Hypercapnia-Based Calibration Techniques for Measurement of Cerebral Oxygen Metabolism with MRI

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Introduction

Magnetic resonance imaging may be used to measure fractional changes in cerebral oxygen metabolism via a metabolic model. One step commonly used in this measurement is calibration with image data acquired during hypercapnia, which is a state of increased CO_2 content of the blood. In this study the most commonly used hypercapnia-inducing stimuli were compared in order to assess their suitability for the calibration step. The following stimuli were investigated: (a) inspiration of a mixture of 4% CO_2, 21% O_2 and balance N_2; (b) breath holding; and (c) inspiration of a mixture of 4% CO_2 and 96% O_2 (i.e., carbogen). Measurements of BOLD and cerebral blood flow were made on six subjects during the different hypercapnia-inducing stimuli, and carefully analysed using the metabolic model, revealed that of the aforementioned stimuli, inspiration of 4% CO_2, 21% O_2 and balance N_2 should be preferred for the calibration.

Theory & Methods

A mathematical model that uses MRI data to calculate fractional changes in the cerebral metabolic rate of oxygen consumption ($CMRO_2$) has been proposed[3, 4]. The $CMRO_2$ response is closely related to neuronal activation because the increased energy demand of the activated neurons is met by an increase in the metabolic rate of O_2 consumption. The MRI $CMRO_2$ model requires a calibration step that effectively estimates the maximum theoretical BOLD fMRI signal change. Typically this is achieved by imaging during a hypercapnia challenge in which the CO_2 content of the blood in increased. Hypercapnia is chosen because it is assumed that it increases the cerebral blood flow (CBF) without changing the metabolism (i.e. the $CMRO_2$), thereby providing ideal conditions for the calibration. Several different techniques for inducing hypercapnia have been used in the literature, including a) breathing CO_2-enriched air (with 21% O_2)[1-3, 6]; b) various breath holding tasks[7, 8]; and c) breathing a CO_2/O_2 mixture without nitrogen[9, 10]. However, these techniques may not be equally suitable for calibration of the $CMRO_2$-model. A study that directly compared methods (a) and (b) found that both methods are equally suitable for the calibration of the $CMRO_2$-model[5], yet that study drew this conclusion from CBF measurements that are not in agreement with those reported elsewhere[1-3, 6]. We therefore wished to study each of these hypercapnia challenges in detail, in order to determine their suitability as an MRI $CMRO_2$ calibration step. Six non-smoking healthy volunteers (male, aged 23±2) were recruited to the study. Each subject gave informed consent and the protocol was approved by the appropriate research ethics committee. The three CO_2 stimuli were (a) breathing of a mixture of 4% CO_2, 21% O_2 and balance N_2 ("4% CO_2 in air") for 3 minutes, (b) repeated periods of breath holding/normal breathing for 30s/30s, and (c) breathing of 96% O_2 and 4% CO_2 ("carbogen") for 3 minutes. Images were acquired on a 3 Tesla Siemens MRI scanner, and an interlaced BOLD/pulsed arterial spin-labelling (ASL) sequence was used to collect T_2^*-weighted conventional EPI images and macrovascular-crushed Q2TIPS[11] cerebral perfusion images. BOLD measurements had TR/TE=4.5 s/32 ms, and ASL experiments had TR/TE/TI=4.5 s/23 ms/1.4 s. The data were analysed with tools from the FMRIB Software Library (FSL).

Results & Discussion

All three stimuli led to hypercapnia, indicated by a statistically significant increase ($p < 0.05$) in the percentage of end-tidal expired CO_2. The breath holds and 4% CO_2 in air resulted in similar end tidal CO_2 levels, as designed. However the same $FiCO_2$ in oxygen results in a lower end tidal value, most likely due to the tendency towards hyperventilation induced by hyperoxia which would blow off more CO_2. The different effects of each stimulus on the end tidal oxygen levels display the significant differences between the techniques, most notably that breath holding induces a significant decrease in $P_{ET}O_2$ compared to normal air and 4% CO_2 in air, whereas carbogen induces a substantial increase. Fig. 1 shows the BOLD signal changes (cBOLD) induced by the challenges plotted against the percent change in the raw ASL signal ($c\Delta M(t)$), lines with $CMRO_2/(CMRO_2)_0 = constant$ have been estimated to illustrate that the different states of hypercapnia do not lie on the same iso-metabolic contour and therefore lead to different calibration constants M. The M value used in Fig. 1 has been obtained from the inter-subject mean of the 4% CO_2 in air stimulus, for which it was assumed that $CMRO_2/(CMRO_2)_0 = 0$. By using this value of M, the "apparent" inter-subject mean change of $CMRO_2$ with respect to baseline during breath holding was determined to be (+53±11)%.

