Cerebral oxygen extraction fraction MRI: Techniques and applications

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Funding information
NIH (R01 NS106702, R01 NS106711, R01 AG064792, R1F AG071515, R1F NS110041, R21 AG058413, and P41 EB031771).

INTRODUCTION

The human brain constitutes 2% of the body’s total mass but uses 20% of the oxygen.1 The brain has limited capacity to store oxygen, and its oxygen utilization primarily relies on extraction from incoming arterial blood in real time. Therefore, the oxygen extraction fraction (OEF) is a key physiological parameter of the brain’s energy metabolism and has been suggested to be a potential biomarker in several diseases, such as Alzheimer disease (AD),2,3 carotid steno-occlusive disease,4 sickle cell disease (SCD),5,6 and brain tumor.7

Measurement of OEF and the related cerebral metabolic rate of oxygen (CMRO2) in humans used to be a niche market of PET with 15O-labeled radiotracers.8-10 Although 15O-PET is still widely regarded as the gold standard for OEF and CMRO2 mapping, its broad clinical applications have been hampered by the complex logistics,
exposure to radiation, and the requirement for an on-site cyclotron to produce the $^{15}$O isotope, which has a short half-life of 2 min.

With the advances in MRI, several techniques have been developed to quantify OEF, based on the associations between blood oxygenation and MRI properties, such as $T_2$, susceptibility, and magnetization phase, or by exploiting gas modulations. Among these techniques, some provide a global or whole-brain measure of OEF, while others aim to estimate OEF in specific brain regions. Some of these techniques have demonstrated potential clinical utility in brain diseases. The goal of this article is to provide a review of MRI-based OEF measurements. We will first introduce the physiological importance of OEF. We will then review major categories of MRI-based OEF techniques, including their signal mechanisms, acquisition methods, and data analyses. Finally, we will highlight key clinical applications of these techniques, although they are not meant to be exhaustive.

2 | OEF AND BRAIN OXYGEN HOMEOSTASIS

As illustrated in Figure 1, when fully oxygenated arterial blood flows through the capillaries, it releases oxygen to the surrounding tissues. The fraction of oxygen extracted by the tissue is the OEF. Specifically, OEF is defined as:

$$OEF = \frac{Y_a - Y_v}{Y_a} \times 100\%$$  (1)

where $Y_v$ is the venous oxygenation, defined as the fraction of oxyhemoglobin in the venous blood, and $Y_a$ is the arterial oxygenation. Under normal conditions, $Y_a \approx 100\%$ and is relatively uniform throughout the body. Thus, OEF can often be simplified to:

$$OEF \approx 1 - Y_v.$$  (2)

$Y_a$ can also be conveniently measured by a pulse oximeter at the fingertip, especially when abnormalities in $Y_a$ are expected. The major challenge is, therefore, the measurement of $Y_v$.

In blood, oxyhemoglobin and deoxyhemoglobin have distinct magnetic properties: oxyhemoglobin is diamagnetic, while deoxyhemoglobin is paramagnetic. Inside the vessel, an increased concentration of deoxyhemoglobin leads to a larger microscopic magnetic field gradient. Diffusion and exchange of water molecules in this induced inhomogeneous field results in a reduction in blood $T_2$, similar to the well-known BOLD effect. A higher concentration of deoxyhemoglobin also increases the magnetic susceptibility of voxels containing blood. This susceptibility difference between blood and tissue results in an additional phase angle in the transverse magnetization of blood. Outside the blood vessel, the local field inhomogeneity induced by the paramagnetic deoxyhemoglobin in the vessel networks results in additional decay of the tissue signal. Finally, BOLD signal changes during hypercapnic and hyperoxic gas inhalations can be modeled as a function of deoxyhemoglobin, and the non-linear nature of this function enables the differentiation of different variables and the estimation of OEF (among other physiological parameters). The OEF methods described in this review are based on one or more of the above-mentioned effects.

Once OEF is quantified, it can be combined with cerebral blood flow (CBF) to calculate CMRO$_2$ based on the Fick's principle:

$$CMRO_2 = CBF \cdot \left( Y_a - Y_v \right) \cdot C_{hb} \cdot [Hb]$$
$$= CBF \cdot OEF \cdot Y_a \cdot C_{hb} \cdot [Hb]$$  (3)

where [Hb] is the total hemoglobin concentration (in gram hemoglobin/dL blood). $C_{hb}$ is the oxygen carrying capacity of hemoglobin (1.34 ml or 59.8 μmol O$_2$/gram hemoglobin). The term $\left( Y_a - Y_v \right) \cdot C_{hb} \cdot [Hb]$ is sometimes called the arterio-venous difference in oxygen content (AVDO$_2$). CBF can be measured globally by using phase-contrast MRI to quantify blood flow in the feeding arteries, or regionally by using arterial spin labeling (ASL) MRI.

It should be pointed out that OEF reflects a balance between CBF (blood supply) and CMRO$_2$ (oxygen consumption), which can be considered the driving variables of OEF. In clinical applications, for some diseases, such as neurodegenerative diseases, CMRO$_2$ may be a better biomarker since it is more directly associated with neural function. For other diseases, such as stroke, OEF may be a more sensitive biomarker since it is also related to blood supply.

It is worth noting that non-invasive quantification of OEF and CMRO$_2$ is also possible with MR spectroscopic imaging of $^{17}$O, which is the only MR-active stable isotope...
of oxygen. Due to the very low natural abundance of $^{17}\text{O}$, $^{17}\text{O}$ MRI is typically performed with $^{17}\text{O}$-enriched tracers. A detailed review of $^{17}\text{O}$ MRI is beyond the scope of this article, and interested readers are referred to other dedicated reviews. In this article, we will focus on MRI OEF techniques that do not require exogenous tracers.

3 MRI TECHNIQUES FOR OEF MEASUREMENT

3.1 T$_2$-based methods

3.1.1 Measurement of venous T$_2$

Under a fixed hematocrit (Hct) level, blood oxygenation has a one-to-one correspondence to blood T$_2$. Therefore, $Y_v$ (and OEF) can be measured by quantifying blood T$_2$. It is important to obtain a pure venous blood signal in this measurement, as partial volume contamination from tissue or CSF can cause bias in T$_2$ determination. While some researchers have relied on high image resolution to separate blood signal in large cerebral veins, more recent work has used special sequence designs to isolate the blood signal.

One example is T$_2$-relaxation-under-spin-tagging (TRUST) MRI. Figure 2A shows the TRUST pulse sequence diagram. TRUST labels blood spins on the venous side (Figure 2B), and uses the subtraction between control and labeled images (Figure 2C) to yield pure venous blood signal in the superior sagittal sinus (SSS). The venous blood T$_2$ is quantified by applying T$_2$-preparation with a varying number of refocusing pulses, which is characterized by the effective TE (eTE). The T$_2$-preparation pulses are applied to the entire brain, i.e., non-selectively, so that the degree of T$_2$ attenuation is not dependent on the flow velocity of the blood. Simple mono-exponential fitting of the blood signal as a function of eTE then yields venous T$_2$, which is converted to $Y_v$ through a calibration model, based on the Hct level of the subject. Since the SSS drains the majority of the cerebral cortex, TRUST MRI is thought to assess the global OEF level of the brain.

