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The effects of altered intrathoracic pressure on resting cerebral blood flow and its response to visual stimulation

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ABSTRACT

Investigating how intrathoracic pressure changes affect cerebral blood flow (CBF) is important for a clear interpretation of neuroimaging data in patients with abnormal respiratory physiology, intensive care patients receiving mechanical ventilation and in research paradigms that manipulate intrathoracic pressure. Here, we investigated the effect of experimentally increased and decreased intrathoracic pressures upon CBF and the stimulus-evoked CBF response to visual stimulation.

Twenty healthy volunteers received intermittent inspiratory and expiratory loads (plus or minus 9 cmH_2O for 270 s) and viewed an intermittent 2 Hz flashing checkerboard, while maintaining stable end-tidal CO_2. CBF was recorded with transcranial Doppler sonography (TCD) and whole-brain pseudo-continuous arterial spin labeling magnetic resonance imaging (PCASL MRI).

Application of inspiratory loading (negative intrathoracic pressure) showed an increase in TCD-measured CBF of 4% and a PCASL-measured increase in grey matter CBF of 5%, but did not alter mean arterial pressure (MAP). Expiratory loading (positive intrathoracic pressure) did not alter CBF, while MAP increased by 3%. Neither loading condition altered the perfusion response to visual stimulation in the primary visual cortex. In both loading conditions localized CBF increases were observed in the somatosensory and motor cortices, and in the cerebellum.

Altered intrathoracic pressures, whether induced experimentally, therapeutically or through a disease process, have possible significant effects on CBF and should be considered as a potential systematic confound in the interpretation of perfusion-based neuroimaging data.

Introduction

The brain regulates its blood supply in order to ensure adequate delivery of oxygen and nutrients in the face of changing systemic blood pressure and regional changes in metabolic demand. Cerebral autoregulation is the hemodynamic process that keeps cerebral blood flow (CBF) within tight physiological limits during changes in perfusion pressure via adaptations in cerebrovascular resistance (van Beek et al., 2008), while neurovascular coupling matches local CBF to changes in underlying neuronal activity (Nielsen and Lauritzen, 2001).

CBF can be affected by physiological modulations or pharmacological agents, which in turn can affect the CBF-derived blood oxygen level dependent (BOLD) response (Brown et al., 2003; Cohen et al., 2002). Altered intrathoracic pressures could potentially affect CBF via direct pressure effects on the great arteries and veins of the chest, causing systemic changes in arterial blood pressure and in venous return from the brain (Kolbitsch et al., 2000).

Classical physiology teaching states that CBF is affected by systemic factors (e.g. systemic vascular resistance, arterial blood pressure, venous return, arterial carbon dioxide and oxygen tensions) and by local factors within the brain (e.g. autoregulation). It is therefore important to examine how these effects might confound the interpretation of CBF-derived functional neuroimaging methods, such as arterial spin labeling (ASL) or BOLD contrast, when intrathoracic pressures are changed. In order to correctly interpret FMRI to examine brain activity of patients with altered intrathoracic pressure or of healthy volunteers undergoing respiratory loading, we need to establish the effects of respiratory loading, both on baseline CBF and on CBF changes during neuronal activation. This understanding of the effects of altered intrathoracic pressure on CBF may be important in a number of clinical and experimental scenarios.

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The ability to quantify CBF regulation in patients following neurological injury is commonly required in both research and clinical practice. As these patients can often require intensive care interventions such as sedation and mechanical ventilation, changes in intrathoracic pressure may potentially affect measurements of CBF. During mechanical ventilation, gas is forced into the lungs, increasing intrathoracic pressures to +15 to +30 cmH_2O. Additionally, positive end expiratory pressure (PEEP) of up to +10 cmH_2O is often applied to prevent lung collapse. Any known effect of mechanical ventilation on CBF would need to be taken into consideration when interpreting CBF measures.

Changes in intrathoracic pressure might also be a potential confound when interpreting functional neuroimaging in patients with respiratory diseases. There is currently much interest in using FMRI to understand the relevance of brain processes in these often chronic and debilitating conditions. In COPD, there is fixed obstruction of airways and inspiratory pressure of approximately −13 cmH_2O, and expiratory pressures of +3 cmH_2O have been reported (Montes de Oca et al., 1996). Acute bronchoconstriction in asthma can generate negative intrathoracic pressures of −30 cmH_2O (Stalcup and Mellins, 1977). In addition to clinical asthma, methacholine, a compound that is inhaled to create bronchoconstriction, is used to test for bronchial hyperreactivity or model asthma for experimental purposes, and could conceivably be used to investigate brain mechanisms of asthma with FMRI.

