Does pulsed arterial spin-labeling selectively underestimate responses to global challenges?

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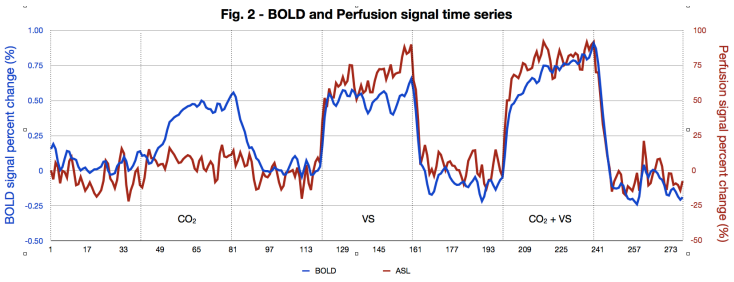
Introduction: Hypercapnic manipulation of global cerebral blood flow has shown promise in various applications, including measures of cerebrovascular reactivity [1], detection of large venous BOLD responses [2], and calibrated MRI for estimation of CMRO2 [3, 4]. Blood oxygenation level-dependent (BOLD) imaging provides a simple and robust means of detecting CO_2-induced flow changes, but the responses observed depend on both vascular and metabolic factors and are therefore ambiguous. Arterial spin-labeling (ASL) provides a specific measure of cerebral blood-flow, making it of particular interest in the applications mentioned above. In their general kinetic model of the pulsed ASL signal, Buxton et al. [5] pointed out that changes in transit delay could result in substantial underestimation of blood flow changes, a pitfall that is of particular concern during global manipulations because flow velocity in the major arteries may be substantially accelerated. We have noted that pulsed arterial spin-labeling (e.g. PICORE Q2TIPS [6] using standard literature parameters) often appears to depict little or no change in response to moderate hypercapnia (e.g. inhalation of 5% CO_2), even though simultaneously recorded BOLD signals appear to reveal a substantial hemodynamic response. This could be due to the reduced signal-to-noise ratio of ASL relative to BOLD, but we have found that, even after extensive averaging, the apparent flow response was below the threshold of detectability. To investigate this apparent paradox, we sought to test whether moderate hypercapnia was imposing a "ceiling" on the ASL signal (due to transit time shortening) by measuring flow responses to a visual stimulus at normocapnia and then again during simultaneous induction of mild hypercapnia. If a shortened transit delay were responsible for the apparent lack of an ASL response to CO_2, we might expect that the focal visual response would be similarly reduced or eliminated during hypercapnia.

Methods: Imaging was performed on a 3 Tesla scanner using a 32 channel receive-only head coil. A pulsed ASL sequence was used with the following parameters: TR/TE/α = 3000ms/12ms/90º. PICORE labeling was performed [7] with a tag width of 150 mm, a gap of 15 mm, and an inversion time of 1400 ms. The Q2TIPS technique [6] was used to impose a tag duration of 700 ms, with a Q2TIPS stop time of 1350 ms (TI1/TI2=700ms/1400ms in the QUIPSS2 nomenclature). An EPI readout was used to image seven slices of 6 mm thickness on a 64x64 matrix with an in-plane resolution of 3.5 mm. Functional scans lasted 14 minutes, during which the subjects were presented with two-minute blocks of the following three conditions: hypercapnia (achieved using inhalation of 5% CO_2 in medical air), visual stimulation (while breathing 100% air) with a high-contrast radial checkerboard contrast reversing at 8 Hz, followed by simultaneous hypercapnia and visual stimulation with the same checkerboard. Between these blocks, and at the beginning and end of the scans, were two-minute blocks of baseline (grey screen with fixation marker while breathing 100% air). This was repeated twice for each of the three subjects scanned thus far (all subjects gave informed consent and the protocol was approved by our institutional ethics committee). Image series were first motion-corrected and spatially smoothed (6 mm FWHM 3D Gaussian kernel), and ASL and BOLD series separated by surround subtraction. The amplitudes of BOLD and ASL responses were then estimated by performing a GLM fit with a different regressor for each of the three conditions: CO_2, visual stimulation, and CO_2+visual stimulation. Fits using only two regressors (visual stimulation and CO_2) were also performed for delineation of a region-of-interest based on the conjunction of the visual responses detected in ASL and BOLD maps. The average GLM effect size for each regressor was computed within the visual ROI for each subject, then divided by the ROI-averaged DC term from the same model fit and multiplied by 100 to convert to percent change. Time series signals, converted to percent change, were also averaged within the ROI for each scan. The percent effect sizes and time series thus obtained were then averaged over all subjects (two scans per subject times three subjects).



Discussion: Our results suggest a weak ASL response (11.3±5.17%) to 5% CO_2, one that is somewhat lower than reported by others under similar conditions [3] and difficult to detect due to the low SNR of the ASL signal. If there is a systematic underestimation of the CO_2 response, the mechanism for this does not seem to prevent the robust detection of the focal response to a simultaneously presented visual stimulus. Moreover the percent flow change observed during visual stimulation is increased by the simultaneous addition of hypercapnia. The BOLD responses show a clearly visible response to CO_2, both alone and in combination with visual stimulation. The apparent lack of an ASL response to CO_2 likely reflects the low SNR of the signal, combined with the relatively low "true" response amplitude for CO_2 compared with sensory stimulation (63.4±16.29% for visual).

Bibliography: 1. Mikulis, D.J., Neuroimaging Clin N Am, 2005. **15**(3): p. 667-80, xii. 2. Bandettini, P.A. and E.C. Wong, NMR Biomed, 1997. **10**(4-5): p. 197-203. 3. Ances, B.M., et al., Hum Brain Mapp, 2009. **30**(4): p. 1120-32. 4. Davis, T.L., et al., Proc Natl Acad Sci U S A, 1998. **95**(4): p. 1834-9. 5. Buxton, R.B., et al., Magn Reson Med, 1998. **40**(3): p. 383-96. 6. Luh, W.M., et al., Magn Reson Med, 1999. **41**(6): p. 1246-54. 7. Wong, E.C., R.B. Buxton, and L.R. Frank, NMR Biomed, 1997. **10**(4-5): p. 237-49.

Results: In spite of the short echo time (12 ms), BOLD effect sizes and time series showed significant increases during both CO_2 inhalation and visual stimulation, as well as a linear combination of the responses from CO_2 and visual stimulation (note that percent changes are smaller than with longer echo times normally used in BOLD imaging). ASL measurements indicated a percent effect size for CO_2 that only marginally achieved statistical significance, and a time series in which the CO_2 was not qualitatively apparent (see Fig. 1-2). Visual responses were, however, robust in the ASL data. Moreover the visual+CO_2 flow response was higher than the pure visual response by an amount equal to the estimated flow response to CO_2 alone, consistent with a linear combination of flow responses to CO_2 and visual stimulation (and inconsistent with "saturation" of the ASL signal due to the global response to CO_2).