TRUST has a scan time of 1.2 min, and its signal mechanism is relatively straightforward. Rater dependence in TRUST data processing is minimal, as it uses the top signal voxels for T$_2$ estimation and the manual region of interest (ROI) plays a negligible role in the final result as long as it contains the SSS. The test–retest reproducibility of TRUST MRI has been examined, with a same-day test–retest coefficient of variation (CoV) of 3% and a day-to-day CoV of 8% for OEF quantification. The sensitivity of TRUST to OEF changes has been evaluated in several physiological challenges, such as caffeine ingestion, hypercapnia, hypoxia, and hyperoxia, all of which showed expected OEF changes using TRUST. The reliability of TRUST MRI has also been studied in the context of multiple sites and different MR vendors. In a recent study, TRUST MRI was validated with $^{15}\text{O}$-PET, which found a global OEF of 36.44 ± 4.07% with TRUST MRI and 36.45 ± 3.65% with $^{15}\text{O}$-PET in 16 healthy adults. The two modalities also revealed a correlation (intraclass correlation coefficient = 0.90) in OEF measures. In addition to human studies, TRUST has also been implemented on animal MR imaging systems for OEF assessment in mice and rats.

Other interesting technical work on global T$_2$ assessment includes the use of high-spatial-resolution echo-planar or turbo-field-echo acquisition to obtain pure blood voxels, the combination of a T$_2$-preparation sequence with inversion recovery to simultaneously measure blood T$_1$ and the integration of flow measurement in the sequence to allow CMRO$_2$ measurement from a single sequence. While global OEF estimation has the obvious limitation of a lack of spatial information, these techniques tend to have a high reproducibility with a short scan duration, which makes them easy to incorporate into the workflow of clinical or research imaging. The global OEF can also serve as a useful reference or validation measure for comparison with regional OEF techniques.

T$_2$-based regional OEF techniques have also been reported. O’Brien et al. proposed to incorporate spatially selective saturation pulses into TRUST to isolate venous blood signal from localized regions of the brain, so that OEF can be measured for a specific hemisphere or a volume of interest. Another technique, T$_2$-relaxation-under-phase-contrast (TRUPC), uses phase-contrast complex subtraction to isolate flowing blood signal in the vessels. With this technique, OEF can be measured in regional cerebral veins, such as the internal cerebral vein (ICV), the great vein of Galen, the straight sinus, as well as the pial veins. TRUPC has a same-day CoV of 6% for OEF quantification. An accelerated version of TRUPC has also been proposed, which shortens the acquisition time from 5 min to approximately 2 min. TRUPC MRI has been validated against blood-gas oximetry of direct blood samples from the SSS on a piglet model. Three-dimensional and T$_2$-based implementations of TRUPC have also been demonstrated.

Further advancement of T$_2$-based methods attempted to provide voxel-wise OEF mapping. QUantitative Imaging of eXtraction of Oxygen and Tissue Consumption (QUIXOTIC) and Velocity-Selective Excitation with Arterial Nulling (VSEAN) are two techniques that use velocity-selective labeling or excitation to isolate the...
FIGURE 2 Illustration of TRUST MRI. A, The TRUST pulse sequence starts with a pre-saturation (pre-sat) pulse to suppress static tissue signal. Then, a label/control module is used to magnetically label the incoming venous blood. Images are acquired after a waiting period. This waiting period is selected to allow the labeled blood to flow into the imaging plane and to allow the inverted blood signal to recover to the positive magnetization, so that the phase of the magnetization is not a confounding factor for control-label subtraction. Before data acquisition, non-selective T2-preparation pulses are applied to modulate T2-weighting. The spin history is cleared by post-saturation (post-sat) pulses at the end of TR. B, Position of TRUST MRI. Imaging slice (yellow box) is placed approximately parallel to the anterior-commissure–posterior-commissure line and 20 mm above the sinus confluence. Blue box represents the labeling slab. C, Representative TRUST data. Subtraction between control and labeled images yields strong venous blood signal in the SSS (red box). The scatter plot shows venous signal as a function of eTEs. The resulting blood T2, Yv, and OEF are also shown.

post-capillary venous blood signal from tissues in the same voxel, allowing voxel-wise mapping of venous blood T2 and OEF. However, since the post-capillary venous blood comprises only 1–3% of the volume of a voxel,67 SNR and partial volume contamination represent potential obstacles in clinical applications. Approaches to shorten scan time,68 enhance SNR, and reduce CSF contamination69 have been proposed.

3.1.2 T2-Y conversion

All T2-based oximetry methods require the use of a calibration model to convert blood T2, which is an MR property, to oxygenation (Y), which is a physiological parameter. It should be noted that, under most circumstances, the same calibration plot can be used for different subjects and different studies. That is, it is not necessary to develop a calibration plot for each subject or each study. For applications in children and adults who have no hematological pathologies, the most commonly used T2-Y calibration model was proposed by Lu et al. (Figure 3),43 which was based on in vitro experiments on bovine blood samples. Bovine blood has characteristics similar to those of adult human blood in terms of the hemoglobin structure, red blood cell (RBC) shape and size,70 and diffusional water permeability.71 This bovine model has been demonstrated to provide Yv and OEF quantifications consistent with 15O-PET in healthy human adults.41

Some studies have also considered the effect of Hct on the T2-Y relationship. Blood T2 is indeed also dependent on Hct, although to a much lesser degree compared to oxygenation.43 To take Hct into consideration in the conversion, the calibration model can be used to obtain an Hct-specific T2-Y curve (most models provide a three-way relationship of Y, Hct, and T2; thus, it is straightforward to obtain Hct-specific curves). Then, based on the individual’s Hct value, which is sometimes available from the
Figure 3. The bovine T₂-Y calibration model: A. 3D mesh plot showing the dependence of blood T₂ on Y and Hct; B. Exemplary T₂-Y conversion curves extracted from the 3D mesh plot. With a fixed Hct, T₂ increases monotonically with Y; with a fixed Y, a lower Hct leads to a higher T₂.

Future work should consider individual-specific, in vivo calibrations for patients with hematological conditions such as SCD. Such calibration can be conducted by applying MRI T₂ measurements to the superficial veins in the arm, for example, followed by blood sampling to obtain its oxygenation. The venous oxygenation in the arm can be varied by using intermittent cuff occlusion to restrict blood flow, or by using hyperoxic/hypoxic gas inhalation, providing multiple data points to determine the subject-specific T₂-Y calibration curve. Such calibration data can then be applied to the venous T₂ of the brain to provide a more accurate estimation of OEF in the patient. Compared to previous calibration efforts, this approach can preserve the cell integrity of erythrocytes and their natural shape in vivo and will not have confounding factors related to blood preparation.

Finally, the above-mentioned models were primarily calibrated at 3T, with some conducted at 7T. Since T₂ varies with magnetic field strength, for applications at other field strengths, specific calibration models should be used. A unified calibration model based on quantitative theory and aggregated experiments has also been proposed.

