

CBF was measured via the $^{133}$Xenon inhalation technique. A mixture of the isotope in air (5-7 mCi/liter) was administered through a sterilized, close-fitting face mask for one minute. Clearance of the isotope from the brain was traced by recording the progressive decline in radioactivity with 32 suitably collimated scintillation detectors mounted on a helmet and applied to the scalp. Blood flow values were computed from these clearance curves using a bicompartamental model by an online mini-computer. The use of multiple detectors permitted the measurement of capillary perfusion in different brain regions. The influence of air passage contamination on the scalp clearance curves was minimized by commencing the clearance curve analysis from the point at which the end-tidal isotope concentration had fallen to 20 percent of its peak value. End-tidal isotope concentrations were also used for the correction of xenon recirculation to the brain. The bicompartamental curve analysis permitted the separation of the highly perfused gray matter from white matter and extracranial tissues. Differences between subjects on the blood-brain partition coefficient for Xenon were corrected for using predetermined values corresponding to their hemoglobin levels.

All measurements were made in a quiet, semi-dark room with eyes open. Blood pressure (before and after the measurement), respiratory rate, end-tidal carbon dioxide (PCO$_2$) and a one channel EEG recording (to detect any sleep onset) were monitored during the entire procedure. None of the subjects became drowsy during the measurements. The Xenon-air mixture was turned on only after the respiration and PECO$_2$ levels had stabilized. All the measurements were carried out under identical laboratory conditions. Levels of anxiety experienced during each measurement were quantified via the State Anxiety Scale of the State Trait Anxiety Inventory administered immediately after each measurement. Subjects who received caffeine and placebo were compared on the three sets of CBF values (each set consisted of right and left hemispheric and 32 regional flow values), (figs. 1 and 2), physiological indices and State Anxiety Scores via analysis of variance with repeated measures and post hoc Newman-Keuls tests. Post hoc tests (multiple comparisons) were used to find out where the significant differences between the variables lie after significant F ratios were obtained.

**Results**

Analysis of the 32 regions indicated significant reductions in blood flow for the caffeine group both at the 30 and 90 minute periods which were not present in the placebo group as indicated by statistically significant interactions in almost all regions (figure 3). These findings were substantiated by post-hoc testing which indicated no differences between the two groups on resting cerebral blood flow and between the three sets of CBF values in the placebo group. However, the post-caffeine blood flow to most regions and the two hemispheres during the latter two measurements were significantly lower ($p < .05$) than the resting values and the corresponding values obtained by the placebo group (figs. 3 and 4). Differences between the pre- and post-caffeine CBF values were much greater than the corresponding values obtained by the placebo group. Levels of PECO$_2$, blood pressure, respiratory rate and State Anxiety were stable across the three measurements for both groups.

**Discussion**

Several investigators have reported cerebral vasoconstriction following the intravenous administration of caffeine and other xanthene drugs. The results of this study indicate significant reductions in CBF, thirty and ninety minutes after the oral administration of 250 mg of caffeine. Twelve (7 females and 5 males) of the 14 subjects who received caffeine showed reduced cerebral blood flow and none had CBF increases. Both males and females showed similar CBF responses to the drug. These findings are also comparable to those of the previous open study conducted in this laboratory. Similar results were obtained with both compart-
mental and noncompartmental indices of cerebral blood flow and identical flow changes were found in both hemispheres. Mathematical correction of the CBF values for differences in end-tidal carbon dioxide levels (which were non-significant) did not alter the results. The double-blind feature of the present experimental design considerably reduces the influence of chance and nonspecific factors. The robustness of the "Xenon inhalation technique has been demonstrated by reports of high degrees of test/retest stability of the CBF values obtained via this technique." The observed CBF changes were uniform across all brain regions, bilaterally.

The precise mechanism responsible for the caffeine-induced cerebral vasoconstriction is unclear. Under normal conditions, CBF is insulated from the vicissitudes of peripheral circulation through autoregulatory mechanism. There were no significant changes in blood pressure after the administration of the drug. In our previous open trial, we evaluated the changes in pulse and extracranial circulation via forehead skin temperature. The caffeine-induced reduction in cerebral circulation was not associated with any changes in pulse or extracranial blood flow. Carbon dioxide is well known for its powerful effect on CBF. The changes in cerebral perfusion reported here and in our previous report were not accompanied by fluctuations in PECO2, and corrections for PECO2 differences did not alter the results. Similarly, levels of anxiety also remained constant during the three measurements. Thus, the caffeine-induced cerebral vasoconstriction seemed unrelated to changes in carbon dioxide, peripheral circulation or level of arousal (anxiety).

Low doses of caffeine have been shown to bind to adenosine receptors in a dose dependent manner. Several pharmacological actions of the drug have been explained on the basis of this mechanism. Adenosine is a powerful cerebral vasodilator. Therefore, adenosine receptor blockade by caffeine would seem to be the most plausible explanation for the reduction in cerebral perfusion seen after the administration of the drug.

The ubiquitousness of caffeine consumption makes this finding of considerable clinical significance. The dose of caffeine used in this study is comparable to the quantities in which it is typically consumed (roughly equal to two cups of brewed coffee — 1). Blood is the vehicle through which CNS-acting drugs reach the brain. The reduction in cerebral perfusion maintained up to ninety minutes after caffeine administration can thus reduce the effectiveness of several of these agents. Indeed, caffeine has been reported to antagonize several sedatives and hypnotics and cause exacerbation of psychiatric illnesses in patients on maintenance medication. It also has been found to reduce neuroleptic-induced catalepsy in animals without producing significant changes in plasma levels of the drug. Cerebral ischemia is of paramount clinical significance since severe reduction in cerebral circulation causes brain damage. Though the CBF reduction following caffeine administration does not seem severe enough to cause symptoms of cerebral ischemia in normal individuals, it is unclear whether it may increase the risk for transient ischemic attacks and cerebral infarction in high risk individuals and in those recovering from cerebrovascular accidents. Over-the-counter diet preparations and illicit stimulants which contain caffeine and phenylpropanolamine (a sympathomimetic agent) have been reported to cause confusion, psychosis, seizures and stroke. Phenylpropanolamine induced hypertensive crisis is generally considered to be re-
sponsible for this. 3.36 Cerebral vasoconstriction secondary to caffeine may be an additional contributing factor. Caffeine induced CBF changes in dementias which are associated with reduced cerebral perfusion 3.34 may also be of relevance.

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