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Baseline oxygenation in the brain: Correlation between respiratory-calibration and susceptibility methods

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ABSTRACT

New MRI methods for noninvasive imaging of baseline oxygen extraction fraction (OEF) in the brain show great promise. Quantitative O_2 imaging (QUO2) applies a biophysical model to measure OEF in tissue from BOLD, cerebral blood flow (CBF), and end-tidal O_2 (ETO_2) signals acquired during two or more gas manipulations. Alternatively, quantitative susceptibility mapping (QSM) maps baseline OEF along cerebral vessels based on the deoxyhemoblogin (dHb) susceptibility shift between veins and water. However, these approaches have not been carefully compared to each other or to known physiological signals. The aims of this study were to compare OEF values by QUO2 and QSM; and to see if baseline OEF relates to BOLD and CBF changes during a visual task.

Simultaneous BOLD and arterial spin labeling (ASL) scans were acquired at 7 T in 11 healthy subjects continuously during hypercapnia (5% CO_2, 21% O_2), hyperoxia (100% O_2), and carbogen (5% CO_2, 95% O_2) for QUO2 analysis. Separate BOLD-ASL scans were acquired during a checkerboard stimulus to identify functional changes in the visual cortex. Gradient echo phase images were also collected at rest for QSM reconstruction of OEF along cerebral veins draining the visual cortex.

Mean baseline OEF was (43.5 ± 14)% for QUO2 with two gases, (42.3 ± 17)% for QUO2 with three gases, and (29.4 ± 3)% for QSM across volunteers. Three-gas QUO2 values of OEF correlated with QSM values of OEF ($P = 0.03$). However, Bland–Altman analysis revealed that QUO2 tended to measure higher baseline OEF with respect to QSM, which likely results from underestimation of the hyperoxic BOLD signal and low signal-to-noise ratio of the ASL acquisitions. Across subjects, the percent CBF change during the visual task correlated with OEF measured by 3-gas QUO2 ($P < 0.04$); and by QSM ($P = 0.035$), providing evidence that the new methods measure true variations in brain physiology across subjects.

Introduction

Adequate oxygen supply is critical to the health of cerebral tissues, and cerebral oxygen extraction fraction (OEF) is thought to be highly conserved across the brain (Hatazawa et al., 1995; Ishii et al., 1996b). While OEF is preserved across a wide range of physiological states in normal brain function, it is also known to be altered by cerebrovascular (Derdeyn et al., 1998; Yamauchi et al., 1999) and neurodegenerative disorders (Ishii et al., 1996a). The ability to noninvasively image OEF would thus provide important clinical information in patients where the brain oxygen supply may be disrupted. This information may also improve our understanding of the baseline physiology that underlies vascular and metabolic blood-oxygen-level-dependent (BOLD) signal changes. Although [^{15}O] positron emission tomography (PET) is the accepted reference method to quantify OEF maps in the brain (Ito et al., 2005), it is rarely used in the clinic due to the need for a cyclotron on site to produce short half-life [^{15}O]-tracers, experimental complexity, and use of ionizing radiation. Recognition of the importance of

Abbreviations: ANOVA, analysis of variance; ASL, arterial spin labeling; BOLD, blood oxygenation level dependent; CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen; BOLD, blood oxygenation level dependent; dHb, deoxyhemoglobin; ETO2, end-tidal O2; GCM, generalized calibration model; Hct, hematocrit; OEF, oxygen extraction fraction; QSM, quantitative susceptibility mapping; QUO2, quantitative oxygenation imaging; ROI, region of interest; SNR, signal-to-noise ratio; TV, total variation.

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sophisticated OEF mapping and the current limitations in its measurement has prompted recent efforts to develop magnetic resonance imaging (MRI) alternatives. A variety of MRI methods have been proposed to measure global and local OEF from T_2 relaxation (Bolar et al., 2011; Guo and Wong, 2012; Lu and Ge, 2008), respiratory calibration (Bulte et al., 2012; Gauthier and Hoge, 2012; Wise et al., 2013), and magnetic susceptibility contrasts (Fan et al., 2012; Haacke et al., 1997; Jain et al., 2010).

