Effect of acute and chronic caffeine use on the cerebrovascular, cardiovascular and hormonal responses to orthostasis in healthy volunteers

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1. The effects of acute and chronic caffeine ingestion on supine- and tilt- (60 min at 70°) induced changes in middle cerebral artery velocity (V_{mca}), heart rate, blood pressure and counter-regulatory hormone levels (catecholamines, growth hormone and cortisol) were studied in nine healthy volunteers. A double-blind, placebo-controlled design was used to study acute effects followed by an open study after 6 days of chronic caffeine use.

2. In the supine position, acute ingestion of caffeine (250 mg) was associated with a fall in V_{mca} [-11 cm/s, point estimate of difference versus placebo (95% confidence interval: -17, -6) cm/s, \( P < 0.001 \)] and a rise in mean arterial pressure [+4 (1, 6) mmHg, \( P < 0.01 \)] and plasma adrenaline levels [+138 (53, 223) pmol/l, \( P < 0.01 \)]. After chronic caffeine use, the pressor and adrenaline responses, but not the drop in V_{mca}, were significantly attenuated.

3. On tilting to 70° the fall in V_{mca} was greater with placebo than after acute caffeine ingestion [-10 (-14, -15) cm/s, \( P < 0.01 \)], whereas increments (above supine values) in heart rate, mean arterial pressure and hormone levels were unchanged by caffeine. In contrast, the adrenaline [+126 (29, 282) pmol/l, \( P < 0.01 \)] and noradrenaline [+0.6 (0.1, 0.9) nmol/l, \( P < 0.05 \)] responses to tilting were augmented after acute caffeine ingestion. Chronic caffeine supplementation did not alter the fall in V_{mca} associated with tilting, but significantly attenuated the adrenaline response (\( P < 0.01 \) compared with the acute study).

4. Acute caffeine ingestion and orthostasis are both associated with a reduction in V_{mca} and a rise in mean arterial pressure and adrenaline levels. The acute effects of caffeine on mean arterial pressure and adrenaline but not on V_{mca} are lost with sustained caffeine intake. These results suggest dissociation between the development of central and peripheral tolerance after chronic caffeine use.

INTRODUCTION

Ingestion of moderate doses of caffeine, a common constituent of coffee, tea, confectionery and over-the-counter cold remedies, is generally considered to be mildly stimulating and helpful in relieving fatigue with little risk of harmful effects. Early reports of a caffeine-mediated rise in blood pressure did raise the possibility of a link between caffeine and hypertension, possibly as a consequence of activation of the sympathetic nervous system [1]. However, it is now clear that any such rise is transient and confined to caffeine-naive subjects, as tolerance to this pressor response rapidly develops [2].

In the brain, acute caffeine ingestion simultaneously decreases cerebral blood flow and increases brain glucose metabolism [3]. When continuous caffeine use is stopped abruptly, characteristic withdrawal symptoms appear quickly, suggesting dependence [4], although it is not known whether the central nervous system can also become tolerant to chronic caffeine use [5].

The aim of this study was to examine the effect of caffeine ingestion, after a period of abstinence, on the haemodynamic and hormonal changes associated with changing posture, a recognized stimulus for activation of the sympathetic nervous system [6]. A further aim was to determine whether tolerance to these effects develops with chronic caffeine use.

METHODS

Nine healthy, non-obese (body mass index 23 ± 1.0 kg/m²) volunteers (four men and five women, age range 21–28 years) gave their written, informed consent to the study which was approved by the local ethics committees. None was taking any prescribed or over-the-counter medications and all...
were regular caffeine users (average daily intake <200 mg). Each volunteer participated in three identical studies performed at least 1 week apart.

The initial two studies examined the effect of acute caffeine ingestion, after 48 h abstinence, on the physiological responses to a change in posture using a double blind, randomized, placebo-controlled design. The third, open study, examined identical physiological parameters after 6 days of continuous caffeine supplementation (250 mg daily), to determine the effect of chronic caffeine use (chronic study). The final caffeine capsule was taken 12–16 h before the start of the third study.

All studies were performed the morning after a 12 h overnight fast using an identical experimental protocol at each visit. A retrograde intravenous catheter was inserted under local anaesthesia into a dorsal hand vein for sampling of arterialized venous blood. The hand was placed in a heated box (60°C) and the cannula was kept patent by slow infusion of 154 mmol/l NaCl. Subjects then rested in the supine position for 30 min, after which duplicate baseline measurements were recorded of middle cerebral artery velocity \(v_{\text{mca}}\), heart rate (HR) and blood pressure, and arterialized venous blood was taken for subsequent measurement of plasma catecholamines, growth hormone and cortisol levels, \(\text{PCO}_2\) and haematocrit.

