Caffeine reduces cerebral blood flow in patients recovering from an ischaemic stroke

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Abstract

Background: caffeine is present in a variety of beverages and food and is widely consumed. In a previous study of patients recovering from an acute ischaemic stroke using transcranial Doppler ultrasound we demonstrated a fall in middle cerebral artery blood velocity of 12% following ingestion of 250 mg caffeine. The aim of this study was to investigate if this velocity change affected a change in cerebral blood flow.

Methods: the study used a randomised, double blind, cross-over design. Nineteen patients recovering from an acute ischaemic stroke in the middle cerebral artery territory and 10 controls attended two sessions, having abstained from caffeine for 48 hours previously. At each session cerebral blood flow was measured four times using xenon clearance, twice before the oral administration of 250 mg caffeine or matched placebo, and twice after. Similarly, three middle cerebral artery blood velocity readings using transcranial Doppler were made prior to administration and four after.

Results: the caffeine resulted in a significant fall in cerebral blood flow and middle cerebral artery blood velocity compared to placebo.

Conclusions: since caffeine is present in the diet of most patients recovering from an acute ischaemic stroke this effect may have adverse clinical consequences.

Keywords: cerebral blood flow, stroke, ischaemic, caffeine, transcranial Doppler, elderly

Introduction

Caffeine is one of the most widely consumed drugs worldwide. In Britain the average daily intake per person is close to 300 mg [1]. The main sources of caffeine are coffee, tea and caffeinated cola drinks. Caffeine is completely absorbed after oral administration, is metabolised via a complex set of reactions and has a plasma half-life of 2½–4½ hours [2].

The pharmacological effects of caffeine are consistent with its ability to block adenosine receptors. In the brain adenosine inhibits the release of excitatory neurotransmitters, decreases the rate of firing of central neurones and is a potent vasodilator of cerebral blood vessels.

Several trials have demonstrated that caffeine reduces cerebral blood flow (CBF) in normal volunteers [3–5]. A similar reduction in CBF in subjects with impaired cerebrovascular reserve may have adverse clinical consequences. In a previous study of 20 patients recovering from an acute ischaemic stroke using transcranial Doppler ultrasound a 13% fall in blood velocity in the middle cerebral artery (Vmca) was demonstrated after acute ingestion of 250 mg caffeine [6–8]. This reduction was similar for both the affected and unaffected cerebral hemisphere.

In the present study the aim was to investigate if these cerebral blood velocity changes previously demonstrated with caffeine in stroke patients reflect changes in CBF. The Xenon inhalation technique was chosen as the method of measurement of CBF as the robustness of the technique has previously been validated by high test/retest stability [9, 10].

Subjects and methods

Subjects
In total, 19 subjects (11 males and 8 females) were studied, aged between 48 and 86 years. The sample size was
determined by a power calculation based on the authors’ previous work on blood velocity [7, 8]. That study showed that the mean reduction (95% CI) in blood velocity in stroke patients after taking caffeine was 6.3 cm/s (3.8 cm/s, 8.7 cm/s) greater than in the same patients after taking placebo, and that the standard deviation of these differences was 5.5 cm/s. With 19 patients the present study has 80% power to detect a mean reduction of 3.8 cm/s (equivalent to the lower confidence limit of the previous study) in the caffeine phase of the trial compared to the placebo phase.

These subjects were recruited from a Stroke Rehabilitation Unit. All subjects had suffered an ischaemic stroke in the distribution of the middle cerebral artery 2–10 weeks prior to entry into the study. This was based on clinical findings and CT brain scanning. According to the Bamford Oxfordshire Community Stroke Project classification all subjects were in the TACS and PACS group [11]. The Barthel Index, a validated score of general disability based on activities of daily living, was measured on admission to the study [12].

Furthermore, a separate group of 10 controls (6 males and 4 females), aged between 52 and 85, were studied. A control was defined as a person who had no indication or history of cerebrovascular disease. All subjects and controls gave written informed consent. The Southampton and South West Hants Joint Research Ethics Committee and the East Dorset Local Research Ethics committee granted ethical approval.

