

## Comparison of caffeine-induced changes in cerebral blood flow and middle cerebral artery blood velocity shows that caffeine reduces middle cerebral artery diameter

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### Abstract

Changes in cerebral blood flow (CBF) can be assessed directly with xenon clearance (XeC) or indirectly by measuring changes in middle cerebral artery blood velocity (Vmca) with transcranial Doppler (TCD). The aim of this study was to compare the changes in CBF and Vmca following caffeine ingestion.

Nineteen patients (age 48–86, recovering from an acute stroke) and ten controls (age 52–85) were each studied twice. Bilateral measurements of CBF and Vmca were made before and after ingestion of 250 mg caffeine or matched placebo. The percentage change in CBF and Vmca after caffeine was calculated. Full results (CBF and Vmca) were obtained from 14 patients and 9 controls. There was no significant difference between patients and controls, so results were combined.

Caffeine reduced CBF by 22% (95% confidence interval (CI) = 17% to 28%) and reduced Vmca by 13% (95% CI = 10% to 17%). The fall in Vmca was significantly less than that in CBF ( $p = 0.0016$ ), showing that caffeine reduces mca diameter. Analysis based on Poiseuille flow in the arterioles suggests that caffeine reduced arteriole diameter by 5.9% (95% CI = 4.6% to 7.3%) and mca diameter by 4.3% (95% CI = 2.0% to 6.6%).

TCD is being used as an alternative to XeC for assessing the effect of vasoconstrictors and vasodilators on CBF. This study has demonstrated that mca diameter can be changed by the vasoactive agents, and that changes in Vmca do not necessarily reflect changes in CBF.

Keywords: cerebral blood flow, blood flow velocity, caffeine, transcranial Doppler, xenon clearance, arterial diameter

## 1. Introduction

Changes in cerebral blood flow (CBF) can be assessed either directly with xenon clearance (XeC) or indirectly with transcranial Doppler (TCD) (Obrist and Wilkinson 1990, Newell and Aaslid 1992). XeC uses an array of gamma-ray detectors around the head to measure the rate of washout of radioactive xenon administered in the inhaled air. TCD uses an ultrasound probe on the side of the head to measure the time average of the instantaneous maximum blood velocity in the middle cerebral artery (Vmca). Fractional change in Vmca should be equal to fractional change in CBF provided vessel diameter and velocity profile remain constant (Kontos 1989).

It is well known that caffeine ingestion causes an acute reduction in CBF. Oral administration of 250 mg caffeine to healthy young volunteers after at least 2 h abstinence reduced CBF by 18% (Mathew and Wilson 1985) and intravenous infusion of 250 mg of caffeine after 12 h abstinence reduced whole brain CBF by an average of 31% (Cameron *et al* 1990). There is no evidence that this reduction in CBF causes any problems in the normal population in whom there is an adequate cerebral perfusion reserve, but there may be implications in ischaemic stroke patients. An ischaemic stroke is caused by a reduction in blood supply to an area of the brain leading to localized infarction, and there may be regions of hypo-perfusion around the infarct which could be vulnerable to any further flow reduction (Kaufmann *et al* 1999).

We have already used TCD to show that 250 mg caffeine reduces Vmca by 13% in patients recovering from an ischaemic stroke in the middle cerebral artery (mca) territory (Lunt *et al* 2002). Caffeine of 250 mg is equivalent to two 150 ml cups of filter coffee or four cups of instant coffee or five to nine cups of tea depending on the brewing time (Bunker and McWilliams 1979). The aim of this study was to compare the changes in Vmca and CBF in stroke patients following caffeine ingestion to determine whether the change in Vmca does reflect a change in CBF.

## 2. Materials and methods

Nineteen patients (age 48–86) and ten controls (age 52–85) were each studied twice using a randomized double-blind cross-over design. Patients were selected from the Stroke Rehabilitation Unit at Christchurch Hospital and from Acute Stroke Units at Royal Bournemouth and Southampton General Hospitals. All were recovering from an ischaemic stroke in the territory of a middle cerebral artery, diagnosis having been confirmed by clinical findings and consistent computed tomography scan appearances. The studies were performed at Southampton General Hospital. Ethical approval was obtained from the local Ethics Committees.

Before each study, subjects abstained from caffeinated drinks for 48 h. Each study was performed with the subject lying supine in a quiet room. Two baseline CBF measurements and three baseline Vmca measurements were obtained bilaterally. Subjects were then given a capsule containing either 250 mg of caffeine or placebo, and the CBF measurements repeated 40 and 60 min after administration. Four further Vmca measurements were obtained, two at 30 min and two at 90 min after administration.