One new class of MRI methods utilizes respiratory calibration with multiple gas challenges to quantify tissue OEF in the brain. Traditional calibrated BOLD techniques have relied on a single isometabolic gas challenge, such as hypercapnia or hyperoxia, to measure relative changes in oxygen metabolism during a functional task (Chiarelli et al., 2007; Davis et al., 1998). These approaches typically assume a baseline OEF value and estimate the M parameter, the maximum achievable BOLD signal at rest due to deoxyhemoglobin (dHb), as an intermediate step in the processing. On the other hand, the recently proposed generalized calibration model (GCM) enables biophysical modeling of BOLD MRI, perfusion MRI, and end-tidal O_2 (ETO_2) responses to arbitrary combinations of hyperoxia and hypercapnia (Gauthier and Hoge, 2013). Through use of multiple gas manipulations and the GCM, local baseline values of M and OEF are available per tissue voxel. Several variants of this respiratory calibration approach have been implemented with pure hyperoxia and hypercapnia (Bulte et al., 2012; Germuska and Bulte, 2014), or multiple combinations of gases with different combinations of O_2 and CO_2 concentrations (Wise et al., 2013). In this work, we focus on a specific variant known as QUantitative O_2 (QUO2) MRI (Gauthier et al., 2012), which provides a graphical interpretation of the GCM and was originally proposed with use of three gases.

On the other hand, magnetic susceptibility represents a distinct MRI contrast mechanism that reflects the magnetizability of a tissue and is thus sensitive to brain oxygenation. The OEF level in cerebral veins directly relates to the concentration of paramagnetic dHb molecules in the vessels (Weisskoff and Kiihne, 1992). The presence of dHb molecules changes the magnetic susceptibility in venous blood relative to reference tissue, such as the cerebrospinal fluid, which can be measured using gradient echo phase images. These magnetic field perturbations are non-local and depend on the geometry of the object and its orientation with respect to the main magnetic field, B_0. Based on the observed MRI field maps, quantitative susceptibility mapping (QSM) methods (Bilgic et al., 2014; de Rochefort et al., 2008; Liu et al., 2009, 2012) have been proposed to invert the dipole imaging kernel and reconstruct the underlying susceptibility distribution. These QSM reconstructions typically rely on prior information about the spatial "smoothness" of the desired susceptibility, and allow measurement of susceptibility, and thus OEF, along brain vessels of arbitrary orientation and geometry. Given sufficient resolution to measure susceptibility within the veins, quantitative oxygenation venograms that measure baseline OEF along the venous vasculature of the brain are then available (Fan et al., 2014; Haacke et al., 2010; Xu et al., 2014).

While these new MRI approaches to assess absolute OEF are promising, they have not been carefully compared to each other or to known physiological signals, such as BOLD contrast and cerebral blood flow (CBF). Only a few studies have investigated the reproducibility of MRI-based oxygenation mapping across different sites (Liu et al., 2015), begun to compare global measurements of baseline OEF in healthy volunteers (Barhoum et al., 2015; Rodgers et al., 2015), or estimated relative changes of OEF compared to corresponding changes in BOLD and CBF (Donahue et al., 2009; Lu and van Zijl, 2005). Our aims were thus to compare two variants of QUO2 (with two and three gases, respectively) against independent OEF values by QSM analysis; as well as to see if baseline OEF measurements by these methods relate to BOLD and perfusion signals elicited during a visual functional task. These experiments were performed at 7 Tesla (7 T) to achieve high spatial resolution and localize OEF values to the visual cortex for comparison.

