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Effects of inspiratory and expiratory loading upon global and stimulus evoked CBF

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Introduction: Cerebral blood flow (CBF) is affected by alterations in intrathoracic pressure, via effects on arterial blood pressure (ABP), heart rate (HR) and venous outflow from the brain. These effects (illustrated in Figure 1) are clearly observed during a Valsalva manoeuvre [1] and the Mueller manoeuvre [2]. Alterations in intrathoracic pressure occur in disease states such as asthma and chronic lung disease. In order to understand the neural processing in a wide range of respiratory disorders it is important to understand the CBF effects of altered intrathoracic pressure, and how such changes may interact with stimulus-evoked signal changes. The aim of this study was to investigate how resistive inspiratory and expiratory loading, a tool for the investigation of breathlessness, affects CBF and the stimulus-evoked CBF response. We used trans-cranial Doppler (TCD) to investigate short-lived temporal effects and whole brain pseudo-continuous ASL to assess longer term and spatial effects.

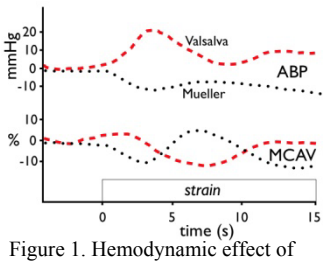

Figure 1. Hemodynamic effect of Valsava and Mueller Maneuvers [1,2]

Methods: 13 healthy volunteers (2 female; age 28+/-7(SD)) were examined on two occasions, first in a physiology laboratory and second in a Siemens 3T Verio scanner. In both sessions, participants breathed room air via a custom designed breathing system in which the internal diameter of the inspiratory and expiratory limb could be altered remotely by inflation/deflation of a water-filled balloon. Subjects were trained to maintain end-tidal carbon dioxide ($PETCO_2$) constant via real-time visual feedback [3]. Alternating 270-second blocks of inspiratory loading (-10cmH20), expiratory loading (+10cmH20) and no loading were delivered. Subjective ratings of breathlessness (0-10 on a visual analogue scale) were acquired after each block. A 2Hz flashing checkerboard was displayed for 120 seconds during each block. In the first experimental session, continuous recordings were made of middle cerebral artery velocity (MCAV; trans-cranial Doppler) and blood pressure (Finapres). During the second session, pseudo continuous ASL (TE= 14ms, TR= 4000ms, 450 volumes, voxel size 3.8x3.8x5.0mm) was acquired on a Siemens Verio 3T MRI scanner with a 32-channel radiofrequency receive coil. Analysis of the ASL data was carried out using FSL (http://www.fmrib.ox.ac.uk/fsl). A region-of interest approach was used to calculate mean perfusion changes across whole brain grey matter in response to inspiratory and expiratory loading and mean perfusion changes in the visual cortex (anatomical mask based on standard atlas template in FSL) in response to visual stimulation. The interaction between visual stimulation and the two loading conditions was modelled in the first level analysis, and explored using the same ROI approach. Voxel-wise statistical analysis was extended to a second (group) level in a fixed effects analysis using cluster threshold of Z>2.3 and a (corrected) cluster significance threshold of P=0.05. Physiological data were analyzed with a custom written script in Matlab.

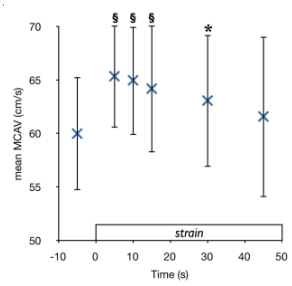

Figure 2: MCAV changes after application of inspiratory resistive load § p<0.01, * p<0.5

Results: ***Laboratory session*:** The main results are depicted in Table 1 and Figure 2. We observed a transient increase in CBF (TCD) in the first 30 seconds following application of an inspiratory load that was associated with an increase in $PETCO_2$, but not in blood pressure. We did not observe physiological changes in response to removal of the inspiratory load nor in response to application or removal of an expiratory load. ***FMRI session*:** Perfusion changes in the regions of interest are demonstrated in Table 2. This shows no effect of inspiratory or expiratory loading upon global CBF. As expected there was a robust CBF response to visual stimulation in the visual cortex, but no interaction was observed between loading and visual stimulation. Physiological data is summarized in Table 3. This shows that $PETCO_2$ was maintained constant across all experimental blocks. The voxel wise analysis (Figure 3) demonstrated robust activation in the visual cortex in response to visual stimulation (not pictured), no significant activations in response to inspiratory loading, activation in the right sensorimotor and bilateral lobe VI of the cerebellum in response to expiratory loading, and activation in the right insula and ventroposterolateral thalamic nucleus that correlated with the subjective dyspnea ratings.

