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Multiplexed MRI Methods for Rapid Estimation of Global Cerebral Metabolic Rate of Oxygen Consumption

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Abstract

The global cerebral metabolic rate of oxygen (CMRO₂), which reflects metabolic activity of the brain under various physiologic conditions, can be quantified using a method, referred to as ‘OxFlow’, which simultaneously measures hemoglobin oxygen saturation in a draining vein (Y_v) and total cerebral blood flow (tCBF). Conventional OxFlow (Conv-OxFlow) entails four interleaves incorporated in a single pulse sequence – two for phase-contrast based measurement of tCBF in the supplying arteries of the neck, and two to measure the intra- to extravascular phase difference in the superior sagittal sinus to derive Y_v [Jain et al, JCBFM 2010]. However, this approach limits achievable temporal resolution thus precluding capture of rapid changes of brain metabolic states such as the response to apneic stimuli. Here, we developed a time-efficient, multiplexed OxFlow method and evaluated its potential for measuring dynamic alterations in global CMRO₂ during a breath-hold challenge. Two different implementations of multiplexed OxFlow were investigated: 1) simultaneous-echo-refocusing based OxFlow (SER-OxFlow) and 2) simultaneous-multi-slice imaging-based dual-band OxFlow (DB-OxFlow). The two sequences were implemented on 3T scanners (Siemens TIM Trio and Prisma) and their performance was evaluated in comparison to Conv-OxFlow in ten healthy subjects for baseline CMRO₂ quantification. Comparison of measured parameters (Y_v , tCBF, CMRO₂) revealed no significant bias of SER-OxFlow and DB-OxFlow, with respect to the reference Conv-OxFlow while improving temporal resolution two-fold (12.5 versus 25 s). Further acceleration shortened scan time to 8 and 6 seconds for SER and DB-OxFlow, respectively, for time-resolved CMRO₂ measurement. The two sequences were able of capturing smooth transitions of Y_v , tCBF, and CMRO₂ over the time course consisting of 30 seconds of normal breathing, 30 seconds of volitional apnea, and 90 seconds of recovery. While both SER- and DB-OxFlow techniques provide significantly improved temporal resolution (by a factor of 3 – 4 relative to Conv-OxFlow), DB-OxFlow was found to be superior for the study of short physiologic stimuli.

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Keywords

magnetic resonance imaging (MRI); cerebral blood flow (CBF); hemoglobin oxygen saturation; cerebral metabolic rate of oxygen (CMRO₂); simultaneous-echo-refocusing (SER); simultaneous-multi-slice (SMS) imaging

Introduction

The cerebral metabolic rate of oxygen consumption (CMRO₂), unlike cerebral blood flow (CBF) or blood-oxygen-level-dependent (BOLD) contrast, directly reflects aerobic metabolism of glucose for brain energy generation, and thus is an important marker for physiologic or pathologic states of the brain. Changes in CMRO₂ under physiologic challenges such as hypercapnia (Chen and Pike, 2010; Jain et al., 2011), hypoxia (Xu et al., 2012), and apnea (Rodgers et al., 2013) have been investigated. Alterations in resting-state CMRO₂ have been reported in patients with neurologic disorders such as Alzheimer's disease (Ishii et al., 1996), Parkinson's disease (Borghammer et al., 2010), and multiple sclerosis (Ge et al., 2012). Additionally, it has been shown that CMRO₂ varies with developmental stage of the neonatal brain (Liu et al., 2014) as well as aging (Peng et al., 2014). Thus, accurate and reliable quantification of CMRO₂ is important for investigation of neuro-pathophysiologic conditions and provide insight on the interrelationships between neuronal activity, hemodynamics, and metabolism.

The rate of brain oxygen consumption (CMRO₂ in units of oxygen consumed per unit time and tissue mass) is typically described in terms of a conservation of mass equation (Fick's principle (Kety and Schmidt, 1945)), as:

$$\text{CMRO}_2 = C_a \cdot \text{CBF} \cdot (Y_a - Y_v) \quad (1)$$

where C_a is the oxygen carrying capacity of arterial blood in $\mu\text{Mol}/100\text{ml}$, CBF is in units of blood volume per unit time and tissue mass, and Y_a and Y_v are the percent hemoglobin oxygen saturation levels of arterial and venous blood, respectively, ranging from 0 to 100 %. Thus, both brain cerebral flow and arteriovenous difference in O₂ saturation need to be ascertained. In positron emission tomography (PET)-based CMRO₂ mapping (Ito et al., 2005; Mintun et al., 1984), radioactive $^{15}\text{O}_2$ -labeled gas is inhaled for measurement of oxygen extraction fraction ($\text{OEF} = (Y_a - Y_v)/Y_a$), while H_2^{15}O -labeled water injected through a vein allows for CBF quantification. While generally being regarded as the gold standard method, PET-based CMRO₂ quantification is not used widely because of high radiation exposure, long imaging time, as well as the complexity and cost of the procedure.

More recently, MRI-based, non-invasive techniques for global CMRO₂ quantification have been introduced (Jain et al., 2010; Xu et al., 2009). One of the methods builds on an approach referred to as 'T₂-relaxation-under-spin-tagging' (TRUST) (Lu and Ge, 2008), in which T₂ relaxation of labeled venous blood is estimated and subsequently converted to Y_v according to a calibration curve obtained *in vitro*. In combination with phase-contrast (PC) MRI for measurement of total CBF (tCBF) that enters the brain, CMRO₂ is obtained via

Fick's equation. The method has since demonstrated its potential for reliable and reproducible quantification of global CMRO₂ (Liu et al., 2013). However, the relatively long acquisition times resulting from the need for measurements with multiple T_2 preparation times, somewhat limits its utility in dynamic studies involving physiologic challenges or functional tasks. Additionally, since data for measurements of Y_v and tCBF are acquired in a separate, sequential manner, TRUST-derived CMRO₂ may not be applicable if the steady-state brain metabolism is not maintained over the two imaging sessions.

