Comparison of ASL measures of cerebrovascular reactivity to CO_2 using different respiratory manipulations

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Introduction: ASL measurements of the cerebrovascular reactivity to CO_2 (CVR) may provide a clinical index of the cerebral vasculature's health status[1] and are also an essential component of calibrated MRI to estimate the rate of oxidative metabolism in the brain[2]. CVR is usually expressed as the increase in cerebral blood flow (CBF) per mmHg increase in end-tidal PCO_2 ($P_{ET}CO_2$) that are measured during a respiratory manipulation. A common method for inducing hypercapnia, i.e. CO_2 increases, consists of administering air mixtures with a fixed concentration of CO_2 (FI). In FI-based manipulations the $P_{ET}CO_2$ changes depend on different physiological parameters, rendering reproducibility of the stimulus challenging. Moreover, accelerated breathing during hypercapnia can lead to incidental changes in end-tidal PO_2 ($P_{ET}O_2$), an effect that may confound the CVR estimates. As an alternative to FI, several groups have utilized more complex systems to prospectively control (PC) CO_2 and O_2 levels[3]. Based on a specially designed sequential rebreathing circuit and incorporating a physiological modeling of CO_2 fluxes in the body, the RespirAct system, an implementation of the PC method, can target $P_{ET}CO_2$ and $P_{ET}O_2$ levels individually. Another approach that has been used to induce hypercapnia is to have subjects to execute a breath hold (BH)[4]. Although very simple, requiring minimal equipment and setup time, BH methods are limited to subjects who are able to understand and comply with the breath-hold instructions. Disadvantages include the associated hypoxia and difficulty estimating the changes in $P_{ET}CO_2$ for the normalization of CBF responses. We sought to determine whether these different types of respiratory manipulation lead to consistent measurements of CVR.

Methods: Ten young healthy subjects were scanned in a Siemens 3T using pseudo-continuous ASL (pCASL) to measure CBF, during 4 different respiratory manipulations of ~10 min duration each (Fig. 1). pCASL parameters were: labeling time = 1.5s, delay = 0.9s, TR/TE = 3000/10ms, 11 slices with 7x4x4mm^3 resolution. In the PC manipulation a commercial system (RespirAct^{TM}, Thornhill Research Inc.) was used to control $P_{ET}CO_2$ and $P_{ET}O_2$. The system was programmed to increase the subjects' $P_{ET}CO_2$ by 5mmHg in two different instances of 2m:20s while keeping $P_{ET}O_2$ unchanged. In the FI, the paradigm followed the same block design as in PC, with subjects breathing air during the baseline condition and a 5%-CO_2 air mixture to stimulate hypercapnia. In the BH, subjects hold their breath for 20s in 12 different instances, separated by 30s of paced breathing (PB). In the latter 3 manipulations subjects were instructed to pace their breath at 16 breaths per min (bpm)[3]. In a fourth manipulation that mimicked the block design of PC and FI, the baseline condition consisted of hyperventilation (HV) – with subjects breathing at 24bpm – and stimuli of 2 compounded blocks of breath-hold. Respiratory levels of CO_2 (and O_2) were continuously monitored using a nasal cannula and a gas sampler/analyzer (Biopac MP150). The baseline levels and amplitude of the hypercapnic responses were obtained through linear modeling of the end-tidal points in the capnographs (Fig. 2, left panel: capnographs in grey, models in solid black). As to the CBF measures, the ASL image series were first motion corrected, flow series were obtained by subtracting tag-control images and the difference signal was then fit with a GLM consisting of the monitored values of $P_{ET}CO_2$ plus a 3rd order polynomial representing the drift terms and a constant offset (Fig 2, right panel: ASL signal in grey, models in black). The missing values of $P_{ET}CO_2$ during breath-holds were completed with the estimates obtained with the capnograph modeling. The ASL signal was converted to physiological units of CBF as in ref 5. The GLM fit yielded estimates of the baseline CBF and related increases. CBF was averaged within a grey matter probability ROI, obtained with the segmentation of anatomical acquisitions (MPRAGE of 1mm^3 resolution). The resting "normal" $P_{ET}CO_2$ and CBF levels were obtained from additional scans in which subjects breathed air spontaneously. End-tidal and CBF/CVR values were compared during conditions and against the resting levels using paired t-tests.

