**In Vivo \(^{17}\)O MR Imaging and Quantification of CMRO\(_2\), CBF and OEF in Human Visual Cortex at Rest and during Activation**

Xiao-Hong Zhu\(^1\), Xiao Lin\(^1\), Ming Lu\(^1\), Hannes M Wiesner\(^1\), Kamil Urgubil\(^1\), and Wei Chen\(^1\)

\(^1\)CMRR, Department of Radiology, University of Minnesota Medical School, Minneapolis, MN, United States

**Introduction**

Oxygen consumption occurs in the mitochondrial respiratory chain to form ATP for supporting the energy needs in the brain and other aerobic organs. In vivo \(^{17}\)O MRSI has unique ability for assessing cerebral oxygen metabolism via imaging the dynamic change of the metabolic H\(_2\)O\(_2\) according to the reaction of \(4H^+ + 4e + \ ^{17}O_2 \rightarrow 2H_2O\). However, the cerebral metabolic rate of oxygen (CMRO\(_2\)) in human is difficult to quantify due to the large body size and slow exchange between the labeled and non-labeled oxygen gases in the lung as compared to small animals. This issue could become more problematic for a short \(^{17}\)O inhalation experiment. In this study, a simple and practical approach was proposed for measuring gas exchange rate of lung, which was incorporated into a comprehensive modeling for simultaneously determining three important physiology parameters of CMRO\(_2\), CBF and OEF in the human brain with a brief \(^{17}\)O inhalation time of 2-3 minutes. This new approach was tested in the human visual cortex under resting and visual stimulation conditions.

**Theory**

The quantification method is based on following mass balance equation 3.4

\[
\frac{dC(t)}{dt} = 2 \cdot \text{CMRO}_2 \cdot \alpha(t) + \text{CBF} \cdot \left(C(t) - \frac{C(t)}{\lambda}\right) \quad \text{Eq. [1]}
\]

where \(C(t), C_i(t)\) and \(C_f(t)\) are the metabolic \(^{17}\)O\(_2\) concentration in excess of the natural abundance \(^{17}\)O\(_2\) concentration in the arterial blood, brain tissue and venous blood; respectively; \(\alpha(t)\) is the \(^{17}\)O enrichment fraction of oxygen molecule in the artery blood; CBF is cerebral blood flow; \(\lambda\) is the brain/blood partition coefficient (\(\approx 0.90\)ml/g). For a small animal, \(\alpha(t)\) can be approximated as a constant equal to the \(^{17}\)O enrichment fraction of inhaled \(^{17}\)O\(_2\) gas (\(\phi\)) due to fast gas exchange occur in the lung and rapid blood circulation. Unfortunately, this approximation does not apply to human, since \(\alpha(t)\) varies with the inhalation time especially during the initial \(^{17}\)O\(_2\) inhalation period. In this study, we proposed to experimentally determine the oxygen exchange function of \(\alpha(t)\) in the human, where \(k\) represents the exchange rate constant, and this function can be incorporated into Eq. [2].

\[
\frac{d\alpha(t)}{dt} = \frac{F_{AV} \cdot \left(\alpha_i - (1 - e^{-\phi}) \cdot \alpha(t)\right)}{T_{i1}} \quad \text{Eq. [2]}
\]

\(\frac{d\alpha(t)}{dt} = \frac{F_{AV} \cdot \left(\alpha_i - (1 - e^{-\phi}) \cdot \alpha(t)\right)}{T_{i1}} \quad \text{Eq. [2]}
\]

where \(F_{AV} = 0.3\) is the arteriovenous difference of oxygen saturation fraction and \(T_{i1} = 20\)s is the averaged blood circulation time from lung to lung. Solving Eq. [2] led to an analytical solution of \(\alpha(t)\), then \(C_i(t)\) can be estimated according to the integral of \(\alpha(t)\) function: \(C_i(t) = A \cdot \int_0^t \alpha(t) dt\) (\(A\) is a scaling factor); thus