An alternative approach to MRI-based, quantitative assessment of global CMRO₂, referred to as 'OxFlow' (Jain et al., 2010), is based on susceptibility-based oximetry (Fernández-Seara et al., 2006) that yields Y_v by measuring the blood water protons' phase in a large draining vein relative to surrounding brain tissue, which serves as a calibration-free reference. OxFlow enables quantification of global CMRO₂ within a single imaging pulse sequence by incorporating susceptibility-based oximetry for measuring Y_v of superior sagittal sinus (SSS) in a brain slice and PC MRI in the feeding neck arteries. The method has subsequently been used to study the effect of hypercapnia at a temporal resolution of 30 seconds (Jain et al., 2011). Higher temporal resolution for investigating global CMRO₂ changes in response to an apneic challenge was achieved with a single-slice version of OxFlow (Rodgers et al., 2013), in which blood flow in the SSS (SSSBF) was measured along with Y_v in the same vein and imaging slice, and subsequently converted to tCBF using pre-calibrated ratio of SSSBF to tCBF. The authors found the ratio between SSSBF and tCBF not to vary significantly over the time course of a gas breathing study in healthy subjects (Rodgers et al., 2013). However, this may not hold true in patients with hemodynamic impairments.

Multiplexed data acquisition for multi-slice MR imaging (Feinberg and Setsompop, 2013), which can be achieved via simultaneous multi-slice (SMS) (Larkman et al., 2001) or simultaneous echo refocusing (SER) (Feinberg et al., 2002), is widely used, in various applications, including arterial spin labeling (Feinberg et al., 2013; Kim et al., 2013), diffusion imaging (Feinberg et al., 2010; Setsompop et al., 2012), and fMRI (Feinberg et al., 2010; Moeller et al., 2010). In the SMS technique, two or more slices are simultaneously excited by a single, multi-band radio-frequency (RF) pulse, leading to echo formation at the same time point. Overlapping signals are then resolved using parallel imaging algorithms (Griswold et al., 2002; Pruessmann et al., 1999) by exploiting data redundancy in multiple receiver coils. In contrast, the SER method applies a series of single-band RF pulses sequentially in such a manner as to achieve spin refocusing originating from different slices at distinct time points with a short inter-echo spacing.

Since OxFlow acquires data at two different scan locations in a slice-interleaved fashion, multiplexing can be readily applied for enhancing efficiency of data acquisition. Here, we aimed to develop two multiplexed OxFlow strategies based on SMS and SER schemes, respectively, and investigated their performance for global CMRO₂ quantification. Baseline CMRO₂ values were measured using the two multiplexed OxFlow methods and statistically compared to those derived from Conv-OxFlow. Finally, time-varying global CMRO₂ under an apneic challenge was investigated to evaluate the method's performance in response to a physiologic stimulus.

Materials and Methods

1. Principle of OxFlow for global CMRO₂ quantification

The fundamental principle of OxFlow is to simultaneously measure both Y_v and tCBF, yielding global CMRO₂ from the Fick's relationship (Eq. (1)). Y_v is derived in a large draining vein (internal jugular vein or SSS) (Fernández-Seara et al., 2006) by quantifying the magnetic susceptibility of the vein's blood relative to surrounding tissue, as given by:

$$\Delta\chi = Hct \cdot \Delta\chi_0 \cdot (1 - Y_v) \quad (2)$$

Here, Hct is the hematocrit and χ_0 is the susceptibility difference between fully deoxygenated and fully oxygenated red blood cells ($\chi_0 \sim 0.27$ ppm in CGS units (Jain et al., 2012; Spees et al., 2001)). Provided that the blood vessel can be approximated as long straight cylinder, the induced local magnetic field shift B can be expressed as (Schenck, 1996):

$$\Delta B = \frac{2\pi}{3} B_0 \Delta\chi (3\cos^2\theta - 1) \quad (3)$$

Here, B_0 is the strength of the static magnetic field and θ is the angle of the vessel with respect to B_0 . By acquiring two echoes with an inter-echo time of TE , B is obtained as $B = \phi / \gamma TE$ where ϕ is the phase difference between the two echoes and γ is the gyromagnetic ratio. In Eq. (3), the term $1/3$ accounts for the effects of the Lorentzian sphere (Chu et al., 1990) while B is in CGS units. Y_v is quantified using Eqs. (2,3) from a measurement of the intra to extravascular difference in ϕ . The model underlying Eq. (3) had previously been validated theoretically and experimentally (Langham et al., 2009a; Li et al., 2012) for various vessels with different geometries.

The conventional OxFlow (Conv-OxFlow) pulse sequence (Fig. 1a) (Jain et al., 2010), which consists of four interleaves corresponding to two slice locations (Fig. 1d), provides both tCBF and Y_v from neck and head images, respectively, thereby enabling global CMRO₂ quantification with a single pulse sequence. However, due to the application of four interleaves the temporal resolution of Conv-OxFlow is limited to ~ 30 seconds (Jain et al., 2011), making it challenging to capture relatively rapid changes in brain metabolic activity, as for example, in response to apneic events. To address this limitation, we propose to incorporate multiplexed MRI methods into the OxFlow principle in the next section.