The CBF measurements were made using a Novo Cerebrograph 32c instrument, (manufactured by Novo Diagnostic Systems, Denmark). The subject inhaled air containing  $^{133}\text{Xe}$  in a concentration of  $110 \text{ MBq l}^{-1}$  by means of a re-breathing administration system for 1 min and then continued to breathe normal air through the mask for the next 4 min to collect exhaust xenon. The rate of removal of the isotope from the brain was monitored throughout the 4 min and for a further 6 min by tracing the progressive change in radioactivity with a system of 16 collimated scintillation detectors mounted on a helmet. The impulse response function was determined by deconvolution with the curve of activity in the airway. CBF was calculated from the rate of washout of the impulse response using the initial slope index (Risberg and Prohovnik 1981).

The  $V_{mca}$  measurements were made using a transcranial Doppler unit (PCDop842, Scimed Ltd, Bristol, UK). The unit displayed the Doppler spectrum continuously, identified the maximum frequency envelope and converted frequency to velocity assuming blood flow was directly towards the probe. Once an optimum signal had been obtained, an 8 s sample was saved and the average of the maximum velocity envelope ( $V_{mca}$ ) read from the TCD display. For each reading the operator manipulated the probe to find the maximum velocity signal through the temporal window. Each measurement consisted of three readings on each side.

At the end of each study, the subject was allowed to take their normal beverages until 48 h before any subsequent study. There was a gap of at least one week between studies to allow washout of any administered caffeine.

For each subject the mean CBF on each side of the brain before and after medication was calculated by averaging the results from the eight detectors on that side. The two initial measurements were then averaged to obtain the baseline CBF and the subsequent two measurements averaged to obtain the post-medication CBF. For the  $V_{mca}$  measurements, the maximum of each set of three readings was used. Baseline  $V_{mca}$  on each side was obtained by averaging the three measurements before medication, and post-medication  $V_{mca}$  obtained by averaging the four post-medication measurements.

After the code was broken, the effect of caffeine was found for each hemisphere separately by subtracting the change after placebo from the change after caffeine and these were averaged over all subjects. Overall percentage changes were calculated using averages of the pre-medication measurements as baselines. Statistical significance was assessed using Student's *t*-test with 5% significance level.

### 3. Results

Full CBF results (both sides and both visits) were available from 19 patients (mean age 71 years, range 48–86 years) and 10 control subjects (mean age 69 years, range 52–85 years). In some of these patients, it was not possible to obtain good TCD signals from both sides. Full  $V_{mca}$  results were available from only 14 patients (mean age 70, range 48–86) and 9 control subjects (mean age 68, range 52–85) (table 1 and figures 1 and 2).

In the patients, there was no significant difference between the affected and unaffected sides, so results from both were combined. Overall, the caffeine reduced CBF by 23.7% (SD 13%, 95% confidence interval 18% to 30%) and  $V_{mca}$  by 15.5% (SD 9%, 95% CI 10% to 20%). There was no significant correlation between the reduction in CBF and the age of the patient ( $r = 0.23$ ,  $p > 0.1$ ).

In control subjects, there was no significant difference between the right and left sides so results from both were combined. Overall, the caffeine reduced CBF by 18.9% (SD 10%, 95% CI = 12% to 26%) and  $V_{mca}$  by 11.2% (SD 11%, 95% CI = 3% to 19%). There

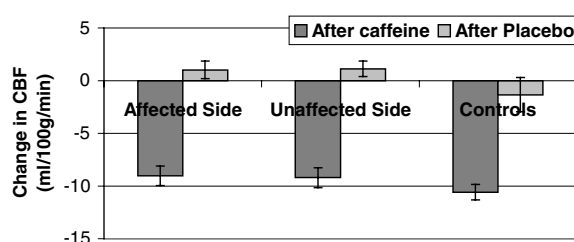


Figure 1. Change in CBF after tablet—patients and controls (mean  $\pm$  1 SEM).

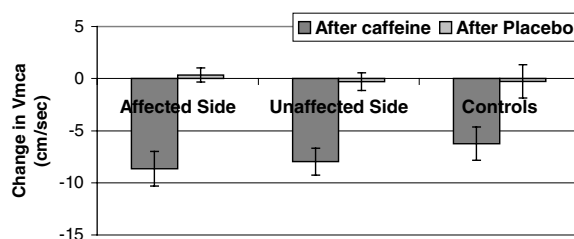


Figure 2. Change in Vmca after tablet—patients and controls (mean  $\pm$  1 SEM).

