Comparison of CO_2 in Air versus Carbogen for the Measurement of Cerebrovascular Reactivity with Magnetic Resonance Imaging

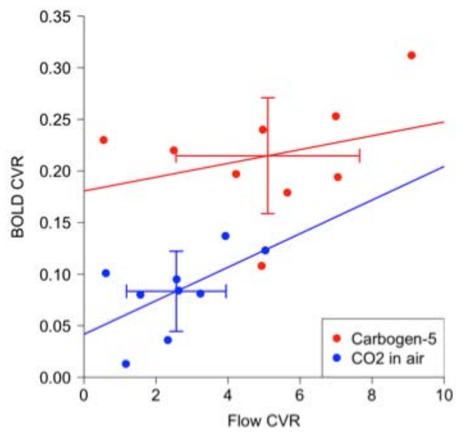
Hannah Hare[1], Michael Germuska[1], and Daniel Bulte[1]
[1]*FMRIB, University of Oxford, Oxford, Oxon, United Kingdom*

Introduction

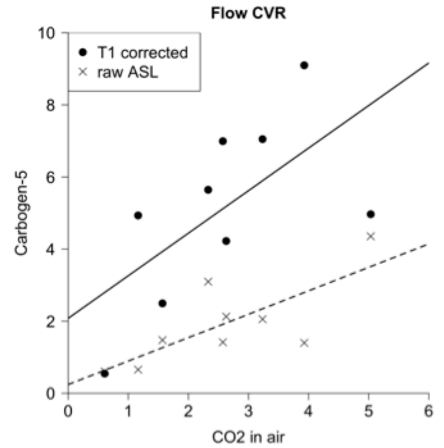
Measurement of cerebrovascular reactivity (CVR) can give valuable information about existing pathology and the risk of adverse events such as stroke. Regional values of CVR are typically acquired by measuring the flow response to CO_2 enriched air using arterial spin labelling (ASL) or blood oxygen level dependent (BOLD) imaging. Recently several studies[1,2] have used carbogen gas (composed of CO_2 with balance oxygen) as an alternative stimulus, implicitly assuming that increasing the oxygen fraction of inspired air will have no effect on CVR measurement. We tested this hypothesis by acquiring values for CVR using ASL and BOLD data taken during a single scan with stimuli of (a) 5% CO_2 in air and (b) 5% CO_2 in oxygen (carbogen-5).

Theory & Methods

Both ASL and BOLD imaging are sensitive to changes in cerebral blood flow (CBF). Provided all other variables (CBV, PaO_2, $CMRO_2$) remain approximately constant, as is assumed with an air/CO_2 stimulus, either imaging technique can be used to measure CBF correlated signal changes and hence estimate CVR. However, when carbogen is used, both the arterial partial pressure of CO_2 ($PaCO_2$) and the venous partial pressure of oxygen (PvO_2) are significantly increased, causing the BOLD signal to be elevated through more than one mechanism: increased blood flow due to CVR *and* increased venous oxygen saturation of the blood. We aimed to highlight the considerations required when using BOLD in conjunction with carbogen gas when attempting to measure CVR, and to investigate the effect that breathing carbogen has on CVR as measured by ASL. 9 healthy volunteers were recruited (mean age 25±4 years, 2 female), and scanned on a 3T Siemens Verio scanner using a 32 channel receive-only head coil. Subjects wore a close fitting gas mask over the mouth and nose, through which we implemented the following paradigm: 30s breathing medical air, then 1 min 5% CO_2 in air; 1 min carbogen-5; 1 min 5% CO_2 in air; 1 min carbogen-5; where each 1 min block was followed by 1 min of medical air. Gas delivery was 25L/min, and a sampling tube was used to measure the gas composition in the mask using oxygen and CO_2 analysers. A single TI dual echo pulse sequence was used to acquire data for both ASL and BOLD following a single RF excitation. Using a pseudo-continuous ASL scheme[3] and an EPI readout (TR=4s, TE(1)=16ms, TE(2)=35ms) 23 slices (each 64×64 voxels, voxel size 3×3×5mm or 3.4×3.4×5mm to ensure full brain coverage) were acquired for each subject, where slice thickness was 5mm with inter-slice gap of 0.5mm.



Comparison of CVR values as measured by flow (ASL) and BOLD response, with linear models fitted. Crosshairs show mean ± standard deviation. For 5% CO_2 in air R^2=0.33, p=0.10; for carbogen-5 R^2=0.092, p=0.43.



Comparison of flow CVR values during stimuli of CO_2 in air versus carbogen-5, with linear models fitted. For corrected values R^2=0.41, p=0.064.

Results & Analysis

Most subjects responded well to the protocol. One subject requested the scan be stopped near the end of the final carbogen block, but sufficient data had already been collected to be included in the results and further analysis. No subjects exhibited significant changes in breathing rate between the 3 gas mixtures. Values for end tidal partial pressure of CO_2 ($PETCO_2$) were extracted from respiratory data as an average of the last 3 breaths taken during each stimulus block; average baseline $PETCO_2$ was visually determined for each subject. $PETCO_2$ was used to deduce the change in PCO_2 in units of mmHg[4]; 5% CO_2 in air increased $PETCO_2$ by 9.8±2.7mmHg, carbogen-5 by 12.0±2.1mmHg. The FEAT tool in FSL (http://www.fmrib.ox.ac.uk/fsl/) was used to extract % increases in CBF (from absolute ASL signal, taking tag/control signal modulation into account) and BOLD signal during stimuli, which were used to calculate CVR values, as summarised in the table below and the graph on the right. Correlation between BOLD and flow CVR for CO_2 in air was R^2=0.33, p=0.10; for carbogen-5 R^2=0.092, p=0.43. Note that for ASL data taken during a carbogen stimulus it was necessary to correct for the change in T_1 of the blood compared to baseline due to increased PaO_2[5].

	Age	CVR for CO_2 in air *(% change per mmHg)*		CVR for carbogen-5 *(% change per mmHg)*	
		ASL	BOLD	ASL	BOLD
Mean ± SD	25±4	2.563±1.380	0.083±0.039	5.105±2.549	0.215±0.056

Discussion & Conclusions

Our key findings were that 1) CVR as measured by BOLD and ASL response appear to be correlated for CO_2 in air (in agreement with previous findings[6]) but not when using carbogen as a stimulus and 2) intrasubject flow CVR as measured by ASL is strongly affected by PO_2 and is not consistent between the two gas stimuli. Because of the high oxygen content of carbogen-5 gas it is not possible to identify how much of an ensuing increase in BOLD signal is due to increased blood flow (as opposed to simply an increase in venous oxygen saturation), so CVR cannot be accurately determined. Therefore, BOLD imaging should never be used with a carbogen stimulus to determine CVR. We also found that although flow CVR values (as measured by ASL) to air/CO_2 versus carbogen are correlated, the values obtained are not directly comparable. A further potential confound of using carbogen gas is that the interplay between the Bohr and Haldane effects is likely to influence diffusion gradients in the lungs affecting the process of gas exchange and partial pressure relationships in the lungs, blood, and tissues. Under these conditions changes in $PETCO_2$ measures may no longer be accurate indicators of arterial PCO_2 changes.

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