The effect of caffeine on cerebral blood flow in a test-retest study using pseudo-continuous ASL

Joost PA Kuijer[1], Petra JW Pouwels[1], Ajit Shankaranarayanan[2], David Alsop[3], Frederik Barkhof[4], and Rudolf Verdaasdonk[1]

[1]Physics and Medical Technology, VU University Medical Center, Amsterdam, Netherlands, [2]Global Applied Science Laboratory, GE Healthcare, Menlo Park, CA, United States, [3]Radiology, Beth Harvard Medical School, Israel Deaconess Medical Center, Boston, MA, United States, [4]Radiology, VU University Medical Center, Amsterdam, Netherlands

Introduction Dietary caffeine consumption is known to decrease the cerebral blood flow (CBF) [1]. It has been shown that both caffeine consumption and abstinence are potential confounding variables in cerebral perfusion and functional MR imaging [2]. Additionally, it may be hypothesized that scanner habituation may have an effect on the CBF. In this study we considered mean CBF and variance of a homogeneous group of female healthy volunteers as a function of caffeine intake and scanner habituation, assessed in a test-retest study design with intervention (intake of coffee) and control conditions (intake of caffeine-free coffee or tea).

Methods The study was approved by the local ethical committee and subjects gave written informed consent. Nineteen female students, age range 19-24 years were included. Three male students were scanned but excluded from data analysis to avoid between subjects variance from gender [3]. Subjects declared no use of tobacco. Dietary caffeine intake was scored by a survey including daily intake of coffee, tea, cola and energy drinks. Subjects were divided between low (<100mg/day) and high (≥100mg/day) caffeine intake groups. Subjects were instructed to refrain from caffeine intake for at least 4 hrs before scanning, and to refrain from alcohol intake for at least 20hrs. Scanning took place between 5 and 9 PM thus subjects were allowed their regular caffeine intake in the morning. Given the clearance rate of caffeine of 50% per 5 hours, the 4-hour period was considered a reasonable balance between acute effects of coffee intake, and long-term effects of abstinence.

Subjects were divided into a caffeine intervention (n=9) and a control group (n=10). Subjects were blinded for intervention and were presented one standard serving of either caffeine-free (3 mg caffeine) or regular (91 mg caffeine) coffee brewed on a Philips Senseo coffee machine (caffeine content: personal communication with manufacturer). Only subjects with a strong dislike of coffee (n=5) were not blinded and assigned to the control group and were presented caffeine-free tea.

The scan protocol consisted of a localizer, followed by baseline ASL (scan time approx. 4 min). During intervention, the subjects were removed from the head coil and remained seated on the patient table during oral intake of their beverage. Intervention was followed by localizer, an ASSET calibration scan and two T1-weighted IR-FSPGR scans (total duration approx. 10 min, providing time for uptake of caffeine). Finally, the intervention ASL scan was performed.

For ASL, pseudo-continuous labelling was combined with a 3D FSE spiral acquisition on a 3T MRI scanner (Signa HDxt, GE Medical Systems, Milwaukee, WI). Background suppression was used; no vascular crushers were applied. Details are described in [4]. Labeling and imaging parameters were: label duration 1.5s, post-label delay 1.5s, TR 4.3s, TE 4.7ms, spiral readout with 8 arms x 512 samples, RBW 62.5kHz, in-plane resolution 3.2x3.2mm, reconstructed pixel size 1.7x1.7mm, 36 x 5.0mm axial slices, NEX 2, scan time approx. 4 min). An approximately PD-weighted image was obtained by a one-NEX saturation recovery (SR). Scan parameters for the 3D T1-weighted scan were: IR-FSPGR, TI 450ms, TR 7.8ms, TE 3.0ms, voxel size 0.97x0.97x1mm). All scans were 3D corrected for gradient non-linearity. CBF maps were calculated using single compartment model [5]: $CBF = \lambda * (1 - \exp(-T_{sat}/T_{1GM})) * \exp(w/T_{1B}) / (2 * T_{1B} * (1 - \exp(- \tau/T1b)) * \varepsilon) * (\Delta S / S_0)$, parameters post-label delay w=1.5s; labelling time τ = 1.5s; partition coefficient λ = 0.9; labelling efficiency ε = 0.8 * 0.75 (label PCASL * background suppression); T1 of blood T_{1B} = 1.4s; SR time for PD image T_{sat} = 2.0s; correction for SR in PD image T_{1GM} = 1.2s; ASL difference image ΔS; PD reference image S_0.

