Cerebral blood volume changes in arterial and post-arterial compartments and their relationship with cerebral blood flow alteration during brief breath-holding and visual stimulation in human brain

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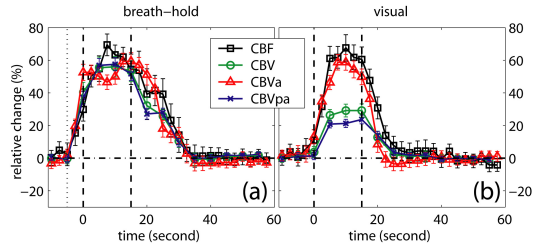
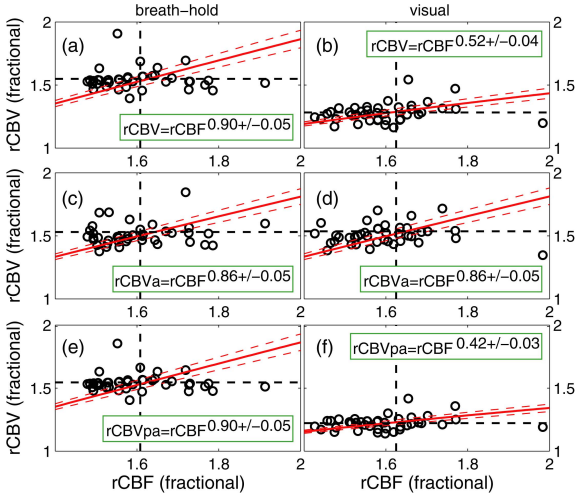
Introduction: Arterial and post-arterial cerebral blood volumes (CBV) have different physiological and functional roles in the brain. Arterial vessels are the major active regulator of cerebral blood flow (CBF), while post-arterial (capillary, venous) vessels mostly dilate passively to accommodate changes in CBF. A change in CBV is one of the primary factors affecting the stimulus evoked BOLD signal change. As the extravascular tissue R_2^* has a value between arterial and post-arterial blood R_2^*s (1), an alteration in arterial CBV (CBV_a) or post-arterial CBV (CBV_{pa}) alone would affect the overall BOLD signal, even without any change in the blood oxygenation level. In many previous studies (2), CBV_a change was assumed to have negligible influence on BOLD signal, mainly because CBV_a occupies only around 20% of total CBV at baseline. Nevertheless, recent MRI and optical imaging studies in animal brains revealed that the largest relative vasodilation during hypercapnia (3) and neural activation (4,5) occurs in arterioles. Therefore it is essential to measure CBV_a and CBV_{pa} responses separately. Detailed investigations of CBV_a and CBV_{pa} changes in human brain under global hypercapnic and focal neuronal stimulations remain scarce. In this study, we employ vascular-space-occupancy (VASO) (6) and inflow VASO (iVASO) (7) MRI to detect total CBV and CBV_a responses, respectively, in human visual cortex during short breath-hold or visual stimulation, and investigate their relationships with CBF alterations.

Methods: Eleven subjects were scanned on a 3T Philips MRI scanner using 6 pseudo-randomized fMRI sessions including CBF, CBV and CBV_a measurements during a visual task (4 blocks of 55s cross-hair fixation+15s 8Hz flashing checkerboard) and a breath-hold task (4 blocks of 50s normal breathing+5s exhaling+15s breath-holding), *respectively*. Common parameters: voxel=3x3x3mm^3, single slice centered on calcarine fissure, single shot turbo spin echo (TSE) readout, TE=6ms, SENSE=2.5. *CBF*: The transfer-insensitive-labeling-technique (TILT) ASL technique (8) was employed: TR/TI=2.5s/1.6s, label thickness=80mm, label/slice gap=12.5 mm, crushing gradients V_{enc}=3cm/s, b=1.7s/mm^2. *CBV*: long-TR VASO MRI (6) sensitized to total CBV change: TR/TI=5s/1054ms. *CBV_a*: A recently developed iVASO technique (7) was used, in which a non-selective inversion is followed by a slab-selective inversion that flips back the water spins within the imaging slice and superior brain region. By choosing a proper TI that is comparable to the mean arterial transit time in human visual cortex, the inverted blood water spins will be nulled by the time they perfuse the arterial compartment but before reaching capillaries and venules, allowing assessment of arterial CBV effects. TR/TI=2.5s/811ms, flip-back slab thickness=80mm, flip-back/slice gap=10mm. *Analysis*: Images were co-registered and baseline drift corrected. A two-tailed Z-test was engaged for activation detection (Z-score>2.5, cluster>4, SNR>20). Only voxels activated in all scans were analyzed. $\Delta CBV/CBV$ and $\Delta CBV_a/CBV_a$ were quantified with VASO (6) and iVASO (7) theory, respectively. Baseline CBV was assumed as 0.055ml/ml (9) for calculating $\Delta CBV_{pa}/CBV_{pa}$ from $\Delta CBV/CBV$ and $\Delta CBV_a/CBV_a$.