2. Multiplexed OxFlow

The fundamental idea of multiplexing in multi-slice MRI (Feinberg and Setsompop, 2013) is that imaging components for RF excitation, gradient encoding/spoiling, and data acquisition, are partially (SER) or fully (SMS) shared by magnetization created at multiple slice locations, allowing for rapid volumetric imaging. Since a global CMRO₂ value is ascertained from dual-slice image information in the OxFlow method, we conjectured that multiplexing data acquisition of OxFlow would substantially enhance the temporal resolution and thus

might be beneficial in dynamic CMRO₂ experiments. In the following subsections, two possible implementations for multiplexed OxFLOW are described; 1) SER-based OxFLOW (SER-OxFLOW) and 2) SMS imaging-based dual-band OxFLOW (DB-OxFLOW).

As in Conv-OxFLOW, both the multiplexed OxFLOW methods achieve flow sensitization along the slice selection (SS) direction by time-shifting the last gradient pulse of the velocity compensation module for a given value of velocity encoding (VENC) (Fig. 1). Compared with bipolar gradients based flow-encoding which results in accumulation of eddy-current induced phase errors upon image subtraction, the gradient-sliding scheme employed here minimizes such errors in the velocity calculation at the expense of slightly increased flow-encoding duration (Thompson and McVeigh, 2003). Additionally, the readout polarity of two echoes for Y_v quantification is identical to keep their velocity sensitivity the same in the readout direction.

2.1. SER-OxFLOW—A timing diagram of the SER-OxFLOW pulse sequence is shown in Fig. 1b. A pair of excitation RF pulses are successively applied to brain and neck slices. During the short inter-RF pulse interval of T_{prep} , velocity compensation is achieved in the slice-selection axis while a de-phasing gradient (G_{prep}) is inserted in the frequency encoding (FE) direction to refocus magnetization in the head slice after data sampling in the neck slice. Following the second RF pulse, three consecutive gradient echoes are generated pertaining to neck (echo 1) and head (echoes 2 and 3), the latter separated by TE (Fig. 1b). To ensure adequate temporal separation between the first two echoes and thus avoiding image artifacts resulting from signal interference, a dephasing gradient pulse (G_d) is placed in between the two signal encoding windows while the zeroth moment of G_{prep} (A) is set to (Fig. 1b):

$$A=B+C+D \quad (4)$$

$$B=\pi/\gamma\Delta x_n, D=\pi/\gamma\Delta x_h \quad (5)$$

where x_h and x_n are the pixel sizes of the neck and head slices in the FE direction, respectively, and C is the zeroth moment of G_d .

Since the two echoes in the head slice are acquired with uni-polar readout gradient pulses, they have identical sensitivity to flow in all directions within each TR. Thus, corresponding signals between flow-compensation and flow-encoding blocks were averaged prior to data processing for signal-to-noise ratio (SNR) enhancement.

2.2. Dual-band OxFLOW—Figure 1c shows the pulse sequence diagram of dual-band OxFLOW. The RF pulse, which is to simultaneously excite both neck and head slices, is designed as a linear combination of two single-band RF pulses for the two slice locations as:

$$RF_{db,n}(t)=RF_{neck,n}(t)+(-1)^n \cdot RF_{head,n}(t) \cdot e^{i\Delta\omega t} \quad (6)$$

where n is the RF pulse index, ω is the modulation frequency given as $\omega = \gamma G_z z$ with z being the inter-slice spacing and G_z the SS gradient amplitude. The alternating polarity of RF_{head} over the entire pulse train, which shifts the head slice by one half of field-of-view (FOV) along the phase encoding (PE) direction, is to exploit sensitivity variations of receive coils along both PE and SS directions during the slice separation process, thereby reducing geometry-factor-induced noise amplifications in resolved images (Breuer et al., 2005).

The acquired, sliced-aliased image signal at each voxel location and receive coil can be written as:

$$I_{db,l}(x, y) = C_{neck,l}(x, y) \cdot \rho_{neck}(x, y) + C_{head,l}(x, y + FOV_y/2) \cdot \rho_{head}(x, y + FOV_y/2) \quad (7)$$

where x and y are spatial positions on FE and PE axes, l is the coil index, C is the receive coil sensitivity, and ρ is the unknown voxel profile in each slice. A matrix equivalent to Eq. (7) is formulated in each voxel:

$$\begin{aligned} I &= C\rho \\ \begin{bmatrix} I_{db,1}(x, y) \\ I_{db,2}(x, y) \\ \vdots \\ I_{db,N_c}(x, y) \end{bmatrix} &= \begin{bmatrix} C_{neck,1}(x, y) & C_{head,1}(x, y + FOV_y/2) \\ C_{neck,2}(x, y) & C_{head,2}(x, y + FOV_y/2) \\ \vdots & \vdots \\ C_{neck,N_c}(x, y) & C_{head,N_c}(x, y + FOV_y/2) \end{bmatrix} \begin{bmatrix} \rho_{neck}(x, y) \\ \rho_{head}(x, y + FOV_y/2) \end{bmatrix} \end{aligned} \quad (8)$$

Where N_c is the number of receive coil elements. Then, the solution of Eq. (8) can be found by solving a weighted linear least squares problem as described in (Pruessmann et al., 1999):

$$\rho_e = (C^\dagger \Psi^{-1} C)^{-1} C^\dagger \Psi^{-1} I_e, \quad e = TE_1, TE_2 \quad (9)$$

where ρ_e are the disentangled slice images at each TE, $\dagger$ is the adjoint operator (complex conjugate transpose), Ψ is the noise covariance matrix, and I_e are the acquired images at each TE. Prior to dual-band imaging, single-band, calibration data were acquired for measurements of C and Ψ . Since the level of flow encoding is identical between neck images at TE_1 and TE_2 within each TR, those two were averaged prior to velocity calculation. Additionally, the individual brain images obtained with flow-encoding and flow-compensation were averaged for each TE as in SER-OxFlow.

