# An artifact-free imaging protocol for the mapping of cerebrovascular reactivity.

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**INTRODUCTION:** Cerebrovascular reactivity (CVR) is an indicator of the ability of vasculature to dilate and is an important biomarker for vascular reserve [(1)]. CVR can be measured by brief inhalation of CO2 while simultaneously acquiring perfusion-sensitive MR data such as the BOLD image. This index is thought to be a more specific vascular marker compared to baseline perfusion, and is increasingly utilized in studies of cerebrovascular diseases [(2.)]. A logical expectation is that large, positive CVR would indicate healthy vasculature, and low or negative CVR would signal a depletion of vascular reserve, implicating diseased blood vessels. However, a disturbing finding that has been noted by several researchers is that *negative CVR* values have been observed even in healthy brain [(3,4)], which can potentially compromise the interpretability of CVR data in clinical applications. Recently, our group characterized this phenomenon by showing that the apparently negative CVR is predominantly located in brain ventricles. It is attributed to a dilation of blood vessels during $CO_2$ inhalation, which displaces the bright CSF signal in ventricle causing an "artifactual" reduction in BOLD signal [(5)]. In this work, we performed simulation and experimental studies to re-optimize the BOLD imaging parameters such that negative CVR is no longer present. SNR, CNR, and test-retest reproducibility were also evaluated for the "old" and "new" protocols.

**METHODS:** Simulation: We first conducted numerical simulations to determine how BOLD imaging parameters need to be adjusted to remove the negative artifact. Specifically, based on a multi-compartment BOLD signal model and typical relaxation parameters described in our earlier study [(5)], we have conducted simulations to compute TR, TE, and flip angle combinations that can meet the criterion $S_{CSF}=S_{blood}$ (details not shown due to space limit). From this calculation, we can make a recommendation on what the optimal TE is for a given TR, which is plotted in Fig. 1. It can be seen that, in order to avoid negative CVR artifact, TE of the BOLD sequence needs to be reduced and this is more so for scans using a longer TR. Experiment: To verify the simulation predictions with experimental results, we conducted three CVR scans using 1) an "old" protocol before optimization (TR/TE=1500/30ms, square symbol in Fig. 1); 2) a "new1" protocol (TR/TE=1500/21ms, triangle in Fig. 1), 3) a "new2" protocol (TR/TE=800/23ms, circle in Fig. 1). The "new2" protocol was performed to examine whether the longer TE afforded by shorter TR can help improve sensitivity. All experiments were performed on a 3T Philips scanner. Six healthy volunteers (Age 31±8 years) were scanned using the three protocols in randomized order. Inhalation paradigm was identical across protocols: the subject inhaled 5% $CO_2$ gas mixture for 50 seconds followed by 70 seconds of room air, and this cycle was repeated 4 times for a total duration of 9 minutes. This entire scan session was repeated after a 30-min break outside the scanner, to examine the test-retest reproducibility. Data analysis: General linear regression was used between the BOLD time course and end-tidal $CO_2$ (ETCO2), yielding CVR map in %BOLD/mmHg CO2 [(1)]. SNR per image was estimated by temporal mean divided by temporal standard deviation of room-air BOLD signal. CNR per unit time (i.e. overall sensitivity) was calculated by SNR*CVR/sqrt(TR).