ΔS/S (%)	CBF	CBV	CBV_a	CBV_{pa}
Breath-hold	60.8+/-7.2	54.9+/-5.8	53.1+/-6.2	54.5+/-4.9
Visual	62.5+/-7.5	28.2+/-5.2	53.6+/-5.5	22.2+/-3.8





Results & Discussions: Average relative signal changes (ΔS/S) and time courses of CBF, CBV, CBV_a and CBV_{pa} during stimulation are summarized in Table 1 (n=10) and Fig.1, respectively. Fig.2 displays the scatter plots of relative (normalized by baseline) $CBV/CBV_a/CBV_{pa}$ vs. CBF values during the two tasks. Each point represents the average value from one block of a subject (40 points total). Linear regression was performed to fit the power law relationship between volume and flow. The black and red broken lines depict the mean values and 95% confidence intervals, respectively. Our major findings are: **(i)** $\Delta CBV/CBV$ and $\Delta CBV_{pa}/CBV_{pa}$ during breath-hold were twice as large as those during visual stimulation, respectively, whereas $\Delta CBV_a/CBV_a$ was comparable between the two tasks. This suggests that the larger $\Delta CBV/CBV$ during hypercapnia, observed in human brain using VASO MRI (10) and in animal studies using MION CBV imaging (11), originates primarily from the post-arterial compartment. **(ii)** During breath-hold, CBV_a and CBV_{pa} increases were the same (P>0.1), whereas, during visual stimulation, CBV_a rose twice as much as CBV_{pa}. The dilation in the arterial compartment accounted for 20% and 40% of total CBV increase during breath-hold and visual stimulation, respectively. Compared to the results from animal studies ($\Delta CBV_a/\Delta CBV \approx 64\%$ during hypercapnia (3) and 100% during neural stimulation (4)), our data are in agreement in general trend but smaller in absolute amounts, possibly due to the difference between animal and human brains, use of anesthesia in animal studies and different spatial resolutions. **(iii)** The relative changes in CBV_{pa} and CBV were comparable during breath-hold while $\Delta CBV_{pa}/CBV_{pa}$ was smaller (P<0.05) than $\Delta CBV/CBV$ during visual stimulation. This smaller $\Delta CBV_{pa}/CBV_{pa}$ accords with studies employing the VERVE approach, which reported 10-16% $\Delta CBV_{pa}/CBV_{pa}$ during neural stimulation with various intensities in human brain (12). **(iv)** The relative changes in CBF were comparable (P>0.1) between the two tasks. This indicates that the coupling between CBV/CBV_{pa} and CBF differed markedly between breath-hold and visual stimulation (P<0.01), whereas the power law relationship between CBV_a and CBF was largely preserved during both tasks, which can be expected as CBF is primarily controlled by arterial vessels. The power law relationships between $CBV/CBV_a/CBV_{pa}$ and CBF during visual stimulation were generally consistent with the literature (12-14), while the fitted exponents during breath-hold were larger than those reported in studies of CO_2 inhalation (15,16), which may induce hypercapnic conditions that differ from breath-hold (17). According to the central volume theorem (flow=volume/transit time), our data also imply that the reduction in arterial transit times during both stimuli were small (5-10%), while the changes in mean transit times were larger during visual stimulation (≈25%) than during breath-hold (5-10%). Similar observations were reported in an independent study in rat brain (4). These results have critical implications for methods that use hypercapnia as a calibration state to quantify $\Delta CMRO_2$ during neural activation (18). Such methods commonly assume a constant relationship between CBF and CBV during both tasks, negligible signal contribution from arterial blood and approximate $\Delta CBV_{pa}/CBV_{pa}$ with $\Delta CBV/CBV$. In contrast, our data suggest that these assumptions may not hold and their influence on $\Delta CMRO_2$ calculation may be sizable. Therefore, for accurate $\Delta CMRO_2$ quantification, individual $\Delta CBV_a/CBV_a$ and $\Delta CBV_{pa}/CBV_{pa}$ measurements during both stimuli may be necessary, and the signal contribution from $\Delta CBV_a/CBV_a$ (R_2^* difference), which is about twice as large as $\Delta CBV_{pa}/CBV_{pa}$ during neural activation, may need to be incorporated into the model.

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