3.2 Phase-based methods

Because of the paramagnetic property of deoxyhemoglobin, the susceptibility difference (Δχ) between blood and tissue has a linear relationship with blood oxygenation:

$$\frac{\Delta \chi}{Hct} = \Delta \chi_{do}(1 - Y) + \Delta \chi_{oxy}$$

where Δχ_{do} is the susceptibility difference between fully oxygenated and deoxygenated blood, and has been characterized in the literature. Δχ_{oxy} is the susceptibility difference between fully oxygenated blood and tissue. Δχ_{oxy} is much smaller than Δχ_{do} and is often omitted in many studies. The susceptibility of blood induces a
local magnetic field offset \( \Delta B_{\text{bl}} \), which results in an additional phase difference, \( \Delta \Phi \), between successive echoes. Although, in general, the inverse problem to solve \( \Delta \chi \) from \( \Delta \Phi \) is complex and ill-conditioned, in a special case where the blood vessel can be modeled as a long straight cylinder approximately parallel to the main magnetic field \( B_0 \), we have:

\[
\Delta \Phi_{\text{ie}} = \Delta \phi_{\text{intra}} - \Delta \phi_{\text{extra}} \tag{5}
\]

where \( \Delta \phi_{\text{intra}} \) and \( \Delta \phi_{\text{extra}} \) are the inter-echo phase difference within the vessel and in the neighboring extravascular tissue, respectively, and can be written as:

\[
\Delta \phi_{\text{intra}} = \gamma \cdot \Delta T E \cdot (\Delta B_{\text{bl,intra}} + \Delta B_{0,\text{intra}}) \tag{6}
\]

\[
\Delta \phi_{\text{extra}} = \gamma \cdot \Delta T E \cdot (\Delta B_{\text{bl,extra}} + \Delta B_{0,\text{extra}}) \tag{7}
\]

where \( \gamma \) is the gyromagnetic ratio and \( \Delta T E \) is the TE difference between successive echoes. \( \Delta B_{\text{bl,intra}} \) and \( \Delta B_{\text{bl,extra}} \) are the intra- and extravascular background \( B_0 \) inhomogeneity, respectively. \( \Delta B_{0,\text{intra}} \) and \( \Delta B_{0,\text{extra}} \) are the blood-induced field inside and outside the vessel accounting for the Lorentz sphere effect, respectively, and can be written as:

\[
\Delta B_{\text{bl,intra}} = \frac{\Delta \chi}{2} \left(\cos^2 \theta - \frac{1}{3}\right) B_0 \tag{8}
\]

\[
\Delta B_{\text{bl,extra}} = \frac{\Delta \chi}{2} \left(\sin^2 \theta - \frac{r^2}{\rho^2} \cdot \cos 2\omega\right) B_0 \tag{9}
\]

where \( \theta \) is the angle between the cylinder axis and \( B_0 \), \( r \) is the vessel radius, \( \rho \) is the distance to the vessel axis, and \( \omega \) is the azimuthal angle (Figure 4A). Assuming that the intra- and extravascular ROIs are sufficiently adjacent to each other, and thus, the effects of background \( B_0 \) inhomogeneity, that is, \( \Delta B_{0,\text{intra}} \) and \( \Delta B_{0,\text{extra}} \), are the same, \( \Delta \Phi_{\text{ie}} \) is primarily related to the deoxyhemoglobin content in the blood. Figure 4B shows a simulated blood-induced field map (Equations 8 and 9) for a hypothetical cylindrical vessel oriented at \( \theta = 20.1^\circ \). It can be seen that the extravascular term, \( \Delta B_{\text{bl,extra}} \), is very small when \( \theta \) is small, and also decays rapidly with the distance from the vessel. Therefore, in most experimental studies where the vessel is approximately parallel to \( B_0 \), \( \Delta B_{\text{bl,extra}} \) is negligible and Equation (5) can be written as:

\[
\Delta \Phi_{\text{ie}} = \frac{\Delta \chi}{2} \left(\cos^2 \theta - \frac{1}{3}\right) B_0 \gamma \Delta T E. \tag{10}
\]

Note that \( \theta \) can be measured from localizer or time-of-flight (TOF) vessel images. Combining Equations (4 and 10) and ignoring \( \Delta \chi_{\text{oxy}} \), \( Y_v \) can be calculated by:

\[
Y_v = 1 - \frac{2|\Delta \Phi_{\text{ie}}|}{\gamma B_0 \cdot \Delta T E \cdot \Delta \chi_{\text{do}} \cdot \text{Hct} \left(\cos^2 \theta - \frac{1}{3}\right)} \tag{11}
\]

To quantify OEF using the phase-based method, gradient-recalled-echo (GRE) sequences with multiple TEs are typically used. Flow compensation is usually applied to minimize the flow-induced phase accumulation. Figure 5A shows an exemplary flow-compensated multi-echo GRE sequence. Because the vessel is assumed to be a long straight cylinder, phase-based methods usually focus on large cerebral veins that are relatively parallel to \( B_0 \), such as internal jugular veins (IJVs) and the SSS, which can provide an estimation of global \( Y_v \) (and OEF) similar to the TRUST method. Figure 5B shows exemplary data of phase-based OEF at the level of the SSS. Some studies have also extended this technique to quantify OEF in selected regional veins that can be approximated as a long cylinder (length to diameter ratio >5).

The accuracy of phase-based \( Y_v \) quantification relies on the calibration of \( \Delta \chi_{\text{do}} \). For normal human adult blood, early work by Weisskoff et al. found a \( \Delta \chi_{\text{do}} \) around 0.18 ppm (centimeter-gram-second [cgs] system of units). A later study by Spees et al. obtained a
\( \Delta \chi_{do} \) of 0.27 ppm (cgs) using three independent methods, including MR measurements, superconducting quantum interference device measurements, and theoretical estimates based on Curie’s law and blood magnetic properties reported by Pauling and Coryell. Another study by Jain et al. also found a \( \Delta \chi_{do} \) of approximately 0.27 ppm (cgs). A recent study by Eldeniz et al. reported that \( \Delta \chi_{do} \) was 0.19 ppm (cgs) for normal adult blood and the \( \Delta \chi_{do} \) of sickled blood was not significantly different. For human neonatal blood, Portnoy et al. found a \( \Delta \chi_{do} \) of 0.21 ppm (cgs).

The sensitivity of phase-based methods to OEF changes have been demonstrated in various physiological challenges, such as hypercapnia, hypoxia, acetazolamide administration, caffeine ingestion, and breath-hold apnea.

Phase-based methods have been integrated with phase-contrast MRI to simultaneously measure global OEF and CBF levels in a single sequence dubbed OxFlow. OxFlow demonstrated a CoV of 5% for global OEF quantification in same-day and day-to-day test–retest experiments. Recently, OxFlow has been shown to provide global OEF values with no systematic bias compared to \( ^{15} \)O-PET measurements on a porcine model. The original OxFlow sequence took 30 s. With extensive acceleration, the variants of OxFlow can achieve a temporal resolution of a few seconds.

It should be noted that actual cerebral veins often exhibit curvature and noncircular cross-sections, and thus, rarely conform to the straight cylinder model. For example, the SSS has a triangular cross-section. Fortunately, it has been demonstrated that the absolute error in \( Y_v \) caused by a non-circular cross-section is <5% when the vessel tilt angle is small \(( \theta < 30^\circ \)) . Alternatively, Driver et al. proposed using a forward field calculation that takes into account the exact shape of the vessel to estimate \( Y_v \). Another major source of error is the phase errors induced by background \( B_0 \) inhomogeneities, which can be approximated as a second-order polynomial and then removed from the phase difference calculations in Equations (6 and 7). In addition, to minimize partial-volume effects, sufficient image resolution is required. Finally, the processing of the data requires the manual drawing of extravascular ROIs, which must be approached carefully to minimize rater dependence.