Protocol

This was a double blind, randomised, cross-over, placebo control study. Each subject attended for 2 studies, 1 or 2 weeks apart and was given 250 mg caffeine in one study and matched placebo in the other. Ten of the 19 subjects and 4 of the 10 controls were randomised to receive caffeine on their first visit followed by placebo on their second. The dose of caffeine used was comparable to the quantities in which it is typically consumed (roughly equal to two cups of brewed coffee) [13]. For 48 hours prior to each study the subjects abstained from caffeine.

Each study was carried out with the subject lying supine in a quiet room. Two baseline measurements of CBF using Xenon inhalation were made under identical laboratory conditions. Three baseline Vmca measurements were obtained bilaterally using transcranial Doppler. Subjects were then given a capsule containing either 250 mg of caffeine or placebo. Subjects were assigned caffeine/placebo on a random basis independently determined by the pharmacy department. The caffeine and placebo tablets were identical in appearance. The caffeine/placebo administrations were completed in <2 minutes.

Blood flow measurements were repeated twice more, 40 and 60 minutes after the administration of the caffeine/placebo. Two repeat measurements of Vmca were recorded 30 minutes post ingestion of caffeine/placebo and a further two measurements at 90 minutes.

Venous blood samples were obtained 40 minutes before and 80 minutes after ingestion of caffeine/placebo. These were analysed for blood concentration of caffeine by an enzyme immunoassay technique (EMIT; Behring Diagnostics, Milton Keynes, UK) on an Olympus AU560 auto-analyser (Olympus Optical, Eastleigh, UK). Blood Pressure (BP) measurements using a sphygmomanometer were recorded at the beginning and end of each pair of xenon measurements (i.e. four times).

Cerebral blood flow measurements

Cerebral blood flow measurements were made using a Novo Cerebrograph 32c instrument, (manufactured by Novo Diagnostic Systems, Denmark).

The subject inhaled air containing Xenon 133 in a concentration of 3 mCi (110 MBq)/litre by means of the rebreathing Xenon-133 administration system for 1 minute. The subject then continued to breathe normal air for the next 4 minutes with the mouthpiece in to collect exhaust xenon. At 3 minutes into each xenon measurement the End Tidal Carbon Dioxide (ETCO2) was recorded as measured by the integrated CO2 monitor. The CO2 monitor is an integrated part of the machine and is based on the measurement of infra-red absorption by carbon dioxide.

Throughout inhalation and then for a further 6 minutes after the mouthpiece was taken out the rate of removal of the isotope from the brain was monitored by tracing the progressive decline in radioactivity with a system of 16 collimated scintillation detectors mounted on a helmet. The rate of washout of the xenon formed the basis for the flow calculations. The Initial Slope Index (ISI), which is a modification of the ISI described by Risberg, was used to express CBF results [14]. This was chosen as the most reliable measure of CBF because it is independent of the partition coefficient of xenon (which is unknown for ischaemic tissue) and is little affected by the extra-cerebral matter.

For each subject the mean of the CBF values for the eight detectors on each side of the brain was calculated. The two initial measurements were averaged to obtain the baseline CBF value and the subsequent two measurements were averaged to obtain the after table CBF value. The mean CBF values were then averaged for the 19 subjects and the 10 controls to calculate the overall mean and SEM in each group.

Cerebral blood velocity measurements

Each Vmca measurement was carried out by the same operator using a transcranial Doppler unit (PCDop842, Scimed Ltd, Bristol, UK).

During each measurement the operator manipulated the probe to find the maximum velocity signal through the temporal window. Each measurement consisted of three Vmca readings on each side, of which the maximum value was used for analysis. Vmca refers to the time averaged maximum velocity envelope over 3–4 cardiac cycles and is calculated automatically after frequency analysis using a Fast Fourier Transformation.

