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Cerebrovascular reactivity measured with arterial spin labeling and blood oxygen level dependent techniques

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ABSTRACT

Purpose: To compare cerebrovascular reactivity (CVR) quantified with pseudo-continuous arterial spin labeling (pCASL) and blood oxygen level dependent (BOLD) fMRI techniques.
Materials and Methods: Sixteen healthy volunteers (age: 37.8 ± 14.3 years; 6 women and 10 men; education attainment: 17 ± 2.1 years) were recruited and completed a 5% CO_2 gas-mixture breathing paradigm at 3 T field strength. ASL and BOLD images were acquired for CVR determination assuming that mild hypercapnia does not affect the cerebral metabolic rate of oxygen. Both CVR quantifications were derived as the ratio of the fractional cerebral blood flow (CBF) or BOLD signal change over the change in end-tidal CO_2 pressure.
Results: The absolute CBF, BOLD and CVR measures were consistent with literature values. CBF derived CVR was 5.11 ± 0.87%/mmHg in gray matter (GM) and 4.64 ± 0.37%/mmHg in parenchyma. BOLD CVR was 0.23 ± 0.04%/mmHg and 0.22 ± 0.04%/mmHg for GM and parenchyma respectively. The most significant correlations between BOLD and CBF-based CVRs were also in GM structures, with greater vascular response in occipital cortex than in frontal and parietal lobes (6.8%/mmHg versus 4.5%/mmHg, 50% greater). Parenchymal BOLD CVR correlated significantly with the fractional change in CBF in response to hypercapnia ($r = 0.61$, $P = 0.01$), suggesting the BOLD response to be significantly flow driven. GM CBF decreased with age in room air (−5.58 mL/100 g/min per decade for GM; $r = -0.51$, $P = 0.05$), but there was no association of CBF with age during hypercapnia. A trend toward increased pCASL CVR with age was observed, scaling as 0.64%/mmHg per decade for GM.
Conclusion: Consistent with previously reported CVR values, our results suggest that BOLD and CBF CVR techniques are complementary to each other in evaluating neuronal and vascular underpinning of hemodynamic processes.

1. Introduction

1.1. Cerebrovascular reactivity

Cerebrovascular reactivity (CVR) describes the compensatory dilatory capacity of cerebral vasculature in upregulating perfusion. An inadequate dilatory response contributes to a higher risk of stroke and other ischemic injuries and is implicated in many pathologic conditions, such as diabetes mellitus and carotid artery disease [1–3]. Historically, CVR has been quantified by measuring the change of cerebral blood flow (CBF) during physiologic stress, using techniques such as MR phase-contrast/angiography, positron emission tomography, and Doppler sonography [4–6]. Some drawbacks of these methods include side effects from contrast agents and poor reproducibility. Alternatively, CVR is calculated as the relative difference between the challenge-induced absolute CBF or blood oxygen level dependent (BOLD) signal change relative to baseline levels using relatively new MRI sequences [7]. Advances in multi-parametric functional neuroimaging have allowed quantification of challenge-induced CBF together with BOLD signal change [8,9]. Additionally, such quantification allows for measurement of CVR by way of comparing pre- vs. post-stress blood flow changes [10]. By examining the effects of hypercapnia on the physiologic perfusion baseline, a model of CVR assessment can be developed, with or without functional stimulus [8,11].

1.2. BOLD fMRI

The BOLD effect is the basis of most fMRI methods, which exploit the increase in T2* during functional activation resulting from a

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fractional increase in intracellular oxyhemoglobin. The increased metabolic demand induces a greater than required increase in CBF, leading to a transient decrease in the deoxyhemoglobin to oxyhemoglobin ratio, which manifests as the BOLD effect [12]. Measurements of CVR based on breath-holding (BH) and hyperventilation have produced interesting results that could better define the biophysical origins of hemodynamics [13–15]. However, the tasks usually require subjects to be co-operative and cued, and results are also prone to intra-subject variability. Further, BH may induce a mixed hypercapnic–hypoxic state during which the $CMRO_2$ level is not constant [16]. Quantification of CVR based on well-validated hypercapnic BOLD measurement alone has been reported recently, with a slight drop of $CMRO_2$ levels observed during hypercapnia [17,18]. Since the BOLD signal change in response to increased CO_2 is relatively small (1–2%), a block design with several repetitions interleaving hypercapnia (similar to task condition) and resting state (baseline) has been used to enhance signal to noise ratio (SNR) [19]. In the present study, BOLD is used for quantifying CVR under the assumption that mild hypercapnia does not change $CMRO_2$ [20].

