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Multiparametric imaging of brain hemodynamics and function using gas-inhalation MRI

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ABSTRACT

Diagnosis and treatment monitoring of cerebrovascular diseases routinely require hemodynamic imaging of the brain. Current methods either only provide part of the desired information or require the injection of multiple exogenous agents. In this study, we developed a multiparametric imaging scheme for the imaging of brain hemodynamics and function using gas-inhalation MRI. The proposed technique uses a single MRI scan to provide simultaneous measurements of baseline venous cerebral blood volume (vCBV), cerebrovascular reactivity (CVR), bolus arrival time (BAT), and resting-state functional connectivity (fcMRI). This was achieved with a novel, concomitant O_2 and CO_2 gas inhalation paradigm, rapid MRI image acquisition with a 9.3 min BOLD sequence, and an advanced algorithm to extract multiple hemodynamic information from the same dataset. In healthy subjects, CVR and vCBV values were 0.23 ± 0.03%/mmHg and 0.0056 ± 0.0006%/mmHg, respectively, with a strong correlation (r=0.96 for CVR and r=0.91 for vCBV) with more conventional, separate acquisitions that take twice the scan time. In patients with Moyamoya syndrome, CVR in the stenosis-affected flow territories (typically anterior-cerebral-artery, ACA, and middle-cerebral-artery, MCA, territories) was significantly lower than that in posterior-cerebral-artery (PCA), which typically has minimal stenosis, flow territories (0.12 ± 0.06%/mmHg vs. 0.21 ± 0.05%/mmHg, $p < 0.001$). BAT of the gas bolus was significantly longer (p=0.008) in ACA/MCA territories, compared to PCA, and the maps were consistent with the conventional contrast-enhanced CT perfusion method. FcMRI networks were robustly identified from the gas-inhalation MRI data after factoring out the influence of CO_2 and O_2 on the signal time course. The spatial correspondence between the gas-data-derived fcMRI maps and those using a separate, conventional fcMRI scan was excellent, showing a spatial correlation of 0.58 ± 0.17 and 0.64 ± 0.20 for default mode network and primary visual network, respectively. These findings suggest that advanced gas-inhalation MRI provides reliable measurements of multiple hemodynamic parameters within a clinically acceptable imaging time and is suitable for patient examinations.

1. Introduction

Medical imaging has provided a wealth of tools to evaluate the brain's vascular function. It plays an important role in the management of various cerebrovascular diseases and conditions, including arterial stenosis (Donahue et al., in press; Gupta et al., 2012; Mandell et al., 2008; Mikulis et al., 2005), stroke (Geranmayeh et al., 2015), small vessel disease (Greenberg, 2006), brain tumors (Lu et al., 2008), traumatic brain injury (Chan et al., 2015), and substance abuse (Han et al., 2008).

In current clinical practice, Computed Tomography Perfusion (CTP) and magnetic resonance imaging (MRI) with gadolinium-based dynamic susceptibility contrast (DSC) are often used to examine baseline vascular properties such as cerebral blood flow (CBF) (Detre et al., 1992; Wintermark et al., 2000), cerebral blood volume (CBV) (Ostergaard et al., 1996) and arterial arrival delay (Lv et al., 2013; Reichenbach et al., 1999). In situations where baseline measurements are found to be insufficient to make treatment decisions, a “stress-test”

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of brain vasculature is usually required to collect cerebrovascular reactivity information (Burt et al., 1992; Chollet et al., 1989; Pillai and Zaca, 2011). This requires a separate visit during which a vasoactive challenge, e.g. injection of acetazolamide, is applied and vascular reactivity is assessed using radionuclide methods such as Single-Photon-Emission-Computer-Tomography (SPECT) or Positron Emission Tomography (PET) (Hirano et al., 1994; Ogasawara et al., 2003). Additionally, resting-state functional MRI is being increasingly used in patients with cerebrovascular diseases to evaluate their brain function (Carter et al., 2012; Park et al., 2011), which requires another imaging exam in the patient's workup schedule.

A major limitation of the current clinical practice is that collection of all information described above requires separate exams and, sometimes, separate visits. This limitation increases patient burden and significantly escalates the cost of care. Moreover, PCT, SPECT and PET scans involve the exposure to ionizing radiation (Hirano et al., 1994; Ogasawara et al., 2003; Reichenbach et al., 1999; Wintermark et al., 2000). MRI based perfusion studies do not require ionizing radiation; however, the most commonly used MR contrast agent, gadolinium-based chelate, cannot be applied to patients with poor renal function, due to risk of development of nephrogenic systemic fibrosis (NSF) (Marckmann et al., 2006). Even for patients with healthy renal function, residuals of the injected gadolinium-based contrast agent (GBCA) can apparently cross the blood-brain-barrier and deposit in the brain (McDonald et al., 2015). While no clinical symptoms have been characterized, it nonetheless presents a safety concern when used repeatedly (http://www.fda.gov/Drugs/DrugSafety/ucm455386.htm). Due to the concerns of radiation safety and dose-restrictions, these methods are generally not used for disease surveillance and treatment monitoring. In all, current clinical practice of hemodynamic imaging of the brain could be improved in terms of efficiency, cost, and risk management.