### 3.3 Methods based on quantitative susceptibility mapping

To estimate OEF in local veins with an arbitrary orientation and geometry, quantitative susceptibility mapping (QSM) methods have been developed. QSM solves the general inverse problem of determining regional \( \Delta \chi \) from \( \Delta \Phi \). Assuming that the vein is at least one-voxel wide, and thus, the \( \Delta \chi \) measured is linearly proportional to blood oxygenation but not due to blood volume fraction, regional \( Y_v \) can be estimated using Equation (4). As mentioned earlier, this inverse problem is complex and ill-conditioned. Various algorithms have been proposed to solve this problem and quantify \( Y_v \) and OEF in local veins, such as thresholded \( k \)-space division and L1-regularization. To further correct for the flow-induced phase errors in the veins, an adaptive-quadratic fitting method has been proposed. A potential caveat of these methods is that they may be sensitive to partial volume effects, i.e., the voxel is not 100% blood, which will result in an overestimation of venous oxygenation (thus underestimation in OEF), especially for small veins. Partial volume correction algorithms may be useful in improving the accuracy of OEF quantification.

In addition to local veins, QSM-based methods have been extended to measure voxel-wise OEF. This method does not require the vein(s) to occupy the entire...
voxel. For an arbitrary voxel in the brain, its susceptibility has contributions from various sources, including blood and non-blood tissues. To decouple these factors, QSM and CBF (e.g., using ASL) can be acquired in two isometabolic brain states to correct for the non-blood contributions (e.g., from tissue ferritin), which are assumed to remain the same between the two states. This has been carried out by using physiological challenges, such as caffeine ingestion, hyperventilation, hypercapnia, or hyperoxia. These challenges are generally considered to be isometabolic (i.e., does not change CMRO₂), although controversial findings exist in the literature. The blood contribution arises from both venous and arterial blood and is modulated by their respective cerebral blood volume (CBV). In these QSM-based methods, total CBV was estimated from CBF data by assuming CMRO₂ to have minimum local variance. A caveat of these methods is the large number of assumptions, for example, CBF-CBV relationship, arterial–venous CBV fractions, isometabolic challenge, and registration between EPI-based low-resolution ASL and GRE-based high-resolution QSM images. In addition, the accuracy of the measurement is expected to strongly depend on the reliability of the ASL CBF estimation in both baseline and challenged states, in the presence of confounding factors such as labeling efficiency, bolus arrival time, and arterial contaminations.

A few studies have compared QSM-based OEF measurements to PET-based OEF in healthy volunteers and in patients with arterial steno-occlusive diseases, in which the affected hemisphere is likely to have an elevated OEF. These studies showed significant correlations between QSM and PET in both the absolute OEF values and the affected/contralateral OEF ratio, although systematic biases were also reported.

### 3.4 Quantitative BOLD

Unlike the T₂-based and susceptibility-based methods that focus on the effect of blood oxygenation on “intravascular” signals, the quantitative BOLD (qBOLD) model focuses on the signal decay in the “extravascular” space due to the local field inhomogeneities induced by the paramagnetic deoxyhemoglobin in the vessel network. When studying the transverse signal decay due to deoxyhemoglobin, conventional BOLD models consider that the decay rate is related to both oxygenation level (i.e., OEF) and blood volume, but are unable to separate the effects of these two terms. That is, a faster BOLD signal decay could be due to either lower blood oxygenation or larger blood volume. Yablonskiy and colleagues, on the other hand, proposed a “static dephasing regime” BOLD model, in which the vessels were considered an ensemble of randomly oriented cylinders. The key advantage of this model is that the oxygenation and blood volume effects can be separated experimentally. Specifically, two asymptotic equations can be derived to describe the signal behavior around a spin-echo:

\[
\ln(S_s(\tau)) = \ln(S(0)) - (TE + \tau) \cdot R_2 \cdot 0.3 \cdot DBV \cdot (\delta \omega \cdot \tau)^2, \\
\text{if } |\tau| < 1.5/\delta \omega
\]

\[
\ln(S_v(\tau)) = \ln(S(0)) - (TE + \tau) \cdot R_2 \cdot R_2' \cdot |\tau| + DBV, \\
\text{if } |\tau| > 1.5/\delta \omega
\]

where \(\tau\) is the time gap between image acquisition and the spin-echo (\(\tau\) is negative if the image is sampled before the spin-echo); \(S_s\) and \(S_v\) are the extravascular tissue signal for short and long \(\tau\), respectively; \(R_2\) is the tissue transverse relaxation rate; and \(DBV\) is the deoxygenated blood volume, to which the veins mainly contribute, but which also contains the part of capillary adjacent to the venous side. TE here is the time of the spin-echo. \(\delta \omega\) is the deoxyhemoglobin-induced frequency shift; \(R_2'\) is the radiofrequency reversible transverse relaxation rate (\(R_2' = R_2 - R_2\)) and has the following relationship:

\[
R_2' = DBV \cdot \delta \omega = DBV \cdot \gamma \cdot \frac{4}{3} \cdot \pi \cdot \Delta \chi_{\text{do}} \cdot Hc \cdot (1 - Y_t) \cdot B_0
\]

Figure 6 shows a schematic of the qBOLD model. The linear part of the model (Equation 13) is used to measure \(R_2'\), while the mismatch between the fitted linear intercept and the spin-echo signal allows estimation of DBV. OEF can then be calculated using Equation (14).

To quantify OEF using the qBOLD model, many studies have used a Gradient-Echo-Sampling-of-Spin-Echo (GESSE) sequence, in which multiple gradient echoes are acquired with varying \(\tau\) from the spin-echo of a fixed TE. Figure 7 shows exemplary \(R_2'\). DBV, and OEF maps acquired with GESSE-based qBOLD. However, one drawback of this sequence is the varying \(R_2\)-weighting among the gradient echo signals (Equation 13), which must be accounted for when quantifying \(R_2'\). Alternatively, An et al. proposed an Asymmetric-Spin-Echo (ASE) sequence in which the position of the 180° refocusing pulse was varied to yield a different \(\tau\) while keeping...
FIGURE 6 Schematic of the qBOLD model describing the transverse MR signal decay in the presence of a blood vessel network. $R_2'$ is inferred from the monoeponential regime ($T_c = 1.5/6\omega$, Equation 13) and DBV is inferred from the mismatch between the linear intercept of this fit and the spin echo signal ($\tau = 0$ ms). Baseline OEF can then be estimated by combining these two measurements. Adapted from Stone et al.\textsuperscript{132} with permission

Because the separation of the DBV and OEF effects in the qBOLD model relies on subtle differences in decay patterns (Equations 12 and 13), accurate estimation of DBV and OEF from the GESSE or ASE signals requires high SNR.\textsuperscript{131,144,145} To address this problem, several groups have developed a multiparametric-qBOLD (mqBOLD) scheme, in which CBV is measured using dynamic susceptibility contrast (DSC) MRI and $R_2'$ is estimated by separately mapping $R_2$ with a multiple spin-echo sequence and $R_2'$ by a multi-echo GRE sequence.\textsuperscript{146-148} However, the CBV measured by DSC is the total CBV rather than DBV. Therefore, the OEF produced by mqBOLD is a relative OEF.\textsuperscript{147,148}

Alternatively, DBV could be separately measured through a hyperoxia challenge\textsuperscript{149} or by using velocity-selective labeling techniques,\textsuperscript{150,151} while $R_2'$ could be quantified using sequences similar to GESSE or ASE.\textsuperscript{138,152,153} Stone et al. reported that OEF values obtained with separate DBV measurement had substantially better agreement with TRUST global OEF than those obtained using DBV values estimated from the ASE signal.\textsuperscript{152,153} This highlighted the importance of accurate DBV measurement in qBOLD-based OEF quantification.

