Noninvasive Quantification of Cerebral Blood Volume in Humans during Functional Activation

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Introduction

Cerebral Blood Volume (CBV) is a fundamental parameter in brain physiology. Measurement of CBV and its changes during physiological challenges will not only improve our understanding of brain hemodynamics and the BOLD fMRI signal mechanism, but is also of great clinical relevance, including evaluating vascular reserve for many cerebrovascular diseases and the alteration of vascular functions following drug administration. However, there is a lack of MRI methods that can be used for noninvasive, quantitative assessment of CBV in the human brain. Dynamic imaging with injections of exogenous contrast agents is an invasive method and is not suitable for fMRI studies due to its poor temporal resolution (1). VASO imaging detects CBV-weighted signal changes between rest and activation states, but does not provide absolute CBV values at these two states (2). We present here a new method that is able to noninvasively quantify CBV values at rest and during activation. This was achieved by measuring the VASO fMRI signal as a function of inversion time (TI), thereby varying the weightings of CBV and blood oxygenation contrasts. The data were fitted to a biophysical model comprised of multiple tissue components to obtain blood volume values at rest and activation states. Experiments on healthy volunteers were conducted to evaluate this method.

Methods

Biophysical Model for Determination of CBV and Venous Oxygenation. A three-compartment model was used in this study, in which a voxel in the activated region contains F_{CSF} fraction of cerebral-spinal fluid (*CSF*) and *1-*F_{CSF} fraction of brain parenchyma. The parenchyma, in turn, contains f_b fraction (also known as CBV) of blood and *1-*f_b fraction of extravascular tissue. Note that the volume fraction of the blood in the whole voxel is given by: $F_b = (1-F_{CSF})\cdot f_b$. The modulus MR signal can be written as: $S = abs(S_{CSF} + S_b + S_t)$, where S_i *(i=CSF, b or t)* is the signal contribution from different compartments, and *abs* denotes the operator to take the absolute value. Considering the volume fractions, water proton densities and MR relaxation rates, the signal from individual compartments are given by:

$S_{CSF} = F_{CSF}\cdot C_{CSF}\cdot M_{CSF}(TI)\cdot e^{-TE\cdot R^*_{2,CSF}}$ [1]; $S_b = (1-F_{CSF})\cdot f_b\cdot C_b\cdot M_b(TI)\cdot e^{-TE\cdot R^*_{2,b}}$ [2]; $S_t = (1-F_{CSF})\cdot(C_p - f_b\cdot C_b)\cdot M_t(TI)\cdot e^{E(TE)}$ [3];

where C_i *(i=CSF, b or p)* is the water proton density for CSF, blood and parenchyma, respectively; $M_i(TI)$ is the signal dependence on longitudinal relaxation rate during an inversion recovery experiment; *TI* is the inversion time and *TR* is the repetition time. The transverse relaxation terms are dependent on the venous oxygenation fraction, Y_v. $Y_{v,\,rest}$ was assumed to be 0.61. During visual stimulation, the MR signal changes can be written as a function of TI with three unknown parameters: CBV_{rest}, CBV_{act}, and $Y_{v,\,act}$. Therefore, by performing experiments with a range of TI values, the data can be fitted to the model to obtain the three parameters.

Functional MRI Experiments. To assess the feasibility and efficacy of the proposed method, MRI experiments were performed on healthy volunteers on a 3T Siemens Allegra scanner. A single oblique axial slice (5mm in thickness) encompassing the primary visual cortex was chosen for functional imaging with a visual stimulation of 8-Hz black-white radial flashing checkerboard. An EPI sequence was used to acquire partial (75%) k-space data with TE of 7.6ms and TR of 3s, FOV of 22 cm and in-plane matrix size of 64x64. An adiabatic inversion pulse was used to invert magnetization in the entire brain, followed by an inversion time (TI) of 499, 649, 679, 709, 724, 739, 754, 769, 799, 829, 859, 889, 919 and 949 ms, respectively. At each TI, a visual stimulation paradigm that started with 30s "off" and followed by 3 cycles of 30s "on" / 30s "off" was used. Each fMRI run lasted 210s during which 70 VASO images were collected, and a total of 14 runs were collected.