**RESULTS AND DISCUSSION:** Fig. 2a shows (raw) BOLD images for the three protocols. It can be seen that CSF is substantially brighter than brain parenchyma in the "old" protocol. In the "new" protocols, on the other hand, signals across the brain are more equivalent, in accordance with the criteria in the simulation. Averaged CVR maps (N=6) are displayed in Fig. 2b. The color scale is selected such that negative CVR, if any, would be shown in cool color. As expected, CVR map using the "old" protocol shows negative CVR in the ventricular regions (arrows in Fig. 2b). Importantly, negative CVR is eliminated in the "new" protocols, suggesting that the imaging parameters recommended by the simulations (Fig. 1) are generally valid. Comparing CVR maps between session 1 and session 2 (Fig. 2b), it appears that the results are reproducible in general. Coefficient of variation (CoV), defined as the standard deviation across sessions divided by their mean, is plotted in Fig. 3a. The new protocols appear to have a lower CoV compared to the old one. Comparing absolute CVR (Fig. 3b), the old protocol yielded significantly higher CVR values than new1 ($p=0.011$) and new2 ($p=0.035$), because the old protocol used a longer TE. But SNR-per-image in the old protocol was significantly lower than new1 ($p=0.042$) and new2 ($p<0.001$) (Fig. 3c). Thus, CNR (i.e. overall sensitivity) was similar between old and new1, but both were lower than new2 ($p<0.001$ for both comparisons) (Fig. 3d).

In summary, we showed that the negative artifact in CVR map can be eliminated by optimization of BOLD imaging parameters, specifically by reducing TE. We provided recommendations for proper TE choices at different TR. These predictions were validated by experimental findings. Our results also suggested that the use of a shorter TR may yield a greater sensitivity in CVR mapping. Future clinical applications of CVR should use a reduced TE in the BOLD sequence, in order to ensure correct interpretation of lower or negative CVR findings.

**REFERENCES:** 1) Yezhuvath et al. NMR in Biomed., 22:779 (2009); 2) Andrea et al. JMRI, 31:298 (2010); 3) Mandel et al. Stroke 39(7):2021 (2008); 4) Blockley et al. MRM 65(5):1278 (2011); 5) Thomas et al. Neuroimage, 83:505 (2013).

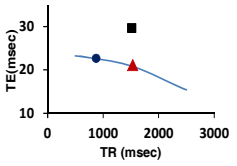


Fig. 1: Simulation results of recommended TE values for a given TR. Symbols represent TR/TE combinations used in experiment. Square – "old"; Triangle – "new1"; Circle - "new2".

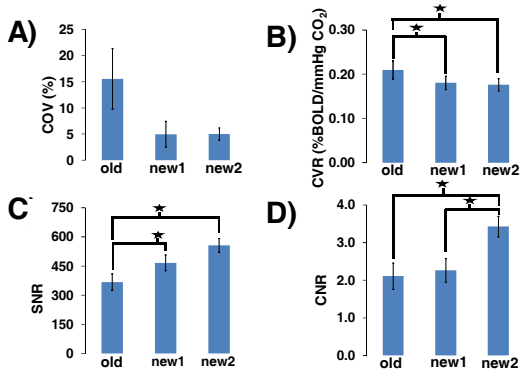


Fig. 3: Summary of experimental results. (A) Coefficient of variation (CoV). (B) CVR values. (C) SNR per BOLD image. (D) CNR per unit time, corresponding to overall sensitivity.

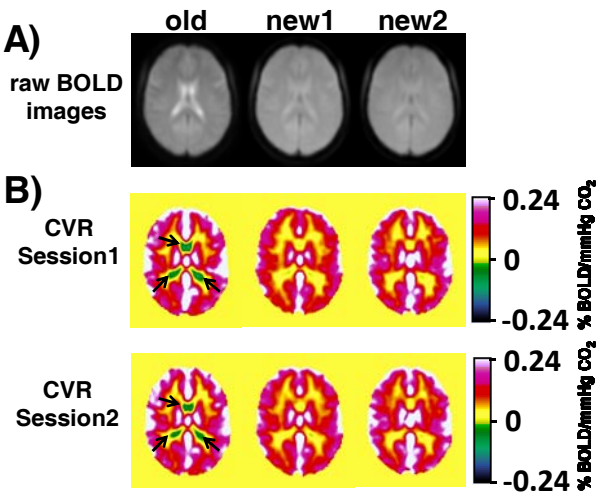


Fig. 2: Group-averaged (A) BOLD images and (B) CVR maps (N=6). Note that, in (A), CSF is bright in "old" protocol, but is not the case in the "new" protocols. Accordingly in (B), negative CVR is seen in "old" but not in "new" protocols.