A caveat of the qBOLD method is that the model described in Equations (12–14) considered a single extracerebral tissue compartment and assumed that $R_2'$ is only related to the deoxygenated blood.\textsuperscript{26,131} However, in reality, $R_2'$ is also sensitive to macroscopic B_0 inhomogeneity, which must be corrected either prospectively, using the z-shimming method,\textsuperscript{132,154} or retrospectively, using a high-resolution field map,\textsuperscript{135} or by modeling the voxel spread function.\textsuperscript{155,156} An actual imaging voxel can also contain other compartments, such as intravascular blood and CSF or interstitial fluid (ISF). To address this issue, He et al. extended the original qBOLD model to incorporate contributions from other compartments.\textsuperscript{135} However, solving this multi-compartmental model requires prior knowledge about the tissue composition and results in a large number of fitting parameters.\textsuperscript{135} Alternatively, contributions from other compartments can be minimized to...

FIGURE 7 qBOLD parametric maps from a representative subject. DBV, OEF, and $R_2'$ maps are presented alongside an anatomic image. Adapted from He et al.\textsuperscript{135} with permission
simplify the model. For example, the intravascular contribution can be reduced by using flow crushing gradients,\textsuperscript{136} and the CSF/ISF signal can be suppressed by using a fluid-attenuated-inversion-recovery preparation pulse.\textsuperscript{132} Another important assumption of the qBOLD model is “static dephasing,” that is, neglecting the diffusion effects. However, it has been shown that diffusion introduces a vessel size-dependent effect on the signal decay, and ignoring this diffusion effect may lead to a systematic underestimation of OEF.\textsuperscript{157–160}

### 3.5 Dual-calibrated fMRI

BOLD-based calibrated fMRI is a method to quantify changes in oxygen metabolism in response to neural stimuli.\textsuperscript{161,162} A detailed review of calibrated fMRI is outside the scope of this article, and interested readers are referred to other dedicated reviews.\textsuperscript{163} In this section, we will focus on a subset of calibrated fMRI techniques, dubbed dual-calibrated fMRI (dc-fMRI), which allows quantification of baseline OEF.\textsuperscript{22–24}

The R\textsuperscript{2}-weighted BOLD signal is dependent on CBV and the concentration of deoxyhemoglobin. Specifically, the relative BOLD signal change can be written as:\textsuperscript{161,162}

\[
\frac{\Delta \text{BOLD}}{\text{BOLD}_0} = M \left(1 - \left(\frac{\text{CBF}_1}{\text{CBF}_0} \right)^a \left(1 - \frac{1}{Y_{v,1}} \right)^{\beta} \right)
\]  \hspace{1cm} (15)

where the parameter M, the so-called calibration constant, is a composite constant related to field strength and TE, among other factors, and represents the maximum possible BOLD signal change that can be observed from the voxel. The subscript “0” denotes the baseline values while the subscript “1” denotes challenged state values. The constant a is the so-called “Grubb exponent” and is used to infer CBV from CBF (CBV \(\propto\) CBF\textsuperscript{a}). The constant a was initially measured to be 0.38 by Grubb et al.,\textsuperscript{121} while later studies have suggested a lower a value of \(\sim 0.2\).\textsuperscript{154,155} The constant \(\beta\) indicates the relationship between deoxyhemoglobin concentration and R\textsuperscript{2}, and is dependent on vascular morphology, water diffusion, and the field strength, typically assumed to be 1.3 or 1.5 at 3T field strength.\textsuperscript{22–24,161,166–168}

Equation (15) is a general expression and is applicable to a variety of challenges, such as task activation and physiological maneuvers. The dc-fMRI OEF method applies this relationship to two gas inhalation regimes, hypercapnia and hyperoxia, to estimate baseline OEF.

First, hypercapnia via CO\textsubscript{2} inhalation is used to determine M. The MRI data acquisition involves the measurement of both BOLD and CBF (via ASL) at baseline and during the hypercapnia challenge. Based on Equations (2, 3, 15), we can derive that:

\[
\frac{\Delta \text{BOLD}_{hc}}{\text{BOLD}_0} = M \left(1 - \left(\frac{\text{CBF}_{hc}}{\text{CBF}_0} \right)^a \left(\frac{\text{CMRO}_{2, hc}}{\text{CMRO}_{2,0}} \right)^{\beta} \right)
\]  \hspace{1cm} (16)

where the subscript “hc” denotes the values during hypercapnia. Under the assumption that hypercapnia is isometabolic (CMRO\textsubscript{2, hc} = CMRO\textsubscript{2,0}), M can then be estimated based on the hypercapnia-induced BOLD signal change and CBF change.

Next, a hyperoxia challenge is applied while BOLD and CBF changes are measured. To apply Equation (15) to hyperoxia, CMRO\textsubscript{2} is again assumed to be unchanged and the \(\frac{1-Y_{v,0}}{1-Y_{v,1}}\) term is rewritten as:\textsuperscript{24}

\[
\frac{1 - Y_{v, ho}}{1 - Y_{v,0}} = \frac{\text{CBF}_0}{\text{CBF}_{ho}} - \frac{1}{1 - Y_{v,0}} \left\{ \frac{1}{C_{hb}[Hb]} \left( \text{CaO}_2, ho \right) - \left( \frac{\text{CBF}_0}{\text{CBF}_{ho}} \right) \left( \text{CaO}_2, ho \right) + \frac{\text{CBF}_0}{\text{CBF}_{ho}} - 1 \right\}
\]  \hspace{1cm} (17)

where the subscript “ho” denotes the values during hyperoxia. [Hb] is the total hemoglobin concentration. C\textsubscript{hb} is the oxygen-carrying capacity of hemoglobin (59.8 \(\mu\)mol O\textsubscript{2}/gram hemoglobin).\textsuperscript{28} CaO\textsubscript{2} is the arterial oxygen content. Here, CaO\textsubscript{2} must consider the dissolved oxygen (which is no longer negligible), in addition to hemoglobin-bound oxygen, and can be written as:\textsuperscript{24}

\[
\text{CaO}_2 = C_{hb} \cdot [Hb] \cdot \frac{1}{\left( \frac{23400}{(P_aO_2) + 150} P_aO_2 + 1 \right)} + P_aO_2 \cdot \varepsilon
\]  \hspace{1cm} (18)

