In Vivo ^{17}O MR Imaging and Quantification of $CMRO_2$, CBF and OEF in Human Visual Cortex at Rest and during Activation

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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 MRS/I has unique ability for assessing cerebral oxygen metabolism via imaging the dynamic change of the metabolic $H_2{}^{17}O$ during an inhalation of ^{17}O-isotope-labeled oxygen gas ($^{17}O_2$) [1-4] according to the reaction of $4H^+ + 4e + {}^{17}O_2 \rightarrow 2H_2{}^{17}O$. 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 compare to small animals. This issue could become more problematic for a short $^{17}O_2$ 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 $^{17}O_2$ 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 [2-4]

$$\frac{dC_b(t)}{dt} = 2 \cdot CMRO_2 \cdot \alpha(t) + CBF \cdot (C_a(t) - \frac{C_b(t)}{\lambda}) \qquad \text{Eq. [1]}$$

where $C_a(t)$, $C_b(t)$ and $C_v(t)$ are the metabolic $H_2{}^{17}O$ concentrations in excess of the natural abundance $H_2{}^{17}O$ 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; λ is the brain/blood partition coefficient ($\approx$ 0.90ml/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 (α_0) due to fast gas exchange occur in the lung and rapid blood circulation[5]. 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 ($\alpha(t)_{lung} = \alpha_0(1 - e^{-kt})$) in the human lung, where k represents the exchange rate constant, and this function can be incorporated into Eq. [2] [4]

$$\frac{d\alpha(t)}{dt} = \frac{F_{AV}}{T_{l\text{-}l}}(\alpha_0 \cdot (1 - e^{kt}) - \alpha(t)) \qquad \text{Eq. [2]}$$

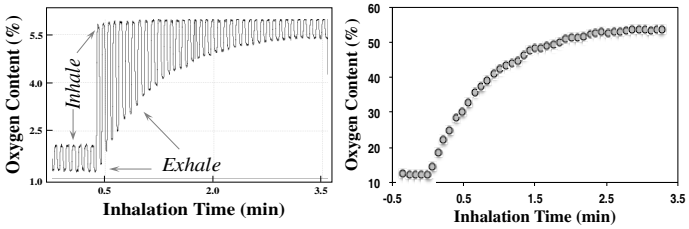

Figure 1. The oxygen time course of a breathing test in a representative human subject when the inhaled gas mixture was quickly switched from normal air to an air mixture containing 60% oxygen (left). The exchange rate of the oxygen gas in the lung can be determined via exponential fitting the signals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

where F_{AV} ($\approx$0.3) is the arteriovenous difference of oxygen saturation fraction[6] and $T_{l\text{-}l}$ ($\approx$20s) is the averaged blood circulation time from lung to lung[4]. Solving Eq. [2] led to an analytical solution of $\alpha(t)$, then $C_a(t)$ can be estimated according to the integral of $\alpha(t)$ function: $C_a(t) = A \cdot \int_0^t \alpha(t)dt$ (A is a scaling factor); thus

$$\frac{dC_b(t)}{dt} = 2 \cdot CMRO_2 \cdot \alpha(t) + A \cdot CBF \cdot \int_0^t \alpha(t) - CBF \frac{C_b(t)}{\lambda} \qquad \text{Eq. [3]}$$

where t_i is the inhalation time, and the solution of Eq. [3] can be presented as $C_b(t) = f$ ($CMRO_2$, A, CBF/λ, t) with known constants of F_{AV}, $T_{l\text{-}l}$, α_0 and t_i (2-3 min) and experimentally measured k. The least square fitting algorism can be performed for each $C_b(t)$ time course measured during and after $^{17}O_2$ inhalation for determining two important physiology parameters of $CMRO_2$ and CBF, then, oxygen extraction fraction (OEF) can be calculated according to Eq. [4]

$$OEF = \frac{CMRO_2}{CBF \cdot C_{a,O_2}} \times 2.24 \qquad \text{Eq. [4]}$$

where C_{a,O_2} is the artery oxygen content (=18.5ml/dL)[7] and 2.24 is a unit conversion factor[8].

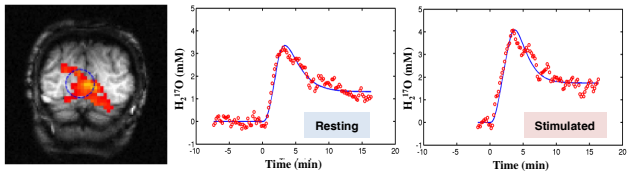

Figure 2. A visual stimulation induced fMRI map with ROI lication indicated on the map. The time courses of the ROI at rest and during visual stimulation are also shown here where both the original signals (red circle) and model fitting (blue trace) were displayed.

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 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 $^{17}O_2$ (α_0=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 $\alpha(t)_{lung}$, 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 $\alpha(t)_{lung}$ 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. It provides readouts of $\alpha(t)_{lung}$ and k, indicating a slow lung gas exchange in the human. The k value could varied significantly among different subjects and was ranging ~1.7 - 3.2 min^{-1} based on measurements in a group of normal subjects (n=6). Figure 2 shows a fMRI map with a selected ROI in the activated visual cortex, and the corresponding $H_2{}^{17}O$ signal dynamics under resting and visual stimulation conditions, as well as the regression lines based on the proposed quantification model, which were used to derive $CMRO_2$, CBF and OEF values with k=2.4 min^{-1}. The results reveals that $CMRO_2$ increased from 1.57 μmole/g/min at rest to 1.78 μmole/g/min under visual stimulation in this particular ROI; in contrast, CBF changed from 0.62 ml/min to 0.93 ml/min for the individual data shown in Fig. 2. The averaged changes of $CMRO_2$, CBF and OEF from activated voxels were 1.59 μmole/g/min, 0.64 ml/min and 0.30 at rest, and 1.75 μmole/g/min, 0.96 ml/min and 0.22 under stimulation, revealed 10% increase of $CMRO_2$, 50% increase of CBF and 27% decrease of OEF.

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 $H_2{}^{17}O$ 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.

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