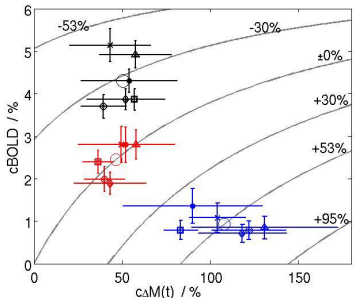

Fig. 1: black, red and blue markers correspond to measurements during inspiration of carbogen, 4% CO_2 in air, and breath holding, respectively.

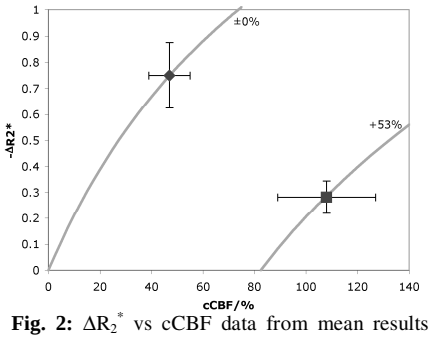

Fig. 2: ΔR_2^* vs cCBF data from mean results shown in Fig. 1. Separation between CO_2 in air and breath-hold data produces an *apparent* change in metabolism with breath holds.

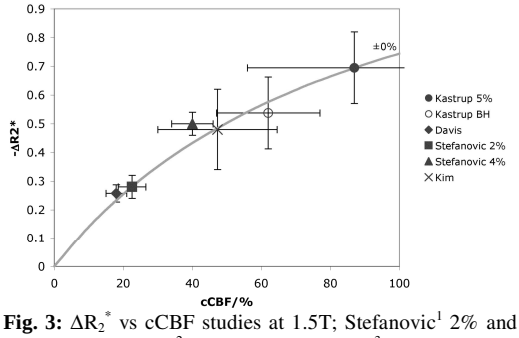

Fig. 3: ΔR_2^* vs cCBF studies at 1.5T; Stefanovic[1] 2% and 4% CO_2 in air, Kim[2] 5% CO_2 in air, Davis[3] 5% CO_2 in air, and Kastrup[5] - breath holds ○, 5% CO_2 in air ●. The line marks the iso-metabolic contour calculated from Kastrup's 5% CO_2 data.

Fig. 2 shows the apparent change in metabolism during breath holds. If relaxation times remain constant then the percent change in ASL signal is proportional to the percent change in blood flow (cCBF). The findings of Kastrup *et al.* that breath holds are isometabolic are not supported by our data (see Figs 2 and 3), although this may in part be due to differences in how the breath hold was performed (on expiration for Kastrup *et al.* rather than on inspiration). In particular, our measurements show that breath holding and inspiration of air with an increased percentage of CO_2 lead to calibration points that appear in different regions of the cBOLD-cCBF map, as illustrated in Fig. 1. Moreover, breath holding also violates the $CMRO_2$-model since the concentration of venous deoxyHb is not necessarily proportional to $CMRO_2$/CBF. In the case of breath holding the venous concentration of deoxyHb may be increased artificially by a decrease in arterial oxygen saturation, since blood that passes through the lungs is no longer oxygenated. This effect leads to an apparent positive $cCMRO_2$ during breath hold, an artefact arising from the artificially lowered cBOLD.

Conclusions

It was found that if using CO_2 as the method of calibration the $CMRO_2$-model should be calibrated with measurements of BOLD signal and CBF changes during the inspiration of CO_2-enriched air. On theoretical grounds, neither breath holding nor inspiration of a CO_2/O_2 mixture without nitrogen should be used, as both stimuli lead to BOLD signal changes that cannot be accounted for within the $CMRO_2$-model. Experimentally, this leads to a large apparent fractional change in $CMRO_2$ of +53±11% during breath holding (when referenced to a $CMRO_2$-model that is calibrated with measurements during the inspiration of CO_2-enriched air).

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