3. Experiments and analyses

3.1. Experimental protocols—All experimental studies performed in this work were approved by the Institutional Review Board of the University of Pennsylvania and informed written consent was obtained from all study participants (seven males; three females; age (mean $\pm$ standard deviation (SD)) = 35 ± 7 years).

The three imaging methods, Conv-, SER-, and DB-OxFlow, were implemented in SequenceTree software (Magland et al., 2016). Unless otherwise stated, the following imaging parameters were used for all three sequences: FOV = $208 \times 208 \text{ mm}^2$, slice thickness = 5 mm, matrix size = 208×208 , bandwidth per pixel = 481 Hz, VENC = 60 cm/s, and TE = 3.71 ms. TR_{prep} in SER-OxFlow was set to 2.3 ms.

Prior to running OxFlow, a time-of-flight MRA scan was performed in each subject. Based on the resulting vessel-scout image (Fig. 1d), we manually selected a neck slice above the carotid bifurcation and a head slice with the SSS approximately orthogonal to the axial plane, followed by calculation of the tilt angle θ in Eq. (3).

3.2. Data processing—Data were processed in Matlab (Mathworks Inc. Natick, MA). A blood flow velocity map in the neck slice was calculated as $v = \eta \cdot \text{VENC}/\pi$ where η is the phase difference between velocity encoded and compensated images. The derived velocities in the four feeding arteries, left/right internal carotid artery (ICA) and left/right vertebral artery (VA), were converted to tCBF and normalized to brain mass obtained from an MP-RAGE image dataset (Mugler and Brookeman, 1990). In the brain slice, the effect of macroscopic magnetic field on the phase difference of images at TE₁ and TE₂ (ϕ) was removed as described in (Langham et al., 2009b), yielding a background field corrected phase map (ϕ_{corr}). Subsequently, the pixel average of ϕ_{corr} in SSS was subtracted from that in a surrounding brain tissue region to yield Y_v of SSS using Eqs. (2,3) (Jain et al., 2010). Hb was measured via fingerprick test using HemoCue Hb 201⁺ (HemoCue, Ängelholm, Sweden). Finally, global CMRO₂ was computed from the derived tCBF and Y_v values via Eq. (1).

3.3. Baseline CMRO₂—To evaluate the performance of the two fast CMRO₂ sequences, data was acquired in ten healthy subjects at 3 T (TIM Trio; Siemens Medical Solutions, Erlangen, Germany) using Conv-, SER-, and DB-OxFlow techniques with a 16-channel head/neck coil for signal reception. For each method, five successive scans were done in the same imaging session to obtain intra-subject mean and SD of quantified parameters. Imaging parameters specific to Conv-OxFlow were: TR_{head} = TR_{neck} = 30ms, $\alpha = \beta = 22^\circ$, temporal resolution = 25 sec, and imaging time = 125 sec. Parameters specific to SER- and DB-OxFlow: TR = 30 ms, $\alpha = \beta = 16^\circ$, temporal resolution = 12.5 sec, and imaging time = 62.5 sec. Five sets of images were generated for a representative subject in each method: magnitude of neck slice ($|\rho_{\text{neck}}|$), v , magnitude of head slice at TE₁ ($|\rho_{\text{head,TE1}}|$), ϕ , and ϕ_{corr} . Subsequently, the extracted values for Y_v , tCBF, and CMRO₂ from each method in the ten subjects were tabulated and subjected to repeated measures analysis of variance (RM-ANOVA) using JMP (SAS, Cary, NC). Additionally, correlation analysis was performed between Conv- and SER-OxFlow and between Conv- and DB-OxFlow for each of the three parameters derived in the ten subjects.

To ascertain the maximally achievable temporal resolution of multiplexed OxFlow methods yielding parameter estimates comparable to those obtained with the reference technique (Conv-OxFlow with 25 seconds of temporal resolution), data was additionally acquired in all ten subjects using SER-OxFlow with TR = 25 and 20 ms and DB-OxFlow with TR = 25, 20, and 15 ms, respectively. Flip angles were optimized accordingly in each experiment to $\alpha =$

$\beta = 14^\circ$ and 12° in SER-OxFlow and $\alpha = \beta = 14^\circ, 12^\circ$ and 10° in DB-OxFlow. Thus, eight sets of data were collected: reference, SER-OxFlow (temporal resolution = 12.5, 10.4, 8.3 sec), and DB-OxFlow (temporal resolution = 12.5, 10.4, 8.3, 6.2 sec). For each method, v and ϕ_{corr} maps were generated in a representative subject for visual comparison while the derived parameters, Y_v , tCBF, and CMRO₂, in all subjects were scatter plotted for quantitative comparison.

3.4. Dynamic CMRO₂ under apneic challenge—The feasibility of the proposed, multiplexed OxFlow methods for a time-resolved measurement of global CMRO₂ was investigated at 3 T (Magnetom Prisma; Siemens Medical Solutions, Erlangen, Germany) in three male subjects using a 20-channel head/neck receiver coil. All imaging parameters were kept identical to those above, but based on results in the above section TR was adjusted in each method to yield a temporal resolution of 8 and 6 seconds in SER- and DB-OxFlow, respectively. Flip angles were set to 12° (SER-OxFlow) and 10° (DB-OxFlow). VENC was set to 80 cm/s in each method.