Figure 1 – The 4 respiratory manipulations

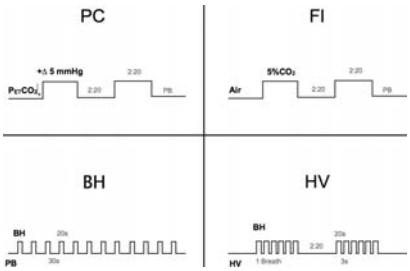
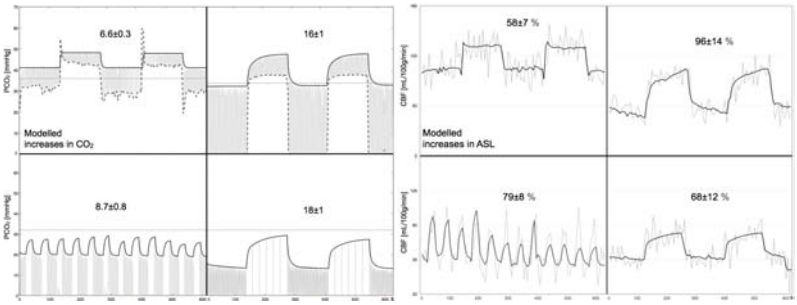
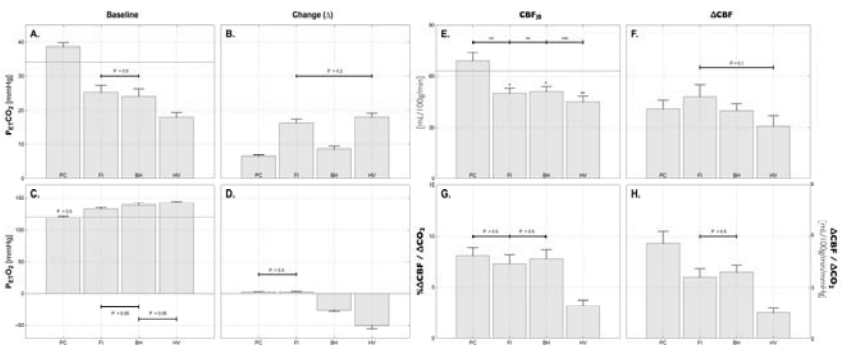


Figure 2 – Average increases in $P_{ET}CO_2$ and grey matter CBF



Results: Results are summarized in Fig. 3. Differences between $\Delta P_{ET}CO_2$ were generally statistically significant, with the exception of the pair FI and HV (B). Baseline levels of $P_{ET}CO_2$ were significantly different than resting values (A). Whereas FI, BH and HV had baseline $P_{ET}CO_2$ levels that were lower than the spontaneously arising values, the PC manipulation had levels that were higher. Baseline $P_{ET}CO_2$ levels were, as expected, lowest in HV, where ventilatory rate was 50% higher than in the rest of the manipulations. The paced breathing of 16bpm caused subjects to go hypocapnic in the FI and BH scans, and baseline $P_{ET}CO_2$ did not differ significantly between the respective manipulations. $P_{ET}CO_2$ levels much below 40 mmHg were difficult to achieve with the RespirAct at the desired breathing rates. Incidental changes in O_2 were all significantly different from zero (D). In PC and FI, changes were minimal and virtually indistinguishable. Baseline levels of $P_{ET}O_2$ were above resting levels except for PC (C). As would be expected, peak baseline levels for $P_{ET}O_2$ were observed for hyperventilation. Differences in the CBF response were only marginally significant between FI and HV (F). The CBF increases contrast with the $P_{ET}CO_2$ increases mostly due to the HV response. Baseline CBF levels (E) were generally correlated with baseline $P_{ET}CO_2$, with PC having considerably higher values than the other manipulations, amongst whom the differences were not statistically significant. When CVR was expressed in terms of the absolute change in CBF per mmHg change in $P_{ET}CO_2$ there were significant differences in the values given by the different methods (H). Absolute CVR values were correlated with the resting $P_{ET}CO_2$ associated with each manipulation. When expressed as the percent change in CBF per unit of change in $P_{ET}CO_2$, PC, FI, and BH yielded comparable CVR estimates that did not differ by a statistically significant amount (G). The HV manipulation, again, gave a significantly lower CVR, indicating that CBF responses are significantly attenuated for lower doses of CO_2.

Figure 3 – End-Tidal levels and CBF reactivity



Discussion: Reproducibility of the hypercapnic stimuli in all 4 manipulations were comparable. Incidental changes in O_2 were well controlled in the FI manipulation using the paced breathing. In BH, the hypoxia may have stretched the respective CVR value, but the effect seems to be minor. Values of CVR expressed in terms of the absolute change in CBF per unit of change in $P_{ET}CO_2$ depended on the range of $P_{ET}CO_2$ levels considered, indicating that the non-linearity of the CBF-CO_2 dose-response curve [6] exerts significant influence on the CBF reactivity observed using ASL. Variability between methods was reduced when CVR was expressed in terms of the percent change in CBF, but with HV producing a significantly lower and less robust estimate. We conclude that manipulations involving significant hypocapnic baseline should be avoided.

References: 1) Stroke 2006;37(4):1010-5 2) NeuroImage 2012;60(2):1212-25 3) MRM 2010;64(3):749-56 4) NeuroImage 2011;54(1):369-79 5) JMRI 2012;36(2):312-21 6) J. Physiol 2011;589(Pt 12):3039-48