Simultaneous Voxel-wise Mapping of Oxygen Extraction Fraction, Blood Flow and Cerebral Metabolic Rate of Oxygen

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Introduction: Simultaneous mapping of cerebral blood flow (CBF), oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen ($CMRO_2$) would provide insight into neurovascular and metabolic coupling and probe oxygen delivery and consumption at rest and activation [1]. However, all current methods are extremely involved and not practical in a clinical setting. Here we developed an MRI imaging protocol that integrates acceleration-based arterial spin labeling (Acc-ASL) for CBF and gradient echo sampling of free induction decay and echo (GESFIDE) [2] for OEF mapping [3], into a single sequence, and evaluated its performance by comparison to a recently reported whole-brain oximetry method [4].

Methods: The GESFIDE sequence used for R2′ mapping consisted of a train of 16 gradient echoes each before and after a refocusing π-pulse (echo spacing=1.47 ms, TE/TR=70/100 ms, matrix size =80x80, spatial resolution=2.75x2.75x7 mm^3, 16 slices; positive readout only, bandwidth=2129 Hz). The GESFIDE block was inserted into the "post-label delay" period (PLD=1.66s) in the "control" module of the Acc-ASL block (**Figure 1**). During the repetition period of each control condition (in the ASL "label-control pair"), a phase encoding (PE) gradient was inserted at each multi-slice multi-echo GRE readout, in the GESFIDE portion of the sequence, to encode the y-dimension. The Acc-ASL sequence matched the spatial resolution of GESFIDE; and TE/TR=15/3924 ms. Total acquisition time was 405 sec with partial Fourier factor of 5/8 for GESFIDE PE. For the labeling module, a pair of identical non-selective 180° adiabatic refocusing pulses were placed symmetrically between the two anti-phase 90° RF pulses to reduce effects from magnetic field inhomogeneity (i.e. to correct phase shifts) and eddy currents. Acceleration parameters were chosen as in [5] to minimize signal loss from diffusion and cerebrospinal fluid signal contamination as well as to maximize gray matter (GM) SNR. Motion sensitizing gradients (MSG; G= 30 mT/m, MSG duration Δ=30 ms, and gradient duration δ= 1 ms; MSG gradients amplitude was set to zero for control module). The cut-off acceleration was 2.3 m/s^2. Background suppression using adiabatic inversion pulse was applied 50 ms after labeling. To evaluate the performance of the integrated sequences, separate scans of Acc-ASL and GESFIDE were also performed; and in two subjects test-retest scans were performed. Eight healthy volunteers (mean age = 30.4 ± 5.4 years) were examined at 3T (Siemens TIM Trio) at rest. From the time-course of the echo amplitudes before and after the π-pulse in the GESFIDE sequence, R_2' was derived, and a field map computed from the phase difference of two adjacent gradient echoes, to correct for macroscopic magnetic field inhomogeneity using the spatial finite difference algorithm of [6]. Finally, OEF was derived as in [3] and CBF was quantified from the Acc-ASL data as described in [5].

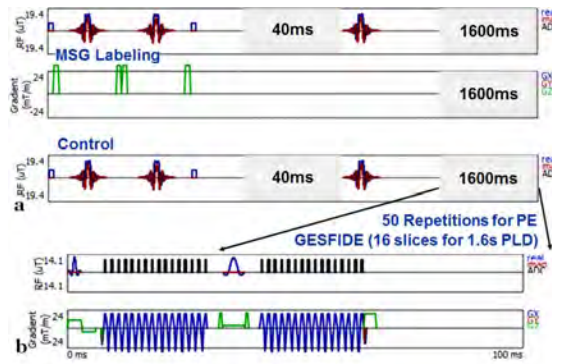

Figure 1. Integrated AccASL (a) and GESFIDE (b) sequence for simultaneous mapping CBF and OEF.

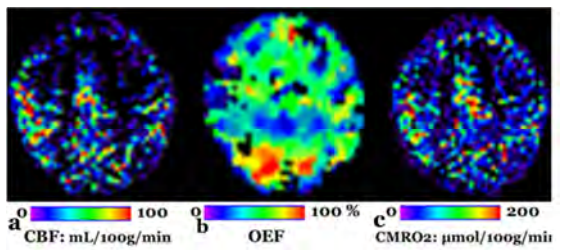

Figure 2. Voxel-wise one-slice map of OEF (a), CBF (b) and $CMRO_2$ (c) for a representative subject at rest.

Results: Parametric maps of CBF, OEF and $CMRO_2$ are shown in **Figure 2**. Estimated mean OEF values obtained with separate and integrated sequences were not significantly different (32.7±2.6% from integrated sequence vs. 34.7±3.2% from separate GESFIDE sequence, paired t-test P=0.19). Test-retest scans showed good repeatability of parameters estimated, with inter-scan variability <5%. As expected, CBF was much greater in brain GM than in white matter (WM) (**Figure 2a**). OEF was relatively constant, with higher values in the occipital lobe and small prefrontal regions (**Figure 2b**). Regional $CMRO_2$ paralleled that of CBF, with higher values in GM than in WM, as well as areas of greater metabolic demand, such as frontal and posterior occipito-parietal regions (**Figure 2c**). Across-subject group means of global OEF, CBF and $CMRO_2$ were 32.7±2.6 %, 47.7±4.8 mL/100g/min and 123.8±11.1 µmol/100g/min, respectively. The data are also suggestive of the expected negative correlation between global OEF and CBF across subjects (r=-0.6, P=0.06) (**Figure 3a**). CBF was significantly correlated with $CMRO_2$ (r=0.81, P=0.016), consistent with tight vascular-metabolic coupling in the resting state. There was no significant difference between global $CMRO_2$ measures using the present method and those obtained with a previously reported whole-brain susceptometry technique applied to the same study subjects (123.8±11.1 vs. 121.2±6.0 µmol/100g/min, P=0.75). Lastly, whole-brain [4] and voxel-wise derived average $CMRO_2$ obtained in the same subjects were correlated with each other (r=0.77, P=0.04) (**Figure 3b**).

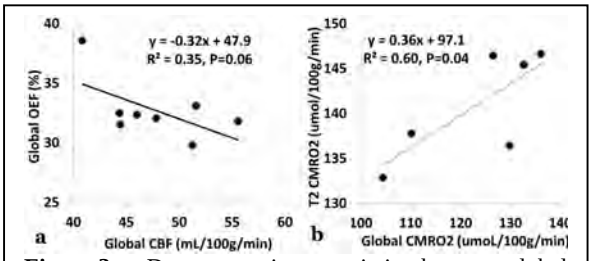

Figure 3. a: Data suggesting association between global CBF and OEF (r=-0.6, P=0.06). b: Correlation between global voxel-wise $CMRO_2$ measures and $CMRO_2$ values based on the T_2-Yv method (r=0.77, P=0.04).

Discussion and Conclusion: The new integrated method for OEF and CBF quantification allows for $CMRO_2$ mapping in scan times of less than 7 minutes. CBF, OEF and $CMRO_2$ values obtained with the new integrated sequence are in good agreement with those from susceptometry and Yv-T2 fitting methods [4,7]. Rigorous testing in larger study cohorts will be necessary to determine the method's robustness and reproducibility.

References: [1] Mintun et al, PNAS, 2001. [2] Ma and Wehrli, JMR, 1996. [3] He and Yablonskiy, MRM. 2007.
[4] Rodgers et al, JCBFM, 2013. [5] Schmid et al, MRM, 2014. [6] Jensen et al, MRM 2006. [7] Xu et al, MRM 2009.