Changes in cerebral physiology with ageing assessed by respiratory-calibrated MRI

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Purpose: Recently, respiratory-calibrated MRI methods capable of providing a non-invasive, quantitative assessment of cerebral physiology have been developed[1-3]. Although differing slightly in detail, the aim of these methods is the same: to calibrate the MRI signal using a combination of hyperoxic and hypercapnic gas stimuli, and thereby allow quantification of brain energy metabolism and perfusion. To date, work in this area has focussed on methodological development and consequently data published have been acquired exclusively from healthy young volunteers. In order to move towards using respiratory-calibrated MRI techniques in studies of patient groups, the effect of healthy ageing on the quantifiable parameters must first be investigated. Of particular interest when studying a healthy aged subject group is the greater degree of variability in physiological parameters such as blood pressure (BP), body mass index (BMI) and pulse rate. We applied respiratory-calibrated MRI to a group of healthy aged subjects in order to investigate the effect of potentially altered baseline physiology on the parameters quantified by respiratory-calibrated MRI.

Methods: 23 healthy adult volunteers aged 50 to 70 years (mean±std dev 60±6 years, 13 female) were scanned on a 3T Siemens Verio with a 32-channel head coil. The subjects' age, BP, pulse rate and BMI were recorded. Measurement of cerebral physiology was achieved using the method described in Bulte et al[1]. The paradigm consisted of delivering respiratory gases via a 2-tube nasal cannula. Medical air, 100% oxygen (O_2) and a mixture of 10% carbon dioxide (CO_2), 21% O_2 balance nitrogen were supplied during rest, hyperoxia and hypercapnia blocks respectively. Respiratory data were measured using a Biopac MP150 (Biopac, Goleta, CA, USA). The respiratory paradigm was 16 mins 33 secs long, consisting of 33 secs of air followed by 2 x 2 min blocks of hypercapnia interleaved with 2 x 3 min blocks of hyperoxia. Data from 3 male subjects were removed from the subsequent analysis due to poor or negligible end-tidal CO_2 and O_2 response to the gaseous stimuli. Whole brain perfusion and BOLD data were acquired during the respiratory paradigm using a dual-echo, pseudo-continuous arterial spin labelling (PCASL) gradient echo EPI sequence (TE_1/TE_2=13/30ms, TR = 4.17ms, 24 slices, flip angle 90^0, voxel dims=3.4x3.4x5mm^3, PCASL labelling duration=1200ms, PLD=600ms). Cerebral blood flow (CBF) was measured using a separate multi-TI PCASL sequence (single echo gradient echo EPI, TE=13ms, TR=4s, labelling duration=1.4s, 6 x PLD times=0.25, 0.5, 0.75, 1.0, 1.25 and 1.5s) with identical planning to the dual-echo sequence. Additional scans included a time-of-flight angiography scan acquired in the neck to allow optimal placement of the PCASL labelling plane, a high resolution structural scan (MPRAGE) for registration of functional datasets and two PCASL calibration scans for quantification of CBF in absolute units.[4] CBF and arterial arrival time (AAT) were quantified by performing a nonlinear fit of the general kinetic model[5] to the multi-TI PCASL data using a variational Bayes approach.[6] Analysis of the respiratory-calibrated dual-echo data was performed using Matlab (Mathworks, Natick, MA, USA) and FSL. Cerebrovascular reactivity (CVR) was calculated from the CBF response to CO_2.[7] The BOLD calibration constant, M, was calculated on a voxel-wise basis from the BOLD response to CO_2. The M value was then used with the end-tidal O_2 and the BOLD response to hyperoxia to calculate the oxygen extraction fraction (OEF). The cerebral metabolic rate of oxygen ($CMRO_2$) was calculated from the OEF and CBF. Cerebral blood volume (CBV) was calculated from the BOLD response to hyperoxia[8]. The parameter maps were registered to MNI152 standard space using FLIRT in order to compare regional (cerebellum, frontal lobe, occipital lobe, temporal lobe, parietal lobe, hippocampus and thalamus), grey matter and whole brain values. Potential correlations between baseline physiological parameters and the parameters quantified by respiratory-calibrated MRI were investigated using SPSS (ver. 21).

Results: The mean ± std dev systolic blood pressure, diastolic blood pressure, pulse rate and BMI across all subjects were 140±23mmHg, 90±13mmHg, 75±8bpm and 26.7±4.4kg/m^2 respectively. Bivariate linear correlation testing of mean grey matter (GM) and regional respiratory-calibrated MRI parameters (CBF, AAT, OEF, $CMRO_2$, CBV and CVR) with age, BP, pulse rate and BMI revealed no significant correlations (Pearson correlation coefficient, two-tailed test, level of significance p=0.05). Mean GM CBF and OEF values were found to be significantly inversely correlated, as shown in Fig.1(a) ($p<0.01$, R^2 linear=0.429), while mean GM CVR and CBF were found to be significantly correlated, as shown in Fig.1(b) ($p<0.01$, R^2 linear=0.402).

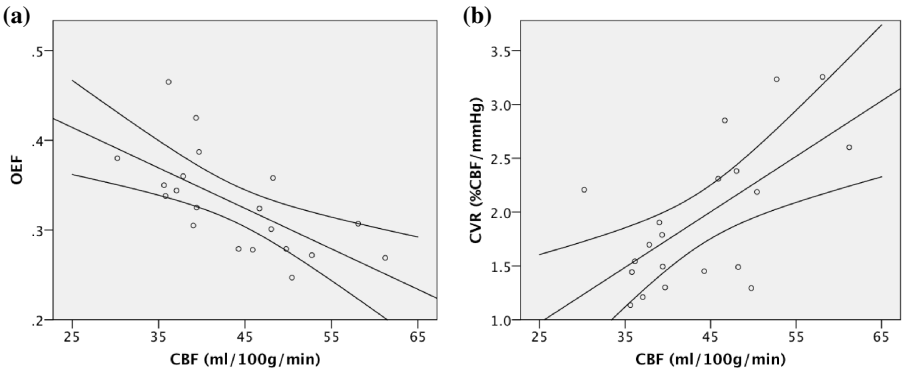

Fig.1:(a) Inverse correlation of OEF and CBF (R^2 linear=0.429, significant at 0.01 level) **(b)** Correlation of CVR and CBF (R^2 linear =0.402, significant at 0.01 level)

Discussion: The results demonstrate that respiratory-calibrated MRI can be applied to subject groups with a large degree of variability in parameters such as age, BMI, BP and pulse rate. The quantified parameters were found to be independent of variations in baseline physiology. The strong inverse linear relationship of OEF and CBF, and linear relationship between CVR and CBF provides validation of the method. The inverse relationship between OEF and CBF is in agreement with recent PET research reporting increased OEF with decreased CBF due to ageing, with a resultant decline in oxygen delivery to brain tissue.[9] However, in this study, CBF was not found to decline significantly with age.

References: **1**.Bulte et al. *NeuroImage* 2012; 60: 582-591. **2**.Gauthier et al. *NeuroImage* 2012; 63: 1353-1363. **3.**Wise et al. *NeuroImage* 2013; 83: 135-147. **4.**Okell et al. *JCBFM* 2013; 33: 1716-1724. **5**.Buxton et al. *MRM* 1998; 40: 383-396. **6.**Chappell et al. IEEE Trans Sig Proc 2009;57:223. **7**.Hare et al. *JCBFM* 2013; 33: 1799-1805. **8**.Bulte et al. JMRI 2007; 26: 894-899. **9**.Aanerud et al. *JCBFM* 2012; 32: 1177-1187.