An apneic challenge paradigm was implemented consisting of three successive periods of normal-breathing (referred to as baseline), apnea, and recovery, under visual and auditory cueing. During the last seven seconds of the baseline, the subjects were instructed to breathe in, breathe out, and hold to smoothly transition to an apneic state. Durations of the three stages were: 32, 32, and 88 seconds for SER-OxFlow and 30, 30, and 90 seconds for DB-OxFlow. The three blocks were consecutively repeated four times during 10 minutes of data acquisition in each method. Arterial oxygen saturation (Y_a) was also continuously monitored from a fingertip using a digital pulse oximeter (Medrad Veris; Bayer Healthcare, Whippany, NJ). Since it takes approximately seven seconds for blood to transport from the lungs to brain or peripheral body locations (Batzel et al., 2007), the arterial resaturation in the brain and fingers can be expected to be delayed by the same amount after the cessation of breath-hold. Thus, the entire time course of the measured Y_a was shifted accordingly to correct for the unknown temporal delay in Y_a measurements as done previously (Rodgers et al., 2013).

Data averaged over the four repeats was subsequently processed to produce time courses for Y_a , Y_v , tCBF, and CMRO₂ for each method. Time points during the first 24 seconds of baseline were employed to calculate average of the four quantities at resting state. CMRO₂ at two time points at the end of the apneic period was averaged to represent its end-apneic response. For a representative subject, spatial maps of v and ϕ_{corr} were also generated at time points that correspond to baseline, minimum and maximum of derived tCBF and Y_v values over the entire time course, respectively.

Results

Figure 2 shows five sets of images ($|\rho_{\text{neck}}|$, v , $|\rho_{\text{head,TE1}}|$, ϕ , ϕ_{corr}) in a representative subject acquired using Conv- (Figs. 2a–e), SER- (Figs. 2f–j), and DB- (Figs. 2l–p) OxFlow methods, respectively. In DB-OxFlow, the initially acquired, slice-overlapped image is additionally shown in Fig. 2k. As compared with Conv-OxFlow, both SER- and DB-OxFlow methods, despite a two-fold reduction of imaging time, produced visually similar contrast in both v and ϕ_{corr} maps while yielding quantitatively comparable parameter values.

Table 1 lists the functional parameters, Y_v , tCBF, and CMRO₂, in the ten study subjects, derived from Conv-, SER-, and DB-OxFlow methods. Figure 3 represents corresponding scatter plots of Y_v (Fig. 3a), tCBF (Fig. 3b), and CMRO₂ (Fig. 3c). Group-averages ($\pm$ SD) of the measured quantities were: $Y_v = 68.1 \pm 2.7$, 69.3 ± 3.1 , and 68.7 ± 2.5 %; tCBF = 49.9 ± 4.6 , 49.8 ± 3.9 , and 50.0 ± 3.9 ml/min/100g; and CMRO₂ = 132.4 ± 12.9 , 127.4 ± 12.8 , and 130.7 ± 14.0 μ mol/min/100g (Conv-, SER-, and DB-OxFlow, respectively). RM-ANOVA indicated that none of the parameters were different between the three methods (all $p > 0.1$). Figure 4 shows correlation plots comparing Conv- vs SER- OxFlow (Figs. 4a–c) and Conv- vs DB-OxFlow (Figs. 4d–f) for quantified Y_v (Figs. 4a,d), tCBF (Figs. 4b,e), and CMRO₂ (Figs. 4c,f) for all ten subjects. Strong correlations are observed for all three correlations with R^2 values ranging from 0.86 to 0.96 yielding intra-class correlation coefficients (ICC) 0.89 to 0.96.

Figure 5 shows eight sets of v and ϕ_{corr} maps in one subject for TR values ranging from 15 to 30 ms (in 5 ms increments) for SER- (Figs. 5b–d) and DB- (Figs. 5e–h) OxFlow along with those in Conv-OxFlow (Fig. 5a). For the eight sets of data, the measured Y_v , tCBF, and CMRO₂ values in the ten subjects are plotted in Fig. 6. The three quantities derived from both SER- and DB-OxFlow methods are consistent over the entire range of TR values (temporal resolutions), and agree well with reference values. Thus, it is inferred that the use of the shortest TR values (20 ms for SER-OxFlow and 15 ms for DB-OxFlow) is a feasible option for dynamic CMRO₂ studies.

Figure 7 shows three pairs of v and ϕ_{corr} distributions in a subject along with group-averaged time-courses of four physiologic quantities (Y_a , Y_v , tCBF, CMRO₂) under apneic challenges, derived from SER- (Figs. 7a–d) and DB- (Figs. 7e–h) OxFlow. Alterations of brain metabolism in response to apneic stimuli are highlighted in the functional maps with visually apparent contrast changes. Further, the time-course plots capture smooth transitions in the physiologic quantities at the temporal resolutions of 8 (SER-OxFlow) and 6 (DB-OxFlow) seconds. The derived functional parameters for each study subject are provided in Table 2. Arterial oxygen saturation was slightly reduced during the stimulus in all subjects. Group-averaged Y_v , tCBF, and CMRO₂ estimates were increased by 6.4 ± 0.4 %, 34.4 ± 2.7 %, and 7.9 ± 4.9 % in SER-OxFlow and 7.2 ± 0.8 %, 26.8 ± 2.3 %, and 7.4 ± 3.8 % in DB-OxFlow, respectively.