where the first term represents O\textsubscript{2} bound to hemoglobin while the second term is the dissolved O\textsubscript{2} in blood plasma. P\textsubscript{a}O\textsubscript{2} is the arterial oxygen partial pressure and can be approximated by the end-tidal oxygen partial pressure (P\textsubscript{ET}O\textsubscript{2}) measurement. \(\varepsilon\) is the coefficient of solubility of oxygen in blood (0.138 \(\mu\)mol O\textsubscript{2}/dL blood/mm Hg O\textsubscript{2} tension).\textsuperscript{48,169} Finally, based on Equations (2, 15–17), we can derive that:

\[
\text{OEF}_0 = 1 - Y_{v,0}
\]

\[
= \frac{1}{C_{hb} \cdot [Hb]} \left( \text{CaO}_2, ho - \left( \frac{\text{CBF}_0}{\text{CBF}_{ho}} \right) \text{CaO}_2, ho \right) + \frac{\text{CBF}_0}{\text{CBF}_{ho}} - 1
\]

\[
= \frac{\text{CBF}_0}{\text{CBF}_{ho}} \left( 1 - \frac{\Delta \text{BOLD}_{ho}}{\text{BOLD}_0} M \right) \left( \frac{\text{CBF}_0}{\text{CBF}_{ho}} \right)^{\frac{1}{\beta}} \left( \frac{\text{CBF}_0}{\text{CBF}_{ho}} \right)^{\frac{1}{\beta}}
\]  \hspace{1cm} (19)

Therefore, baseline OEF can be measured by acquiring the BOLD signal, CBF, and P\textsubscript{ET}O\textsubscript{2} (to estimate CaO\textsubscript{2} per Equation 18) at baseline and during two gas challenges: hypercapnia to calibrate M and hyperoxia to factor out
(1 − \(Y_{V,0}\)). A schematic of dc-fMRI experiments is shown in Figure 8.\(^{170}\) The total duration of a dc-fMRI experiment is typically about 18 min.\(^{22–24,170}\)

To simultaneously acquire both BOLD and CBF images at the baseline and during gas challenges, one approach is to use an ASL sequence with a relatively long TE (\(\sim 20\) ms) to increase the BOLD weighting. The BOLD signal is then extracted by averaging the adjacent ASL label and control images, while CBF is calculated from the label-control difference.\(^{23}\) However, the TE used in this approach is suboptimal for both ASL and BOLD, leading to a compromised contrast-to-noise ratio.\(^{170}\) Later studies of dc-fMRI have mainly used dual- or multi-echo ASL sequences in which the CBF images are acquired at an early echo with shortest TE to maximize SNR, while the BOLD images are acquired at a later echo with optimal BOLD contrast.\(^{22,24,119,167,171,172}\) The dual-echo sequence contains greater cross-talk between the CBF and BOLD effects. Thus, some studies have used dual-excitation schemes in which a conventional ASL readout is immediately followed by another excitation to acquire BOLD images.\(^{173–175}\)

Data processing of dc-fMRI is relatively complicated. One approach is to compute \(M\) and OEF separately using the hypercapnia and hyperoxia data,\(^{23}\) as described above, but may suffer from error propagations along the analysis pipeline. Alternatively, these parameters can be jointly estimated by fitting a generalized model using all data, which has been suggested to improve the robustness of OEF estimation.\(^{176}\) Machine-learning-based methods have also been proposed.\(^{177}\)

dc-fMRI allows simultaneous measurement of OEF, CBF, and CMRO\(_2\). In addition, cerebrovascular reactivity (CVR) can also be extracted from the dc-fMRI data,\(^{23,176}\) which itself is an important index of cerebrovascular health.\(^{178,179}\) Figure 9 shows exemplary parametric maps produced by dc-fMRI.\(^{23}\) The reproducibility of dc-fMRI measurements has been evaluated in two studies. Lajoie et al. reported a same-day CoV of 13.6% for OEF averaged across gray matter.\(^{180}\) Merola et al. showed that the CoV of OEF averaged across gray matter was 6.7% and 10.5% for same-day and day-to-day test–retest experiments, respectively.\(^{181}\) These CoV values are generally higher than some of the previously described methods. However, the advantage of the dc-fMRI method is that it provides spatially resolved maps of multiple hemodynamic and metabolic parameters in one scan. The sensitivity of dc-fMRI to OEF changes has been demonstrated in caffeine challenges.\(^{119}\)

A key assumption in dc-fMRI is that hypercapnia and hyperoxia do not change CMRO\(_2\). However, it is under debate whether these two challenges are truly “isometabolic.”\(^{47,48,58,94,115–118}\) Simulations have demonstrated that violation of the isometabolic assumption results in a bias toward OEF estimation.\(^{182,183}\) Several approaches have been developed to account for possible alterations of CMRO\(_2\) during gas challenges. Bulte et al. incorporated a fixed 10% reduction of CMRO\(_2\) during hypercapnia in the model fitting.\(^{23}\) Englund et al. proposed measuring global \(Y_v\) together with CBF and BOLD to relax the isometabolic mandate, assuming that \(Y_v\) changes induced by gas challenges are spatially uniform.\(^{184}\) Driver et al. proposed using graded hypercapnia to determine \(M\) and dose-wise CMRO\(_2\) alterations.\(^{117}\)

A limitation of dc-fMRI is the need for gas challenges, which require complex set-ups and can lead to a considerable dropout rate for patients due to the discomfort of hypercapnia.\(^{171}\) A recent study has proposed replacing gas challenges with breath-hold modulations to quantify OEF using the BOLD signal model.\(^{185,186}\)

Another limitation of the dc-fMRI method is that the reliability of the measure primarily hinges upon the quality of the ASL MRI data. ASL is known to suffer from low SNR even for basal perfusion measurement. The reliability of quantifying changes in CBF due to hypercapnia or hyperoxia requires further examination. In addition, the ASL signal may have confounding factors, such as bolus
arrival time, $T_2^*$, and labeling efficiency, which are also expected to alter during physiological challenges.\textsuperscript{123–126}

### 3.6 Comparison and combination among techniques

Table 1 shows a brief summary of the techniques described in previous sections and their strengths and weaknesses. In general, global OEF measurements have high SNR and some, such as TRUST and OxFlow, have been extensively tested and validated against gold standards.\textsuperscript{20,41,44,49,95,103} For the regional OEF measurement, a major challenge is the low SNR, because the local blood volume is very small and many techniques rely on complex model fittings that are sensitive to noise. Some authors have proposed exploiting machine-learning methods to denoise the OEF maps and reduce the computational cost.\textsuperscript{177,187,188} Future technical developments designed to improve the SNR are critical for the robustness of regional OEF measurement.

