Estimation of CBF Based on the Metabolic $H_2{}^{17}O$ Decay Rate in $CMRO_2$ Measurement Using *In Vivo* ^{17}O MR Approach

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INTRODUCTION *In vivo* ^{17}O MRS imaging (MRSI) approach at high/ultrahigh field has been established for non-invasively mapping the cerebral metabolic rate of oxygen ($CMRO_2$) in small animals [1-3]. However, imaging of the cerebral blood flow (CBF) using the same ^{17}O MR approach usually requires invasive procedures for introducing the NMR-visible $H_2{}^{17}O$ as exogenous tracer [2, 4]. In the previous study, we have observed that the metabolic $H_2{}^{17}O$ water generated from a brief $^{17}O_2$ gas inhalation, which was commonly used for the $CMRO_2$ measurement, had a much slower washout (or decay) rate compared to that of $H_2{}^{17}O$ tracer, suggesting possible permeability restrictions in the mitochondrial and/or cellular membranes [1]. In the present study, we found that the decay rate of the metabolic $H_2{}^{17}O$ is still closely related to cerebral perfusion and its change; and a linear relationship between CBF and $H_2{}^{17}O$ decay rate can be determined experimentally from combined CBF and $CMRO_2$ measurements in the rat brains under varied physiological or pathological conditions.

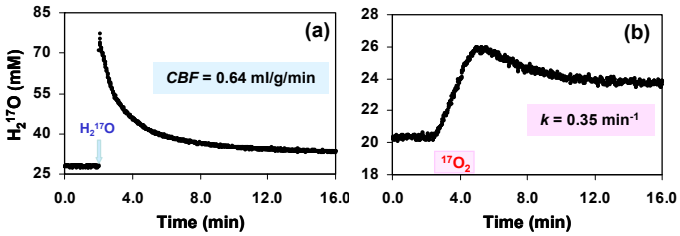

Figure 1 Typical ^{17}O MR approaches for imaging: (a) CBF following a bolus injection of $H_2{}^{17}O$ (blue arrow) into an internal carotid artery; and (b) $CMRO_2$ with an $^{17}O_2$ gas inhalation (purple bar). The value of CBF was determined by the $H_2{}^{17}O$ decay rate (k = 0.60 min^{-1}) in (a); while the $H_2{}^{17}O$ decay rate (k = 0.35 min^{-1}) in (b) after the $^{17}O_2$ inhalation is much slower than that of CBF measurement using the $H_2{}^{17}O$ bolus in the same rat brain.

METHOD All ^{17}O MRS/MRSI data and anatomic brain images were acquired on 9.4T/31cm horizontal animal magnet (Magnex Scientific, UK) interfaced with Varian INOVA console (Varian Inc., Palo Alto, CA). Male SD rats (250-350 g, n=9) were used in this study. These rats were divided into sub-groups and underwent different preparation. ***Group A*** (n=3): four-blood vessel occlusion (4BVO) model was used for performing acute (12 minutes) global forebrain ischemia in these rats anesthetized with α-chloralose (25mg/kg/hour). ***Group B*** (n=2): normocapnia ($FiCO_2$<1%) and hypercapnia ($FiCO_2$=3-7%) were applied for the rats in this group under isoflurane (~2%) and/or α-chloralose (25mg/kg/hour) anesthesia. ***Group C*** (n=1): this rat underwent three different anesthesia conditions which include isoflurane (~2%), low-dose pentobarbital (30mg/kg/hour) and high-dose pentobarbital (70mg/kg/hour), respectively. ***Group D*** (n=3): the rats in this group were studied under normothermic (37°C) and hypothermic (32°C) conditions, respectively. Multiple $CMRO_2$ measurements (at least two) were carried out on every animal at different stages of the experiment. The CBF measurements were performed using Laser Doppler Flow (LDF) technique and Dual-channel OxyLab LDF/OxyFlo instrument (Oxford Optronix, UK) with the LDF probe(s) located in the rat cerebral cortex for the experimental ***Groups A-C***. The CBF values of the rats in ***Group D*** were measured using conventional tracer technique through a bolus injection of $H_2{}^{17}O$ (~40% enrichment; 0.05 ml) into one internal carotid artery within 1-2 s [2, 4].

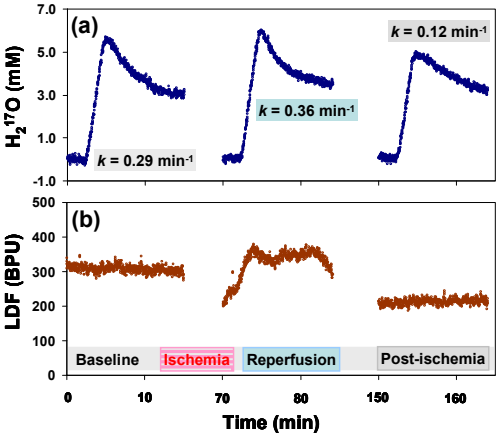

Figure 2 (a) Multiple $CMRO_2$ and (b) LDF measurements in a representative rat brain with global forebrain ischemia (4BVO model) preparation. The $H_2{}^{17}O$ decay rates during the baseline, reperfusion and post-ischemia periods were quantified in (a) and they correlate well with the relative CBF changes in shown in (b).