For each subject, both CBF maps were registered to the T1W scan using FSL 4.1. The T1W scan was processed with SIENAX to obtain a whole brain mask and partial volume estimates (PVE). The brain mask was applied to the ASL scans yielding the whole brain CBF. The PVE maps were transformed to the ASL voxels, and linear regression was used to correct for partial volume effects [6], using a gaussian weighted kernel with σ=4mm (FWHM 9.5mm). For statistical analysis a repeated measures univariate general linear model (GLM) with regular caffeine intake as covariate (effect on baseline and on intervention) was used in SPSS 15.0.

Results The mean CBF for baseline and after intervention are listed in Table 1, and Figure 1 shows the whole brain CBF. CBF changed significantly after caffeine intervention, while no change was found in the control group. The within-subjects coefficient of variation (wsCV) of the control group expresses reproducibility. The heart rate during ASL scanning was 65±10 bpm (mean±SD). No significant effects were found for regular caffeine intake on baseline CBF (low/high caffeine intake: 48.1±6.9 / 43.0±6.6 ml/100g/min) and no significant effect modification of regular caffeine intake on intervention was found. No significant difference in heart rate for group of regular caffeine users was found. No significant correlation between baseline CBF and heart rate or between ΔCBF and change in heart rate after intervention. Table 2 lists the group CV (calculated as group SD / group mean) for all subjects pooled, and for the two subgroups (RMS averaged over groups).

Discussion The baseline CBF is in general agreement with the (wide range of) published values. A direct effect of change in CBF due to scanner habituation was not found, while the caffeine intervention produced highly significant effect. The wsCV (which included repositioning) is similar to reported values in literature, e.g. the 1-hour wsCV of 5.5% for GM and 9.3% for WM [7].

The group variance for all subjects (pooled) at baseline was considered a model for a 'conditioned' group with instructions to refrain from caffeine intake for at least four hours, while the group variance after intervention modelled a 'mixed' group without instructions, where some subjects may have taken coffee. It was expected that caffeine intake would increase group heterogeneity, and thus the pooled CV after intervention would be larger compared to baseline pooled CV. In contrast, the results suggest that the pooled group variance is not different after caffeine intake (intervention pooled vs baseline pooled). However, the variance within subgroups was lower after intervention compared to baseline (intervention within group vs baseline within group). This suggests that the additional variance introduced by the caffeine intervention for half the subjects was compensated by a reduction in variance between subjects in the repeated scan. This suggests a habituation time in the scanner reduced the variation between subjects to a similar extent as the caffeine intervention increased it. However, group sizes need to be increased for sufficient reliability of variance estimates and between-subjects variance estimates for statistical significance. These findings might also have implications for results of other studies in view of scanner habituation time of subjects and patients.

References [1] Addicott, HBM 2009; 30: 3102–3114. [2] Field, Radiology 2003; 227:129–135. [3] Parkes, MRM 2004; 51:736–743. [4] Xu, NMR Biomed. 2010; 23: 286–293. Buxton, MRM 1998; 40:383-396. [6] Asllani, MRM 2008; 60:1362-1371. [7] Chen, JMRI 2011; 33:940–949.

Table 1: mean CBF at baseline and intervention. Group difference at baseline was not significant and average was pooled over control and caffeine groups.

CBF [ml/100g/min] Mean ± SD	Baseline	Intervention Control ΔCBF	wsCV for Control	Intervention Caffeine ΔCBF
whole brain	45.2 ± 7.0	0.5 ± 4.1	6.8 %	-5.4 ± 4.7 **
GM	66.2 ± 11	1.1 ± 6.8	7.9 %	-7.4 ± 7.6 ***
WM	33.0 ± 5.0	0.2 ± 2.6	5.2 %	-4.6 ± 3.4 *

*Significance in GLM: * p<0.05 ** p<0.01 *** p<0.005*

Table 2: Group coefficient of variance for all subjects (pooled) and sub-groups (within-group), for baseline and after intervention.

group CV[%]	baseline pooled	baseline within group	intervention pooled	intervention within group
WB	16	16	16	13
GM	17	17	16	14
WM	15	15	18	15

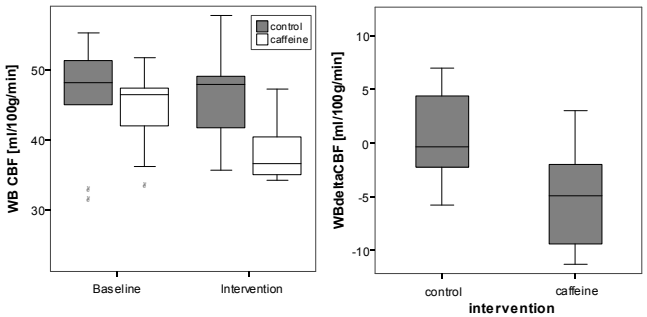

Figure 1a: box plot of whole brain CBF of control and caffeine groups at baseline and intervention. b: change in whole brain CBF for both groups.