Ultra-fast In Vivo Measurement of CMRO2 in Rat Brain in Seconds: A ^{17}O NMR Study at 9.4 Tesla

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Introduction: The determination of the cerebral metabolic rate of oxygen utilization ($CMRO_2$) is essential for understanding the central role of oxidative metabolism in brain function under physiological and pathological states. The simplest MR method for measuring $CMRO_2$ is the use of ^{17}O MRS to directly detect the labeled $H_2{}^{17}O$, which is metabolized from inhaled $^{17}O_2$ (1-3). The complete model for $CMRO_2$ calculation is based on the equation established by Kety and Schmitz as shown in Eq. [1], in which α is ^{17}O enrichment of inhaled $^{17}O_2$, C_a, C_b and C_v are the $H_2{}^{17}O$ concentration expressed *in excess of the natural abundance* $H_2{}^{17}O$ *concentration* in the arterial blood, brain tissue and venule blood, respectively, as a function of $^{17}O_2$ inhalation time *t*.

$$\frac{dC_b(t)}{dt} = 2\alpha CMRO_2 + CBF(C_a(t) - C_v(t)) \qquad [1].$$

The calculation of $CMRO_2$ using Eq. [1] requires multiple measurements of $C_b(t)$ using ^{17}O MRS or MRS imaging (MRSI), $C_a(t)$ using ^{17}O MRS and implanted artery ^{17}O coil, and CBF using ^{17}O MRS/MRSI and $H_2{}^{17}O$ bolus injection (3). Such comprehensive measurements have been demonstrated to be feasible for imaging $CMRO_2$ in rat brain during 2 minutes of $^{17}O_2$ inhalation at 9.4T due to significant sensitivity gain of ^{17}O NMR signal at high fields (3,4). In this study, we explored the feasibility for ultra-fast measurements of $CMRO_2$ in rat with a temporal resolution of seconds at 9.4T.

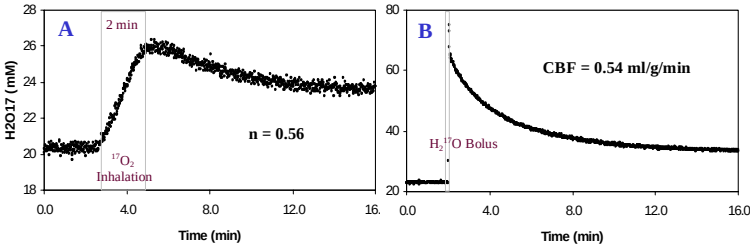

Figure 1. $H_2{}^{17}O$ concentration of a represent rat brain before, during and after (A) 2 min $^{17}O_2$ inhalation and (B) $H_2{}^{17}O$ bolus injection with 1 sec resolution.

Methods: All experiments were conducted on a 9.4 Tesla Magnex magnet interfaced to a Varian INOVA console. The rats were intubated and anesthetized with α-chloralose. Femoral artery and vein were catheterized for physiological monitoring and blood sampling. A multinuclear surface-coil probe consisting of an oval-shape ^{17}O coil (1 cm × 2 cm) and a butterfly-shape ^{1}H coil was used. The spatial localization of ^{17}O signal was achieved through the spatially limited B_1 profile of the ^{17}O surface coil, which covers the most of rat brain and a small portion of muscle. The single-pulse acquisition sequence was used to collect ^{17}O spectra with the acquisition parameters of 10 ms TR, 50 μs pulse width for a nominal 90^0 spin excitation, spectral width=30 kHz and 100 averages (1 second temporal resolution). The same sequence was applied to acquire ^{17}O spectra for determining $C_b(t)$, $C_a(t)$ and CBF. The right internal carotid artery was catheterized for the injection of $H_2{}^{17}O$ bolus and measurements of CBF, which can be calculated from the "wash-out" of the labeled $H_2{}^{17}O$ from the brain tissue (4). Each rat performed a 2-minute inhalation of $^{17}O_2$ (72.1% enrichment) for determining $C_b(t)$. An implanted ^{17}O coil was used to detect $C_a(t)$ in the left carotid artery (5). A complete model (6) was used to calculate the $CMRO_2$ values in each second during the inhalation.

