3D Imaging of Cerebral Blood Flow before and during Global Brain Ischemia and during Reperfusion by using $H_2{}^{17}O$ Tracer and ^{17}O NMR at 9.4 Tesla

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INTRODUCTION: Four-blood vessel occlusion (4BVO) model (1) has been well established for studying hemodynamic and metabolic changes in ischemic brain regions using a variety of animals. However, this model requires complete occlusions of two common carotid arteries. This requirement poses a technical challenge in the measurement of cerebral blood flow (CBF) using the arterial spin tagging MRI methods (2). In this study, we proposed to apply fast 3D ^{17}O MRS imaging combined with $H_2{}^{17}O$ bolus injections for determining spatial distributions and changes of CBF before, during and after a 12-minute global ischemia using 4BVO model at 9.4T. In this approach, one $H_2{}^{17}O$ bolus is injected through one internal carotid artery into one hemisphere 3 minutes before the occlusion. The labeled $H_2{}^{17}O$ washout curves in different voxels measured by 3D ^{17}O MRS imaging provide CBF images in the control condition. After the starting of the occlusion, adequate residues of the labeled $H_2{}^{17}O$ (>25%) are still in the brain tissue. If the brain is completely ischemic, the residue signal should be constant. On the other hand, any residue CBF during the ischemia duration should lead to a slow decay of the labeled $H_2{}^{17}O$ signal that can be used to calculate the residue CBF values. During the reperfusion period, the second $H_2{}^{17}O$ bolus was applied to imaging CBF overshooting with enhanced detection sensitivity.

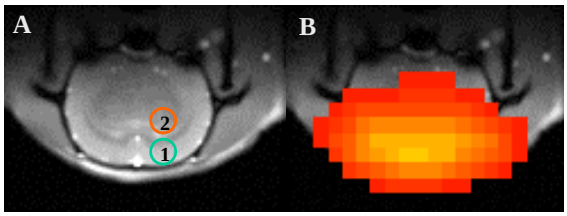

Figure 1. (A) Anatomic imaging of rat brain. (B) Natural abundance $H_2{}^{17}O$ signal map.

METHODS: Male SD rats (250-300g) were used in this study. An electrical occlusion of bilateral vertebral arteries was performed 24-48 hours before MR experiments. The common carotid arteries were exposed and surrounded with two plastic occluders (Harvard apparatus, Holliston, MA). The anesthetization was maintained by continuously α-chloralose infusion (25mg/kg/hour) and 60/40 N2O/O2 gas mixture. The rectal temperature was maintained at 37±0.5°C. The blood pressure and other physiological parameters were monitored and maintained throughout the experiment. The left internal carotid artery was catheterized for $H_2{}^{17}O$ bolus injection. First bolus of $H_2{}^{17}O$ (~0.10 ml; 40% ^{17}O enrichment) was injected 3 minutes before the occlusion. The forebrain ischemia was achieved by inflating the occluders for 12 minutes; the occluders were then deflated for reperfusion. Second bolus of $H_2{}^{17}O$ (~0.08 ml) was injected 4 minutes after the reperfusion. A Varian INOVA console connected to a 9.4 T/31 cm Magnex magnet was used for imaging the labeled $H_2{}^{17}O$ signals in the brain. 3D Fourier series window spectroscopic imaging method (3) was used to map $H_2{}^{17}O$ in brain (TR=10 ms, TE=0.4 ms, spectral width of 30 kHz, voxel size = 75 μl)(4). The total acquisition time for each 3D data set was 11 s. The ^{17}O images were continuously acquired during control (9 min), occlusion (12 min) and reperfusion (20 min).

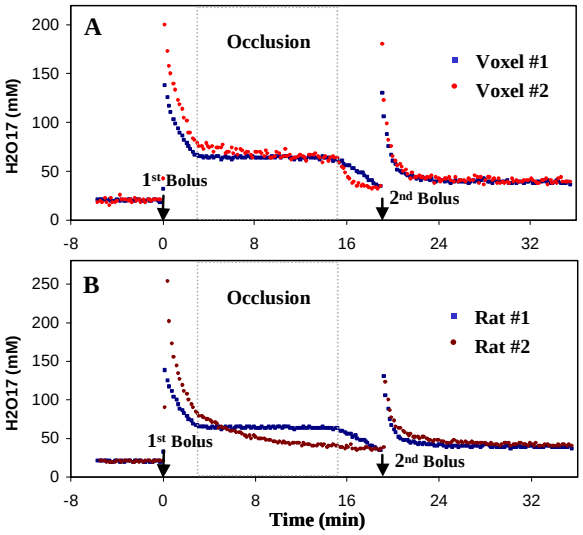

Figure 2. The [$H_2{}^{17}O$] time course pre-, during and post- 12 min occlusion of (A) two voxels in rat #1 as indicated in fig.1A and (B) voxel #1 from two different rat brain.

Table 1. Relative CBF (F: ml/g/min) comparision:

Rat (Vox)	F (1st Bolus)	F (Occlusion)	F (2nd Bolus)
1 (1)	0.58	0.003	1.59
1 (2)	0.59	0.13	2.12
2 (1)	1.13	0.22	1.58

RESULTS and DISCUSSION: Figure 1A shows a coronal image of a rat brain with the voxel positions of ^{17}O image marked: one in superficial cortical area and another in deep sub-cortical area. Figure 1B illustrates a 2D ^{17}O image (extracted from a 3D image set) of natural abundance water, in which the ^{17}O signal intensity was determined by the ^{17}O surface coil B_1. Figure 2A displays the time courses of $H_2{}^{17}O$ signal intensity from two voxels as indicated in Fig. 1A from rat #1. The data points acquired before the zero time point present the natural abundance $H_2{}^{17}O$ concentration (20.35 mM). The time course measured in the first 3 minutes is correlated to CBF, and its decay rate reflects the relative CBF value (4) before the occlusion. The decay rates measured during the occlusion present the residue CBF. For rat #1, the residue CBF in the cortical area (Voxel 1) was near zero. In contrast, the time course of voxel 2 had a slow decay in the occlusion period indicating a non-zero residue CBF (~22% of control CBF). The time decays after the 2nd bolus injection during the reperfusion showed a large CBF overshooting (2.7 times in voxel 1 and 3.6 times in voxel 2 compared to control CBF). Figure 2B compared the time courses of cortical area between rat #1 and rat #2. In comparison with rat #1, rat #2 with much higher blood pressure had a 2-times high control CBF, a significant residue CBF (19%) and a much smaller overshooting CBF (only 1.4 times). The results of CBF measurements are summarized in Table 1. The observations in this study may indicate that an occlusion with less ischemic severity requires less flow compensation (or overshooting) during reperfusion.

CONCLUSION: Our results demonstrate that, due to superior sensitivity of ^{17}O MRS available at 9.4T (4), the proposed ^{17}O imaging method provides a sensitive and reliable approach for imaging CBF changes *in vivo* during brain ischemia and reperfusion. These measurements should be useful for determining the pathological changes in ischemia and stroke. The same method can be applied to other tracers such as D_2O.

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