Materials and methods

MRI acquisitions

Eleven healthy volunteers (9 female, ages 22–32 years, free of vascular abnormalities) were scanned on a MAGNETOM 7 T scanner (Siemens Healthcare, Erlangen, Germany) with a 24-channel head coil (6 volunteers) or a 32-channel head coil (all remaining participants). All procedures were approved by the Ethics Committee of the University of Leipzig and informed written consent was given by all volunteers. Manual shimming was performed to optimize field homogeneity over the imaging and labeling volumes. Dual-echo arterial spin labeling (ASL) data were acquired for simultaneous CBF and BOLD measurements during a 17-min breathing manipulation paradigm, and during a 6.5-minute visual stimulation paradigm. ASL tagging was achieved with a flow-sensitive alternating inversion recovery (FAIR) labeling scheme (Kim, 1995) and QUIPSS II saturation pulses (Wong et al., 1998). To account for specific absorption rate and transmit field constraints of ASL using a head coil at 7 T, an optimized TR-FOCI pulse was used for efficient spin inversion (Hurley et al., 2010). The data were acquired with repetition time (TR) = 3 s; echo times (TE) = 9.2/22.7 ms; matrix = 64 × 64 × 10; nominal resolution = 3 × 3 × 3 mm^3; bandwidth (BW) = 2368 Hz/pixel; GRAPPA acceleration = 2; and inversion times TI_1/TI_2 = 700/1400 ms.

High-resolution 3D gradient echo scans were acquired for QSM reconstruction of baseline OEF_0 along cerebral veins. The imaging slab was in the axial oblique orientation and had first-order flow compensation along all three spatial axes. Additional imaging parameters included TR = 17 ms; TE = 7.5 ms; matrix = 320 × 320 × 104; nominal resolution = 0.6 × 0.6 × 0.6 mm^3; axial oblique slices; flip angle = 9°; BW = 560 Hz/pixel; acceleration = 3; acquisition time (TA) = 4:22 min. To facilitate the generation of phase images from multiple receive channels, low-resolution B_0 field maps were also collected with the same spatial coverage: TR = 28 ms; TE = 5–23 ms spaced by 6 ms; matrix = 64 × 64 × 26; nominal resolution = 3.0 × 3.0 × 2.4 mm^3; FA = 10°; BW = 200 Hz/pixel; TA = 1 min per echo. No shimming was performed between the scans, and data of individual receive channels were saved for offline phase correction before combining the receive channels.

Gas challenges

Three gases were administered sequentially during the 17-min BOLD-ASL acquisition in the following order: 5% CO_2/21% O_2/74% N_2 (hypercapnia), 100% O_2 (hyperoxia), and 5% CO_2/95% O_2 (carbogen). Each gas administration block lasted 3 min and was flanked by 2 min of air breathing. Gases were delivered through a snorkel-like mouthpiece, and participants wore a nose clip to prevent inhalation of room air through the nose. The mouthpiece was connected to the pre-mixed gases by tubes and one-way valves to prevent inflowing gases from mixing with expired gases. Gas flow rates were adjusted manually by a physician within the magnet room and maintained at 15 L/min. The physician also monitored pulse and breathing during the manipulation to ensure the comfort of the participant. Expired gas concentrations were measured using the CO2100C and O2100C modules of the Biopac MP150 system (BIOPAC systems Inc., Goleta, CA, USA). Pulse and oxygen saturation were monitored using a pulse oximeter on the index finger.

End-tidal (ET) values were isolated from the respiratory traces using in-house MATLAB code (Mathworks, Natick, MA, USA). Group mean ETO_2 values (N = 11) were 133 ± 14 mmHg for all room air breathing periods, 126 ± 5 mmHg for hypercapnia, 622 ± 92 mmHg for hyperoxia, and 593 ± 91 mmHg for carbogen manipulations. $ETCO_2$ measurements were only available in 8 of the 11 subjects; group mean $ETCO_2$ values (N = 8) were 38.2 ± 2 mmHg for all room air