Results and Discussion: Figure 1A demonstrates a time course showing the change of the metabolic $H_2{}^{17}O$ concentration as a function of time (i.e., $C_b(t)$) in three periods: control (~3 min), inhalation (2 min) and post inhalation (~11 min). The control concentration presents the natural abundance $H_2{}^{17}O$ concentration (20.35 mM), which can be used to calibrate the absolute $H_2{}^{17}O$ concentrations for the entire time course. The metabolic $H_2{}^{17}O$ concentration increases significantly during the $^{17}O_2$ inhalation and starts a slow decay after the termination of the inhalation. Figure 1B shows the washout of the labeled $H_2{}^{17}O$ in the brain after a $H_2{}^{17}O$ bolus injection. The decay rate was used to calculate CBF and the ratio of this decay rate versus the decay rate measured in post-inhalation period as shown in Fig. 1A gave a constant of n = 0.56, which reflects the limited permeability of $H_2{}^{17}O$ across the mitochondria membranes in cells and it was used in the complete model for calculating $CMRO_2$ values (3). Figure 2A illustrated the time course of $CMRO_2$ during a 2-minute inhalation from a representative rat. The temporal resolution of this curve was 1 second. At initial inhalation period, the $H_2{}^{17}O$ signal increase was similar with the signal fluctuation leading to a large variation of the calculated $CMRO_2$. Another factor leading to offset of the initial calculated $CMRO_2$ from the true $CMRO_2$ is the transition time required to reach equilibrium for binding the inhaled $^{17}O_2$ to hemoglobin in blood. Nevertheless, the calculated $CMRO_2$ value rapidly reaches a constant value after approximately 15 seconds of inhalation. The constant value was similar with the true $CMRO_2$ value (1.32 μmol/g/min) averaged in the later inhalation period. The $CMRO_2$ value of 1.32 μmol/g/min is relatively lower than that measured in cortical areas using ^{17}O MRS imaging (3). This is presumably due to the partial tissue contamination from muscle with much lower $CMRO_2$. These results demonstrate the feasibility for determining $CMRO_2$ in vivo in a small rat brain with a fast temporal resolution of 1 second if the initial inhalation period (~15 seconds) is excluded. In addition, the fluctuations in the $CMRO_2$ time course in Fig. 2A can be significantly reduced by averaging several adjacent data points with reduced temporal resolution in a range of few seconds.

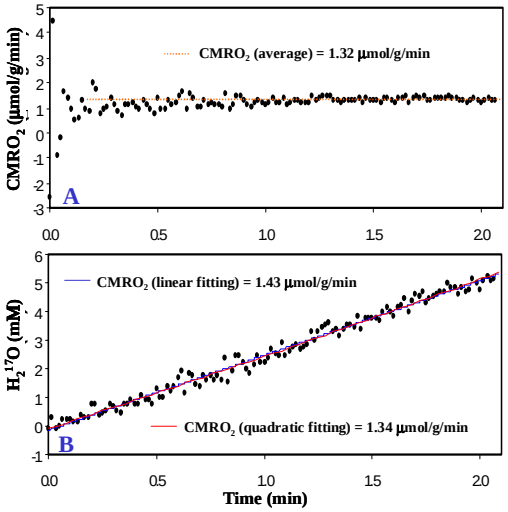

Figure 2. $H_2{}^{17}O$ concentration of a represent rat brain during 2 min $^{17}O_2$ inhalation and $CMRO_2$ values were calculated with completed (A) and simplified model (B) with 1s time resolution.

We have recently proposed a simplified model for noninvasive measurements of $CMRO_2$ using ^{17}O MRS. This model is based on the polynomial fitting of $C_b(t)$ measured in an $^{17}O_2$ inhalation, and the first order polynomial coefficient can be used to calculate $CMRO_2$ (6). The same model was used to test the data measured in this study. Figure 2B shows that both linear and quadratic fittings gave similar results (1.43 and 1.34 μmol/g/min, respectively) compared to the complete model (1.32 μmol/g/min). This result further validates the simplified model for noninvasive measurement of $CMRO_2$ in small animal brain.

Conclusion: In this work, we demonstrate the feasibility for ultra-fast measurements of $CMRO_2$ in rat with a temporal resolution of seconds. Such feasibility should be essential for monitoring the rapid changes of $CMRO_2$ by fast physiological and/or pathological perturbations. The ^{17}O sensitivity gain at high field is crucial for this study.

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