Session Title: **Diffusion & Perfusion**
Talk Title: **MR Imaging of Cerebral Oxygen Extraction and Metabolism**

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Highlights

- Oxygen extraction fraction (OEF) and the cerebral metabolic rate of oxygen ($CMRO_2$) 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 $CMRO_2$ will facilitate understanding of normal brain operation and enable detailed investigation of neuropathology.

- MR-based techniques have been recently developed to quantify OEF and $CMRO_2$. These methods involve first determining OEF and then use a separate cerebral blood flow (CBF) measurement to estimate $CMRO_2$. Three general classes of MR methods exist for OEF quantification:

  - Intravascular T_2-based methods target the relationship between blood oxygenation and the transverse (T_2) 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 $CMRO_2$ from a physiologic perspective
- Learn state-of-the-art MR approaches for imaging OEF and $CMRO_2$
- Identify clinical and basic science applications of OEF and $CMRO_2$ 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 SvO_2 and OEF.

The major challenge in using intravascular T_2 to measure SvO_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 SvO_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_vO_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_vO_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_vO_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_vO_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_vO_2, OEF, and $CMRO_2$ images are subsequently computed (Figure 1c). Notably, QUIXOTIC reports parenchymal S_vO_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_vO_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.
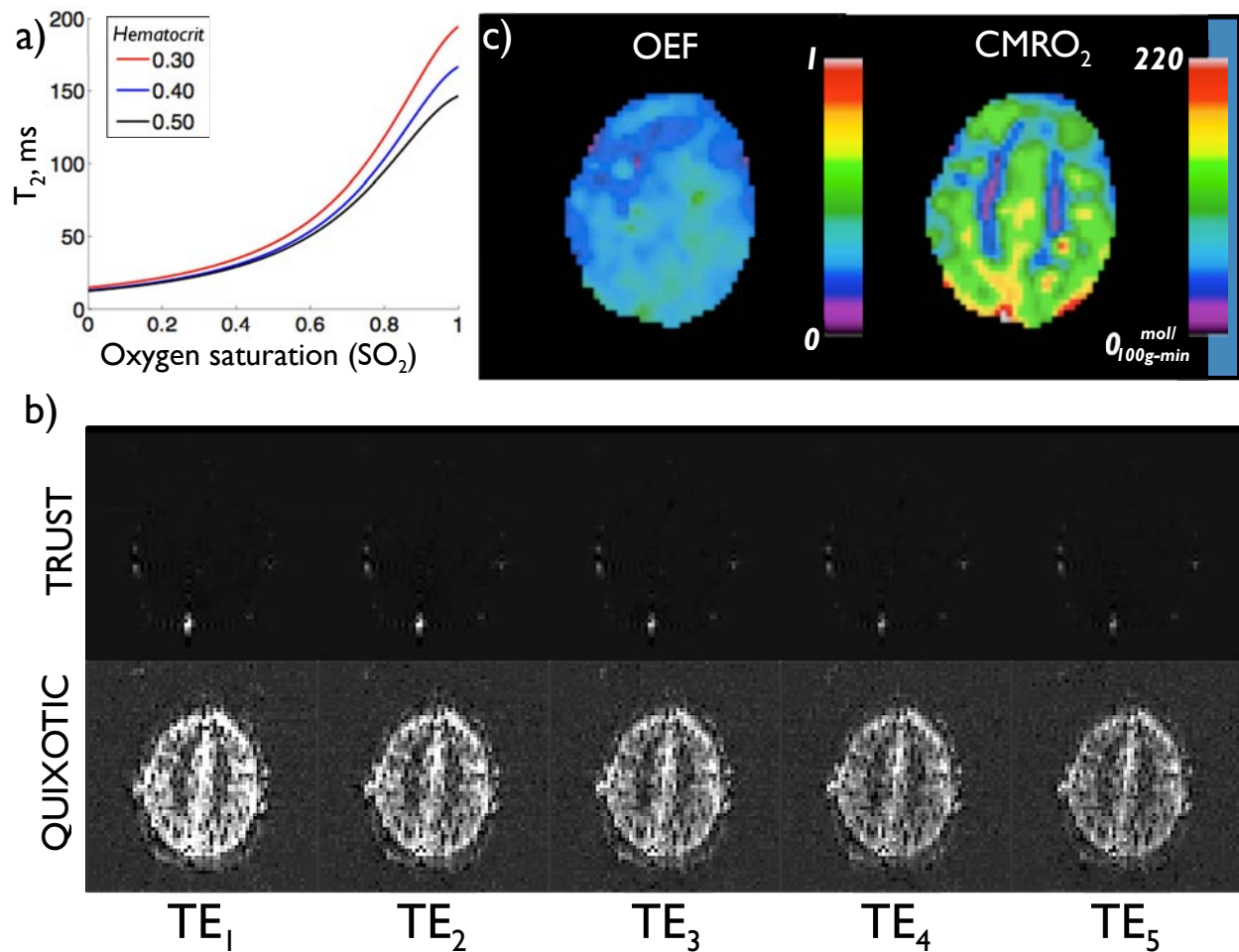
Figure 1. Results from intravascular T2-based approaches. A) sample T2 versus SO_2 calibration curve. B) Representative venous-blood weighted images at multiple TEs for TRUST (top row) and QUIXOTIC (bottom row). C) QUIXOTIC-generated OEF and $CMRO_2$ maps. Adapted from Bolar et. al. (18).