Subjects then received either 250 mg of caffeine (acute study) or matching placebo (placebo study) and remained in a supine position for 60 min, after which they were tilted to 70° for a further 60 min. \(v_{\text{mca}}\), HR and mean arterial pressure (MAP) were recorded at 15–30 min intervals throughout each study with prior blood samples drawn at 30 min intervals.

\(v_{\text{mca}}\) was measured using a transcranial Doppler technique (SciMed, Bristol, U.K.) as previously described [7] and HR and MAP using a semi-automated method (Dinamatt, Critikon Corp, Tampa, FL, U.S.A.). In addition, the pulsatility index (PI) (i.e. systolic minus diastolic velocity divided by the mean velocity), an index of middle cerebral artery resistance, was calculated and expressed as a percentage [8]. Cortisol and growth hormone were measured by double-antibody radioimmunoassays and catecholamines by a radioenzymatic technique (Amersham, Arlington Heights, IL, U.S.A.). Plasma caffeine levels were quantified by EMIT (Enzyme Multiplication Immunoassay Technique; Syva, Palo Alto, CA, U.S.A.) using a BMD Hitachi 717 autoanalyser (Indianapolis, IN, U.S.A.).

**Statistical analyses**

Overall differences between serial measurements were examined by the use of summary measures [9]. Summary responses for each individual were calculated as areas under the curve using the trapezoid method, and were subsequently compared by Student's \(t\)-tests. The change in each variable after tilt was calculated as a difference from the value obtained at the end of the supine period. Results are presented as means with point estimates and 95% confidence intervals for differences between studies. Otherwise data are shown as mean (SEM). As acute and chronic studies were compared with placebo and each other, the level of statistical significance is expressed as \(P<0.02\) although values of \(P<0.05\) are shown.

**RESULTS**

**Caffeine levels**

Caffeine levels were undetectable at the start of the acute and placebo studies whereas the basal level was 10.7 ± 4.2 \(\mu\)mol/l after chronic caffeine supplementation. After acute caffeine ingestion, levels increased above baseline to the same extent in both the acute (+21 ± 2 \(\mu\)mol/l) and chronic (+21 ± 5 \(\mu\)mol/l) studies and were unaffected by head-up tilt.

**Acute versus placebo results**

**Haemodynamic changes** (Fig. 1). Repeatability coefficients for blood flow velocity [mean (95% CI)] for intra-observer and long-term repeatability were 2.06 (±4.12) cm/s and 5.1 (±10.2) cm/s respectively [10].

\(v_{\text{mca}}\), PI, HR and MAP were similar at the start of each study. In the supine position, ingestion of caffeine caused a fall in \(v_{\text{mca}}\) [-12 cm/s compared with +0.3 cm/s during the placebo study; -12 (-17, -6) cm/s, point estimate of difference (95% confidence interval for paired difference), \(P<0.001\)], and a rise in MAP [+6 mmHg compared with +2 mmHg; 4 (1, 6) mmHg, \(P<0.01\)]. HR and MAP increased to the same extent during tilting in each limb of the study, whereas with placebo, tilting was associated with a greater fall in \(v_{\text{mca}}\) than in the acute study [-15 cm/s compared with -6 cm/s; 10 (-14, -5) cm/s, \(P<0.001\)], i.e. absolute values for \(v_{\text{mca}}\) were similar at the end of the tilt period in both studies. In the supine position, PI also rose after acute caffeine ingestion [+9.1% compared with -3.0%; 12 (3, 21)%, \(P<0.01\) compared with placebo]. After tilting, values for PI were similar in both placebo and acute studies (Fig. 1).

**Hormonal changes** (Fig. 2). Baseline values for noradrenaline, cortisol and growth hormone were indistinguishable at the start of each study and were not affected by caffeine ingestion in the supine position. However, there was a caffeine-associated rise in adrenaline levels which was not seen after placebo [+141 pmol/l compared with +3 pmol/l; 138 (53, 223) pmol/l, \(P<0.01\)].

During tilting, growth hormone and cortisol
levels increased to the same extent in both studies, whereas the rise in adrenaline \([+362 \text{ pmol/l]} \text{ compared with } +236 \text{ pmol/l}; +126 (29, 282) \text{ pmol/l}, P<0.01]\) and noradrenaline \([+1.4 \text{ nmol/l]} \text{ compared with } +0.8 \text{ nmol/l}; +0.6 (0.1, 0.9) \text{ nmol/l}, P<0.05]\) levels was greater after acute caffeine load.