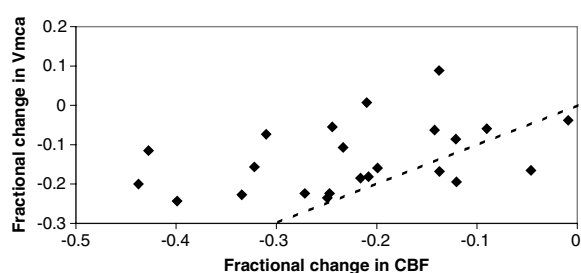
Table 1. Summary of results.

	CBF (ml/100 g min <sup>-1</sup> )		Vmca (cm s <sup>-1</sup> )	
	Affected side	Unaffected side	Affected side	Unaffected side
(a) Patients				
Baseline	42.6	43.2	55.7	52.2
Fall after caffeine	9.0	9.2	8.6	8.0
Fall after placebo	-1.0	-1.1	-0.4	0.3
Fall (caffeine-placebo)	10.0	10.3	9.0	7.7
95% confidence interval	7.2-12.9	7.9-12.8	5.3-12.7	5.4-9.9
(b) Controls	Right side	Left side	Right side	Left side
Baseline	49.3	48.5	52.6	54.2
Fall after caffeine	10.6	10.5	7.1	5.4
Fall after placebo	1.3	1.4	-1.6	2.1
Fall (caffeine-placebo)	9.4	9.1	8.7	3.3
95% confidence interval	5.7-13.0	5.4-12.9	4.7-12.6	2.7-9.2

was again no significant correlation between the reduction in CBF and the age of the subject ( $r = 0.10$ ,  $p > 0.5$ ).

These results confirm that the reduction in Vmca does reflect a real reduction in CBF. However, it appears that the fall in Vmca is less than that in CBF. This was investigated in more detail by comparing the percentage reductions in Vmca and CBF in individual subjects. Full results were available from 23 subjects, 14 patients and 9 controls.

There was no significant difference between patients and controls, and between the affected and non-affected sides of the patients. Results were therefore combined. Caffeine reduced CBF by 22% (95% confidence interval (CI) = 17% to 28%) and reduced Vmca by 13% (95% CI = 10% to 17%). Comparison of the changes in individual subjects (figure 3) showed that the fall in Vmca was significantly less than that in CBF ( $p = 0.0016$ ).



**Figure 3.** Comparison of fractional changes in Vmca and CBF in the individual subjects. The points do not lie on the line of identity (dotted line) and the fall in Vmca was significantly less than that in CBF ( $p = 0.0016$ ).

The consistency of the CBF and Vmca measurements was assessed by comparing measurements made on the same subject on the same occasion. The standard deviation of the difference between CBF measurements was  $4.1 \text{ ml}/100 \text{ gm min}^{-1}$ , and between Vmca measurements was  $4.1 \text{ cm s}^{-1}$ . Baseline CBF and Vmca and their inter-subject standard deviations were estimated by comparing the pre-medication values in the different subjects. For CBF, baseline and standard deviation were 45 and  $7.3 \text{ ml}/100 \text{ gm min}^{-1}$ , and for Vmca they were 52 and  $17.0 \text{ cm s}^{-1}$ .

#### 4. Discussion

The different percentage changes in CBF and Vmca may arise because the two techniques assess different parts of the brain, which respond differently to caffeine. The middle cerebral artery supplies the parieto-temporal region of the brain, while the scintillation detectors were also positioned over the occipital region. CBF results from the 19 patients and 10 controls were therefore re-analysed using only the six parieto-temporal detectors on each side, but this made no significant change in the results. There was a 23% reduction in CBF compared to 22% when all detectors were used.

The CBF measurements will include more of the flow in the superficial cortex, while the middle cerebral artery supplies some deeper structures. Differences may occur if caffeine has a different effect on the grey and white matter and if there are different proportions of grey and white matter in these regions. The CBF measurements were re-analysed using a dual slope model (Obrist and Wilkinson 1990) to determine the effect on grey matter alone, but this made no significant change in the results. There was a 24% reduction in CBF to grey matter compared to 22% to grey and white combined. This is consistent with the findings of Field *et al* (2003) who used magnetic resonance imaging to study the effect of caffeine on CBF to grey and white matter, and found that 250 mg caffeine reduced flow to grey matter by 23% and flow to white matter by 18%.

