Dynamic end-tidal forcing of carbon dioxide and oxygen during FMRI

R. G. Wise[1,2], K. T. Pattinson[2,3], D. T. Bulte[2], P. A. Chiarelli[2], S. Mayhew[2], G. M. Balanos[4], D. F. O'Connor[5], T. Pragnell[5], P. A. Robbins[5], I. Tracey[2,5], and P. A. Jezzard[2]

[1]CUBRIC, School of Psychology, Cardiff University, Cardiff, United Kingdom, [2]FMRIB Centre, Oxford University, Oxford, United Kingdom, [3]Nuffield Department of Anaesthetics, Oxford University, Oxford, United Kingdom, [4]School of Sport and Exercise Sciences, University of Birmingham, Birmingham, [5]Department of Physiology, Anatomy and Genetics, Oxford University, Oxford, United Kingdom

Introduction

Investigations into the BOLD FMRI signal have used respiratory challenges to probe cerebrovascular physiology [1-3]. Such challenges have altered the inspired partial pressures of either carbon dioxide or oxygen, typically to a fixed and constant level (fixed inspired challenge, FIC). Changes in arterial carbon dioxide and oxygen partial pressures are reflected closely in the end-tidal partial pressures ($P_{ET}CO_2$ and $P_{ET}O_2$ respectively) in healthy subjects. The end-tidal values resulting from the FIC are variable as they depend on the subject's metabolism and ventilatory response. In contrast, dynamic end-tidal forcing (DEF) rapidly and independently sets end-tidal oxygen and carbon dioxide to desired levels by altering the inspired gas partial pressures on a breath-by-breath basis. DEF was originally conceived for use outside the FMRI environment [4-6] and has been used extensively with trans-cranial Doppler ultrasound [7]. The present study compares the effects of dynamic end-tidal forcing on respiratory parameters and the BOLD signal with those of the FIC at 3Tesla.

Methods

The DEF technique uses laptop computer feedback control of inspired P_ICO_2 and P_IO_2 (BreatheDP software, v1.0, Department of Physiology, Anatomy and Genetics, University of Oxford, UK). The controlling computer calculates the required inspired partial pressures to achieve target levels of $P_{ET}CO_2$ and $P_{ET}O_2$ throughout the experiment, while also monitoring the end-tidal expired levels actually achieved using signals from rapidly responding gas analyzers (Models CD-3A and S-3A; AEI Technologies, Pittsburgh, PA, USA). On a breath-by-breath basis, P_ICO_2 and P_IO_2 are modified according to an integral proportional feedback algorithm of the deviation between the measured and desired $P_{ET}CO_2$ and $P_{ET}O_2$. CO_2, O_2, N_2 and air are delivered through a fast gas mixing system into a tight fitting face-mask using four mass-flow controllers. The direction and timing of respiratory flow (inspiration or expiration) were measured using an MR-compatible turbine volume flow transducer (VMM-400, Interface Associates, CA, USA). For feedback control it was necessary to minimize delays in gas mixture delivery and sampling from our 7m long gas sampling line. The time to register 95% of a step change in CO_2 partial pressure through the sampling line was reduced to 1.6s. For safety, the volunteer's heart rate and pulse oxygenation were monitored; the volunteer was instructed to actively depress a switch mounted on a handle; an additional (backup) oxygen analyzer provided a continuous display of oxygen supply partial pressure; and a separate emergency oxygen supply was present. For comparison with DEF, each volunteer underwent a FIC in which pre-mixed 5% CO_2 in a balance of air (19.7% O_2) was used to cycle between periods of hypercapnia and normocapnia by manual gas switching.

Four healthy male volunteers (mean age 37, range 32-40) were studied. The FIC was performed first in all volunteers to allow the end-tidal partial pressures from the FIC to be used as targets for the subsequent DEF challenge. The FIC and DEF runs consisted of a period of 3 minutes of normocapnia followed by 4 cycles of hypercapnia (2 mins each) and normocapnia (2 mins each). During DEF the "normocapnic" $P_{ET}CO_2$ target was set to be 1 mmHg above the resting value for each volunteer as DEF can only increase $P_{ET}CO_2$ from basal levels. Identical functional imaging acquisitions were performed for FIC and DEF at 3T using a Siemens Trio system (gradient-echo echo-planar imaging with T2* weighted contrast: TE=32ms, TR=1s, 1140 volumes, flip angle 70º, image matrix of 64x64 voxels, giving in-plane voxel dimensions of 3x3 mm. Each volume comprised 16 contiguous 6 mm thick axial slices. For each subject a T1-weighted structural scan was acquired (1 mm in plane voxel size, 3 mm slices). This was used to segment grey matter in subsequent analyses. $P_{ET}CO_2$, was the intended driver of changes in the BOLD signal. The group mean lag of BOLD signal following change in $P_{ET}CO_2$ was 12 s, established by cross-correlation. We examined the degree of BOLD signal change explicable by the induced changes in $P_{ET}CO_2$ by linear regression of the mean grey matter BOLD time-course with the $P_{ET}CO_2$ waveform.