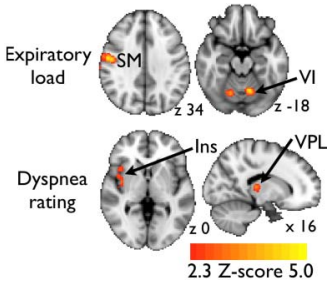

Figure 3. Significant CBF increases during exp loading (top), and in response to subjective dyspnoea ratings (bottom). Abbr: SM sensorimotor cortex, VI cerebellum lobe VI, Ins Insular cortex, VPL ventroposterior thalamic nucleus

Time:	Baseline	5	10	15	30	45
MAP:	96(16)	95(16)	95(17)	94(18)	94(18)	93(16)*
HR:	71(15)	69(12)	70(15)	69(15)	73(18)	72(15)
CO2:	5.5(0.5)	5.7(0.6)*	5.7(0.6)*	5.6(0.5)*	5.6(0.5)	5.6(0.5)

Table 1. Physiological variables over first 45 seconds after inspiratory load

Load	Minimum pressure [cmH_2O]	Maximum pressure [cmH_2O]	PETCO2 [%]	Heart rate [/min]	Dyspnea Rating [0-100]
Insp	-9.0(1.4)*	0.3(0.5)	5.5(0.7)	67(7)*	41(14)***
No	-0.7(0.2)	0.8(0.2)	5.6(0.7)	63(7)	8(12)
Exp	-0.2(0.7)	8.5(2.0)	5.5(0.8)	63(7)	38(14)***

Table 3. Physiological measurements obtained during scanning
* p<0.05, *** p<0.001 compared with baseline

Discussion: These data show that respiratory loading for durations of 270 seconds has no significant effects upon global CBF, nor the stimulus evoked CBF response. This is extremely useful for studies in patients with respiratory disease and for a realistic volunteer model of dyspnoea. However, we have demonstrated significant effects on CBF in the early phase of respiratory loading (i.e. the first 30 seconds). The increase in CBF is most likely due to a raised $PETCO_2$ as subjects find it more difficult to breathe, although rapidly adjusting their breathing pattern. We would expect the negative intrathoracic pressure to cause a transient decrease in CBF (Figure 1), therefore it appears that the transiently increased $PETCO_2$ has a more powerful effect on cerebral perfusion. This finding of altered CBF in the initial stages following an inspiratory load suggests that studies using much shorter breathlessness durations (e.g.[4]) may be confounded by physiological effects upon global cerebral blood flow. The findings of increased CBF in the sensorimotor cortices and lobule VI of the cerebellum (sensorimotor cerebellum) reflect the increased effort participants consciously make. Such changes were not observed with inspiratory loading, which seemed to be more threatening and steered by reflexes. We observed increases in CBF in the right insular cortex and the right ventroposterolateral nucleus of the thalamus that correlated with changes in the subjective ratings of dyspnoea. These findings are supported by other neuroimaging literature on dyspnoea that has used either BOLD FMRI with short stimulus durations (~25 seconds) or positron emission tomography. Arterial spin labeling has the potential to be a useful neuroimaging method for understanding the neural mechanisms of dyspnoea, particularly since stimulus durations can be extended to make a more clinically realistic model.

	%ΔCBF (SD)
Grey matter	
Inspiratory loading	0.5(3.5)
Expiratory loading	6.9(2.0)
Visual cortex (V1)	
Visual stimulation	25.2(37.1)*
Interaction(insp/vis)	0.3(0.5)
Interaction (exp/vis)	0.1(0.6)

Table 2. Perfusion measurements from ASL* p<0.05 compared with baseline

References: [1] J Appl Physiol 86: 675-680, 1999. [2] Clin Physiol 20: 292-303, 2000. [3] J Cereb Blood Flow Metab 27: 414-423, 2007. [4] Am J Respir Crit Care Med. 177 :1026-32, 2008.