

# Brainstem Cerebral Blood Flow in Women with Poly-Cystic Ovary Syndrome (PCOS)

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**Target audience** Researchers and clinicians interested in brainstem perfusion measurements with arterial spin labelling.

**Introduction** Poly-cystic ovary syndrome (PCOS) carries increased risks of hypertension, obstructive sleep apnoea, and insulin resistance and is associated with chronic hyperactivity of the sympathetic nervous system [1]. Sympathetic outflow, as measured by muscle sympathetic nervous activity (MSNA), has been shown to be mediated by nuclei in the brainstem, in particular, in the medulla (MD) [2]. We hypothesize that PCOS patients have a higher cerebral blood flow (CBF) in the medulla than healthy controls. Arterial spin labelling (ASL) measurements of the brainstem are challenging. However, we recently demonstrated such measurements in healthy controls [3]. Here we apply these methods in our ongoing study that aims to quantify potential haemodynamic differences in CBF in the MD between PCOS patients and controls. We present preliminary results from 17 participants.

**Methods** MTI pulsed ASL (PICORE with QUIPSS II cut-off at 700 ms) [3] was performed in 6 healthy women (age:  $29.7 \pm 3.6$  years) and 11 PCOS patients (age:  $29.5 \pm 4.8$  years) at 3 T (HDx, General Electric, Milwaukee, WI). Gradient echo, spiral image acquisition (echo time = 2.7 ms, minimised repetition time, single interleave, voxel size  $3.5 \times 3.5 \times 7$  mm<sup>3</sup>, slice gap 1 mm, 14 slices) was used. Eight control-tag pairs were acquired per inversion time (TI=150, 300, 450, 600, 1000, 1333, 1667, 2000 ms). Cardiac (finger plethysmography) and respiratory (pneumatic belt around abdomen) traces were acquired for physiological noise correction (RETROICOR [4]), which was applied for only 11 participants (4 controls, 7 patients) due to poor quality of the physiological signals in the remainder of participants. The PASL time series were corrected for head motion before tag-control subtraction. Difference images were analysed with a two-compartment model [5] to calculate CBF maps. These maps were corrected for coil sensitivity profiles by dividing the maps by a smoothed (SUSAN, FSL toolbox v5.0, <http://fsl.fmrib.ox.ac.uk>) minimal contrast image (the same geometrical prescription as PASL, TE = 11 ms, TR = 2 s, 8 spiral interleaves). Masks of whole brain gray matter (GM) were created from a T<sub>1</sub>-weighted structural scan (3D FSPGR, TE = 2.9ms, TR = 7.8 ms, voxel size =  $1 \times 1 \times 1$  mm<sup>3</sup>) with FAST (FSL). The brainstem (BS) mask (including medulla) was obtained from the Harvard Oxford Subcortical Atlas in MNI standard space (available within FSL) and registered to subject space via the T<sub>1</sub>-weighted structural scan. The medulla (MD) was delineated as the caudal part of the brainstem ( $Z \leq 14$ , Figure 1). Group mean CBF values were calculated based on individual regional averages. Resting mean arterial blood pressures (MAP) were measured noninvasively before the start of the scan session over a 6 minute period.

**Results** MAP for patients:  $78.8 \pm 12.5$  mmHg, and controls:  $78.6 \pm 9.9$  mmHg (two-sample t-test,  $p > 0.05$ ). Figure 2 shows a representative CBF map. Mean medullary CBF is higher in PCOS patients than in healthy controls ( $64.8 \pm 18.9$  vs  $52.3 \pm 7.5$  ml/100 g/min), although the difference is not significant (two-sample t-test,  $p = 0.15$ ), which strengthens the hypothesis of elevated sympathetic outflow mentioned in the introduction. In controls, average CBF in the MD (and BS) is lower than in GM (not significant, paired t-test MD vs GM CBF,  $p = 0.06$ ), which coincides with previously reported values for healthy volunteers [3]. Interestingly, in PCOS patients CBF in the MD is significantly higher than in the GM (paired t-test,  $p < 0.05$ ).

**Discussion** The trend towards elevated CBF in the MD in PCOS patients is consistent with our hypothesis of elevated sympathetic outflow. However, it must be noted that the study is ongoing. Comparison of CBF with microneurography, a more direct measure of a component of sympathetic nervous activity would be valuable. CBF measurement in the brainstem, in which the nuclei of interest are small, would also benefit from higher resolution image acquisition. Nevertheless our preliminary results suggest that it is feasible to measure brainstem (medullary) blood flow in patient groups for the purposes of clinical research.

**References** 1. Lansdown, A, et al., Clin Endocrinol (Oxf), 6, p: 791-801 (2012). 2. Sander, M, et al., J Appl Physiol, 6, p: 1691-700 (2010). 3. Warnert, EAH, et al., Proc Intl Soc Mag Reson Med, p: 2182 (2013). 4. Glover, GH, et al., Magn Reson Med, 1, p: 162-7 (2000). 5. Chappell, MA, et al., Magn Reson Med, 5, p: 1357-65 (2010).

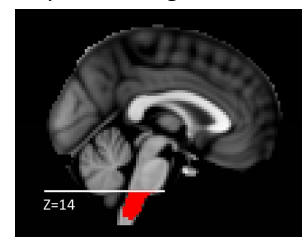


Figure 1. MNI standard image. The medulla mask (red) was based on the brainstem mask as in the Harvard Oxford Subcortical Atlas within the FSL library.

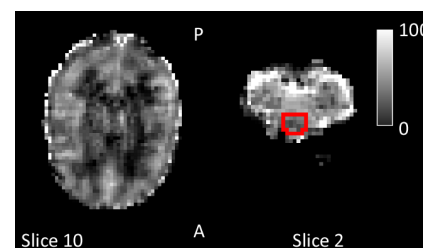


Figure 2. Example of CBF map (ml/100 g/min). Two axial slices (left: slice 10, right: slice 2). Medulla mask outlined in red. A = anterior, P = posterior.

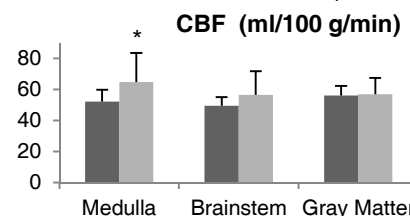


Figure 3. Group mean CBF for medulla, brainstem and gray matter in PCOS patients (light gray,  $N=11$ ) and controls (dark gray,  $N=6$ ). CBF in the medulla of PCOS patients is higher than for controls but not significantly so, two-samples t-test,  $p=0.15$ .

\*Significantly higher than corresponding GM value for patients (paired t-test,  $p < 0.05$ ).