**Chronic versus acute studies**

**Haemodynamic changes** (Fig. 1). Baseline values for \(V_{mca}\), PI, HR and MAP were similar. In the supine position, chronic ingestion of caffeine was associated with a fall in \(V_{mca}\) which was similar to
that seen in the acute study (−6.2 ± 2 cm/s, P = 0.057) but significantly different from placebo (P < 0.01). In contrast, with chronic caffeine use, MAP did not change. In the chronic study, the rise in PI after caffeine ingestion was almost identical to that seen in the acute study (Fig. 1). During tilting, a similar rise in HR and MAP was recorded in both the acute and chronic caffeine studies. The fall in \( V_{mca} \) and rise in PI were unaffected by chronic caffeine use, with absolute values for both being almost identical at the end of the tilt period under all three conditions (Fig. 1).

**Hormonal changes (Fig. 2).** Baseline and supine values for noradrenaline, cortisol and growth hormone were unaffected by chronic caffeine use. Moreover, with tilt, the rise in noradrenaline, cortisol and growth hormone levels, was not significantly different between acute and chronic caffeine studies. However, the caffeine-associated increments in adrenaline in both the supine [+22 pmol/l compared with +141 pmol/l, 119 (190, 48) pmol/l, \( P < 0.01 \)] and tilt [+188 nmol/l compared with +362 nmol/l, 174 (270, 70) pmol/l, \( P < 0.01 \)] positions were attenuated after chronic caffeine supplementation.

**Haematocrit and \( PCO_2 \) (Fig. 3)**

Values for haematocrit and arterialized \( PCO_2 \) did not change during the supine periods. During tilting, haematocrit increased to the same extent in all three studies (\( P < 0.01 \) versus supine values), whereas values for \( PCO_2 \) were slightly lower in the acute and chronic caffeine studies compared with placebo (4.7 ± 0.1 kPa and 4.7 ± 0.2 kPa compared with 5.1 ± 0.1 kPa, \( P < 0.05 \)).

**DISCUSSION**

In everyday life, the amount of caffeine consumed in coffee, tea and other drinks produces effects that are difficult to detect or so subtle as to go unnoticed. This may be a consequence of the development of tolerance to the peripheral effects of caffeine. In this study, after 48 h abstinence, acute caffeine ingestion was associated with a sustained reduction in the velocity and an increase in the PI of the middle cerebral artery, a mild pressor response and a rise in plasma adrenaline levels. After 6 days of chronic caffeine supplementation, tolerance to peripheral pressor and augmented adrenaline responses to caffeine ingestion was demonstrated, whereas the rapid and sustained fall in velocity and rise in the PI persisted despite chronic use. These results suggest dissociation between the development of peripheral and central tolerance to prolonged caffeine use.

In relating changes in \( V_{mca} \) to alterations in cerebral blood flow, measurement of \( V_{mca} \) assumes that calibre changes in the vessel in which the velocity is measured are small. Under certain circumstances (e.g. dynamic exercise) this assumption may be erroneous [11]. Others have suggested that assessment of \( V_{mca} \) correlates well with changes in global and hemispheric cerebral blood flow during hypoglycaemia and in the assessment of cerebral vasoreactivity [12–14]. Recently, Larsen et al. [15] have shown that transcranial Doppler is a valid method for determining the lower limit of cerebral autoregulation and that changes in blood flow may be reliably evaluated by assessment of \( V_{mca} \) during alterations in cerebral perfusion in normal subjects.

After 48 h abstinence, acute ingestion of caffeine, in a dose equivalent to two or three cups of coffee [16], was associated with a rise in blood pressure and fall in HR. This observation is consistent with other reports of an acute pressor response to caffeine in normotensive volunteers of all ages [2, 17]. However, individuals who regularly ingest caffeine show little or no blood pressure response after acute dosing. Even non-users rapidly develop tolerance to the cardiovascular effects of caffeine [2, 18]. The mechanisms involved in the acute pressor response to caffeine ingestion are not established but previous reports have suggested that caffeine-mediated sympathetic activation may be involved.