1.3. Arterial spin labeling (ASL) fMRI

Arterial spin labeling (ASL) fMRI is a noninvasive method for measuring CBF by using water in arterial blood as an endogenous tracer [21]. Since its introduction, ASL has played a key role for assessing CBF in that it has several advantages over other methods. For instance, because blood is being used as the tracer, ASL is a direct gauge of CBF. Furthermore, the quick magnetization decay allows for a relatively short scan time. Moreover, ASL expresses arterial perfusion whereas BOLD has been argued to be a largely venous phenomenon [22]. The reliability of ASL-based measurement of CBF has been shown previously [23]. Conventionally, two techniques are used: continuous ASL (cASL), where labeling is achieved with continuous radiofrequency (RF) irradiation, and pulsed ASL (pASL), where short RF pulses are used. Both techniques have limitations, in that cASL has low labeling efficiency in return for high SNR whereas pASL has lower SNR but high labeling efficiency. Pseudo-continuous ASL (pCASL), conceived more recently, uses a train of RF pulses mimicking continuous labeling [24], combining the advantages of both methods. Further, pCASL, unlike CASL, can be implemented on clinical scanners. Moreover, pCASL has been reported to be superior to pASL for measuring CO_2 induced CVR due to improved label timing control [24]. Recently, pCASL has been applied for mapping oxygen extraction fraction (OEF), $CMRO_2$, and CVR under hypercapnic and hyperoxic conditions [13,25]. pCASL-based CBF values have been reported to reach similar precision to standard PET-based CBF values at both baseline and during hypercapnia [26].

1.4. Coupling between BOLD and CBF signals

While ASL quantifies perfusion (and thus the change in perfusion in response to a stimulus), BOLD measures the combined effect of changes in blood flow, blood volume and metabolism in response to a stimulus. Therefore, the comparison of CBF and BOLD CVR measures could provide insight into the physiologic processes underlying fMRI (e.g. spatiotemporal dynamic brain reserve and plasticity) [27]. Integration of the two techniques into a single scan session is straightforward, and had been implemented under hypercapnia and/or hyperoxia calibration studies [28]. Coupling between direct CBF and the BOLD signal, as well as resulted CBF and BOLD CVR changes under hypercapnia, have been investigated in various animal and human studies [8,16]. Using a vessel-encoded ASL technique with simultaneous acquisitions of BOLD and CBF data, a close correlation has further been reported during hyperoxia [29], though with lower sensitivity in BOLD reactivity compared to CBF reactivity.

Several recent studies have studied the close association between CBF and BOLD changes in normal subjects with aging and in response to carbogen condition [30,31], as well as in patients with moyamoya disease [32]. Moderate to strong associations have been reported between CVR values obtained using ASL and BOLD in steno-occlusive disease patients [7]. The regional dependence of CVR measured by BOLD and CBF in healthy subjects, however, has not been studied extensively, with inconsistent results using the two techniques reported previously [30,31]. For example, the uncoupling of pCASL and BOLD signal is suspected to be secondary to the blood volume effect as previously discussed [7]. That is, the increase in CBV is believed to increase the fraction of the imaging voxel occupied by blood, reducing the BOLD signal. This effect is likely minor, however, as Kastrup et al. concluded that in normal subjects, the BOLD response to hypercapnia is more highly dependent on the flow effects and not blood volume effects [33]. On the other hand, Leoni et al. found that BOLD CVR cannot be inferred from resting baseline CBF directly [16]. Earlier work of measuring both BOLD and ASL simultaneously [34] had revealed significant spatiotemporal (e.g. layer specific and dependent) brain physiological processes with the largest CBF changes occurring in layers IV–V but lagging peak BOLD change in layers I–III in rats. Previous CBF studies with ^{15}O PET and BOLD fMRI under hypercapnia found the fMRI BOLD CVR to be strongly correlated with the PET CBF CVR, albeit with different temporal profiles in gray matter (GM) and white matter (WM) [5]. As there is no "gold standard" measure of CVR [35], understanding the sensitivity and relative agreement of pCASL and BOLD CVRs at the voxel-wise, region of interest (ROI) and whole-brain level is needed.

Investigating the hypercapnia-induced CVR characteristics could also provide physiological clue to the underlying neurovascular mechanism in disease conditions. In this study, BOLD and pCASL measurements were made in room air and during hypercapnia (5% CO_2) challenge to quantify CVR and to compare the functional parameters derived with the two methods. Other factors such as age and brain volume size were also recorded.

2. Materials and methods

2.1. Subjects

A total of 16 healthy volunteers (mean age: 37.8 ± 14.3 years and range: 20–62 years; 6 women and 10 men; education attainment: 17 ± 2.1 years) were recruited. None of the subjects had a diagnosis of cardiovascular or cerebrovascular morbidities. There was no history of medication use or occupational exposure to CO_2. After the institutional review board approval, the subjects were consented regarding the nature and risks of the procedure. For internal reliability control, three subjects repeated the scans with the same protocol one month after the initial scan.

2.2. Implementation of hypercapnia challenge for vascular reactivity measurements

Subjects were briefed on the hypercapnia protocol before the scan. A 10-minute rest period involving inactivity and restriction of verbal communication was instituted to prevent pre-challenge fatigue. During the experiment, the subjects were asked to breathe through an oral breathing tube with a mouthpiece and fitted with nose clips to prevent nasal breathing. The breathing tube was either open to the room air (normocapnia, breathing freely through tube) or supplied with the hypercapnic gas mixture (5% CO_2, 74% N_2, and 21% O_2). The latter was contained in a Douglas bag and delivered to the subjects through a two-way non-rebreathing valve (Hans