Several studies have compared the OEF values measured with different MRI-based techniques. For example, Barhoum et al. showed a significant correlation ($R^2 = 0.50$) between TRUST and OxFlow OEF measurements, while OxFlow yielded slightly lower OEF values.\textsuperscript{95} Significant correlations have also been reported between dc-fMRI and OxFlow\textsuperscript{189} and between dc-fMRI and a QSM-based regional OEF method ($R^2 = 0.39$),\textsuperscript{190} while dc-fMRI gave higher OEF values compared to the other two techniques. Overall, the correlations between different MRI methods were moderate and systematic differences in OEF quantification were observed.\textsuperscript{95,113,190–192}

Combinations of different MRI OEF techniques have been proposed.\textsuperscript{193,194} For example, Cho et al. combined the QSM model of the phase data and the qBOLD model of the magnitude data to estimate OEF from complex multi-echo GRE signals.\textsuperscript{194–196} As mentioned earlier, previous QSM methods required assumptions about the CBF-CBV relationship to estimate CBV from CBF data (measured by ASL).\textsuperscript{17,112–114,122} In the QSM + qBOLD method, CBV, $Y_v$, and non-blood susceptibility are all treated as unknowns and are jointly estimated from the complex GRE signals, although the ratio of CBV to total CBV was still based on an assumption (0.77).\textsuperscript{194} Figure 10 shows representative parametric maps generated by the QSM + qBOLD method.\textsuperscript{194} Recently, this QSM + qBOLD method has been compared to $^{15}$O-PET.\textsuperscript{130} Although the averaged OEF values across subjects were not significantly different between QSM + qBOLD and $^{15}$O-PET, there has been no report of correlation between these two methods.\textsuperscript{130}

### 4 CLINICAL APPLICATIONS OF MRI-BASED OEF

In the following sections, we will highlight several clinical applications for the MRI-based OEF techniques, although this list of applications is not meant to be exhaustive.

#### 4.1 OEF across the human lifespan

A number of MRI studies have investigated the evolution of OEF from the fetus to elderly individuals.

For fetuses, a few studies have used QSM-based methods to measure $Y_v$ in the SSS in the fetal brain,\textsuperscript{197–201} and showed that the median $Y_v$ across fetuses decreased from 67.5% in the second trimester to 60.8% in the third trimester.\textsuperscript{200} Note that oxygen is delivered to the fetus from the placenta through the umbilical vein, which was reported to have an average oxygenation of 84%.\textsuperscript{202}

For newborn infants, several MRI techniques have been adapted to measure OEF in the neonatal brain, including $T_2$-based\textsuperscript{57,62,203–205} and phase-based\textsuperscript{206} methods. In healthy neonates, Liu et al. reported an average
| Method               | Exemplary pulse sequences                                                                 | Pros                                                                 | Cons                                                                                                                                 |
|----------------------|-------------------------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| T2-based global      | • TRUST\textsuperscript{50} • T2-TRIR\textsuperscript{57} • High-resolution T2 mapping\textsuperscript{55} | • High SNR                                                           | • Lack of spatial specificity • Dependence on T2-Y calibration model                                                            |
|                      |                                                                                           | • Short scan time                                                    |                                                                                                                                 |
|                      |                                                                                           | • Straightforward data processing                                   |                                                                                                                                 |
|                      |                                                                                           | • Excellent reproducibility                                          |                                                                                                                                 |
| T2-based regional    | • TRUPC\textsuperscript{62} • QUIXOTIC\textsuperscript{65} • VSEAN\textsuperscript{66}    | • Vessel-specific or voxel-wise mapping of OEF                       | • Low SNR • Dependence on T2-Y calibration model                                                                                   |
| Phase-based global   | • OxFlow\textsuperscript{20} • Flow-compensated multi-echo GRE\textsuperscript{19}       | • High SNR                                                           | • Lack of spatial specificity                                                                                                                                                                |
|                      |                                                                                           | • Very short scan time                                               | • Restriction on vessel orientation and shape                                                                                                                                                 |
|                      |                                                                                           | • Excellent reproducibility                                          | • Dependence on manual drawings of vessel and tissue ROIs • $\Delta\chi_{do}$ of special RBCs not fully characterized                                                                     |
| QSM-based regional   | • Flow-compensated multi-echo GRE\textsuperscript{15–17}                                  | • Vessel-specific or voxel-wise mapping of OEF                       | • Susceptible to partial volume effect • Need for prior assumptions • Relatively long scan time                                                                                             |
| qBOLD                | • GESSE\textsuperscript{135} • ASE\textsuperscript{136}                                  | • Voxel-wise mapping of OEF                                          | • Complex signal model • Confounding factors such as macroscopic field inhomogeneity • Relatively long scan time                                                                          |
| dc-fMRI              | • Dual-echo ASL\textsuperscript{22,24}                                                   | • Voxel-wise mapping of OEF, CBF, CMRO$_2$ and CVR                  | • Need for gas challenges • Complex signal model • Low SNR due to the need to measure ASL during baseline and challenged states • Long scan time |
global OEF of 31.8 ± 4.1%, which was similar to the adult OEF level.\textsuperscript{204}

There is currently a paucity of human studies on age-related OEF changes in children of 1 to 18 years of age. A previous \textsuperscript{15}O-PET study found that OEF values in children were within the range of adult values regardless of the child’s age.\textsuperscript{207}

During adulthood, many MRI-based studies have reported an age-related increase in OEF,\textsuperscript{2,4,9,74,208–210} which was accompanied by a reduction in CBF.\textsuperscript{74,209,210} Results regarding CMRO\textsubscript{2} are mixed.\textsuperscript{74,209–211} An increase in OEF with age has also been suggested in recent studies using non-MRI techniques, such as \textsuperscript{15}O-PET\textsuperscript{212} and near-infrared spectroscopy\textsuperscript{213–215} in human subjects.

4.2 Cognitive impairment

AD and vascular disease, as well as their co-occurrence, are the most common causes of cognitive impairment.\textsuperscript{216} There are some suggestions that OEF is differentially affected by AD and vascular disease.\textsuperscript{2} For example, AD pathology will lead to diminished neural activities, and thereby decreased glucose and oxygen metabolism.\textsuperscript{217} Thus, a decreased OEF is expected in the presence of a relatively intact blood supply. On the other hand, small-vessel vascular pathology will cause a reduction in blood supply\textsuperscript{218,219} and result in an elevated oxygen extraction (Figure 11).\textsuperscript{2} This notion is consistent with other recent MRI studies, which reported reduced OEF in cognitively impaired patients with minimal vascular risk factors.\textsuperscript{3,171} In addition, it has been shown that, among cognitively normal individuals, the carriers of the apolipoprotein-E4 gene, a major genetic risk factor for AD, manifested diminished global OEF.\textsuperscript{75}

4.3 Cerebral large and small vessel diseases

In patients with unilateral stenosis/occlusion of major cerebral arteries, several MRI studies have reported an elevated OEF in the affected hemisphere,\textsuperscript{128,220–224} consistent with the “misery perfusion” pattern observed in previous \textsuperscript{15}O-PET studies,\textsuperscript{4,225–227} while a few other MRI studies found insignificant hemispheric differences in OEF.\textsuperscript{228–232}
MRI techniques have also been used to evaluate OEF in patients before or after carotid stenting/endarterectomy.\textsuperscript{233,234} In patients with Moyamoya disease, Watchmaker et al. found an elevated MRI-based global OEF\textsuperscript{235} while \textsuperscript{15}O-PET studies have reported mixed results.\textsuperscript{236–238} In patients with cerebral small-vessel disease, a recent MRI study found an elevated OEF in white matter and watershed regions, while the OEF in gray matter was decreased.\textsuperscript{239}

\subsection*{4.4 Stroke}

In acute ischemic stroke patients, a few MRI studies have reported that OEF was higher in the affected hemisphere than in the contralateral side.\textsuperscript{240–242} A study by An et al. further attempted to delineate the stroke penumbra using MRI-based OEF and CBF measures.\textsuperscript{243} Several other MRI studies have found a decreased CMRO\textsubscript{2}\textsuperscript{244–246} but increased OEF\textsuperscript{247} in the ischemic core of acute stroke patients.

