Highlights

- Oxygen extraction fraction (OEF) and the cerebral metabolic rate of oxygen (CMRO₂) are fundamental indicators of brain tissue health and function. As such, they are perturbed during functional neuronal activation and in disease states such as stroke and brain tumor. Quantification of OEF and CMRO₂ will facilitate understanding of normal brain operation and enable detailed investigation of neuropathology.

- MR-based techniques have been recently developed to quantify OEF and CMRO₂. These methods involve first determining OEF and then use a separate cerebral blood flow (CBF) measurement to estimate CMRO₂. Three general classes of MR methods exist for OEF quantification:
  - Intravascular T₂-based methods target the relationship between blood oxygenation and the transverse (T₂) MR relaxation of intravascular blood. TRUST MRI uses spatial-based spin labeling to measure whole brain OEF, whereas QUIXOTIC-based MRI uses velocity selective spin labeling to map OEF on a voxel-by-voxel basis.
  - Phase-based MR methods assess oxygenation in individual veins by quantifying susceptibility shift between vessels and tissue. Susceptibility shift is directly related to blood oxygenation; extrapolating shift from MR phase images allows for regional OEF measurement.
  - Quantitative BOLD techniques quantify the effects of inhomogeneous magnetic fields in the extravascular space, as created by deoxygenated intravascular blood. The magnitude of these effects on the MR signal depends on level of intravascular blood oxygenation; careful modeling of the MR signal allows voxel-wise OEF mapping.

Target Audience: MR physicists & developers, neuroscientists, neuroradiologists, neurologists

Outcome/Objectives:

- Understand cerebral OEF and CMRO₂ from a physiologic perspective
- Learn state-of-the-art MR approaches for imaging OEF and CMRO₂
- Identify clinical and basic science applications of OEF and CMRO₂ imaging

Problem Summary

Continuous oxygen delivery to neural tissue is necessary to maintain normal brain function and viability. The brain consumes 20% of total body energy through aerobic metabolism under healthy conditions (1). The ability to easily map brain oxygenation would provide new information about normal cerebral physiology at rest and during functional activity (2), and improve understanding about disorders in which oxygen supply to the brain is disturbed, such as stroke (3), tumor (4), and
multiple sclerosis (5). In acute stroke, for instance, metabolic indicators such as local oxygen extraction can identify tissue at risk of infarction and guide subsequent therapy (6).

Assessing blood oxygenation *in vivo*, however, is technically challenging. Until recently, established *in vivo* methods to measure brain oxygen utilization have relied on positron emission tomography (PET) imaging with $^{15}$O radiotracers (7,8). However, $^{15}$O PET is not used clinically as it requires injection of short-lifetime radiotracers, veno/arterial puncture and blood monitoring, and a large staff for a single experiment. Consequently, clinically feasible MR-based assessment of brain oxygenation is highly desirable. Since MRI is sensitive to oxygenation-dependent modulations in the blood signal, primarily through magnetic properties of deoxygenated hemoglobin (dHb), measuring OEF and CMRO$_2$ become possible. In recent years, quantitative MRI methods have been developed to study OEF and CMRO$_2$ and have shown promise.

**Oxygenation Parameter Definitions**

Because oxygen is not produced endogenously in the brain, it must be delivered by cerebral blood flow (CBF) to meet the metabolic demands of cerebral tissue. The percent of oxygen extracted by tissue from the vasculature is commonly expressed as the oxygen extraction fraction (OEF):

$$OEF = \frac{SaO_2 - SvO_2}{SaO_2}$$  \[1\]

where $SaO_2$ is the blood oxygen saturation level in arteries and $SvO_2$ is the remaining oxygen saturation in the veins after extraction. Often, $SaO_2$ is close to one since arterial blood is typically fully oxygenated.

If local oxygen extraction and blood flow are known, the absolute rate of oxygen consumption by brain tissue (CMRO$_2$), can be determined in micromol O$_2$/100g∙min using Fick’s principle (9):

$$CMRO_2 = OEF \cdot CBF \cdot C_a$$  \[2\]

where $C_a$ is the oxygen carrying capacity of hemoglobin molecules per volume of blood.

**MR method classes to quantify OEF and CMRO$_2$**

**Intravascular T$_2$-based MRI (10)**

One class of approach to measure OEF involves quantifying dHb-induced signal loss in intravascular blood. These techniques invoke an MR signal model that establishes an analytic relationship between the T$_2$ relaxation of blood, SO$_2$, and hematocrit, and exclude signal contributions from extravascular constituents. The model has been extensively described (11-14) and recently applied in humans at 3T (15). Using this model, T$_2$ versus SO$_2$ calibration curves can be generated (figure 1a) and used to convert venous blood T$_2$ to absolute $S_vO_2$ and OEF.