Results

	Fixed Inspired Challenge (FIC)		Dynamic end-tidal forcing (DEF)	
$\Delta S_{BOLD(GM)}$ (%)	1.97 ± 0.31		$1.27^{\dagger}$ ± 0.26	
$\sigma^{I}_{P_{ET}O2}$	3.5 ± 1.1		$1.7^{\dagger}$ ± 0.6	
	Normocapnia	Hypercapnia	Normocapnia	Hypercapnia
Target $P_{ET}CO_2$	N/A	N/A	40.6 ± 1.9	46.8 ± 1.3
$P_{ET}CO_2$	38.2 ± 2.1	45.6 ± 1.4	$40.9^{\ddagger}$ ± 1.8	46.4^{NS} ± 1.6
P_ICO_2	2.4 ± 0.5	32.5 ± 2.8	$17.8^{\ddagger}$ ± 2.5	34.0^{NS} ± 2.1
Target $P_{ET}O_2$	N/A	N/A	108.0 ± 3.9	
$P_{ET}O_2$	110.3 ± 4.2	112.8 ± 1.2	$107.8^{\dagger}$ ± 3.5	$108.2^{\dagger}$ ± 4.7
P_IO_2	144.5 ± 0.7	133.3 ± 0.9	$132.5^{\dagger}$ ± 3.4	$124.7^{\dagger}$ ± 4.2

Table. Respiratory parameters and grey matter BOLD signal variation during periods of normocapnia and hypercapnia (group mean and standard deviation). Partial pressures (mmHg). $\Delta S_{BOLD(GM)}$: % change in cortical grey matter BOLD signal in response to the hypercapnic challenge. $\sigma^{I}_{P_{ET}O2}$: (mmHg) mean of temporal standard deviation of $P_{ET}O_2$.
‡ Indicates a significantly larger value for DEF than for FIC (P<0.05, one-tailed, paired t-test).† Indicates a significantly smaller value for DEF than FIC (P<0.05, one-tailed, paired t-test). ^{NS} (P>0.05, two-tailed, paired t-test)

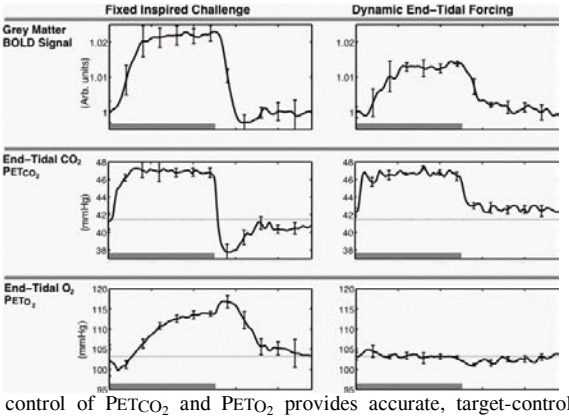

Figure. FMRI BOLD and respiratory recordings. One representative volunteer. Mean across cycles of hypercapnia are shown: error bars are the standard deviation. The period of the hypercapnic challenge is indicated by the grey bar. The dotted line indicates resting values.

DEF produced a consistent hypercapnia while fixing $P_{ET}O_2$. During the hypercapnic periods of DEF, $P_{ET}CO_2$ was not significantly different from that during FIC, confirming that DEF successfully met the chosen $P_{ET}CO_2$ targets. In general, $P_{ET}CO_2$ rose faster at the start of the hypercapnia during DEF than FIC. An undershoot of $P_{ET}CO_2$ was evident after the end of the FIC (140-200 s), also reflected in an undershoot of the grey matter BOLD signal. This undershoot was avoided by DEF, providing a squarer $P_{ET}CO_2$ waveform. Unlike the FIC, DEF successfully maintains a constant $P_{ET}O_2$ by decreasing P_IO_2 when ventilation rises in response to hypercapnia.

Discussion and Conclusions

We have demonstrated the feasibility of dynamic end-tidal forcing (DEF) as a means of delivering respiratory challenges for FMRI [5,6]. The potential rewards of a DEF system for use with FMRI must be balanced against the additional cost and set-up time required for the technique. Computer control of $P_{ET}CO_2$ and $P_{ET}O_2$ provides accurate, target-controlled, repeatable respiratory challenges that could be automatically synchronized with FMRI data acquisition. DEF is able to force fast changes in arterial gas partial pressures. It could also be used to reduce physiological noise related to breathing fluctuations [8,9]. The confounds of the fixed inspired challenge, such as an elevated Pa_{O_2} due to the ventilatory response to CO_2, can be avoided, opening the way for better-controlled quantitative studies of BOLD and perfusion image contrast.

References

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