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Investigating the non-linearity of the BOLD cerebrovascular reactivity response to targeted hypo/hypercapnia at 7 T

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ABSTRACT

Cerebrovascular reactivity (CVR) is a mechanism responsible for maintaining stable perfusion pressure within the brain via smooth muscle mediated modulations of vascular tone. The amplitude of cerebral blood flow (CBF) change in response to a stimulus has been evaluated using Blood Oxygen Level Dependent (BOLD) MRI, however the relationship between the stimulus and the measured signal remains unclear. CVR measured invasively in animal models and using blood-velocity based measurements in humans has demonstrated a sigmoidal relationship between cerebral blood flow and CO_2 partial pressure. Using an ultra-high magnetic field strength (7 T) MRI scanner and a computer controlled gas delivery system, we examined the regional and voxel-wise CVR response in relation to a targeted progressively increasing hypo- to hypercapnic stimulus. The aim of this study was to assess the non-linearity/sigmoidal behavior of the CVR response at varying arterial CO_2 ($PaCO_2$) levels. We find that a sigmoidal model provides a better description of the BOLD signal response to increasing $PaCO_2$ than a linear model. A distinct whole-brain and gray matter BOLD-CVR signal plateau was observed in both voxel-wise and regional analysis. Furthermore, we demonstrate that a progressively increasing stimulus in combination with a sigmoidal response model can be used to obtain CVR values and provides additional physiologically relevant information (such as linear and non-linear response domains, and maximum response amplitudes) that may be more difficult to obtain from blocked CVR experiments. Considering these results, we propose an alternative way in which to define CVR based on the derivative of the BOLD-CVR response curve, which can potentially be used to differentiate between healthy and diseased vascular states.

1. Introduction

Cerebral autoregulation (CA) refers to the mitigation of changes in cerebral blood flow in response to changes in cerebral perfusion pressure (Peterson et al., 2011). Cerebrovascular reactivity (CVR) refers to the change in cerebral blood flow (CBF) and cerebral blood volume (CBV) in response to a vasoactive stimulus. CVR is an essential component of the CA mechanism. Impaired CVR has been linked to an increased risk of stroke in patients with carotid artery occlusion and stenosis (Gupta et al., 2012; Silvestrini et al., 2000), severe depression (Lemke et al., 2010), and has been studied in connection with cognitive decline (Balucani et al., 2012) and Alzheimer's disease (Silvestrini et al., 2012). Mapping of CVR has been used to identify neuro-vascular uncoupling for the purpose of pre-surgical planning in tumor resection procedures (Zaca et al., 2011). Furthermore, CVR maps have been used to evaluate clinical outcomes in patients following corrective cerebrovascular surgery (Han et al., 2011; Heyn et al., 2010; Mikulis et al., 2005). CVR also plays a role during the calibration process for quantitative functional Blood Oxygen Level Dependent (BOLD) imaging (Davis et al., 1998; Gauthier and Hoge, 2013; He and Yablonskiy, 2007; Hoge, 2012; Pike, 2012).

1.1. Measuring CVR

Hypercapnia is the most common vasoactive stimulus used to probe CVR since it serves to iso-metabolically increase CBF and CBV. Hypercapnia can be imposed in a number of ways, including breath-holding, the inhalation of CO_2-containing gas, rebreathing of exhaled gas and automated targeting of arterial CO_2 (Fierstra et al., 2013; Tancredi and Hoge, 2013; Wise et al., 2007). The vascular response to hypercapnia can be assessed using a variety of modalities including transcranial Doppler ultrasound (TCD), near infrared spectroscopy (NIRS), magnetic resonance imaging (MRI) and positron emission tomography (PET)

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imaging (Rostrup et al., 2000). Clinically, non-invasive CVR measurements are generally performed using TCD (TCD-CVR), whereby changes in blood flow velocity are recorded from the middle cerebral arteries, thereby facilitating the measurement of CVR in related perfusion territories. Therefore, TCD measurements are generally insensitive to localized CVR impairment. Alternatively, MRI based measurements can be used to probe CVR and assess local changes by way of the BOLD contrast mechanism (henceforth termed BOLD-CVR), which is sensitive to changes in blood oxygenation (Kim and Ogawa, 2012; Lythgoe et al., 1999; Siero et al., 2013; Vesely et al., 2001). Increasing CBF via vasoactive stimuli will increase venous oxygen saturation due to the de-oxyhemoglobin removal causing a concurrent increase in the BOLD signal from baseline. Recent studies have demonstrated that BOLD MRI is a viable tool for investigating impaired CVR in relation to pathological conditions (da Costa et al., 2013; Spano et al., 2012).

1.2. Linearity of the CVR response

BOLD-CVR experiments generally assume a linear relationship between hypercapnia-imposed CVR and the resultant change in the BOLD signal (van der Zande et al., 2005). However, investigations of CVR using TCD in combination with progressively increasing CO_2 stimuli have demonstrated a sigmoidal relationship between cerebral blood flow velocity and arterial CO_2 partial pressure ($PaCO_2$) (Battisti-Charbonney et al., 2011; Claassen et al., 2007; Ringelstein et al., 1988). This non-linear response of the cerebral vasculature has also been thoroughly documented in animal studies while invasively measuring changes in CBF as a function of $PaCO_2$ (Harper and Glass, 1965; Reivich, 1964). A non-linear CVR relationship will complicate the interpretation of clinical BOLD-CVR results since variations in delivered stimulus magnitude will result in inconsistent CVR values. This issue will also influence the robustness of quantitative BOLD-fMRI experiments that make use of hypercapnic calibration experiments.

