Feasibility Study of the Cerebrospinal Fluid Flow Circulation in the Brain of Dogs with $H_2{}^{17}O$ using Magnetic Resonance Imaging

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Introduction: Cerebrospinal fluid (CSF) is mainly produced in the choroids plexus in the lateral, third, and fourth ventricles, and a minor part is derived from the extracellular space of the brain. The speed of water supply is about 500mL per day and the total volume of CSF in the adult is about 140 ml, being replaced 3 to 4 times a day. In general, choroids plexus is thought to be responsible for 60-80% of CSF production. However, based on previous works [1-3], there is a possibility that the choroids plexus may account for only 30-50% of CSF production. Based on the former theory, the water supply into CSF is about 0.5-0.6mL per min. In the later theory, it is about1.0-1.3mL per min. CSF flows through the ventricles to sites of drainage in the subarachnoid space surrounding the brain and spinal cord. The rates of CSF production and absorption must be equal in the steady state. Once the balance between CSF production and absorption is disturbed, CSF related diseases such as normal pressure hydrocephalus (NPH) and intracranial hypotension symptoms (IHS) can occur. Oxygen-17 (^{17}O) has been utilized and examined in several works using magnetic resonance imaging (MRI) for measurement of absolute cerebral blood flow (CBF), relative tumor blood flow (TBF), and Cerebral Metabolic Rate of Oxygen [4-8]. Two main methods, proton detection technique based on the T_2 shortening effect of ^{17}O and ^{17}O direct detection technique, have been examined. The former technique would have an advantage for its higher spatial resolution and higher availability to conventional MRI scanners. To date, there have been no published investigations about the circulation of CSF mechanism with ^{17}O water ($H_2{}^{17}O$) using MRI. Our purpose was to understand the circulation of cerebrospinal fluid for providing a better diagnosis/treatment of CSF related diseases using ^{17}O, which is the true marker of the water molecule. Therefore, we have investigated the normal CSF circulation in animal studies.

Materials and Methods: Beagle dogs, weighing 5kg, were anesthetized with 1-2 % halothane in mixed gas (N_2O: O_2 = 3 to 4 : 1); after tracheal intubation, they were paralyzed with pancronium, and were mechanically ventilated with an animal ventilator. A catheter was inserted into femoral vein for $H_2{}^{17}O$ injection, $PaCO_2$ was controlled at 40 mmHg by 2-4 % CO_2 inhalation. Imaging was performed on 3T MRI scanner (Signa Excite, GE Healthcare) using a standard quadrature head coil. MRI was performed using fast spin echo (FSE; TR/TE=3000/120ms, ETL=64, number of slices=4, slice thickness=5mm, BW=31.25kHz, FOV=120×120mm, matrix=256×128, scan time=15sec). $H_2{}^{17}O$ (40atm%, 2mL/kg) was injected at a constant speed for 40 seconds. MRI images were acquired at pre and post injection for every 15 sec for 5 min and for every 1 minute thereafter up to 19 min post injection.

Data Analysis: First, as a preprocessing step, dog brain was segmented from non-brain structures manually by outlining the brain in a slice-by-slice manner. Second, all repeat scans were registered to the baseline image with SPM2 tool [9] to compensate the dog head motion. Third, the first three images, acquired before the injection of $H_2{}^{17}O$, served as a baseline image and the remaining 35 images were used for the voxel by voxel based subtraction. The subtracted images in the brain were analyzed with 3 Region of interests (ROIs) at ventricles (red), cortex gap (yellow) and cerebral sulcus (blue) using MATLAB 6.5 (MathWorks, Natick, MA). The main reason behind why we selected those ROIs is given as follow: (i) the ventricle might tell slow dynamics of ^{17}O concentration mainly from choroids plexus but also some from brain parenchyma, (ii) cortex gap might tell fast dynamics mainly from brain parenchyma, (iii) cerebral sulcus might tell the dynamics of ^{17}O from blood supply to parenchyma.

Results & Discussion: Figure 1a-d shows the dog brain at 4-slice location respectively. The manually segmented brain overlaid with 3 ROIs, is shown in Figure 1e-i. After registration procedure, the intensity difference in the brain between pre and post $H_2{}^{17}O$ injection using 3 ROIs is shown in Figure 2. Based on the general theory mentioned in the introduction section, it may be expected that $H_2{}^{17}O$ wash-in into CSF is much slower. However, in our study, the preliminary results indicate that all the ROIs show the very fast uptake of $H_2{}^{17}O$ comparing to the story of water supply from choroids plexus, especially within a few 10 seconds, to the contrary. Furthermore, the peak of ROI-cortex gap and ROI-cerebral sulcus is a bit faster than the peak of ROI-ventricle. This might tell that water flow into CSF is faster at the area around a parenchyma than the area at ventricle. In other words, there might be a much water supply from parenchyma than choroids plexus into CSF. Further studies are needed to further validate this finding.

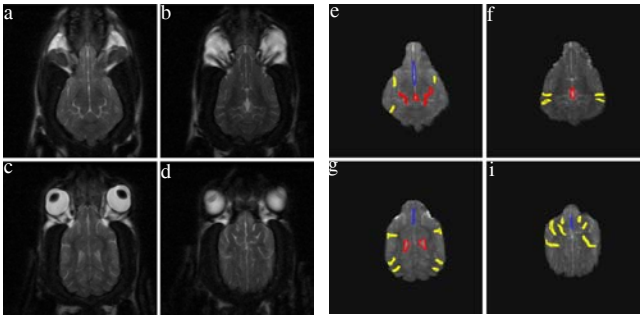

Figure 1. (a-d): The original dog data and (e-i): and manually segmented data overlaid with 3 ROIs, ventricles (red), cortex gap (yellow) and cerebral sulcus (blue), after registration.

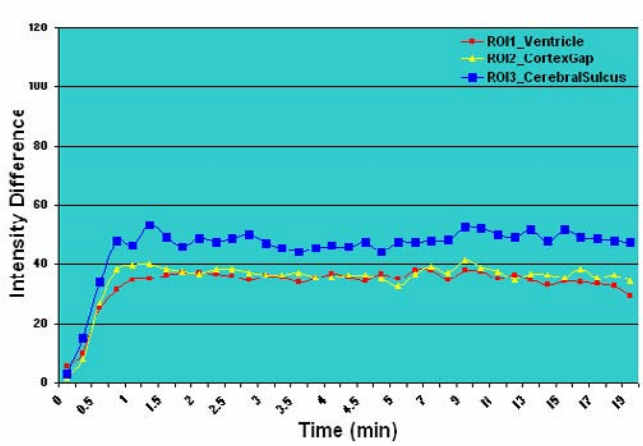

Figure 2. The intensity difference in the brain based on pre and post $H_2{}^{17}O$ injection using 3 ROIs at ventricles, cortex gap and cerebral sulcus.

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