Furthermore, intrathoracic pressure is altered by breathing against an external resistive respiratory loads as an integral part of laboratory models used to investigate the neuronal mechanisms involved in the control of breathing and in the perception of breathlessness, e.g. (Banzett et al., 2008; Sturdy et al., 2004). These models can be used to gain an understanding of the neuronal mechanisms involved in the perception of breathlessness with FMRI (Banzett et al., 2008; von Leupoldt et al., 2007). Although the profound CBF effects of the Valsalva maneuver (Tiecks et al., 1996) and Mueller maneuver (Reinhard et al., 2000) have been well described, these techniques, which involve forced expiration or inspiration against a closed glottis, are extreme, unphysiological, and induce other physiological processes beyond changing thoracic pressure (e.g. hypercapnea). Therefore, to better understand the effects of altered intrathoracic pressure on cerebral physiology, a controlled experimental paradigm is required.

In this study we examined the effects of inspiratory and expiratory loading on CBF measured in two ways, with ASL FMRI and with transcranial Doppler sonography (TCD). We also determined whether or not respiratory loading induces CBF changes that might alter the perfusion response to visual stimulation. Informed by previous studies using TCD during inspiratory loading (decreased inspiratory pressure), we hypothesize that inspiratory loading will lead to increased CBF and that expiratory loading (increased expiratory pressure) will lead to a decrease in CBF. If the induced CBF changes are relatively large, these could potentially alter the CBF response to visual stimulation, similar to the way in which CBF changes affect evoked BOLD responses (e.g. increased arterial CO_2 increases CBF, which decreases the BOLD response to visual activation (Cohen et al., 2002)). We furthermore expect inspiratory and expiratory loading to show locally increased perfusion in brain areas that are engaged in the control of breathing.

Materials and methods

Brief overview

The study consisted of three sessions: a training session, a laboratory session in which CBF was measured indirectly (with TCD) with simultaneous continuous non-invasive mean arterial blood pressure (MAP) measurements and a third session in the MRI scanner during which CBF was measured across the whole brain with ASL FMRI.

TCD enables the beat-by-beat investigation of local blood velocity changes in the middle cerebral artery (MCAV), which reliably correlate with changes in CBF (Bishop et al., 1986) and hence can be used as an indirect measure of CBF, as long as a stable diameter of the insonated vessel and constant blood vessel resistance and permeability throughout the brain can be assumed.

ASL allows serial measurement of relative CBF to be taken over several minutes from the whole brain (Dai et al., 2008). During ASL, water molecules in flowing blood are magnetically labeled at the level of the neck. An image is acquired in the brain once this labeled blood water has exchanged from the vasculature into the brain tissue. Tissue perfusion, or CBF, can then be assessed by subtracting this labeled image from a control image in which the inflowing blood water is not magnetically labeled. We used a recently developed variant of ASL, PCASL (Dai et al., 2008), which provides enhanced labeling efficiency and a resultant increase in the signal-to-noise ratio of the CBF measurements.

Participants

Twenty volunteers (mean age 27 (SD ± 6) years, 6 females) participated in this study after giving written informed consent in accordance with the Oxfordshire Research Ethics Committee. Participants were healthy right-handed non-smokers with no history of significant neurological, pulmonary or cardiovascular disease and free from acute illness (e.g. acute upper respiratory tract infection). Participants abstained from excessive consumption of alcohol (24 h), caffeine (6 h) and heavy meals (2 h) before the experiment and had sufficient sleep the preceding night. Female participants either used hormonal contraception or were at the same stage of their menstrual cycle during both parts of the experiment.

The 20 volunteers were drawn from a total of 27 participants, seven of which were excluded for the following reasons: one did not tolerate the visual stimulus, four did not comply with the study protocol, and two displayed excessive head motion during FMRI. These complete datasets were excluded from all analyses.

Respiratory loading

The same experimental paradigm was performed in both experimental sessions (Fig. 1). In a supine position, participants wore a nose clip (Air Safety Ltd, Morecambe, UK) and standard foam earplugs while breathing room air through a mouthpiece connected to a custom-built respiratory circuit (shown in Fig. 2). Participants were exposed to intermittent inspiratory or expiratory loads of either minus or plus 9 cmH_2O, which was induced by partially occluding either the inspiratory or the expiratory limb of the breathing circuit with a balloon that was remotely controlled by a hydraulic system. Intrathoracic pressure can be inferred through non-invasive measurements of mouth pressure, which is approximately equivalent to measurements of esophageal pressure, the common way to determine intrathoracic pressure (Baydur et al., 1982).

Respiratory control

As a strong cerebrovascular vasodilator, CO_2 has been shown to alter CBF and to induce changes in the BOLD FMRI signal (Cohen et al., 2002). Therefore, participants were trained to maintain the partial pressure of end-tidal CO_2 ($PETCO_2$) stable throughout this study. A $PETCO_2$ baseline value was determined for each individual at the beginning of each experimental session by monitoring $PETCO_2$ over two minutes after an 8-minute habituation period. A $PETCO_2$ target value was set 0.1 kPa lower than the baseline. During the training session, participants learnt to keep their $PETCO_2$ stable. At the beginning of each session, participants were instructed to keep their $PETCO_2$ stable within 1 kPa of their target value throughout the paradigm via