Reliable quantification of cerebrovascular reactivity despite poorly performed breath-holds

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Target audience Clinicians and researchers interested in a reliable BOLD vascular reactivity measure

Purpose Cerebrovascular reactivity, the vascular response to a vasodilatory stimulus, can be measured with BOLD fMRI by increasing end-tidal CO_2 using a breath-hold task. A long end-expiration breath-hold lasting 20s provides a suitably large BOLD response [1]. However, clinical and elderly populations may find such a long breath-hold difficult and it is likely that the length of breath-hold that each participant can achieve will vary greatly, both from trial-to-trial and on average across these groups. The purpose of this study is to demonstrate that by measuring end-tidal CO_2 during the breath-hold task, reliable measures of vascular reactivity can be obtained even if the participant cannot perform the breath-hold to its full length.

Methods FMRI was performed on 8 participants (3 female; age 32.9±6.6) on a 3T GE MRI scanner. Six breath-hold runs and a resting run lasting 330s each were collected in a randomised order. End-expiration breath-holds followed by a short exhalation were separated by 50s and interspersed with paced breathing. In the *All10*, *All15* and *All20* breath-hold runs, the length of the breath-hold was held constant throughout the run at 10s, 15s and 20s respectively. In the *Avg12.5*, *Avg15* and *Avg17.5* runs, a combination of the three breath-hold lengths was chosen so that the average length of breath-hold was 12.5s, 15s and 17.5s respectively. CO_2 traces were recorded using a nasal cannula connected to a capnograph. The functional data were volume registered, time-shifted to a common temporal origin and converted to % BOLD change; a gray matter segmentation map was calculated from the resting dataset using a T1 mapping technique [2]; and average gray matter time courses were calculated for each subject. For each run, the CO_2 baseline was designated to be the minimum end-tidal CO_2 and the CO_2 increase was calculated as the difference between baseline and the 90th-percentile of the end-tidal CO_2 trace. Three analysis pipelines were used. The *All 20s ramps* pipeline considered the situation where all breath-holds were presumed to last 20s. Since the BOLD breath-hold response has been shown to increase linearly with time [1], the breath-holds were modelled as linear ramps lasting 20s with a final amplitude of 1. The *Time-scaled ramps* pipeline assumed that every breath-hold length was known, modelling each with the same constant linear slope for the correct length of time. Finally, the *End-tidal CO_2* pipeline modelled the response with the recorded end-tidal CO_2 values. Repeatability across the runs was measured using intra-class correlation coefficients (ICC).

Figure 1: End-tidal CO_2 increases

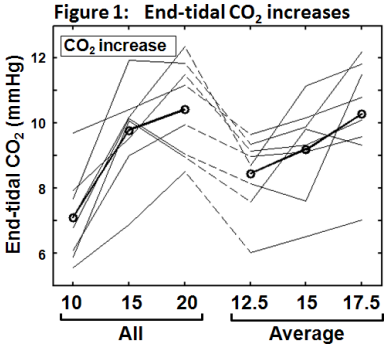
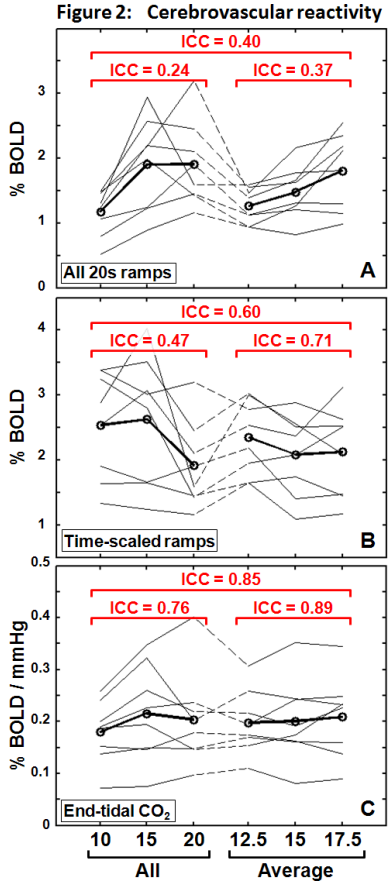


Figure 2: Cerebrovascular reactivity



Results Breath-hold manipulations of varying lengths produced the expected variance in CO_2 changes. In the constant length runs, longer breath-holds induced higher increases in end-tidal CO_2: 7.1±1.4, 9.8±1.4 and 10.4±1.5 mmHg in the *All10*, *All15* and *All20* runs respectively (Fig 1). A similar pattern was observed in the variable length breath-hold runs. In the situation where breathing is unmonitored and 20s breath-holds are assumed (Fig 2 - *All 20s ramps*), the mean %BOLD change to breath-hold varied from 1.2±0.4% (*All10*) to 1.9±0.7% (*All20*) and repeatability across all six runs was low (ICC=0.4). If the timing of the breath-holds is known (e.g from a respiration belt), the *Time-scaled ramps* analysis showed that larger % BOLD change values are found: ranging from 1.9±0.7% (*All20*) to 2.6±1% (*All15*) and that repeatability across all six runs was increased (ICC=0.6). In the *End-tidal CO_2* analysis, measuring the varying BOLD signal changes stemming from varying CO_2 increases, a higher repeatability across all 6 runs was measured (ICC=0.85) with true vascular reactivity measures ranging from 0.18±0.06 %BOLD/mmHg (*All10*) to 0.22±0.09 %BOLD/mmHg (*All15*). For all 3 analysis pipelines, repeatability was higher for the 3 variable vs. the 3 constant breath-hold runs (Fig 2).

Discussion To provide a large BOLD signal for a reliable cerebrovascular reactivity measure, the longest possible duration breath-hold is desired. The *All 20s ramps* results demonstrate that differences in end-tidal CO_2 increases are reflected in %BOLD change (compare with Fig 1 with Fig 2A). In this situation, a participant who could hold their breath for longer would be deemed to have higher cerebrovascular reactivity. If a participant cannot reach the end of the breath-hold, it is vital to know this information. Knowing the length of the individual breath-holds (the *Time-scaled ramps* analysis) helps to improve repeatability; however, it is only by measuring the exact end-tidal CO_2 increases caused by each of the variable length breath-holds that a useful, repeatable measure is obtained. An important benefit of this approach is that by normalising %BOLD change to the mmHg change in end-tidal CO_2, a quantitative measure is obtained that is comparable between participants. Interestingly, in all pipelines the variable length breath-hold tasks provide more repeatable measures than the constant length tasks. This suggests that even in healthy controls, breath-hold tasks consisting of variable lengths rather than constant lengths may be more reliable.

Conclusion By measuring end-tidal CO_2 changes during a breath-hold task, a repeatable measure of cerebrovascular reactivity can be obtained irrespective of whether the participant can perform the task fully or consistently. *Recommendation:* present all participants with a 20s breath-hold task with the instruction that if they unable to reach the end, a short exhale should be performed before taking a breath (to provide an end-tidal CO_2 measure) and the task resumed when the paced breathing restarts.

References: [1] Murphy (2011), NeuroImage:54,369 [2] Bodurka (2007), NeuroImage:34,542
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