For the analysis the maximum of the three Vmca recordings per measurement was used. The mean was calculated for the three baseline measurements and for the four measurements taken after tablet administration. The average of the two sides before and after the tablet was taken across the 14 subjects and 10 controls and the mean and SEM was calculated.
Caffeine reduces cerebral blood flow in ischaemic stroke

Statistical methods
Data on CBF and Vmca in individuals were analysed, both as absolute changes from baseline and as percentage changes from baseline. Changes in CBF, Vmca, blood pressure and carbon dioxide within individuals between the placebo and caffeine phases, and between affected and unaffected cerebral hemispheres were compared using the paired t-test. Comparisons between stroke and control groups were made using the independent samples t-test. Estimates of mean change are presented with 95% confidence intervals. More sophisticated analysis using repeated measures analysis of variance was used to assess whether the order in which caffeine and placebo were given altered the results. The relationship between percentage change in blood velocity and percentage change in blood flow was summarised using Pearson’s correlation coefficient. Data was analysed using SPSS for Windows Version 10 and Microsoft Excel. A 5% level of statistical significance was used.

Results
The concentration of caffeine before administration of the tablet was <0.1 mg/l for all subjects and controls. The mean caffeine concentration 65 minutes after administration of the caffeine tablet was 3.5 mg/l in the subject group and 3.0 mg/l in the control group. The mean duration of time from onset of stroke to entry into the study was 4.5 weeks. The average Barthel Index on admission to the study was 14 (range 6–20).

(a) Cerebral blood flow
The effect of caffeine on CBF was calculated by subtracting changes during the placebo phase from changes during the caffeine phase. The results for subjects and controls can be seen in Table 1 and Figure 1. The effect of caffeine was not significantly different between the affected and unaffected cerebral hemisphere in the subject group (P = 0.47). Combining both sides gives an average decrease in CBF of 10 ml/100 g/min from a baseline of 43 ml/100 g/min (~24% [95% CI 18–30%], P < 0.001). In the control group, the effect of caffeine was not significantly different between the right and the left hemisphere so they were combined with the following result. There was an average decrease with caffeine in CBF of 9 ml/100 g/min from a baseline of 49 ml/100 g/min (~19% [95% CI 12–26%], P < 0.001).

There was no significant difference in the effect of caffeine on cerebral blood flow between subjects and controls (P = 0.23).

Administration of 250 mg caffeine did not significantly alter blood pressure (P = 0.5 for systolic BP, P = 0.96 for diastolic BP). The end tidal carbon dioxide measurements during xenon studies can be seen in Table 3. The change in end tidal carbon dioxide was not significantly different between the caffeine and placebo group (P = 0.06). There was no significant correlation between time since stroke and the reduction in CBF with caffeine (P = 0.4).

(b) Middle cerebral artery blood velocity
Similar reductions in Vmca were demonstrated after caffeine. This data can be seen in Table 2. There was no difference between the effects of caffeine on Vmca on the stroke side compared to the non-stroke side in the subject group (P = 0.34). There was no significant difference in the effect of caffeine in the subjects compared to controls (P = 0.28).

(c) Comparison of CBF with Vmca
This study showed a significant positive correlation between percentage changes in Vmca as measured by TCD and changes in CBF as measured by xenon –133 (r = 0.42, P = 0.045).

There was no change in the results after adjusting for the order in which the subject received caffeine and placebo.

Discussion
Our data demonstrates significant reductions in global cerebral blood flow up to 90 minutes after the oral administration of 250 mg caffeine as measured by the xenon inhalation technique in patients recovering from an ischaemic stroke. Similar results were obtained in the affected stroke hemisphere and the unaffected side. The average reduction in CBF with caffeine was 24% [95% CI 18–30%, P < 0.00001] in the subject group. This reduction was similar in the control group. The results of this study also
The changes in CBF were not being caused by a secondary effect in which caffeine affects CO₂ and/or BP which in turn affect flow/velocity. In the subject group the change in CO₂ was 3.4 mmHg after caffeine and 2.5 mmHg after placebo giving a difference of 0.9 mmHg. The corresponding figures for controls are 4.2 mmHg with caffeine and 0.9 mmHg with placebo giving a difference of 3.3 mmHg. A normal response to hypercapnia is 3.6% per mmHg change in CO₂ [15]. We may therefore expect a drop in blood flow in the order of 3.3% in subjects and 11.7% in controls attributable to changes in CO₂. Clearly this is not sufficient to explain the reduction in CBF observed in this study.

