Calibrated BOLD: measuring task-related changes in $CMRO_2$ at baseline and elevated CBF

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Introduction: By using a gas challenge to determine the maximum possible blood-oxygenation-level-dependent (BOLD) response for a given region, calibrated BOLD techniques can measure relative changes in oxidative metabolism ($CMRO_2$) induced by a task [1-3]. This process requires delivery of CO_2 or O_2 to the subject whilst acquiring ASL data to determine vasculature-related changes in BOLD and cerebral blood flow (CBF). In this study, we determine whether calibrated BOLD techniques perform similarly in baseline conditions and at altered baseline CBF levels by administering CO_2 at two different levels with a concurrent motor task. This provides an experimental simulation of performance of calibrated BOLD in a situation of altered baseline state, such as might be induced by drugs or disease. Verifying the performance of calibrated approaches at modified CBF levels will render calibrated BOLD techniques more pertinent to a clinical setting.

Methods: 15 subjects participated in 2 sessions in which scans were acquired at 3T using a PICORE QUIPSS II dual-echo ASL sequence (12 slices, 64 spiral, TE1=3.3ms, TE2=29ms, TR=2200ms, FOV=22cm, slice thickness/gap=7/1mm, TI1=600ms, TI2=1500ms, reps=490). Twenty to 30s blocks of fingertapping task were presented whilst end-tidal CO_2 levels where changed at 2 minute intervals between baseline, +4mmHg and +8mmHg values (order: 0, 8, 4, 8, 0, 4, 8, 4, 0). CBF time series were calculated from the first echo by separating tag and control time series, interpolating to the TR and subtracting. A similar procedure using averaging rather than subtraction yielded BOLD time series from the second echo. The resulting time series were averaged over grey matter motor cortex voxels across subjects for each session. BOLD and CBF responses to both the task and the CO_2 challenges were determined using a GLM by modelling the +4mmHg and +8mmHg CO_2 levels with a simple block design, all motor events with separate regressors for the +4mmHg and +8mmHg events to allow for differences at elevated CO_2 levels and linear/quadratic trends. Transitions between gas levels have a large impact on the resulting fits, therefore a number of time points (27=~60s) after transitions were ignored. Three values of M, the maximal BOLD signal, were calculated for each session with the Davis model [1]: M_4, M_8 and $M_{8\text{-}4}$, using the CO_2 response of the +4mmHg condition, +8mmHg condition and the difference between the two, respectively. Baseline motor responses were converted to relative $CMRO_2|_4$ and $CMRO_2|_8$ changes calculated using M_4 and M_8 respectively. To simulate $CMRO_2$ changes from an elevated CBF level, $CMRO_2|_{8\text{-}4}$ was calculated using the motor responses at the +4mmHg level along with the $M_{8\text{-}4}$ value.

Results: Averaging across sessions, the CO_2 challenge increased baseline BOLD signal by 1% and 2% and baseline CBF by 28% and 39% in the +4mmHg and +8mmHg conditions respectively (see Fig 1). This leads to reduced average BOLD and CBF motor activity responses: from 1.4% and 58% at baseline, to 1.28% and 50.6% at the +4mmHg CO_2 level and 1% and 51% at the +8mmHg CO_2 level (see Fig 2). Large variation in the calculated maximal BOLD signal M was found, dependent on the CO_2 condition used, but which was repeatable between sessions (see Fig 3). Signal changes from baseline to the +4mmHg condition yielded an M_4 value of ~4.4%. A much higher M value was found when examining changes from baseline to the +8mmHg level, M_8=~6.8%. An intermediate M value was calculated with changes taken between the +4mmHg and +8mmHg conditions, $M_{8\text{-}4}$=~5.5%. The combination of M values (Fig 3) and task-induced responses (Fig 2) in the Davis model leads to the $CMRO_2$ values shown in Figure 4. $CMRO_2$ values are consistently lower in Session 2 than Session 1. It was hypothesised that $CMRO_2|_4$ and $CMRO_2|_{8\text{-}4}$ should be similar since both are derived from +4mmHg CO_2 increases. Although $M_{8\text{-}4}$ is greater than M_4, this is offset by lower task-induced BOLD and CBF responses and thus relatively consistent $CMRO_2$ values are observed, for example, in Session 1, $CMRO_2|_4$ = 11.2% and $CMRO_2|_{8\text{-}4}$ = 12.1%. This suggests that measuring a reliable $CMRO_2$ value at an elevated baseline CBF level is possible. However, both $CMRO_2|_4$ and $CMRO_2|_{8\text{-}4}$ are much lower than $CMRO_2|_8$ which is 22.2% in Session 1 and 18.6% in Session 2. These results are closer to expected values suggesting that, although the $CMRO_2$ values are consistent, an increase in CO_2 of +4mmHg may not provide enough signal increase to yield a reliable estimate of M.

Figure 1: CO_2-induced baseline changes

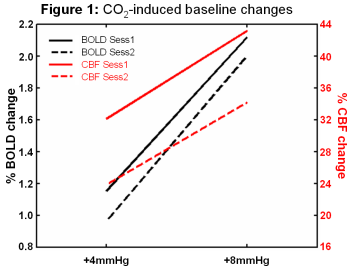


Figure 2: Task response at different CO_2 levels

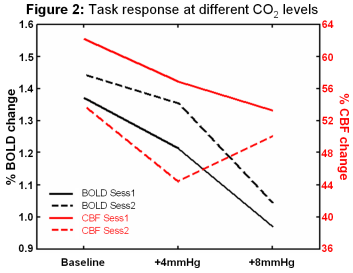


Figure 3: M values in the motor cortex

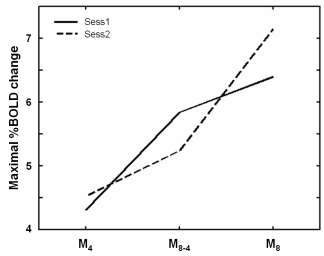
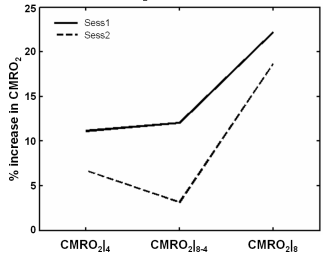


Figure 4: $CMRO_2$ values in the motor cortex



Discussion: This study investigated the effect of baseline condition on the reliability of calibrated BOLD by including 2 levels of increased CO_2 simultaneously with a motor task. Data during the transition between of CO_2 states were ignored since a complicated model of CO_2 changes and task response interactions would be required. A 4mmHg increase in CO_2 at baseline and elevated CBF levels yielded similar $CMRO_2$ results demonstrating the feasibility of calibrated BOLD in a more clinical setting where CBF alterations are expected (e.g. drug and disease conditions). However, the importance of using sufficiently large CO_2 challenge to gain an accurate estimate of M has also been established. The +8mmHg condition provides larger M values and, consequently, relative $CMRO_2$ change estimates that are in better agreement better with previously published results [1-3].

References: [1] Davis, PNAS 95:1834; [2] Hoge, PNAS 96:9403; [3] Chiarelli, NeuroImage 37:808