# Separating the magnitude and temporal responses in a BOLD-based CO2 hypercapnia leads to improved inter-session reliability as well as characterization of hemodynamic impairment: a clinical multi-cohort study

David E Crane[1], Anoop Ganda[1], David J Mikulis[2], Sandra E Black[1], and Bradley J MacIntosh[1]
*[1]Sunnybrook Research Institute, Toronto, ON, Canada, [2]Toronto Western Hospital, Toronto, ON, Canada*

**Target audience:** those interested in modeling hypercapnia and clinical translation of CVR.

**Introduction**: Cerebrovascular response to hypercapnia (CVR) has demonstrated clinical utility [1,2] and is commonly measured by delivering air with increased $CO_2$ concentration while the MRI scanner measures time-varying changes in cerebral blood flow level or the blood oxygenation level dependent (BOLD) contrast signal [3]. CVR is typically calculated as the mean % signal change per unit increase in end-tidal $CO_2$. One disadvantage of this summary measure is the inability to separate magnitude from temporal dynamics effects, since the vascular response may lag for different brain regions. We propose a '*vascular transfer function*' (VTF) method to separate amplitude and temporal lag effects through deconvolution of the BOLD response (**Fig. 1**), which is akin to the hemodynamic response function in fMRI. In this context, the CVR VTF is the BOLD response to an instantaneous input of arterial $CO_2$. We hypothesized that VTF area under the curve (**AUC**) and time-to-peak (**TTP**) metrics will be reliable across sessions and be different between patient groups.

**Methods**: 60 participants were scanned using a Philips Achieva 3T MRI system, and a subset of 20 elderly with white matter hyperintensities (WMH) completed a 1-year follow-up scan. Participants belonged to one of four groups: healthy adult (n=18), moderate WMH (WMH<35ml) burden (n=20), severe WMH (n=12) and a genetic form of WMH called CADASIL (n=10). MRI consisted of a gradient echo BOLD EPI (TR/TE=2000/30ms, matrix=64x64x40, 3.6x2.9x3mm voxels, duration=8min38s) during delivery of two hypercapnia phases, i.e. 10mmHg increase in end-tidal $CO_2$, durations: 45 and 120 sec. Other scanning included: high-resolution T1-images for image segmentation (**Fig. 3A,** TR/TE/TI=9.5/2.3/1400ms, 1x1x1.2mm, flip angle=8° duration=8min56s) and FLAIR images for WMH volume (TR/TE/TI=9000/125/2800ms, 1x1.1x3mm, duration=4min48s). $CO_2$ delivery was conducted with a feed-forward, low gas-flow system (RespirActTM, Thornhill Research Inc., Toronto, Canada). Block-circulant singular value decomposition was used to deconvolve the end tidal CO2 signal from the motion-corrected %ΔBOLD signal and produce the VTF. Summary metrics of the VTF were calculated to represent the CVR magnitude and temporal response phenomenon: the area under the curve (AUC, **Fig 3B**) and time required to reach peak (TTP, **Fig 3C**), respectively. Statistical analysis was conducted on these measures to evaluate correlation across sessions and difference between groups.

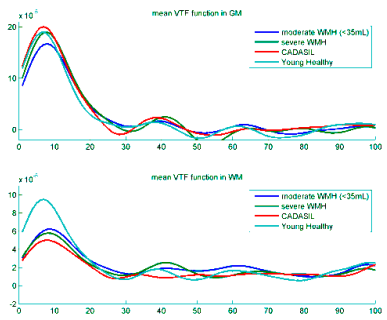


**Figure 1:** Mean VTFs from four groups in GM (top) and WM (bottom). X-axis is time, Y-axis is %BOLD change to a delta function of 1mmHg change in $CO_2$.

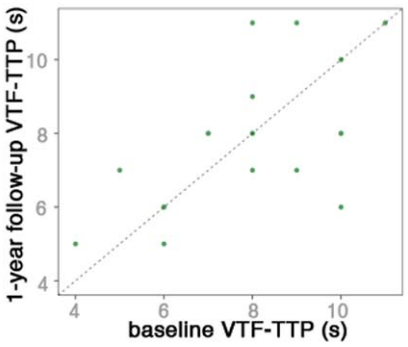


**Figure 2:** Test-retest reliability was assessed using baseline and one year follow-up data from 20 patients for the TTP metric in GM, Pearson correlation r=0.63 (p=0.003).

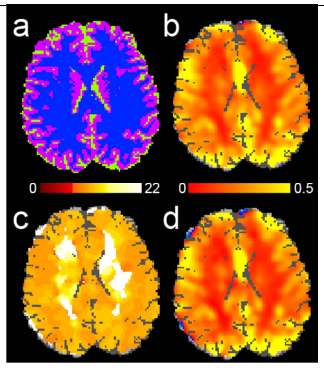


**Figure 3:** Sample images from 24-yr old woman: a) segmented T1 b) VTF-AUC, c) VTF TTP, d) traditional CVR.

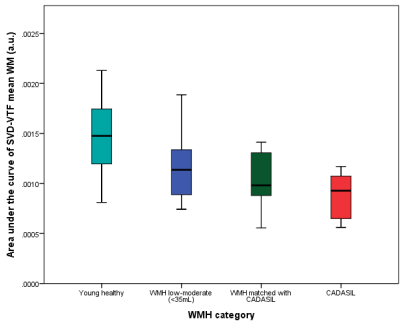


**Figure 4:** VTF-AUC was different between groups for WM (F=12.0, p<0.001) but not GM (f=0.62, p=0.43). Conventional CVR was no significant difference in either tissue (GM: p=0.82; WM: p=0.07).

**Results:** Between-session correlation was robust in GM for VTF-AUC, VTF-TTP and traditional CVR (r=0.41, 0.63, 0.49, respectively) with no correlation across sessions in WM (p>0.25). The CADASIL group had the lowest AUC (**Fig. 4**). As a post-hoc test, we introduced temporal delay into the $CO_2$ signal to test for its effects on AUC and TTP. We found a linear relationship between lag and TTP, while there was no significant effect on AUC for time delays up to 15 seconds.

**Conclusion:** We developed a new method to characterize CVR, which relies on deconvolution of the end-tidal $CO_2$ trace with the BOLD signal to produce a vascular transfer function. The VTF amplitude and timing estimates were more sensitive than conventional CVR metrics, with the ability to detect cross-sectional cohort differences (**Fig.** 4) as well as provide significant test-retest reliability (**Fig. 2**).

**References: 1.** Markus H, et al., Brain. 2001 124(Pt 3):457-67. **2.** Mandell DM et al., Stroke. 2008 39(7):2021-8. 3. Chen JJ, Pike GB, J Cereb Blood Flow Metab. 2010 Jun;30(6):1094-9.