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Comparing cerebrovascular reactivity measured using BOLD and cerebral blood flow MRI: The effect of basal vascular tension on vasodilatory and vasoconstrictive reactivity

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ABSTRACT

Cerebrovascular reactivity (CVR) is an important metric of cerebrovascular health. While the BOLD fMRI method in conjunction with carbon-dioxide (CO_2) based vascular manipulation has been the most commonly used, the BOLD signal is not a direct measure of vascular changes, and the use of arterial-spin labeling (ASL) cerebral blood flow (CBF) imaging is increasingly advocated. Nonetheless, given the differing dependencies of BOLD and CBF on vascular baseline conditions and the diverse CO_2 manipulation types currently used in the literature, knowledge of potential biases introduced by each technique is critical for the interpretation of CVR measurements. In this work, we use simultaneous BOLD-CBF acquisitions during both vasodilatory (hypercapnic) and vasoconstrictive (hypocapnic) stimuli to measure CVR. We further imposed different levels of baseline vascular tension by inducing hypercapnic and hypocapnic baselines, separately from normocapnia by 4 mm Hg. We saw significant and diverse dependencies on vascular stimulus and baseline condition in both BOLD and CBF CVR measurements: (i) BOLD-based CVR is more sensitive to basal vascular tension than CBF-based CVR; (ii) the use of a combination of vasodilatory and vasoconstrictive stimuli maximizes the sensitivity of CBF-based CVR to vascular tension changes; (iii) the BOLD and CBF vascular response delays are both significantly lengthened at predilated baseline. As vascular tension can often be altered by potential pathology, our findings are important considerations when interpreting CVR measurements in health and disease.

Introduction

Cerebrovascular reactivity (CVR) is an important metric of cerebrovascular health. Experimentally, CVR is defined as the degree of vasodilatation or constriction in response to a vasoactive agent or task. CVR is an indication of vascular reserve (Ito et al., 2003) and autoregulatory efficiency (Nur et al., 2009), and CVR impairment has been observed in cerebral steno-occlusive vascular diseases (Mandell et al., 2011; Mandell et al., 2008), lacunar infarction (Birns et al., 2009; Mandell et al., 2011), microbleeding (Birns et al., 2009; Conijn et al., 2012) and cognitive decline in aging as well as dementia (Hurford et al., 2014; Kastrup et al., 1998; Kovács et al., 2010; Suri et al., 2014).

BOLD fMRI during carbon-dioxide (CO_2)-based vascular challenges is the most common CVR imaging approach (Kassner et al., 2010), and has been extensively cross-validated (Herzig et al., 2008). CO_2 is a potent vasodilator, triggering changes in vascular tension through the arterial baroreflex (Ainslie et al., 2008), and the vascular response to CO_2 is well established using transcranial Doppler ultrasound of arterial blood flow (Battisti-Charbonney et al., 2011). Typically, CVR is measured as the ratio between changes in the BOLD fMRI signal and end-tidal CO_2 ($PETCO_2$) change, a surrogate for arterial CO_2 (Robbins et al., 1990).

While the BOLD fMRI method has been the most commonly used due to its high availability and ease of implementation, a well-known concern regarding this approach is that the BOLD signal is not a direct measure of cerebral blood flow (CBF). This concern has been a primary motivation for adopting CBF-based CVR measurement (Noth et al., 2006; Tancredi et al., 2012). While a linear relationship between BOLD- and CBF-based CVR was obtained during hypercapnic vasodilation in healthy controls (Mark et al., 2010) as well as patients (Mandell et al., 2008), these previous experiments imposed iso-oxia during hypercapnic challenges, not the case in the majority of CVR studies. As the BOLD and CBF signals are differentially sensitive to oxygen level changes (Bulte et al., 2007), failure to maintain iso-oxia could introduce biases in the CVR measurements, and the linearity would deteriorate. More importantly, this relationship is still unknown for vasoconstrictive paradigms. In fact, the agreement between BOLD- and CBF-based CVR measurements is potentially dictated by basal vascular

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tension and type of vascular challenge, as BOLD and CBF signals have differing dependences on baseline blood flow and vascular volume, among other variables (Bhogal et al., 2014).

Commonly, CVR-related vascular changes are induced through manually adjusted administration of blended gasses (Bandettini and Wong, 1997; Cohen et al., 2004; Yezhuvath et al., 2009), end-tidal forcing (Poulin et al., 1996) or computerized prospective $PETCO_2$ targeting (Conklin et al., 2011; Han et al., 2011; Mandell et al., 2011; Mandell et al., 2008; Mark et al., 2010; Mikulis et al., 1989; Mutch et al., 2012; Prisman et al., 2008; Slessarev et al., 2007; Spano et al., 2013; Vesely et al., 2001). More recently, breath-holding-based hypercapnia is seen as an increasingly viable alternative (Bright and Murphy, 2013; Murphy et al., 2011). In addition, deep-breathing hypocapnia (Bright et al., 2009; Sousa et al., 2014) has also been proposed as an alternative vascular manipulation. Hypercapnia and hypocapnia result in vasodilation and vasoconstriction, respectively. However, these tasks do not furnish equivalent CVR measurements, as shown by Tancredi and Hoge (2013). Nonetheless, the relationship between simultaneous BOLD- and CBF-based CVR measurements has yet to be clarified for these widely varying types of vascular manipulations. Such knowledge is particularly useful in the context of altered vascular tension, as BOLD and ASL have diverging dependences on baseline conditions.