A multinuclear surface-coil probe consisting of an oval-shape ^{17}O coil (1 cm × 2 cm) and a butterfly-shape ^1H coil was used. The spatial localization of ^{17}O signal was achieved either through the spatially well-defined B_1 profile of the ^{17}O surface coil for covering most of the rat brain or the use of 3D ^{17}O MRSI approach**.** The single-pulse acquisition sequence or MRS imaging sequence were used to collect ^{17}O spectra with the acquisition parameters of 10 ms TR, 50 μs pulse width for a nominal 90° pulse, spectral width=30 kHz and 1 second (for global spectra) or ~11 seconds (for 3D MRSI dataset) temporal resolution. The measured metabolic $H_2{}^{17}O$ washout time course after the cessation of the $^{17}O_2$ inhalation was regressed to an exponential decay function and the fitted decay rate was defined as constant *k*.

RESULTS and CONCLUSIN Figure 1 illustrates typical ^{17}O MR approaches for measuring CBF with a bolus injection of $H_2{}^{17}O$ tracer (Fig. 1a) and $CMRO_2$ with a short $^{17}O_2$ inhalation (Fig. 1b). The $H_2{}^{17}O$ decay rate (k = 0.60 min-1) following the bolus can be used to derive the CBF value as shown in Fig. 1a; while the decay rate of the metabolic $H_2{}^{17}O$ (k = 0.35 min-1) in Fig. 1b is much slower than that of the bolus CBF measurement. This observation is consistent with our previous studies and suggests that the decay rate of the metabolic $H_2{}^{17}O$ following the $^{17}O_2$ gas inhalation can not be directly converted into the CBF value. Figure 2 shows an example of the multiple $CMRO_2$ and CBF (LDF) measurements performed in a representative rat brain (***Group A***) underwent global forebrain ischemia (4BVO model) preparation. The metabolic $H_2{}^{17}O$ decay rates obtained in the $CMRO_2$ measurements during baseline, reperfusion and post-ischemia periods are displayed (see Fig. 2a) and their changes are correlated well with the relative CBF changes determined with LDF (see Fig. 2b). Similar measurements were carried out for each animal in different experimental groups with at least two different physiological conditions. Since the tracer technique can determine the absolute CBF values while the LDF measurements only provide relative CBF information, we decided to use the absolute CBF and decay rate ***k*** values obtained in ***Group D*** to calibrate the <u>baseline</u> CBF values obtained from ***Groups A-C***. Other CBF values (i.e., during reperfusion or post-ischemia for ***Group A***, during hypercapnia for ***Group B*** or during pentobarbital anesthesia for ***Group C***) were determined based on the LDF measurements in each animal. Figure 3 summarizes all paired CBF and *k* data obtained from experimental ***Groups A-D***. It clearly indicates that a linear, strong correlation between CBF values and the metabolic $H_2{}^{17}O$ decay rates following brief $^{17}O_2$ inhalations indeed exists in the rat brain under varied physiological conditions. The linear regression of the experimental data led to CBF ≈ 1.86 × *k* (correlation coefficient R = 0.85), therefore, the measured *k* should provide a good approximation for estimating CBF in a wide range of physiological (or pathological) conditions.

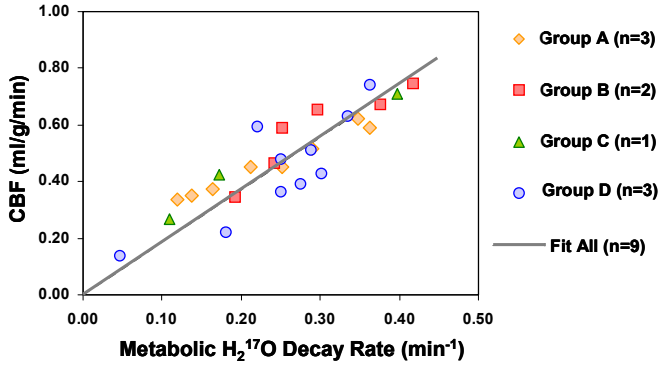

Figure 3 Summary of the correlation between CBF values and the metabolic $H_2{}^{17}O$ decay rates (*k*) following brief $^{17}O_2$ inhalations in rat brains underwent four different types of experimental preparations and/or varied physiological conditions. An linear correlation between CBF and *k* is evident.

In conclusion, the outcomes from the present study and previous research indicate that *in vivo* ^{17}O MRS/MRSI approach is capable of assessing not only $CMRO_2$ but also CBF simultaneously and noninvasively in the rat brain; it should provide new utilities for studying the cerebral oxygen metabolism and tissue perfusion associated with brain function and dysfunction; and it can also be used for imaging oxygen extraction fraction *in vivo*, which is proportional to the ratio of $CMRO_2$ and CBF.

REFERENCES [1]Zhu et al, *PNAS,* 2002; [2]Zhu et al, *NMR Biomed,* 2005; [3]Zhu et al, *JCBFM*, 2007; [4]Zhu et al, *MRM*, 2001.

ACKNOWLEDGEMENTS This work is supported in part by NIH grants NS41262, NS57560, P41 RR08079, P30 NS057091 and KECK Foundation.