Physiologic underpinnings of negative cerebrovascular reactivity in brain ventricles

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INTRODUCTION: With a growing interest for more specific biomarkers of small vessel diseases (1) and the increasing availability of breathing challenge apparatus, over the past few years the field has seen a surging interest to mapping cerebrovascular reactivity (CVR) by combining BOLD MRI and hypercapnia. It is conceivable that, in the near future, CVR mapping may become a new addition to the standard clinical MRI protocol in patients implicated with vascular-related diseases. However, before this promise can be fully exercised, mechanism of BOLD changes during CO2 challenge need to be better understood. In the present work, we report an intriguing but robust observation of apparently *negative* CVR (i.e. BOLD signal decreased during CO2 inhalation) in brain ventricles. We further present evidence that this BOLD signal reduction can be attributed to a shrinkage of CSF space due to ventricular vessel (e.g. choroids plexus) dilation, but not due to T2* reduction. We also show that the negative CVR is not present during O2 challenge, a maneuver known to cause minimal vessel dilation.

METHODS: Two studies were conducted and both used a 3T Philips system. Study 1 (N=14, age 26±4 years) was performed to demonstrate the presence and location of negative CVR in the brain. The subject breathed 5% CO2 (mixed with 21% O2 and 74% N2) for 50 sec and room-air for 70 sec and repeated the cycle for four times, while BOLD images were continuously acquired with the following parameters: TR/TE=1000/30ms, flip angle of 55°, matrix=64x64, 20 slices, 5mm thickness/1mm gap. CVR was calculated from linear regression between BOLD time-course and shifted (to account for time delay from lung to brain) end-tidal CO2 (Et-CO2) curve, as described previously (2). Group-level one-sample t test was conducted to identify voxels with a significantly negative CVR value.

Study 2 (N=9, age 26±5 years) was performed to elucidate the physiologic mechanism of the negative CVR. Two possible hypotheses were considered: 1) Blood oxygenation level in the ventricular vessel decreased, causing a reduction in T2*; 2) CSF (which is bright in BOLD image due to high water density and long T2*) volume fraction decreased as a result of blood volume increase. To differentiate these two hypotheses, we performed an Inversion Recovery (IR) spin-echo EPI sequence with CO2 inhalation. We reasoned that, since CSF is now dark in the IR image, volume fraction change would result in a signal *increase* during CO2. On the other hand, if oxygenation reduction was the cause, the signal should still *decrease* (due to spin-echo BOLD effect). The IR sequence used TR/TI/TE=7000/2500/25ms, TI=2500ms, matrix=64x64, 20 slices, 5mm thickness/1mm gap. We used a TI such that CSF signal was not completely nulled, but instead was suppressed to about 10% of equilibrium. This was to ensure that SNR in the ventricle was still sufficiently high. For comparison, the same BOLD sequence as in Study 1 was performed.

To further confirm that that negative CVR observed using the BOLD sequence was attributed to vasodilatation, we also performed the BOLD sequence with another physiologic challenge, inhalation of 98% O2, which is known to cause oxygenation change but not vasodilatation. We reasoned that negative CVR should not be seen with the O2 challenge.

RESULTS AND DISCUSSION: Study 1: Fig. 1a shows averaged CVR map. The color scale is such that positive CVR is shown in warm color whereas negative CVR, if present, is shown in cool color. As expected, brain parenchyma manifests positive CVR. On the other hand, negative CVR values can be clearly noted. Fig. 1b displayed voxels that had significantly negative CVR. It can be seen that spatial distribution of these voxels is in excellent agreement with the location of brain ventricle. Fig. 1c shows BOLD time-course (red curve) in these voxels, which is clearly anti-correlated with the Et-CO2 time-course (blue curve, cc=-0.89±0.12 for N=14). Although the intuitive explanation for these negative CVR values is a T2* reduction associated with a blood oxygenation decrease, one must also consider the possibility of volume fraction changes. Specifically, given the prominent CSF signal in BOLD images (Fig. 1d), a reduction in CSF volume as a result of blood volume increase would cause a signal decrease too. This is tested in Study 2.