Differences between changes in CBF and Vmca can also be caused by changes in velocity profile (Lunt *et al* 2000). However, profile changes will cause a larger change in Vmca than in CBF (Lunt *et al* 2000), so cannot account for the lower change in Vmca found in the present study.

Blood flow depends on the ratio of blood pressure and peripheral resistance. The reduction in CBF after caffeine must therefore be caused by a reduction in blood pressure, an increase in peripheral resistance, or a combination of the two. After caffeine, systolic blood pressure fell by 1.4% (2.0 mmHg from a mean of 139 mmHg) and diastolic pressure fell by 0.7%

(0.5 mmHg from a mean of 78 mmHg). These changes are far too small to account for the 22% fall in blood flow, so there must have been an increase in peripheral resistance.

The flow of an ideal fluid through a rigid tube is described by Poiseuille's law. Under the ideal conditions of steady established laminar flow, the resistance is proportional to the fourth power of the tube radius. Under these conditions, a 22% fall in flow would be caused by a 6% change in radius. Cerebral blood flow is controlled by arterioles, and many of the assumptions of the theoretical analysis will not strictly apply. In particular, the arterioles are elastic and the flow is pulsatile. In spite of these differences, our results (22% change in CBF and 13% change in  $V_{mca}$ ) are similar to those predicted by a steady-state model in which arteriolar and  $mca$  radii change by the same proportion. If arteriolar radius reduces by 6%, the flow through the arterioles would fall by 22% and the flow through the  $mca$  would also fall by 22%. But, if the  $mca$  radius also reduces by 6%, the  $V_{mca}$  would only fall by 12%, since the relation between velocity and flow would have changed. The validity of this model is discussed further in section 5.

Even though the quantitative analysis may not be applicable, the difference between the reduction in flow and the reduction in velocity indicates that caffeine reduces middle cerebral artery diameter. This is an important result, since the use of transcranial Doppler as an alternative to xenon clearance is often justified by the assumption that there is no change in  $mca$  diameter.

There have been other studies examining whether vasoconstrictors or dilators change  $mca$  diameter. Huber and Handa (1967) used angiography to show that the diameters of cerebral arteries between 0.5 and 1.0 mm diameter were increased about 25% by the contrast agent (Urografin 60%). Increasing  $PaCO_2$  from 40 to 57 mmHg through  $CO_2$  inhalation or injecting 30 mg papavarine also caused a 25% increase. However, the  $mca$  and vessels of similar calibre (2.0 to 2.5 mm diameter) were increased by a much smaller amount (4% with  $CO_2$  inhalation). Giller *et al* (1993) obtained similar results by measuring vessel diameters directly using an operating microscope during craniotomy. End tidal  $CO_2$  was increased by an average of 14 mmHg, and this caused 18% diameter increase in  $mca$  branches but only 2% in the  $mca$  itself.

There have also been other studies examining the relationship between changes in blood velocity and changes in flow. Dahl *et al* (1992) performed simultaneous TCD and XeC measurements to validate the use of TCD for cerebral vasoreactivity studies with acetazolamide as the stimulus. Intravenous administration of 1 g acetazolamide to 20 control subjects increased average CBF and  $V_{mca}$  by 30% and 34%, respectively. Demolis *et al* (1996) performed a similar study on 52 patients referred for cerebral vasoreactivity studies and found a 39% increase in CBF and a 41% increase in  $V_{mca}$ . These results suggest that acetazolamide causes similar changes in CBF and  $V_{mca}$ . However, Brauer *et al* (1998) also used 1 g acetazolamide and found a 25% increase in CBF and a 41% increase in  $V_{mca}$ . Although these results are somewhat inconsistent, there is no evidence that acetazolamide dilates both the arterioles and the  $mca$ , since this would cause a lower increase in  $V_{mca}$  than in CBF. This is important clinically, since acetazolamide is administered to stroke patients to assess cerebral vasoreactivity. The effect of the acetazolamide is assessed by measuring changes in CBF using XeC or changes in  $V_{mca}$  using TCD and the two have been shown to be equivalent (Dahl *et al* 1992).

In summary, different vasodilators and vasoconstrictors have different effects on the  $mca$  diameter. Acetazolamide appears to have little effect, carbon dioxide has some effect and caffeine may have a greater effect, with the percentage change in  $mca$  radius comparable to that in the flow-regulating vessels. However, if caffeine does have a consistent effect on all vessels, there should be a consistent relationship between the changes in flow and velocity in individual subjects. This is investigated below.