In healthy volunteers, Robertson et al. [1] reported that caffeine caused a rise in plasma noradrenaline and adrenaline levels in association with the pressor response. However, in that study, basal catecholamine levels were surprisingly low. Subsequent reports have described little or no change in plasma noradrenaline (an indirect indicator of sympathetic
activity) after a caffeine load, suggesting that caffeine ingestion *per se* does not cause clinically important sympathetic activation. More consistently, plasma adrenaline levels increase after a caffeine load, probably due to direct adrenal medullary stimulation [19–21].

This study also compared the effects of acute and chronic caffeine use on the physiological and hormonal responses to head-up tilt, a recognized stimulus for activation of the sympathetic nervous system [6, 12]. Tilting caused similar increases in blood pressure, HR and levels of growth hormone and cortisol, irrespective of acute or sustained caffeine use. The posture-associated rise in growth hormone and cortisol levels is a well-recognized "stress" response and probably catecholamine-mediated. After caffeine ingestion, the adrenaline and noradrenaline responses to tilting were augmented, although this effect was lost when the subjects were tilted after 6 days of chronic caffeine supplementation. Thus, after a short period of abstinence, caffeine ingestion potentiates the catecholamine responses to orthostasis but tolerance to this effect also develops with chronic caffeine use. It has also been known for many years that assuming the upright posture causes a significant fall in cerebral blood flow [23].

Here, after a combination of tilting and caffeine, the failure of \( V_{mca} \) to fall to the same extent as that seen with placebo, may be explained by the fact that cerebral perfusion had already been compromised by a caffeine-induced reduction in brain blood flow.

Changes in \( PCO_2 \) can affect cerebral blood flow [24]. It is also recognized that caffeine can attenuate anoxia- and hypercapnia-induced increases in cerebral blood flow [5]. In this study, \( PCO_2 \) fell below baseline levels in both caffeine studies after tilting, possibly as a consequence of hyperventilation [25]. However, this change in \( PCO_2 \) is unlikely to have had a major effect on \( V_{mca} \) as tilting also caused a fall in \( V_{mca} \) without any change in \( PCO_2 \) after placebo. Using inhaled \(^{133}\)Xe to assess cerebral blood flow, others have also reported that caffeine-induced cerebral vasoconstriction is unrelated to any change in \( PCO_2 \) [25].

Acute ingestion of caffeine appears to reset the coupling between cerebral blood flow and energy metabolism by decreasing brain blood flow while simultaneously increasing brain glucose utilization. This effect of caffeine is likely to be mediated through antagonism of adenosine and may be prolonged because of its long half-life [3, 26]. Ingestion of caffeine was associated with a sustained reduction in \( V_{mca} \) which persisted despite chronic use, although there was a tendency for the fall to be less marked after chronic caffeine ingestion. This suggests that complete tolerance to the cerebrovascular actions of caffeine does not develop. Animal studies have also indicated that tolerance to the effect of caffeine on brain glucose metabolism does not occur after chronic caffeine administration [27]. Here, in both the acute and chronic caffeine studies, baseline values for \( V_{mca} \) were similar despite plasma caffeine levels being higher at the start of the chronic study. Although the effects of caffeine on the cerebral circulation are well recognized [25, 28, 29], the duration of this effect is unknown. Previously, we have observed that the fall in \( V_{mca} \) after caffeine ingestion may last for at least 4 h in young caffeine-naive subjects given a 400 mg load [30]. Conversely, studies in young and middle-aged normotensive individuals suggest a minimum period of 12 h abstinence is needed to avoid developing tolerance to the peripheral haemodynamic effects of acute caffeine ingestion [31].

In summary, after a period of abstinence, acute ingestion of caffeine is associated with a reduction in \( V_{mca} \), a pressor response and a rise in plasma adrenaline levels. After head-up tilt, prior ingestion of caffeine both adds to and potentiates the adrenaline and noradrenaline responses to orthostasis. Although \( V_{mca} \) falls on assuming the upright posture, this effect is not altered by prior caffeine use. Tolerance to the peripheral effects of acute caffeine ingestion, but not its effect on the cerebral circulation, develops with chronic caffeine use. The development of cardiovascular tolerance to caffeine may explain the lack of convincing data implicating caffeine ingestion as an important risk factor for coronary artery disease or stroke [32]. Recent studies have suggested that caffeine can prevent postprandial hypotension in subjects with autonomic failure and in healthy and frail elderly patients, although the benefit may be less for those with predominantly postural hypotension [33–35]. However, although the sustained reduction in brain blood flow induced by caffeine is not enough to cause ischaemia in healthy volunteers, it is unclear whether a combination of caffeine and orthostasis increases the risk for ischaemia in individuals with established cerebrovascular disease.

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**REFERENCES**