Study 2: Results using the BOLD sequence reproduced the findings in Study 1 (not shown due to space limit). In the IR-EPI image (Fig. 2a), the CSF signal is effectively suppressed as expected. When examining the IR-EPI time-course in voxels that manifested a negative CVR, a positive correlation (cc=0.93±0.06, p<0.001, N=9) with the Et-CO2 time-course is now observed (Fig. 2b). In fact, we were not able to identify any voxels with negative signal change when the IR-EPI sequence was used. These data suggested that the negative CVR observed in the BOLD scan can be attributed to a CSF volume reduction instead of oxygenation decrease. To further demonstrate that vasodilatation is necessary in order for negative CVR to be observed (when using BOLD sequence), we employed a hyperoxia challenge, which alters oxygenation (like CO2 challenge) but does not cause vasodilatation. In the hyperoxia data, no voxels showed a negative signal change (Fig. 3).

In summary, the present work shows that negative CVR is to be expected in brain ventricles, when BOLD sequence is used for image acquisition. This should not be viewed as a sign of blood oxygenation decrease (or vasoconstriction) but rather reflects a dilation of these vessels, causing a relative CSF volume reduction in the voxel. Thus, this observation is a CBV effect, in some sense similar to the VASO effect (3). For physiologic challenges that do not cause vasodilatation (e.g. hyperoxia), negative CVR is not seen. This study also presents interesting evidence that blood vessels in the ventricle related to the choroids plexus are capable of dilating. The choroid plexus is responsible for producing CSF and is a type of soft tissue consisting of foldings of numerous capillaries. Since they are not equipped with smooth muscles, it was previously not known whether they are capable of dilating. The present work provides evidence that they indeed can.

REFERENCES: 1) Greenberg et al. NEJM, 354: 1451 (2006); 2) Yezhuvath et al. NMR in Biomed., 22:779 (2009); 3) Lu et al. MRM, 50:263 (2003).

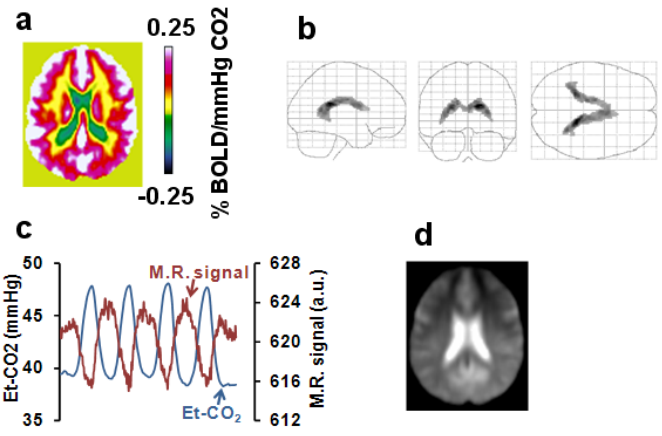

Fig. 1: CVR results from Study 1. (a) Averaged CVR map (N=14) illustrating regions with negative CVR (cool color). (b) Voxels with significantly negative CVR. (c) BOLD time-course (red) in negative CVR region and the corresponding Et-CO2 (blue). (d) BOLD EPI image illustrating that CSF has bright signal.

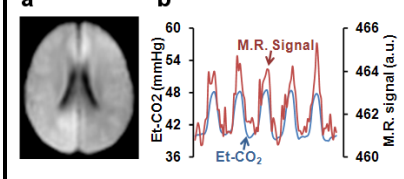

Fig. 2: Results of IR-EPI experiment. (a) Representative image using the IR-EPI sequence, illustrating the suppressed CSF signal. (b) IR-EPI signal time-course in ventricles (red) and the corresponding Et-CO2.

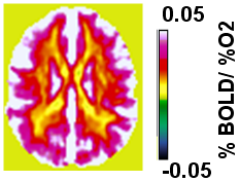

Fig. 3: Map of BOLD responses to hyperoxia (inhalation of 98% O2). Compared to Fig. 1, no negative voxels are seen.