### 5. Comparison of changes in velocity, flow and pressure in individual subjects

We have suggested above that caffeine may be causing the same percentage reduction in the radius of mca and arterioles. This was based on the application of Poiseuille's formula,

$$Q = \frac{\pi}{8\eta} \frac{\partial P}{\partial L} r^4$$

where  $Q$  is the flow through a straight, rigid capillary tube;  $\eta$  the viscosity of the fluid,  $\partial P/\partial L$  the pressure gradient and  $r$  is the radius of the tube.

This formula will not strictly apply to arterioles because they are branched, curved, elastic and carry pulsatile flow, but it suggests that mean flow in arterioles may be proportional to (pressure gradient)  $\times r^4$ . There is only a small pressure drop in vessels proximal to the arterioles, so the pressure gradient can be assumed to be proportional to the difference between arterial blood pressure (ABP) and venous pressure. If cerebral venous pressure is assumed to be zero, pressure gradient will be proportional to ABP and mean flow in the arterioles will be proportional to ABP  $\times r^4$ . Hence, if  $q$ ,  $P$  and  $r$  are the CBF, ABP and arteriole radius in a subject and suffices 1 and 2 are before and after medication (caffeine or placebo),

$$\left(\frac{r_2}{r_1}\right)^4 = \frac{q_2 P_1}{q_1 P_2}. \quad (1)$$

This can be used to find the medication-related change in arteriole radius  $r$  in a given subject. It is important to include the blood pressure, since changes in individual subjects were as high as 15 mmHg between the pre-caffeine and post-caffeine measurements, although the average change across all subjects was less than 1.5 mmHg.

Mca blood flow  $Q$ , radius  $R$  and mean blood velocity  $V_{\text{mean}}$  are related by

$$Q = \pi R^2 V_{\text{mean}}.$$

Transcranial Doppler measures the time-averaged maximum velocity ( $V$ ) instead of the mean. The exact relationship between these depends on the velocity profile (Lunt *et al* 2000) but they will be proportional if the profile remains constant. In this case,

$$\left(\frac{R_2}{R_1}\right)^2 = \frac{Q_2 V_1}{Q_1 V_2} \quad (2)$$

where subscripts 1 and 2 denote before and after medication.

Assuming that the percentage changes in flow in the arterioles and mca are equal to the percentage change in CBF, equations (1) and (2) can be used to examine the changes in arteriole and mca radii ( $r_2/r_1$  and  $R_2/R_1$  respectively) after caffeine and placebo. Results are given in table 2. Caffeine causes significant changes in arteriole radius ( $r_2/r_1 = 0.941$ ,  $p < 0.001$ ) and in mca radius ( $R_2/R_1 = 0.957$ ,  $p < 0.001$ ). Changes after placebo are not statistically significant.

Comparison of  $r_2/r_1$  and  $R_2/R_1$  in individual subjects does not provide hard evidence that these ratios are the same. In fact, the hypothesis that they are the same can be rejected at the 10% significance level ( $p = 0.08$ ).

**Table 2.** Mean fractional change in vessel radius assuming Poiseuille flow in the arterioles. Both caffeine-induced changes are statistically significant.

	Mca (mean change)	Mca (95% CI)	Arteriole (mean change)	Arteriole (95% CI)
After caffeine	0.957	0.934–0.980	0.941	0.927–0.954
After placebo	1.004	0.982–1.026	0.996	0.979–1.013

The above analysis, based on Poiseuille flow in the arterioles, therefore suggests the 250 mg caffeine reduces arteriole diameter by 5.9%, and mca diameter by 4.3%. Both changes are statistically significant.

## 6. Conclusions

This study has demonstrated that 250 mg caffeine reduces CBF by an average of 22% in healthy volunteers and in patients recovering from an acute ischaemic stroke, and that both cerebral hemispheres are affected equally. The caffeine causes a significantly smaller change of 13% in  $V_{mca}$ , and this shows that caffeine reduces the mca diameter. Analysis based on Poiseuille flow in the arterioles suggests that the 250 mg caffeine reduced arteriole diameter by 5.9%, and mca diameter by 4.3%.

Transcranial Doppler is being used as an alternative to xenon clearance for assessing the effect of vasoconstrictors and vasodilators on cerebral blood flow. This study has demonstrated that mca diameter can be changed by the vasoactive agents, and that changes in  $V_{mca}$  do not necessarily reflect changes in CBF.

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