Therefore, we aim to develop an MRI procedure to provide a one-stop-shop imaging of baseline CBV, cerebrovascular reactivity (CVR), bolus arrival time (BAT), and functional connectivity (FC) in one exam, with no exogenous contrast agent. The technique is based on concomitant modulation of CO_2 and O_2 content in inspired gas while collecting blood-oxygenation-level-dependent (BOLD) MRI images. Both CO_2 and O_2 are endogenous to the body, thus modulation within the typical physiological range is safe (Brueckl et al., 2006; Donahue et al., 2014; Spano et al., 2013). CO_2 is a potent vasodilator (Brian, 1998) and can cause perfusion (thereby BOLD MRI signal) changes in healthy vasculature (Bright et al., 2011; Donahue et al., in press; Han et al., 2008; Lu et al., 2011; Mandell et al., 2008; Marshall et al., 2014; Mikulis et al., 2005; Sheng et al., 2015; Yezhuvath et al., 2012). Short-duration O_2 inhalation does not cause vasodilation or vasoconstriction (Mark and Pike, 2012; Xu et al., 2012), but it can serve as an intravascular contrast agent and alters BOLD MRI signal via its effect on the concentration of deoxyhemoglobin. Thus, MRI signal changes associated with O_2 inhalation provides an estimation of baseline venous cerebral blood volume (vCBV) (Blockley et al., 2013; Bulte et al., 2007). In our technique, the timing of CO_2 and O_2 modulation was designed such that their contributions to BOLD signal could be separately assessed. Outputs of the technique include CVR, vCBV, BAT, and FC. CVR is obtained from BOLD response to arterial CO_2 change. Baseline vCBV is obtained from BOLD response to arterial O_2 change. BAT is obtained from the voxel-wise delay between the physiological (i.e. end-tidal CO_2 and O_2 measured from the exhaled air) and MRI signals. FC is obtained from the residual BOLD signal after factoring out the CO_2 and O_2 modulation effects.

In the present study, we provide the first evidence of the proposed multiparametric imaging technique in a group of healthy volunteers. We further demonstrate the clinical utility of the technique in detecting hemodynamic deficits in patients with Moyamoya syndrome, which is a cerebrovascular disease characterized by non-atherosclerotic intracranial stenosis. We compared the concomitant CVR and vCBV measurements to the results of separate CO_2 and O_2 modulation sessions. The BAT measurement was validated by comparison with similar measurements obtained by the current standard, CT Perfusion (CTP). FC maps obtained with our technique were compared with conventional resting-state fMRI scans. We hypothesized that the hemodynamic maps obtained from our method is comparable to those obtained from conventional methods.

2. Materials and methods

2.1. Participants

A total of sixteen human participants were studied, seven of which were healthy volunteers (4 males, age 29.4 ± 5.4 years, range 22-36 years) and nine of which were patients with clinical diagnosis of Moyamoya syndrome. The subjects had no contraindications to MRI scanning (e.g., pacemaker, implanted metallic objects, claustrophobia). Each of the Moyamoya patients received a CT perfusion scan as part of their clinical workup, which allowed the validation of the new method with an existing technique. Each subject gave informed written consent before participating in the study. The study protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center.

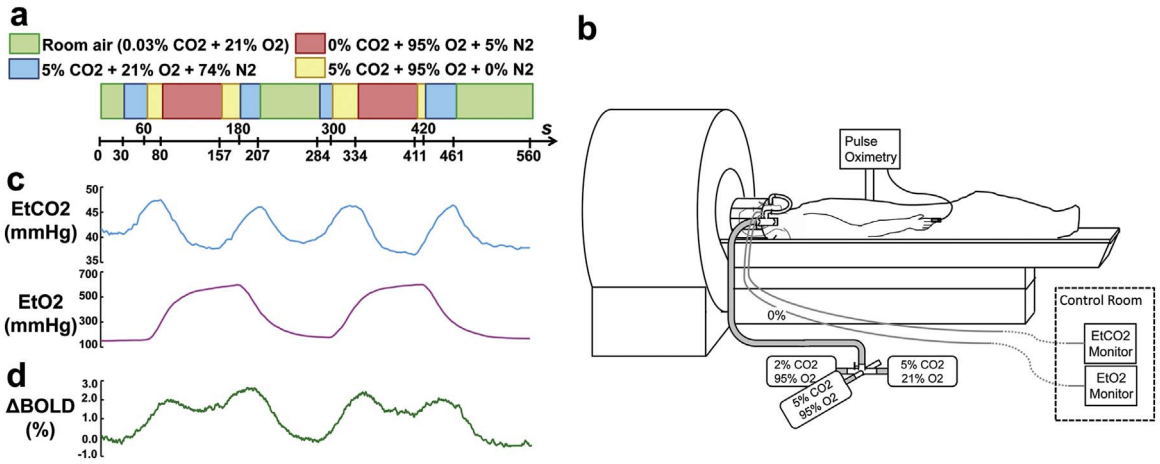

Fig. 1. Illustration of the concomitant CO_2 and O_2 modulation. (a) Paradigm of the gas inhalation. (b) Demonstration of the MRI-compatible gas delivery system. (c) Averaged $EtCO_2$, EtO_2 and ΔBOLD signal time courses from the healthy subjects.