

Measuring vascular reactivity with breath-holds after stroke: implications for fMRI study interpretation

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Target Audience Researchers and clinicians using BOLD fMRI to measure neural recovery after stroke

Purpose Blood oxygenation level dependent (BOLD) contrast fMRI is a widely used technique to map brain function and monitor its recovery after stroke. Since stroke has a vascular aetiology, the neurovascular coupling relationship between the cerebral blood flow (CBF) and neural activity may be altered causing problems for interpretation of BOLD signal changes. Impairments in cerebrovascular reactivity (CVR), the response of cerebral blood vessels to a vasodilatory stimulus, are associated with stroke risk [1,2] and will alter neurovascular coupling. Recently, a simple method to measure BOLD CVR in patient groups using a breath-hold task has been developed [3]. The purpose of this study is to demonstrate the feasibility of this technique in stroke patients and to determine whether alterations in penumbral CVR over time will adversely affect the interpretability of task-related BOLD signal changes.

Methods Forty-six stroke patients with left lateralised lesions and 26 healthy controls were scanned on a Siemens Trio 3T MRI scanner. Of the 46 stroke patients, 24 were scanned in the subacute phase post stroke (SPPS – mean 15 days, range 5–35) and 42 in the chronic phase post stroke (CPPS – mean 111 days, range 84–189) with 20 scanned in both SPPS and CPPS. Of the 26 healthy controls, 17 were scanned twice, approximately 100 days apart. Whole brain BOLD EPI images (TR=2s, TE=31ms, voxel-size=3.5x3.5x3mm³, slices=36) were collected during a breath-hold (BH) task which consisted of 6 cycles of 30s paced breathing followed by 15s breath-hold [3]. End-tidal CO₂ traces were recorded throughout using a nasal cannula connected to a capnograph. Data were motion corrected and converted to a %BOLD signal time series. Each participant's end-tidal CO₂ trace was used as a regressor in a general linear model (GLM), taking the best fit to each voxel's data after allowing for multiple lags (-10s to +10s from the CO₂ lag to the global signal). This yielded a voxelwise map of BOLD BH responses in units of %BOLD change per mmHg change in end-tidal CO₂. Regions of interest (ROIs) for each stroke patient were determined from an anatomical scan: lesions were manual drawn on a T1-weighted image (*Lesion*); penumbra was defined by dilating that lesion maps by 10mm (*Penumbra*); the remaining left hemisphere (*LH-healthy*); the homologous region to the *Lesion* in the right hemisphere (*Lesion homo*); the entire right hemisphere (*Right Hemi*). These regions were further restricted to voxels that displayed a significant fit to the BH model in the GLM using a liberal threshold ($R^2=0.0288$, $p=0.05$). Differences between ROIs and groups were determined using t-tests.

Results Figure 1 shows the lesion distribution across patients. At the SPPS time point, the percentage of voxels in the *Lesion* and *Penumbra* ROIs showing a BH response (61% and 62%, respectively) is significantly less than in the *LH-healthy* ROI (67%; paired $t=4.76$ and 4.8 , $p=1.2 \times 10^{-4}$ and 1.0×10^{-4} respectively) with no difference between *Lesion* and *Penumbra*. Similar results at the CPPS time point demonstrate that vascular reactivity in the *Lesion* and *Penumbra* remain impaired. Figure 2 summarises the CVR measure across all ROIs and groups. At the SPPS time point, CVR is lower in the *Lesion* (0.023 ± 0.13) than in the *Penumbra* (0.048 ± 0.12) which in turn is lower than in the *LH-healthy* ROI (0.10 ± 0.12). A similar trend is observed at the CPPS time point. No significant difference was observed in the *Right Hemi* between patients and controls. To investigate if CVR recovers over time, comparisons were made between patients who were scanned at both timepoints (Figure 3). No significant CVR differences were observed with pairwise comparisons between SPPS and CPPS in any ROI. CVR in the *Lesion* remained significantly lower than in the *LH-healthy* and *RH* ROIs ($p=5 \times 10^{-4}$, $p=3 \times 10^{-4}$) at the CPPS time point. Importantly, although a trend for significantly lower CVR was observed in the *Penumbra* compared to the *LH-healthy* ROI ($p=0.06$ for SPPS, $p=0.02$ for CPPS), no significant CVR difference was observed in the *Penumbra* over time ($p=0.53$).

Discussion This study demonstrates that CVR can be measured successfully in a patient population using the breath-holding task and analyses described by Bright and Murphy [3].

The resulting CVR measures can be used to disentangle vascular and neural changes caused by stroke, increasing confidence in BOLD results. A lack of CVR differences in the right hemisphere between patients and controls suggest that BOLD signal in this region should be unaffected. Since CVR is reduced in the stroke penumbra, a lack of BOLD signal in that area compared to controls may not accurately reflect neural deficits. However, since CVR in the penumbra remains unchanged over time, a finding of increased penumbral activity in the chronic phase in a longitudinal study is less likely to be due to changes in vascular reactivity.

References [1] Gupta (2012), Stroke 43:2884; [2] Markus (2001), Brain 124:457; [3] Bright (2013), NeuroImage 83:559

