Quantitative and Simultaneous Imaging of $CMRO_2$, CBF and OEF in Resting Human Brain

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Introduction Noninvasive and simultaneous imaging of cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral blood flow (CBF) in human brain is essential for studying brain oxygen metabolism, energetics and function in human health and disease. *In vivo* ^{17}O MR-based approach is the only alternative to the positron emission tomography (PET) technique for noninvasively and directly determining the regional $CMRO_2$ in the human brain [1-3]. We have demonstrated that by incorporating the *in vivo* ^{17}O-MR imaging technique with a simple breathing test and a sophisticated quantification model, three important physiology parameters of $CMRO_2$, CBF and oxygen extraction factor (OEF) can be simultaneously obtained in the human brain via a brief inhalation of ^{17}O-labeled oxygen gas [4]. In the present study, this novel ^{17}O MR imaging technique was applied to assess the regional $CMRO_2$, CBF and OEF in healthy human subjects under resting state using a 7 Tesla (T) magnet.

Method *In vivo* ^{17}O-MR spectroscopy imaging (MRSI) experiments were conducted on a 90 cm bore 7T human scanner (actively shielded Agilent magnet and Siemens console) using a passively decoupled surface coil probe consists of a quadrature ^1H coil for anatomic imaging and a single loop ^{17}O coil (7.5cm diameter) placed underneath the human occipital lobe for collecting ^{17}O MRSI data. The ^{17}O MR images were acquired with 3D Fourier series window (FSW) technique (~12 s per image volume, 1.1 cc nominal or 3.5 cc real voxel size) before, during and after a 2-3 minutes inhalation of $^{17}O_2$ (^{17}O enrichment: 75-92%) gas that was mixed with N_2 as in the normal air [5]. Four normal young volunteers were recruited (age: 22-28 years old, 1 male / 3 female) for the study; one of them was scanned twice at two different days. For each subject, a simple breathing test was performed in addition to the MR measurement to determine the gas exchange rate in the subject's lung [4]. This rate together with other known parameters was used in the previously described quantification model to calculate the $CMRO_2$, CBF and OEF values in each ^{17}O imaging voxel [4]. High-resolution 3D-MPRAGE T_1-weighted and proton density (PD) images were acquired (TR=3s, FA=7°, and 1mm isotropic resolution); imaging process including de-nosing, co-registration and segmentation was performed based on the ^1H anatomic (T_1/PD ratio) images. The ^{17}O MRSI voxels were superimposed on the segmented anatomic images to identify the voxel location and determine the fractions of gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) in each voxel. All data are presented as mean ± stdev.

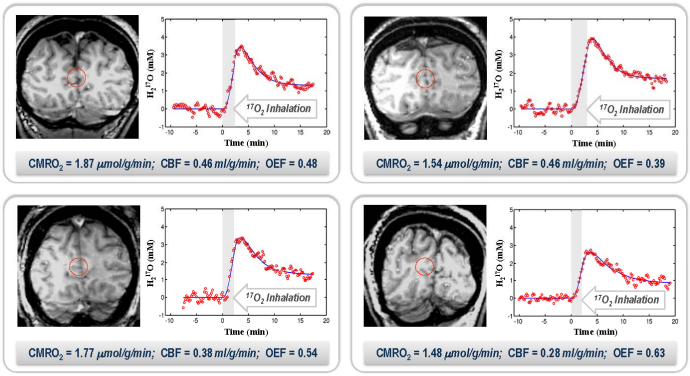

Figure 1. Anatomic images and the dynamic changes of the $H_2^{17}O$ water signal during and after a brief $^{17}O_2$ gas inhalation (indicated by a grey bar) obtained from central voxels (red circles) in four resting human brains. The 3D ^{17}O-MR images were acquired with 12s temporal resolution and nominal voxel size of 1.1cc. The voxel time courses are presented with experimental data (red dots) and corresponding model fitting (blue curves). The calculated $CMRO_2$, CBF and OEF values in these voxels are displayed at bottom of the panel for each subject.