The aim of this work was to investigate the non-linearity of the BOLD-CVR response and to determine whether the response followed a sigmoidal curve, as has been observed using other modalities. Normoxic, slowly increasing hypo- to hypercapnic challenges were administered, allowing closer examination of incremental vascular responses to increasing $PaCO_2$. Blocked hypercapnic challenges were administered to assess whether the BOLD signal changes resulting from rapid increases in $PaCO_2$ were comparable to those administered using a progressive ramp protocol. Breathing challenges were delivered using a computer controlled prospective targeting system, which facilitated precise control of arterial CO_2 and O_2 partial pressures (Fierstra et al., 2013). BOLD signal measurements were performed at ultra-high field strength (7 T). The increased BOLD contrast to noise (CNR) ratio at this field strength (Polders et al., 2011; van der Zwaag et al., 2009) allowed for the production of high resolution CVR and fitted parameter maps, which facilitated voxel-wise analysis of the BOLD-CVR response as well as the comparison of regional GM and WM CVR response.

2. Materials and methods

2.1. Data acquisition

This study was approved by the Medical Ethics Committee of our institution and informed consent was obtained from all volunteers. Eight healthy volunteers (three females) were scanned on a Philips 7 T MRI scanner using a 32 channel receive coil in combination with a volume transmit coil (Nova Medical, Wilmington, MA, USA). Third order image-based shimming was performed using in-house IDL software (v6.3 RSI, Boulder, CO, USA) to minimize B_0 field inhomogeneities. Multi-slice single-shot GE-EPI BOLD images (flip angle: 90°, TR/TE: 3000/25 ms, EPI/SENSE factor: 47/3, reconstructed resolution: 1.5 × 1.5 mm^2, slice thickness: 1.6 mm, FOV: 217.6 × 192 mm^2, acquisition matrix: 133 × 120, slices: 43, image volumes: 204, scan duration: 601 s) with whole brain coverage were acquired throughout a hypo- to hypercapnic breathing challenge. Block stimulus CVR-response data was acquired in five of eight subjects (total scan duration: 369 s) using the same EPI sequence. Following BOLD data acquisition, high resolution 3D multi-shot GE-EPI T_2^* weighted scans were acquired for anatomical reference (flip angle: 24°, TR/TE: 77/27 ms, EPI factor: 13, SENSE factor RL/FH: 2.3/1, reconstructed resolution: 0.5 mm isotropic, FOV: 240 × 150 × 192 mm^3, acquisition matrix: 480 × 381 × 300, scan duration: 385 s) (Zwanenburg et al., 2011).

2.2. Apparatus and breathing protocol

End-tidal CO_2 was targeted by using a RespirAct™ device (Thornhill Research Inc, Toronto, Canada). This computer-controlled gas blender and sequential gas delivery system runs a feed-forward algorithm (Slessarev et al., 2007) whereby measured end-tidal CO_2 partial pressure has been shown to be equal to $PaCO_2$ (Ito et al., 2008). A 600 s breathing challenge (protocol shown in Fig. 3-A) consisting of 4 parts was delivered as follows: (1) 120 s baseline period — $PaCO_2$ values targeted at resting state levels of individual subjects. (2) Hyperventilatory period in which targeted $PaCO_2$ was set to 10 mmHg below baseline. (3) 300 s progressively increasing $PaCO_2$ ramp. The maximum targeted $PaCO_2$ values were adapted on a per-subject basis based on the individual tolerances to RespirAct calibration experiments done outside of the scanner, as well as individual resting baseline values. This lead to maximum targeted values between 46 and 60 mmHg $PaCO_2$. (4) 120 s baseline. In order to compare and validate regional signal changes from the ramped protocol with those acquired using a block stimulus design, an additional 90 s block stimulus ($PaCO_2$ targeted at 10 mmHg above the individual baseline $PaCO_2$ value) in between two 120 s baseline periods was applied in five subjects (protocol shown in Fig. 3-B). Normoxia was maintained throughout both protocols.

2.3. Processing and ROI segmentation

Processing and segmentation of image data was done using the Functional MRI of The Brain (FMRIB) Software Library (FSL) (Jenkinson et al., 2012). A mean-timeseries volume was created by averaging signal intensities across the GE-EPI timeseries. Mean-timeseries voxels containing signal from brain tissue were extracted using the FSL Brain Extraction Tool (BET) (Smith, 2002). A whole brain (WB) mask was then created by binarizing the BET mean-timeseries volume. Multiplication of this WB mask with the individual timeseries volumes extracted the brain tissue from the GE-EPI timeseries data. The extracted volumes were then re-aligned to the mean-timeseries volume using the FSL Motion Correction Linear Image Registration Tool (MCFLIRT) (Jenkinson et al., 2002). Re-aligned volumes were spatially smoothed using a 3D Gaussian kernel (kernel size: 3 × 3 × 3 voxels, $\sigma = 0.65$ mm). The mean-timeseries volume was segmented using the FSL Automated Segmentation Tool (FAST) (Zhang et al., 2001) creating partial volume tissue maps segmenting gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) components. Conservative tissue specific ROI masks were generated by thresholding partial volume maps obtained from FAST output at unity (Zhang et al., 2001) followed by erosion using a 1 × 1 × 1 voxel 'diamond' shaped kernel. Thus, boundary voxels potentially consisting of mixed tissue were discarded. Known CSF regions in GM and WM ROIs, which were not properly segmented, were removed manually. Finally, the mean-timeseries volume was aligned to the high resolution T_2^* anatomical scan using rigid-body registration (FLIRT) (Jenkinson and Smith, 2001; Jenkinson et al., 2002).

2.4. De-trending, smoothing and $PaCO_2$ alignment

To account for scanner drift, ROI and voxel timeseries data were linearly de-trended using their respective pre- and post-stimulus baseline

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