\[
\frac{dC(t)}{dt} = 2 \cdot \text{CMRO}_2 \cdot \alpha(t) + A \cdot \text{CBF} \cdot \int_0^t \alpha(t) dt \quad \text{Eq. [3]}
\]

where \(t\) is the inhalation time, and the solution of Eq. [3] can be presented as \(C_i(t) = f(CMRO_2, A, CBF, t)\) with known constants of \(F_{AV}, T_{i1}, \alpha_i\), and \(t\) (2-3 min) and experimentally measured \(k\). The least square fitting algorithm can be performed for each \(C_i(t)\) time course measured during and after \(^{17}\)O\(_2\) inhalation for determining two important physiology parameters of CMRO\(_2\) and CBF, then, oxygen exchange fraction (OEF) can be calculated according to Eq. [4]

\[
\text{OEF} = \frac{\text{CMRO}_2}{\text{CBF} \cdot C_{a,o}} \times 2.24 \quad \text{Eq. [4]}
\]

where \(C_{a,o}\) is the artery oxygen content (\(\approx 18.5\)ml/dL) and 2.24 is a unit conversion factor.

**Method**

In vivo \(^{17}\)O MRSI experiments of human occipital lobe were conducted on a 90 cm bore 7T human magnet (Magnex Scientific, UK) using a \(^{17}\)O\(_2\) surface coil (7.5cm diameter) tuned to 40 MHz and 3D Fourier series window (FSW) MRSI technique (11 s per image volume and 3.5 ml voxel size). The \(^{17}\)O MRSI was acquired before, during and after a 2-3 minutes inhalation of \(^{17}\)O\(_2\) (\(\approx 89\%)\) with a total data acquisition time of 18 minutes. Two \(^{17}\)O\(_2\) inhalations were carried out on the same subject with and without visual stimulation (an 8Hz reversal checkerboard was used for visual stimulation starting one minute before \(^{17}\)O\(_2\) inhalation and lasted for 10 minutes). For measuring \(\alpha(t)_{\text{inhalation}}\) we designed an breathing experiment, in which the level of exhaled oxygen gas and its rate to reach a new steady-state were monitored when the inhaled gas was quickly switched from normal air to a gas mixture containing higher level oxygen for several minutes. The dynamics of the oxygen content in the exhaled air was captured with a commercial gas monitor commonly used in hospitals, which approximates \(\alpha(t)_{\text{inhalation}}\) and can be used to fit the constant of \(k\).

**Results**

Figure 1 shows the breathing test for determining \(k\) constant in a representative human subject and the time courses of exhaled oxygen gas when the inhaled mixture was switched from normal air to an air mixture containing 60% oxygen (left). The exchange rate of the oxygen gas in the lung can be determined via exponential fitting the signals of exhaled oxygen gas (right), which provides \(k\) value.

**Discussion and Conclusions**

Our preliminary results suggest that: 1) in vivo \(^{17}\)O MRSI at high field is sensitive and reliable for assessing brain oxygen metabolism and perfusion; 2) the proposed quantification model provides good fitting to the experimental data of brain H\(_2\)O\(_2\) signals; 3) the measurement of \(k\) is robust and critical for the CMRO\(_2\) quantification in human; 4) the measured CMRO\(_2\) values in resting human brains agree well with the literature; 5) CMRO\(_2\) increases significantly during visual stimulation, however, its percent change is smaller than that of CBF; 6) the unmatched CBF and CMRO\(_2\) changes in response to visual stimulation leads to an OEF decrease, thus, an increase of venous blood oxygenation level or positive BOLD contrast. In summary, the present study clearly demonstrates that high-field \(^{17}\)O MR-based neuroimaging modality together with a sophisticated quantification model are capable of noninvasive imaging three important physiology parameters of CMRO\(_2\), CBF and OEF under resting and activated human brain, and it should be useful for studying abnormal oxygen consumption in various brain diseases.

**Acknowledgement**

NIH grants N5057560, N5041262, N5070839, P41 EB015894, S10 RR026783 and P30 N5076408.

**References**