Data Analysis. As shown in Fig.1, the relative signal change $\Delta S/S$ becomes very large in certain TI ranges, because the baseline signal (S) approaches zero during the inversion recovery process. The experimental results measured at such TIs tend to have large errors. However, it was found that the location of this singular TI value was mainly sensitive to fraction of CSF in the voxel (F_{CSF}). Therefore, the following procedure was used to determine F_{CSF} first: for each possible physiological F_{CSF} value (0-1 at interval of 0.01), the $\Delta S/S$ was simulated for the two TIs that have opposite signs; a F_{CSF} is included as an admissible value when the signs of simulation and experiment data are consistent for both TIs. This procedure can typically result in a limited number of F_{CSF} values, e.g. 0.09-0.13. Next, the experimental data for the remaining TIs were fitted to the biophysical model with 3 unknowns: $f_{b,rest}$, $f_{b,act}$ and $Y_{v,act}$. This fitting was performed for each F_{CSF} value determined in step 1. The residual errors were used to determine the final F_{CSF}.

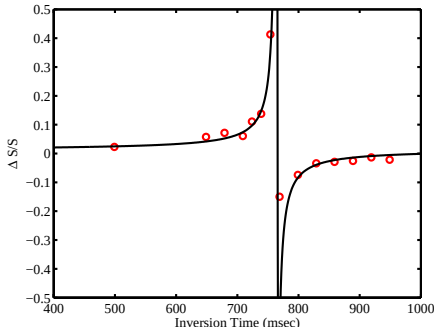

Fig.1 Relative signal change ($\Delta S/S$) measured as a function of TI (red dots) and the curve fitted to the biophysical model (black lines).

Subj	CBV_{rest} (%)	CBV_{act} (%)	$Y_{v,\,act}$ (%)
1	7.64	9.68	81.9
2	9.12	11.2	78.9
3	8.45	11.2	86.4
4	3.56	4.72	70.0
5	9.78	10.7	73.6
Mean	7.71	9.49	78.2
S.D.	2.45	2.73	6.52

Tab.1 CBV at rest and activation, and venous oxygenation values during activation.

Results and Discussions

Activated voxels ($p<0.005$) in the visual cortices were selected as a ROI and the MR signals were averaged to improve CNR. A typical data set ($\Delta S/S$ vs. TI) and the fitting of the data to the biophysical model is shown in Fig.1. Experiments on five healthy volunteers showed that CBV was 7.71±2.45% at resting state and increased to 9.49±2.73% during activation, and venous oxygenation during activation state was 78.2±6.52% (Tab.1). The increase of CBV from rest to the activation (24.7%) is in a similar range as that obtained by other techniques (1). The absolute CBV values are slightly higher than those previously reported in the literature (~5%) (3) using non-MR methods. This may be attributed to the higher spatial resolution of MRI. For instance, the resolution was 12mm in a PET study with ^{11}CO inhalation (3). To assess the effects of spatial resolution on CBV measurement, we smoothed our images to 12mm resolution and found that the resting CBV reduced to 4.38%, suggesting partial volume dilution in the previous studies. In addition, recent studies on brain vascular density suggest that capillary distribution in brain areas may be directly related to the metabolic demand of local neurons, and therefore primary sensory areas, such as the primary visual cortex, would be explained to have higher capillary density (4). The venous oxygenation change ΔY_v between activation and resting states (78.2% – 61.0% = 17.2%) obtained in this study is in good agreement with those in the literature (5).

In summary, we have developed a new method for noninvasive quantification of CBV in humans during functional activation. These absolute CBV values can be obtained without injection of contrast agents. With further improvement to measurement efficiency, this technique will be very useful for quantifying hemodynamic changes associated with neuronal activity.

References

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