The major challenge in using intravascular T$_2$ to measure $S_vO_2$ is isolating pure venous blood signal, free from extravascular and non-venous blood components. This is a nontrivial task due to partial voxel voluming with tissue, CSF, and non-venous blood. To circumvent this issue, initial intravascular T$_2$ studies targeted blood in large veins only, as it was easier to find blood-containing voxels within large-caliber vessels (12,14). These studies used BOLD contrast to first locate draining veins from active sites and then measured T$_2$ and $S_vO_2$ within voxels within these vessels. Despite careful voxel selection, however, limits on spatial resolution made partial volume effects difficult to avoid.
More recently, spin-labeling based approaches have been creatively employed to isolate venous blood signal. Lu and colleagues proposed T$_2$-Relaxation Under Spin Tagging (TRUST) MRI and measure S$_v$O$_2$ in the sagittal sinus (16). TRUST uses pulsed arterial spin labeling (ASL) MRI theory (17), but instead labels blood on the venous side of circulation. Paired subtraction (as in typical ASL data processing) results in an image containing blood signal from large veins only, with tissue and CSF completely subtracted. By acquiring these images at multiple echo times and measuring T$_2$ in a large vein, an estimate of global S$_v$O$_2$ becomes possible. Figure 1b (top row) shows representative multi-echo TRUST images; T$_2$ signal decay within the sagittal sinus is demonstrated. TRUST MRI has been recently applied and validated in humans for both global OEF and CMRO$_2$ measurements. Despite being a spin-labeling technique, TRUST has high SNR due to the large blood volume within draining vein voxels and can thus be accurately performed in minutes. A limitation of TRUST is that measurements are restricted to terminal veins, making regional S$_v$O$_2$ estimation difficult.

A second approach dubbed QUantitative Imaging of eXtraction of Oxygen and TIssue Consumption (QUIXOTIC) extends the utility of spin labeling and isolates venous blood on a voxel-by-voxel basis, thus allowing localized S$_v$O$_2$ measurements (18). QUIXOTIC uses a novel velocity-selective excitation scheme and is related to velocity-selective arterial spin labeling (VS-ASL) (19). In principle, QUIXOTIC applies velocity-sensitive pulses to eliminate signal from blood flowing above preset cutoff velocities. By carefully timing these pulses, it is possible to exploit the physiological blood velocity distribution and create a venular-blood bolus that persists after subtraction (18). Signal from static tissue, CSF, and non-venular blood compartments are eliminated, resulting in a pure venular-blood signal map. As in TRUST, QUIXOTIC blood-weighted images are acquired at multiple echo times (Figure 1b). Voxel-wise exponential fitting generates T$_2$ maps from which S$_v$O$_2$, OEF, and CMRO$_2$ images are subsequently computed (Figure 1c). Notably, QUIXOTIC reports parenchymal S$_v$O$_2$ values higher than those reported by quantitative BOLD and other methods. The source of this discrepancy is currently under investigation; an in-depth discussion can be found in reference (18). The main limitation of QUIXOTIC is low SNR, due to low CBV in a typical parenchymal voxel. This is expected to become less of an issue at higher field strengths and with many-element imaging coils. Notably, like ASL, QUIXOTIC can be used in functional imaging to create quantitative S$_v$O$_2$ and OEF activation maps.

Several novel approaches have been introduced since QUIXOTIC, which offer improvements and address existing issues. VSEAN (Venous Oxygenation Mapping Using Velocity-Selective Excitation and Arterial Nulling) was recently introduced by Guo and colleagues (20), similarly uses velocity-selective excitation (but in a different manner than QUIXOTIC), and adds arterial nulling capabilities. VSEAN reduces contamination from unwanted diffusion-weighting and also offers improved SNR. Schmid and colleagues introduced inflow QUIXOTIC OEF (IQ-OEF) in 2012 (21), which uses a combination of velocity selective labeling and pulsed arterial spin labeling to label the local venous blood pool and eliminates the need for the TO$_1$ inversion pulse. Consequently, a substantial increase in SNR is achieved.
Phase-based Oxygenation Measurements

**MR Susceptometry.** An alternate MR contrast mechanism for oxygenation derives from deoxyhemoglobin (dHb)-induced increases in magnetic susceptibility within veins compared to the surrounding brain tissue. This susceptibility shift creates local magnetic field perturbations (ΔB_{vein-tissue}) that manifest in MR phase images as $\Delta \varphi = \gamma \cdot \Delta B \cdot TE$, where $\gamma$ is the gyromagnetic ratio and TE is the echo time. In this way, MR phase images provide information about susceptibility changes that enable quantification of the underlying SvO$_2$ in individual vessels.