Specifically, vascular tension is an important determinant of the degree of vasoconstriction or vasodilation a blood vessel is capable of, and can be altered by age and neuropathology (Lüscher et al., 1991). Thus, understanding the relationship between CVR measurements and vascular tension would help interpret CVR measurements in patients as well as increase CVR data reliability in healthy controls. For instance, in post-stroke individuals, Zhao et al. (2009) reported a significantly lower increase in CBF during hypercapnic challenges but a greater reduction of CBF during hypocapnic challenges than the control group, which may have been attributable to stroke-related long-term alterations in vascular tension. In support of this theory, Ito et al. (2008) reported higher capacity for CBF reduction in a vasodilated state relative to the resting baseline in healthy controls, whereas Bright et al. (2010) identified a reduction in BOLD signal increase during a predilated baseline. The role of baseline vascular tone is more systematically demonstrated by Ghariq et al. (2014), who found that the BOLD CO_2 reactivity data fit better to a sigmoidal curve whereas the CBF *versus* $PETCO_2$ data fit better to a linear model. Nonetheless, to the best of our knowledge, there has yet to be a comparison of simultaneously measured BOLD- and CBF-based CVR for various vascular-tension conditions. CVR response delay is also a physiologically meaningful parameter (Blockley et al., 2011; Bright et al., 2010) that may become increasingly useful in assessing vascular dysfunction (Poublanc et al., 2013), but there is also limited information on the dependence of CVR response delay on vascular tension.

In this study, we use a dual-echo pseudocontinuous ASL technique to simultaneously assess the behavior of BOLD- and CBF-based CVR measurements under different vascular tensions and in response to different vascular stimuli. The results demonstrate that BOLD- and CBF-based CVR amplitude measurements are differentially sensitive to vascular tension and to the type of vascular stimuli. Our findings also demonstrate that the CO_2 response delay is highly sensitive to baseline vascular tension for both BOLD- and CBF-based CVR measurements. These findings have important implications for comparing BOLD- and CBF-based CVR studies in normal and patient populations.

Materials and methods

Participants

This study was carried out with 18 healthy adult volunteers (10 male, age 26.3 ± 6.5 years; range 18 to 36 years). Participants were recruited through the Baycrest Participants Database, which includes participants from Baycrest and the surrounding community. The study was approved by the Baycrest Research Ethics Board.

MRI acquisition

All images were acquired using a Siemens TIM Trio 3 Tesla System (Siemens, Erlangen, Germany). The scans employed 32-channel phased-array head coil reception and body-coil transmission. A T1-weighted MPRAGE 3D anatomical was acquired at an isotropic resolution of 1 mm. In addition, CBF and BOLD data were acquired concurrently using a dual-echo pseudo-continuous pCASL technique (Dai et al., 2008), with a repetition time (TR) of 4 s, echo times (TE)1/TE2 = 10/25 ms, field of view = 220 × 220 mm, 18 slices (ascending interleaved order), voxel size = 3.4 × 3.4 × 5.0 mm^3, 100 frames, bandwidth = 2520 Hz/pixel and GRAPPA = 2. The labeling duration was 1500 ms, and the post-labeling delay was 1000 ms with a mean G_z of 0.6 mT/m which was selected to achieve transit time insensitivity.

Vascular tension manipulation and vascular challenges

All vascular manipulations were achieved by administering mixtures of O_2, CO_2 and medical air delivered using the RespirAct™ breathing circuit (Thornhill Research, Toronto, Canada), designed to provide computerized and independent targeting of end-tidal O_2 ($PETO_2$) and CO_2 ($PETCO_2$) pressure using the sequential gas delivery method (Slessarev et al., 2007). This method was chosen to maximize steady-state $PETCO_2$-targeting accuracy and stability while minimizing $PETO_2$ confounds during CO_2-based CVR measurements (Chen and Pike, 2010b; Prisman et al., 2008). Within the RespirAct framework, while breath rate was self-regulated, hypocapnia is achieved primarily through increased breathing depths, while hypercapnia is achieved through inhaling air with a higher than normal amount of CO_2. For this method, the CO_2 and O_2 capacity as well as consumption rate for each subject were estimated prior to the scan in order to compensate for the physiology-related resting $PETCO_2$ and CO_2 clearance variations between individuals. The detailed experimental protocol is illustrated in Fig. 1.

During the pCASL scans, $PETCO_2$ was sinusoidally modulated (Blockley et al., 2011) at each baseline $PETCO_2$ with a period of 120 s; 3 periods of sinusoidal $PETCO_2$ variations were induced, following a 1-minute baseline. We chose such a bipolar paradigm as it includes both vasodilatory (upper half of sinusoid) and vasoconstrictive (bottom half of sinusoid) components.

This sinusoidal manipulation was applied at the subject's natural baseline (normocapnic) as well as at hypercapnic and hypocapnic baselines, which are both separated from the normocapnic baseline by 4 mm Hg. The ordering of the different baselines was randomized to minimize biases. These mild $PETCO_2$ changes result in slight changes in the subject's vascular tone without noticeable changes in cerebral oxidative metabolism, a potential confound for CO_2-based vascular assessment (Chen and Pike, 2010a).

Image preprocessing

Functional images, including the tag and control images in the pCASL data, and T_1-weighted anatomical images were separately preprocessed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). In each of the tag and control series, the first four time frames were discarded to ensure MR steady state. Preprocessing for pCASL images included retrospective head-motion correction, slice-timing correction using sinc interpolation, spatial transformation into a Montreal Neurological Institute (MNI) space, and spatial smoothing with a 6-mm full-width at half-maximum (FWHM) Gaussian kernel. Anatomical images were co-registered with their corresponding realigned functional data and segmented into gray and white matter tissue probability maps