Discussion and Conclusion

This work introduces multiplexed MRI-based, rapid OxFlow imaging strategies for measuring global CMRO₂ alterations under an apneic challenge. Both proposed methods, SER- and DB-OxFlow, when compared with conventional OxFlow, have been found to shorten imaging time by 50% without loss of measurement accuracy as demonstrated in Fig. 2 and Table 1. The proposed methods utilize imaging components in a highly efficient manner allowing signal encoding for two slices of interest to occur simultaneously or in rapid succession, thereby achieving a temporal resolution of 6 – 8 seconds, enabling investigation of brain metabolic reactivity to short-time stimuli by capturing changes in hemodynamic parameters in absolute physiologic units. The enhanced temporal resolution achievable with the new OxFlow techniques should be beneficial in the study of a variety of

physiologic processes. A case in point is breath-hold based calibrated BOLD (Kastrup et al., 1999), which requires high temporal resolution since volitional apnea is of intrinsically transient nature (i.e. no steady-state is attainable). In general, the transient response during the transition between two steady states in gas breathing experiments cannot be observed due to inadequate temporal resolution (Jain et al., 2013). Further, in many study populations CMRO₂ measurements are hampered by image corruption caused by involuntary subject motion such as in infants who would otherwise have to be sedated (Jain et al., 2013; Liu et al., 2014).

In the RF-spoiled GRE pulse sequence employed in all three OxFlo methods of the present work, elevated temporal resolution resulting from shortened TR inevitably is traded for reduced SNR in both magnitude and phase images, which may adversely affect precision in parameter estimation. Additionally, systematic errors may also be added to the non-ECG-gated PC velocity measurement due to inflow-induced amplitude modulation in k-space along the PE direction. In spite of such concerns the results in Fig. 6 imply that there is no significant bias in the parameter values at TRs as short as 15 ms. The consistent tCBF estimates over the range of TR values is understood by the observation reported in (Bakker et al., 1995) that as long as the flow waveform is monophasic as in neck blood vessels the inflow effect should be negligible in time-averaged velocity measurements using RF-spoiled GRE imaging with flip angles less than 20°.

An alternative accelerated OxFlo (referred to as 'F-OxFlo') method has recently been reported (Barhoum et al., 2015a). The method uses three interleaves (instead of the four in Conv-OxFlo): 1) flow-compensation and 2) flow-encoding in the neck slice, and 3) a dual-echo acquisition in the head, achieving a temporal resolution of 8 seconds for quantification of time-varying CMRO₂ responses to apneic events. The three-interleave-based approach inevitably causes an imbalance in the steady state due alternation in effective TR (TR_{eff}) between the interleaves 1 and 2. However, as velocity quantification involves measuring the phase of flowing blood, the effect of alternating TR_{eff} on estimation accuracy may not be substantial. Furthermore, the authors did not notice systematic errors in the velocity measurement over a range of TR_{eff} values (Barhoum et al., 2015a). Both SER- and DB-OxFlo methods are potentially superior to F-OxFlo. First, using a constant TR_{eff} over the entire pulse train is more straightforward for velocity quantification; second, it allows averaging of brain signals over flow-compensated and flow-encoded portions of the sequence for SNR enhancement. Nevertheless, an extensive comparison among the methods remains for future investigation. It is further noted that the observed 7.1 % increase in CMRO₂ at end-apnea reported for F-OxFlo is close to that obtained with SER-OxFlo (7.9 %) and DB-OxFlo (7.4 %) in this work (Table 2). These observations lend further credence to the notion that volitional apnea is a hypercapnic-hypoxic stimulus, in accordance with the findings of 6.0 % increase in CMRO₂ at end-apnea by (Rodgers et al., 2013).

In Fig. 7, the peak of tCBF and Y_v coincides in time roughly with the minimum of Y_a, in accordance with the temporal delay of circulatory transport between the lungs and brain by approximately seven seconds (Batzel et al., 2007). Our results are consistent with previous apneic studies (Barhoum et al., 2015b; Rodgers et al., 2013), and possible explanations for

the CMRO₂ increases during apneic stimuli have been provided in (Rodgers et al., 2013), i.e., brain's energy reserves for the anticipated apneic period to generate additional ATP. Nevertheless, the physiological mechanisms underlying our observations warrant further scrutiny outside the scope of the present work.

Both the SER- and DB-OxFlow methods are shown to be capable of a high temporal resolution for time-resolved brain oximetry, with the latter being faster by 33% as a result of simultaneous excitation and acquisition of dual-slice signals. Also worth noting is that since current OxFlow implementations use low flip angles, the RF peak amplitude for DB excitation remains well within hardware limits. Thus, the RF pulse derived from Eq. (6) was directly applied in DB-OxFlow without any modifications to reduce the peak amplitude as required in many SMS imaging applications (Barth et al., 2016). Further, the two slices of interest in the OxFlow (neck and head) are spaced relatively far apart from each other (typically ~ 120 mm), leading to favorable conditions for matrix inversion (Eq. (9)) due to more likely differing receiver sensitivity profiles along the slice direction. However, in DB-OxFlow residual aliasing artifacts and noise signals still exist to some extent in the slice-resolved images (Fig. 2). These may result from inconsistencies in coil maps between the calibration and actual data acquisition, or coil geometry-factor penalties. More advanced multi-band reconstruction techniques (Cauley et al., 2014; Park and Park, 2016) may further attenuate the undesired residual signals, albeit at the cost of computational complexities. Nevertheless, as demonstrated by the data in Figs. 3 and 6 quantification accuracy was not significantly affected.