This approach, termed *MR susceptometry*, has been used to study oxygenation in large draining veins such as the femoral vein of the leg (22) and the internal jugular vein (23) and sagittal sinus of the brain (24). Combining MR susceptometry in the sagittal sinus with whole-brain flow measurements, Jain et al. also recently demonstrated reproducible global CMRO$_2$ estimates in healthy subjects at rest, and during functional changes induced by CO$_2$ gas inhalation (25).

**Phase-based regional oxygen metabolism (PROM).** With sufficient resolution, phase-based oxygenation can be assessed in smaller veins, which is expected to be more reflective of local brain
A recently proposed method called PROM combines susceptometry in parallel pial veins with regional estimates of CBF from arterial spin labeling MRI to estimate local cortical CMRO₂ (26). PROM at 3 Tesla and achieved gradient echo phase imaging with 0.5mm in-plane resolution. In this initial study on 12 healthy volunteers, mean gray matter CMRO₂ was measured as 151 ±mol/100g∙min, which is in line with 15O PET values in the literature. Greater CMRO₂ was observed in the occipital cortex compared to frontal and temporal areas, suggesting that PROM is sensitive to regional variations in metabolism across the brain.

**Quantitative Susceptibility Mapping.** One limitation of PROM its assumption of a long, parallel cylinder model for veins of interest, which restricts the set of vessels amenable to phase-based analysis. It is possible to extend SvO₂ estimates to veins of arbitrary curvature and orientation using quantitative susceptibility mapping (QSM) techniques to directly reconstruct 3D susceptibility distributions from measured field maps (27). In general, recovery of the underlying susceptibility map is challenging due to the complex and nonlocal relationship between susceptibility and magnetic field. Current research aims to utilize new 3D QSM methods to directly assess susceptibility differences between veins and tissue (28). This work potentially can provide whole-brain coverage of SvO₂ in a larger set of veins, and improve applicability of PROM.

**Extravascular-based OEF measurements:**

A third class of methods invokes an MRI signal model that quantifies OEF primarily based on dHb-induced signal loss in the extravascular tissue; in other words, tissue surrounding blood vessels. This model utilizes the so-called “static-dephasing regime”, a regime where the MRI signal is influenced by static magnetic field inhomogeneities. In the static dephasing regime, the phase distribution at a given TE is identical to local magnetic field distribution around vessels containing paramagnetic dHb particles. This allows the derivation of a relationship between the dHb-induced frequency shift and the SvO₂ within the vessels (assuming a random orientation of vessels in the voxel space). It follows that the relaxivity due to these static field inhomogeneities (characterized
by a $R_2'$, which is inversely related to the time constant $T_2'$; i.e. $R_2' = 1/T_2'$ is the product of blood volume and this frequency shift.

$R_2'$ is the difference between $R_2^* (1/T_2^*)$ and $R_2 (1/T_2)$ and can thus be estimated by measuring $T_2$ and $T_2^*$ using gradient echo and spin echo MRI sequences, respectively. Extravascular-based methods typically use a hybrid spin-echo and gradient multi-echo sequence where $R_2'$ is estimated by removing the $R_2$ effect from the net signal collected ($R_2' = R_2^* - R_2$).

Early approaches by An and colleagues used a single compartment model that assumed that MR signal originates from a single extravascular tissue constituent and ignores blood and CSF signal. Using this model, they produced OEF (29) and CMRO$_2$ (30) maps based on the aforementioned $T_2'$ methodology. He and Yabolinskiy took this approach a further by considering a multiple-compartment model, which factors the effects of blood and CSF on the MR signal (31). This technique is called quantitative BOLD (qBOLD), and has been fine-tuned and recently validated in animal and human models, producing OEF and CMRO$_2$ maps (32,33).

Figure 3. Quantification of OEF and CMRO$_2$ using quantitative BOLD methodology. A) T1-weighted anatomical image; (B) cerebral blood flow (CBF) map (in mL/100 g/min), (C) OEF map. D) map of CMRO$_2$ (in mmol/g/min). Adapted from He et. al, (32).
Summary

• Quantitative BOLD, intravascular T2-based spin labeling approaches like QUIXOTIC, and phase-based oxygenation methods like PROM are promising for their ability to quantitatively measure OEF and CMRO₂.

• These MR-based tools to measure oxygenation (previously only accessible by PET) will further our understanding of neuropathology like stroke, brain tumor, and multiple sclerosis, and of normal brain function, for example, through functional MRI.

References


28. Fan AP, Bilgic B, Heberlein KA, Rosen BR, Adalsteinsson E. Quantification of the Cerebral Metabolic Rate of Oxygen (CMRO2) across the Cortex using Phase-based Regional Oxygen Metabolism (PROM) MRI. 2012; Melbourne, Australia. p 2370.