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 ($\Delta B_{vein-tissue}$) that manifest in MR phase images as $\Delta\varphi = \gamma \cdot \Delta B \cdot TE$, where γ 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

physiology. 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 $CMRO_2$ (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 $CMRO_2$ was measured as 151 ⌐mol/100g·min, which is in line with ^{15}O PET values in the literature. Greater $CMRO_2$ 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 SvO_2 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 SvO_2 in a larger set of veins, and improve applicability of PROM.

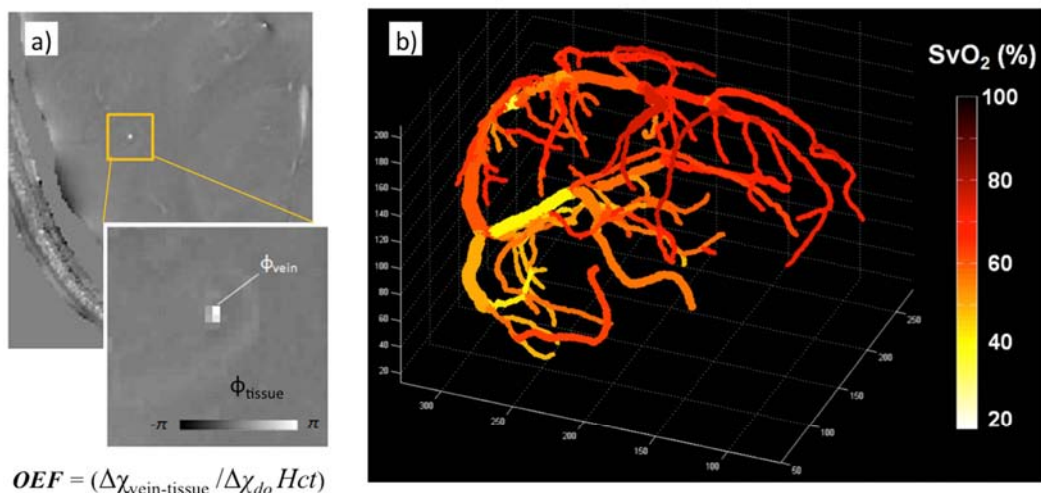$$OEF = (\Delta\chi_{vein\text{-}tissue}/\Delta\chi_{do}\,Hct)$$

Figure 2. A) PROM-based calculation of OEF. B) Quantitative susceptibility mapping to generate SvO_2 projections along draining veins. Adapted from Fan et. al. (26) and (28).

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 SvO_2 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).
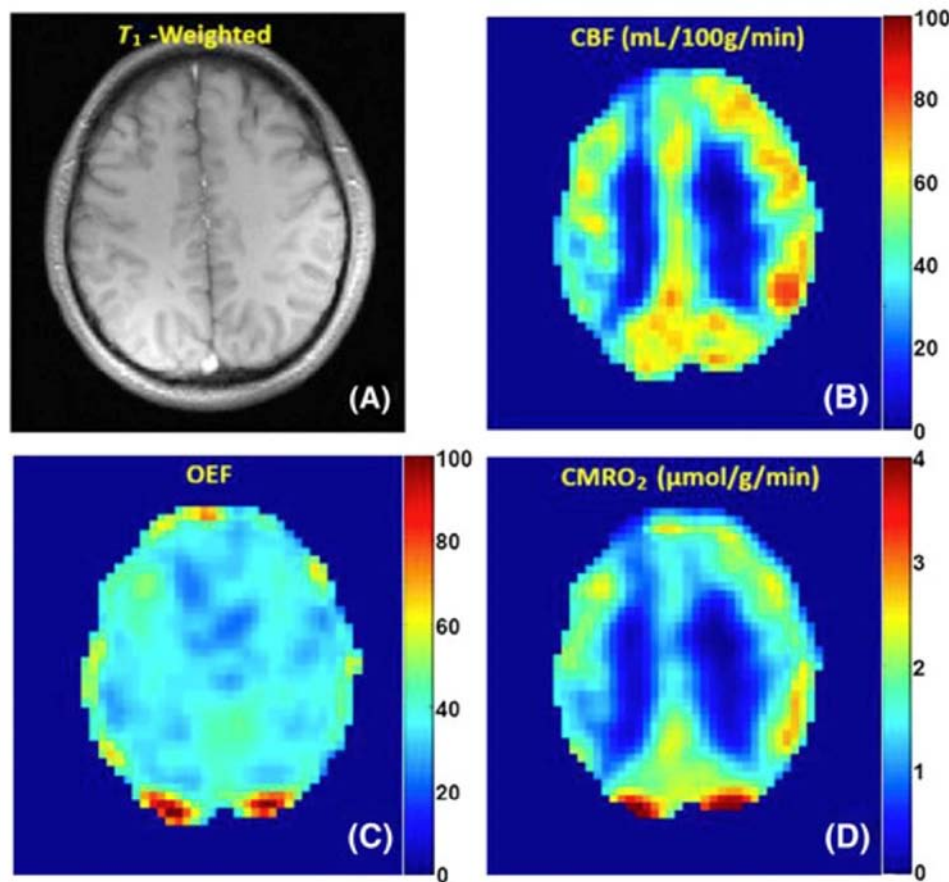

Figure 3. Quantification of OEF and CMRO2 using quantitative BOLD methodology. A) T1-weighted anatomical image; (B) cerebral blood flow (CBF) map (in mL/100 g/min), (C) OEF map. D) map of CMRO2 (in mmol/g/min). Adapted from He et. al, (32).

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 $CMRO_2$.

- 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.

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