In the present work, fully Nyquist-sampled k-space was acquired at each time frame. To further enhance temporal resolution, it should be possible to incorporate in-plane under-sampling into the proposed multiplexed OxFlow sequences. In recent implementations of single-slice OxFlow (Rodgers et al., 2013; Rodgers et al., 2016), a temporal resolution of 2 – 3 seconds was achieved for mapping apnea-induced CMRO₂ alterations by employing view-sharing among neighboring time frames for under-sampling high spatial-frequency data. The observation that justifies high frame-rate CMRO₂ quantification is that the hemodynamic response to events such as apnea is near-global. Additionally, corresponding variations of physiologic quantities are very smooth over the time course as shown in Figs. 7d,h. Thus, the proposed method, in combination with an optimization of k-t sampling trajectory and fast dynamic MRI methods exploiting spatiotemporal correlations (Jung et al., 2009; Lingala et al., 2011), would be worthwhile to pursue. This will also permit a thorough validation of the assumption (a constant ratio between SSSBF and tCBF) made in the single-slice OxFlow methods (Rodgers et al., 2013; Rodgers et al., 2016) in various patients since the proposed multiplexed method should allow extraction of SSSBF from head images in addition to tCBF measurement in the neck.

In conclusion, our work demonstrates the potential of multiplexed MRI-based, rapid time-resolved CMRO₂ quantification at rest and during apneic challenges via direct measurements of tCBF and Y_v from neck and brain locations, respectively. While both new methods, when compared to Conv-OxFlow, are robust alternatives for substantially reducing data acquisition time without loss of estimation accuracy, DB-OxFlow may be the method of choice for high-temporal-resolution quantitative brain oximetry in the presence of short

physiologic stimuli. Lastly, temporal resolution may be further augmented by exploiting spatiotemporal data redundancy in dynamic OxFlo studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Multiplexed MRI based, two global CMRO₂ quantification methods were
- Both methods were applied for baseline CMRO₂ measurements in 10 subjects.
- Compared to conventional method, imaging speed was enhanced 3 – 4 times without loss of accuracy.
- Dynamic CMRO₂ under apneic challenge was attained at 6 – 8 s temporal resolution.
- As apneic response, 7 – 8 % increase in global CMRO₂ was observed in both methods.

Fig 1.

Pulse sequence configuration of Conv-OxFlow (a), the proposed, SER-OxFlow (b) and DB-OxFlow (c), and location of the two slices of interest (d; neck and head). α, β : flip angles for the neck and head slices, ϕ_n : phase of n-th RF pulse, GS: slice selection gradient, GP: phase-encoding gradient, and GR: frequency-encoding gradient. Note that in SER-OxFlow the condition $A=B+C+D$ was met to avoid signal interference between the two slices while in DB-OxFlow RF phase cycling by π radians was applied to the head slice to reduce geometry-factor-induced noise amplification during image reconstruction.

Fig 2.

Five sets of images in a representative subject acquired using Conv- (top), SER- (middle), and DB- (bottom) OxFLOW methods: $|\rho_{\text{neck}}|$ (a,f,l) and v (b,g,m) for the neck slice, $|\rho_{\text{head,TE1}}|$ (c,h,n), ϕ (d,i,o), and ϕ_{corr} (e,j,p) for the brain slice. Measured velocity of the four arteries (left/right ICA and left/right VA) feeding the brain is given in v maps while quantified Y_v of SSS in ϕ_{corr} . Note that in DB-OxFLOW, the slice-overlapped image in k was initially acquired and then subsequently resolved to yield separate neck and brain images in the rest. Note also that the ϕ map in o can be considered as the offset phase relative to the pre-calibrated coil sensitivity, which is subsequently removed upon phase correction (p). Line profiles across the SSS in both $|\rho_{\text{head,TE1}}|$ and ϕ_{corr} for all three methods are given in the Supplementary Material.

Fig 3.

Scatter plots of Y_v (a), tCBF (b), and CMRO₂ (c) at resting state in ten subjects, derived from Conv-, SER-, and DB-OxFlow methods, respectively. In each diamond, vertical vertices represent 95 % confidence interval (CI), while top and bottom horizontal lines are overlap marks ($\sqrt{2}CI/2$) and the middle one a group mean. Three horizontal lines in each box indicate 75th quantile, median, and 25th quantile, respectively, from the top to bottom, while whiskers extending outside from a box are maximum and minimum of each population excluding outliers. Note that statistical comparison of the three OxFlow techniques using RM-ANOVA revealed no significant differences in all the three quantities ($p > 0.1$).

Fig 4.

Correlations comparing Conv-OxFlow vs SER-OxFlow (a–c) and Conv-OxFlow vs DB-OxFlow (d–f) for measured Y_v (a,d), tCBF (b,e), and global CMRO₂ (c,f) in ten subjects. Solid circle and error bar represents mean and SD of corresponding quantity measured over five successive repeats in each subject. Dotted line with corresponding equation is a linear regression of ten data points in each subplot. Note that all pair-wise comparisons yield strong correlations ($0.86 \leq R^2 \leq 0.96$ and $0.89 \leq \text{ICC} \leq 0.96$).

Fig 5.

A pair of v and ϕ_{corr} maps in neck and brain slice locations for a representative subject, acquired using Conv- (a), SER- (b–d), and DB- (e–h) OxFLOW methods with temporal resolutions descending from 25 to 6.2 seconds. Note that as compared to Conv-OxFLOW with the temporal resolution of 25 seconds functional contrasts are well preserved over the range of shorter temporal resolutions in both SER- and DB-OxFLOW.

Fig 6.

Scatter plots of Y_v (a,b), tCBF (c,d), and CMRO₂ (e,f) at resting state in ten subjects, derived from SER-OxFlow with TR of 20, 25, and 30 ms (a,c,e), and DB-OxFlow with TR of 15, 20, 25, and 30 ms (b,d,f), respectively. A temporal resolution corresponding to each TR is given at the bottom. Horizontal dotted line represents a mean of the ten subjects in Conv-OxFlow with the temporal resolution of 25 seconds.

Fig 7.