To our knowledge, the present study is the first to show that caffeine reduces CBF in patients recovering from an acute ischaemic stroke. Previous studies have demonstrated a reduction in CBF after the administration of caffeine in normal healthy volunteers [3–5]. In one study using Xenon-133, clearance reductions of cerebral blood flow of 18% after 250 mg caffeine were demonstrated [3, 4]. A further PET study demonstrated 30% reductions in CBF after 250 mg caffeine [5]. The mechanism of CBF reduction with caffeine is likely to be due to a global effect on the cerebral vasculature since there were no differences between the affected and unaffected cerebral hemisphere in the subject group or between the right and left hemisphere in the control group. Since adenosine is a potent vasodilator of cerebral blood vessels the most plausible explanation for this effect is a direct vasoconstriction due to adenosine receptor blockade.

Though the CBF reduction after caffeine administration is unlikely to cause symptoms of cerebral ischaemia in normal individuals, patients recovering from an ischaemic stroke may have less cerebrovascular reserve and therefore be at more risk. It is well recognised that some patients with major cerebral arterial occlusion may continue to be under chronic haemodynamic stress [16, 17]. In these patients the cerebral vascular bed has reached a maximum vasodilatation to preserve blood flow in compensation for the reduced perfusion pressure. These haemodynamically-compromised areas are exposed to a high stroke incidence and a drop in blood flow in these areas has been postulated as a risk factor for stroke evolution. Therefore, theoretically, caffeine induced falls in cerebral blood flow during the acute stage of recovery may exacerbate pre-existing cerebral ischaemia in areas of misery perfusion.

There have been previous trials investigating the effects of a related methylxanthine (aminophylline) given acutely to patients with acute ischaemic stroke [18, 19]. These trials showed no definite evidence that aminophylline caused harm or benefit [20]. However, the numbers of patients studied was small.

Several experimental animal trials have demonstrated that an acute dose of caffeine or a related methylxanthine prior to an ischaemic insult leads to accelerated ischaemic brain injury [21, 22]. In contrast chronic exposure to caffeine reduces cerebral ischaemia in animal models [22, 23]. The mechanism underlying these effects is likely to be an upregulation of adenosine receptors with chronic caffeine consumption [24]. A significant increase in the number and sensitivity of adenosine receptor occurs with chronic caffeine intake in humans [25–27]. These observations support the idea that activation of adenosine receptors (chronic treatment with caffeine) reduces ischaemic damage while inhibition of the adenosine pathway (acute treatment with caffeine) augments such damage. The absence of a caffeine history from the subjects and controls may be a limitation to this study as the effects of caffeine may be different in caffeine naive people compared to chronic caffeine consumers.

In conclusion, the present study shows that 250 mg caffeine (equivalent to 2–3 cups of instant coffee) significantly reduces CBF up to 2 hours after ingestion in patients recovering from an acute ischaemic stroke. This reduction is similar in the affected and unaffected cerebral hemisphere. In addition this study demonstrates that changes in cerebral blood velocity induced by caffeine reflect changes in CBF. Further research is needed to investigate whether this caffeine induced reduction in cerebral blood flow in patients recovering from an acute ischaemic stroke leads to adverse clinical consequences.

### Key points

- 250 mg caffeine (equivalent to 2–3 cups of instant coffee) significantly reduces cerebral blood flow up to 2 hours after ingestion in patients recovering from an ischaemic stroke.
- There is no difference in the effect of caffeine on cerebral blood flow in ischaemic stroke patients and normal healthy controls.
• There is no difference in the effect of caffeine between the affected and unaffected cerebral hemisphere in stroke patients.
• Changes in cerebral blood velocity induced by caffeine reflect changes in cerebral blood flow.

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**References**

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