A few studies reported elevated R\textsuperscript{′2} in ischemic tissues in acute stroke,\textsuperscript{248–251} but did not quantify OEF. Because R\textsuperscript{′2} is proportional to the product of OEF and DBV (see Section 3.4), consideration of DBV is crucial for the assessment of the extent of OEF changes using the R\textsuperscript{′2} data.\textsuperscript{248}

\subsection*{4.5 Sickle cell disease}

A number of studies have investigated OEF changes in SCD but reported inconsistent results. Several groups have measured global OEF in SCD using T\textsubscript{2}-based techniques,\textsuperscript{5,54,81,235,252–257} but the OEF results varied when different calibration models were used to convert blood T\textsubscript{2} to Y\textsubscript{v} (see Section 3.1.2).\textsuperscript{258} Studies using the bovine calibration model\textsuperscript{43} showed that OEF was higher in SCD patients than controls,\textsuperscript{235,252} and OEF was reduced after blood transfusion.\textsuperscript{253} In contrast, studies using the SCD-specific models\textsuperscript{5,81} have reported either a reduced OEF in SCD patients,\textsuperscript{2,254–256} or no significant difference in OEF between SCD patients and controls.\textsuperscript{54} One study used the neonatal calibration model\textsuperscript{78} and showed that elevated OEF was associated with impaired cognitive processing speed (assessed using National Institutes of Health Toolbox Cognition Battery) in SCD patients.\textsuperscript{257}

Another group used ASE-based qBOLD methods and consistently reported elevated whole-brain and regional OEF in children with SCD.\textsuperscript{6,259–262} In addition, in children receiving chronic transfusion therapy (CTT), CBF and OEF were reduced after transfusion, as shown in Figure 12.\textsuperscript{260}

Two studies used susceptibility-based techniques, and one found reduced OEF in the SSS,\textsuperscript{263} while another study showed elevated OEF in the ICVs in SCD patients.\textsuperscript{264}

The discrepancy in the literature suggests that the application of MRI-OEF techniques to pathological conditions with atypical RBC still presents some challenges. Future studies are needed to resolve the controversies in this field.

\subsection*{4.6 Brain injury}

In neonates, hypoxic ischemic encephalopathy (HIE) is a leading cause of neonatal mortality and neurological disabilities.\textsuperscript{265} A few MRI-based studies have reported that neonates with HIE had lower OEF than controls,\textsuperscript{57,266} and neonates with severe HIE had even lower OEF than those with moderate HIE,\textsuperscript{267} which is presumably due to a lower oxygen consumption rate.

In children and adults, traumatic brain injury (TBI) is among the most severe types of injury in terms of fatality and long-term impairment.\textsuperscript{268} Several MRI-based studies have suggested that OEF was reduced in patients with TBI.\textsuperscript{269–273} In addition, in patients with TBI, higher OEF predicted a better clinical outcome.\textsuperscript{269}

\subsection*{4.7 OEF in response to physiological challenges}

A number of studies have investigated the change in OEF and CMRO\textsubscript{2} under various physiological challenges, including hypercapnia,\textsuperscript{47,58,94,115–117,274} hypocapnia (e.g., induced by hyperventilation),\textsuperscript{112,115,275–277} hyperoxia,\textsuperscript{48,118,278,279} hypoxia,\textsuperscript{48,116,278,280–282} caffeine ingestion,\textsuperscript{17,46,101,119,283,284} acetazolamide injection,\textsuperscript{101,255,285} and acute glucose ingestion.\textsuperscript{286} Table 2 summarizes the OEF, CBF, and CMRO\textsubscript{2} changes under different physiological challenges.

\subsection*{4.8 Other applications}

Elevated OEF was reported in patients with end-stage renal disease,\textsuperscript{287–289} hepatic encephalopathy,\textsuperscript{290} systemic lupus erythematosus,\textsuperscript{291} refractory epilepsy,\textsuperscript{292} and chronic cannabis usage.\textsuperscript{293} Increased OEF was also found in children with primary nocturnal enuresis\textsuperscript{294} and in preterm neonates with anemia.\textsuperscript{295}

Reduced OEF was shown in patients with MELAS syndrome\textsuperscript{296} and multiple sclerosis,\textsuperscript{297,298} as well as in neonates with punctate white matter lesions.\textsuperscript{299}
FIGURE 12  CBF and OEF maps from a child with SCD. This 7-y-old boy was first scanned before the initiation of CTT. After 17 mo of CTT, he was scanned before and after exchange transfusion. The whole-brain CBF was highest at his first scan; after 17 mo of CTT, his pre-transfusion CBF was lower than the initial scan and the post-transfusion CBF was further decreased. OEF was highest at the first scan but was dramatically reduced pre-transfusion and further decreased post-transfusion. Reproduced from Guilliamset al. 260 with permission.

TABLE 2  OEF, CBF, and CMRO2 under physiological challenges

| Physiological challenge | CBF | OEF (or AVDO2) | CMRO2 |
|-------------------------|-----|----------------|-------|
| **Hypercapnia**         | Increased 47,58,94,116,274 | Decreased 47,58,94,116,274 | Mixed literature reporting decreased 47,116,117,274 or unchanged 84,115 |
| **Hypocapnia**          | Decreased 112,115,275–277 | Increased 112,115,275–277 | Unchanged 112,115,275–277 |
| **Hyperoxia**           | Decreased 48,315 or Unchanged 118,278,279 | Decreased 48,118,278,279 | Mixed literature reporting decreased 48 or unchanged 118,278,279 |
| **Hypoxia**             | Increased 48,116,278,280,281 or Unchanged 282 | Decreased 48,278,280–282 | Mixed literature reporting increased 48,116,280,281 or unchanged 278,282 |
| **Caffeine**            | Decreased 17,46,101,119 | Increased 17,46,101,119 | Mixed literature reporting decreased 17 increased 283 or unchanged 46,284 |
| **Acetazolamide**       | Increased 101,255,285 | Decreased 101,255,285 | Unchanged 101,255,285 |
| **Acute glucose ingestion** | Unchanged 286 | Decreased 286 | Decreased 286 |

OEF and CMRO2 have also been studied in patients with glioma, 7,300–306 mountain sickness, 281 cocaine addiction, 307 anorexia, 308 bipolar disorder, 309 metabolic disorder, 310 and obstructive sleep apnea. 311,312 In addition to disease-related changes, alterations in OEF and CMRO2 have also been observed during natural sleep 313 and after fatiguing aerobic exercise. 314

5  | CONCLUSIONS

This review article provides an overview of emerging MRI techniques for OEF measurement. A number of MRI techniques have been developed over the past few years, and each has strengths and limitations. These MRI techniques have been applied in a range of physiological or
pathological conditions. Once further optimized, these techniques have strong potential for use in various basic science and clinical applications.

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**How to cite this article:** Jiang D, Lu H. Cerebral oxygen extraction fraction MRI: Techniques and applications. *Magn Reson Med*. 2022;88:575-600. doi: 10.1002/mrm.29272