Quantification of arterial and total cerebral blood volume: arterial changes dominate during neural activation

T. Kim[1], K. Hendrich[1], S-G. Kim[1]

[1]Neurobiology, University of Pittsburgh, Pittsburgh, PA, United States

Introduction

The BOLD signal has a complicated dependence on venous cerebral blood volume (CBVv), cerebral blood flow (CBF) and oxygen consumption. BOLD signal changes depend on competing factors - changes in CBVv and changes in deoxyhemoglobin concentration in venous blood due to a mismatch between oxygen supply (CBF) and consumption. Since total cerebral blood volume (CBVt) consists of both arterial (CBVa) and venous components, it is important to determine the relationship between CBVt and CBVa or CBVv to understand vascular regulation and to determine BOLD biophysical models. It has been commonly assumed that the CBVv changes, commonly determined by injection of contrast agents, are solely due to CBVv changes (1-3). In the present study, CBVa was measured in the rat somatosensory cortex during neural activation using the modulation of tissue and vessel (MOTIVE) method with arterial spin labeling (ASL) (4), while CBVt was quantified by relaxation rate changes following administration of susceptibility contrast agents (5,6).

Methods

Eight male Sprague-Dawley rats weighing 350-450 g underwent 15 s of forepaw electrical stimulation (1.3-1.6 mA, 6 Hz) under 1.3-1.4% isoflurane anesthesia. Rectal temperature, blood pressure and blood gases were maintained within normal physiological ranges; no significant blood pressure change occurred during stimulation. All experiments were performed on a 9.4 T / 31 cm Varian NMR system. Two actively detunable RF coils were used; a neck coil provided arterial spin labeling, while a head coil detected image signals and generated magnetic transfer (MT) effects. A single 2-mm thick coronal slice covered the forelimb somatosensory area. All images were acquired using the single-shot echo planar imaging (EPI) technique with matrix size of 64 (readout) × 32 (phase-encoding) and FOV = 3.0 × 1.5 cm^2. In all functional studies, the entire pre-stimulus period was defined as baseline, while the time between 2.5 sand 12.5 s after stimulus onset was selected as the stimulation period.

i) *Baseline and stimulation CBVa measurement*: Functional data were acquired using a spin-echo EPI sequence with TR = 2.5 s and TE of 40 ms. The MOTIVE method with ASL was incorporated into each experiment by repeating each functional study with target values of S_{sat}/S_0 = 1, 0.7, and 0.44 in randomized order, where S_{sat} and S_0 are the equilibrium signal in the presence and absence of MT saturation, respectively. Arterial blood volume fraction was determined for baseline and for stimulation periods from ASL data at the three MT levels as described previously (4), and converted to CBVa (units of ml / 100 ml).

ii) *Baseline CBVt measurement*: The transverse relaxation rate changes in tissue were measured before and after injection of ~ 15mg Fe / kg dose of ultrasmall particles of iron oxide (USPIO) using the gradient-echo (GE) EPI sequence with TR = 1 s and TE = 20 ms. Arterial blood was withdrawn to measure the frequency shift of blood water in the presence of USPIO. Baseline CBVt was then determined following the biophysical model (5,6).

iii) *Relative CBVt change induced by stimulation*: fMRI images were obtained using the GE EPI sequence with TR = 1 s before (GE BOLD, TE = 20 ms) and after (GE CBV-weighted, TE = 10 ms) USPIO injection. Stimulation-induced percentage CBVt changes were calculated following ref. 8.

Data from all measurements were compared from within the somatosensory cortex (9-pixel region determined by stereotaxic coordinates and functional maps).

Results and Discussion

The average values of CBVa and CBVt in the somatosensory cortex obtained from all 8 animals are shown in the Table 1. The Figure1. demonstrates a reasonable match between ΔCBVa and ΔCBVt values for all animals. Although ΔCBVa appears to be slightly higher than ΔCBVt, no significant difference were detected (paired t-test, p = 0.22, n = 8). One might expect the measured value of ΔCBVa to be a bit higher than ΔCBVt due to the assumption in the MOTIVE approach that the labeled water in capillaries freely exchanges with tissue water during the spin tagging time (i.e. extraction fraction = 1); during neural stimulation, an elevation of CBF may cause a decrease in extraction fraction in capillaries, resulting in an increase in the measured value of CBVa. Based on our simulation with various physiological parameters, the measured CBVa value can be overestimated by as much as 10%.

Our data demonstrates that blood volume changes during neural stimulation occur mainly in arteries rather than in veins. This observation agrees reasonably well with previous measurements of arterial and venous blood volume changes during global stimulation in α-chloralose anesthetized rats and humans (9). However, our data contradicts the notion of significant CBVv changes proposed by the CBV compliance model and inferred from contrast agent measurements (1-3). Even though these inferences were not validated by direct CBVv measurements, significant CBVv changes are possible under conditions of strong and prolonged stimulation.

One important implication of our study is that ΔCBVv is close to zero, and therefore does not significantly contribute to the BOLD biophysical model. Thus, the BOLD signal is due mostly to the mismatch between CBF and oxygen consumption.

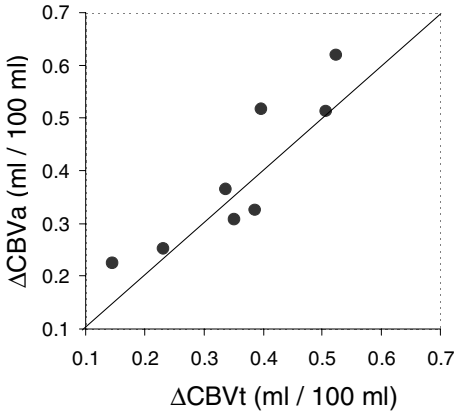

Figure 1. Comparison between absolute changes in ΔCBVa and ΔCBVt shows no statistically significant differences (n = 8). A line of unity is shown.

Table 1. Baseline CBVa and CBVt, and changes due to neural stimulation (mean ± SD, n = 8).

	Baseline CBV (ml / 100 ml)	Stimulation CBV (ml / 100 ml)	ΔCBV (ml / 100 ml)	Relative change (%)
arterial	0.90 ± 0.21	1.29 ± 0.28	0.39 ± 0.14 [a]	44 ± 0.17
total	3.34 ± 0.54	3.70 ± 0.66	0.36 ± 0.12 [b]	11 ± 3.06

[a] $\Delta CBVa = CBVa_{stimulation} - CBVa_{baseline}$

[b] $\Delta CBVt = CBVt_{baseline} \times$ relative CBVt change (%)

References

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