Quantification of time-varying Y_v , $tCBF$, and $CMRO_2$ in response to an apneic challenge using SER-OxFlow (a–d; temporal resolution = 8 sec) and DB-OxFlow (e–h; temporal resolution = 6 sec) methods. Left: A pair of v (neck) and ϕ_{corr} (brain) maps for baseline (a,e), minimum (b,f), and maximum (c,g) of $tCBF$ and Y_v estimates, respectively. Right: group-averaged time-courses of the four physiologic quantities at baseline, volitional apnea (shaded area), and recovery periods. Time points with black circles were used to compute baseline averages, while those with red circles were averaged for $CMRO_2$ at end-apnea (Table 2).

Summary of parameters (Y_v , tCBF, CMRO₂) derived from Conv-, SER-, and DB-OxFlow methods in ten subjects at rest shown in Figure 3. Mean and SD over five successive measurements are provided for each subject while group-mean and SD in the last row.

Table 1

	Y_v (%)			tCBF (ml/min/100g)			CMRO ₂ (μmol/min/100g)		
	Conv-OxFlow	SER-OxFlow	DB-OxFlow	Conv-OxFlow	SER-OxFlow	DB-OxFlow	Conv-OxFlow	SER-OxFlow	DB-OxFlow
Subject 1	65.2 (0.5)	65.8 (1.1)	65.9 (0.7)	48.5 (3.8)	47.6 (3.0)	50.5 (1.0)	146.7 (12.1)	141.5 (4.8)	149.2 (2.3)
Subject 2	69.4 (1.6)	70.2 (1.8)	70.7 (1.3)	54.1 (1.9)	54.0 (2.1)	55.5 (1.5)	123.1 (6.7)	119.7 (5.0)	121.1 (3.7)
Subject 3	66.3 (0.6)	67.3 (1.4)	67.2 (0.9)	52.2 (1.6)	50.9 (0.7)	51.1 (1.4)	132.0 (6.3)	126.4 (4.2)	125.6 (6.8)
Subject 4	71.4 (0.8)	72.6 (1.7)	70.8 (2.1)	49.6 (4.0)	49.5 (3.7)	48.4 (5.8)	120.1 (9.1)	114.7 (14.0)	118.7 (6.5)
Subject 5	65.1 (1.2)	66.3 (0.9)	65.3 (1.0)	47.1 (2.2)	46.7 (1.4)	46.6 (1.3)	162.6 (5.2)	155.3 (2.4)	160.0 (6.1)
Subject 6	71.4 (1.7)	72.6 (0.9)	72.1 (1.4)	58.3 (4.4)	54.4 (2.3)	55.4 (7.9)	117.7 (11.1)	104.9 (7.7)	108.9 (9.7)
Subject 7	64.2 (0.3)	65.7 (0.6)	65.3 (0.9)	39.7 (1.3)	41.6 (1.9)	41.6 (2.1)	130.4 (4.5)	130.5 (7.6)	132.0 (8.4)
Subject 8	67.1 (0.9)	68.0 (0.9)	68.2 (1.1)	47.7 (1.8)	47.5 (3.5)	48.8 (1.9)	136.8 (6.1)	132.0 (7.0)	135.2 (8.8)
Subject 9	70.1 (0.7)	70.0 (1.2)	70.5 (0.4)	50.0 (1.1)	51.1 (1.7)	50.1 (1.3)	129.6 (2.4)	133.1 (8.1)	128.0 (3.7)
Subject 10	71.3 (1.7)	74.7 (1.6)	70.9 (1.7)	51.8 (2.6)	54.9 (4.1)	52.4 (3.3)	125.2 (2.7)	116.3 (14.5)	128.6 (7.3)
Mean (SD)	68.1 (2.7)	69.3 (3.1)	68.7 (2.5)	49.9 (4.6)	49.8 (3.9)	50.0 (3.9)	132.4 (12.9)	127.4 (13.8)	130.7 (14.0)

Summary of the four oximetric parameter estimates (Y_a , Y_v , $tCBF$, $CMRO_2$) in each subject at rest and in response to an apneic challenge, acquired using SER-OxFlow (temporal resolution = 8 sec) and DB-OxFlow (temporal resolution = 6 sec) methods. Values for baseline and end-apnea were calculated at time points indicated in Figs. 7d,h.

Table 2

SER-OxFlow				DB-OxFlow			
	Subject 1	Subject 2	Subject 3	Mean (SD)	Subject 1	Subject 2	Subject 3
Y_a (%)	Baseline	96.6	96.6	97.4	96.9 (0.4)	96.7	98.0
	Minimum	94.8	94.3	92.7	93.9 (0.9)	95.6	93.0
	Change (%)	-1.8	-2.3	-4.8	-3.0 (1.3)	-1.1	-5.1
Y_v (%)	Baseline	63.7	67.9	67.6	66.4 (1.9)	63.6	67.7
	Maximum	67.5	72.5	72.1	70.7 (2.3)	68.5	71.8
	Change (%)	5.9	6.8	6.6	6.4 (0.4)	7.7	6.1
$tCBF$ (ml/min/100g)	Baseline	45.4	40.6	41.9	42.6 (2.0)	47.1	42.3
	Maximum	62.2	53.1	56.9	57.4 (3.7)	58.4	54.7
	Change (%)	36.8	30.7	35.8	34.4 (2.7)	23.9	29.5
$CMRO_2$ (μmol/min/100g)	Baseline	130.4	122.9	119.2	124.2 (4.7)	135.9	122.2
	End-Apnea	149.5	127.3	127.3	134.7 (10.5)	152.5	126.0
	Change (%)	14.7	3.6	5.3	7.9 (4.9)	12.2	3.0