Results Figure 1 displays four data panels obtained from four subjects, respectively. Each panel consists of ^1H anatomic image with identified central voxel location, the corresponding brain $H_2^{17}O$ water dynamics before, during and after a brief $^{17}O_2$ gas inhalation, and the calculated $CMRO_2$, CBF and OEF values of the representative voxel. Excellent ^{17}O-MR sensitivity at 7T, robust and characteristic dynamics of the brain $H_2^{17}O$ signal changes after introducing $^{17}O_2$ gas, and well-fitted experimental data to the quantification model are clearly illustrated in Fig. 1. The $CMRO_2$, CBF and OEF values from various MRSI voxels located in the ^{17}O coil sensitive region were determined and were found to have the following values: $CMRO_2$=1.51±0.21 μmole/g/min; CBF=0.39±0.10 ml/g/min and OEF=0.48±0.10 in the resting human brains (over 100 voxels from 4 subjects). Figure 2 shows a strong positive correlation between the resting state $CMRO_2$ and CBF values observed in different subjects; such correlation is fairly reproducible in the same subject, but varies slightly among different subjects. The measured $CMRO_2$ values from the similar brain region show substantial inter-subject variation (see Fig.1); and can differ significantly across different brain regions within the same subject. Figure 3 shows the distribution of the $CMRO_2$ in human brain tissues, in which the $CMRO_2$ values of various ^{17}O MRSI voxels in four different subjects are plotted against their gray or white matter fraction (F_{GM} or F_{WM}). Strong dependence of the $CMRO_2$ on the tissue composition is revealed, which leads to $CMRO_2$ of 1.97 μmole/g/min for pure GM and 0.91 μmole/g/min for pure WM in the occipital lobe of the resting human brain. Interestingly, we also found a consistent and negative correlation between CBF and OEF.

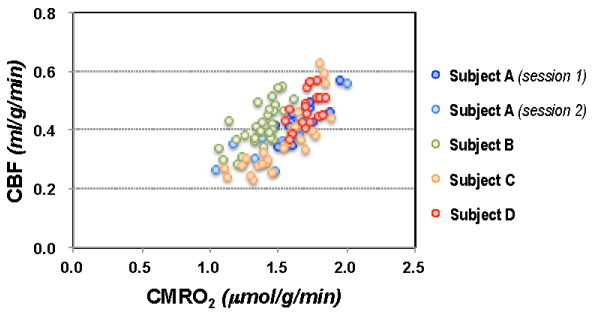

Figure 2. Correlation of the resting state $CMRO_2$ and CBF values obtained in four human subjects, one of them was scanned twice on two different days. Each circle represents data from one ^{17}O-MR imaging voxel, and the data of different subjects or scan sessions is shown in different color.

Discussion and Conclusions The present study confirms the applicability and utility of the newly established *in vivo* ^{17}O-MR imaging technique for studying cerebral oxygen metabolism and perfusion in resting human brain at ultrahigh field strength of 7T. This approach with its simplicity, completely noninvasiveness, superior ^{17}O sensitivity and accurate quantification model is able to reliably imaging the $CMRO_2$, CBF and OEF simultaneously with a brief $^{17}O_2$ inhalation and relatively short MR scan. The resulted resting state $CMRO_2$, CBF and OEF values of the healthy human subjects are in good agreement with the PET literature values [1-2,7]. This novel neuroimaging technique is highly sensitive to differentiate inter-subject variations and tissue-specific differences in regional $CMRO_2$, CBF and OEF. Therefore, the overall findings of the study suggest that the ^{17}O-MR based neuroimaging approach can provide an invaluable tool for quantitatively assessing the $CMRO_2$, CBF and OEF in healthy and diseased human brains.

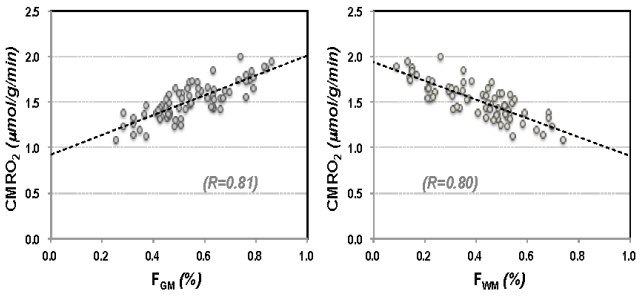

Figure 3. Resting state $CMRO_2$ distributions in different human brain tissues. The $CMRO_2$ values of various ^{17}O-MR imaging voxels in four different subjects are plotted against the fraction of gray or white matter (F_{GM} or F_{WM}) in each voxel. Strong linear correlation is observed, which indicates an over two times $CMRO_2$ difference in the pure gray vs. white matters of the occipital region in normal human brain.

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References [1] Jones *et al. Br J Radiol* **49**:339-43 (1976); [2] Frackowiak *et al. J Comput Assist Tomogr* **4**:727–36 (1980); [3] Zhu *et al. PNAS* **99**:13194-13199 (2002); [4] Zhu *et al. Proc ISMRM* **22**:3763 (2014); [5] Zhu *et al. Proc ISMRM* **14**:409 (2006); [7] Hatazawa *et al. ANM* **9**:15-21 (1995).