Cerebrovascular Reactivity Measured Using Targeted Hypo/Hypercapnia BOLD Imaging at 7T

Alex Bhogal[1], Marielle Philippens[2], Joe Fisher[3], Jeroen Cornelis Willem Siero[1,4], Peter R Luijten[2], and Hans Hoogduin[1]

[1]Radiology, UMC Utrecht, Utrecht, Utrecht, Netherlands, [2]Radiotherapy, UMC Utrecht, Utrecht, Utrecht, Netherlands, [3]Thornhill Research Inc., Toronto, Ontario, Canada, [4]Rudolf Magnus Institute, University Medical Center Utrecht, Utrecht, Utrecht, Netherlands

Introduction: Cerebrovascular Reactivity (CVR) refers to the change in cerebral blood flow in response to a vasoactive stimulus. Observing CVR dynamics can provide insight into the vascular dimension of neurological diseases and may provide information useful for grading and staging brain tumours. Generally CVR is measured using block stimuli in which a CO_2 challenge is administered in a step-wise manner. However, recent studies investigating CO_2 reactivity using transcranial Doppler in conjunction with ramped increases in arterial PCO_2 ($PaCO_2$) have demonstrated a sigmoidal relationship with upper and lower reactivity limits [1][2]. The fitting parameters to this relation may be used to characterize CVR and potentially identify pathological regions or response [3]. For example, malformed vasculature, cancer-related or otherwise, having poor reactivity may demonstrate early plateau, limited CVR span or delayed reactivity. Compromised CVR has already shown to be an indicator of increased risk of stroke [4].

Purpose: To compare BOLD signal changes obtained from ramped CO_2 experiments to those acquired using more traditional block stimulus to improve CVR measurements.

Methods: Three healthy subjects were scanned on a Philips 7T system. Dynamic BOLD-EPI images of at least 20 cranial slices (TR/TE 3000/25ms, EPI/SENSE Factor 47/3, voxel dim: 1.5x1.5x1.6mm) were acquired during CO_2 breathing challenges. $PaCO_2$ was targeted by using a computer-controlled gas blender and sequential gas delivery system running a feed-forward algorithm described by Slessarev et al. [5] (Respiract, Thornhill Research Inc, Toronto, Canada). With this system, end-exhaled PCO_2 are equal to $PaCO_2$ [6]. After a 60-180s subject specific baseline period, the 'ramp' breathing sequence consisted of $PaCO_2$ at 25-35 mmHg followed by a normoxic uniformly progressive increase of $PaCO_2$ over 300 s to 55-65 mmHg; followed by return to baseline. Additionally, 90s block paradigm data was acquired from 2 subjects during a targeted $PaCO_2$ step between 40-50mmHg. Brain tissue was masked and image volumes were co-registered. BOLD signal data was temporally aligned with end-exhaled PCO_2 values to produce ΔBOLD vs. $PaCO_2$ curves. Data was spatially smoothed (3D Gaussian kernel σ = 2.9mm) and voxel time-courses were temporally smoothed with a loess filter with 8% local regression window. ΔBOLD/$PaCO_2$ curves were fit to sigmoidal and linear CVR models in a voxel-wise manner. Fits were constrained to include positive functions only. Thus, any possible steal effects, or otherwise, were ignored due to low R^2 [3]. The sigmoidal function is described by:

$$\mathbf{y = a+[b/(1+exp(-(x-c)/d))]}\ [2].$$

Where 'a' is initial signal level, 'b' is signal span, 'c' is the sigmoid midpoint (mmHg) and 'd', the length of the linear portion of the curve (inverse slope in mmHg). R^2 response maps and sigmoid parameter maps were created.

Fig 1-A

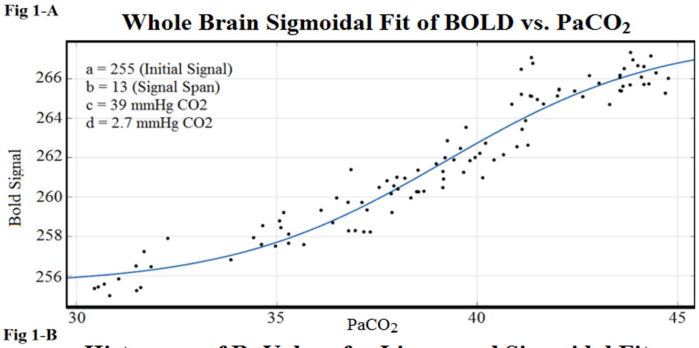


Fig 1-B

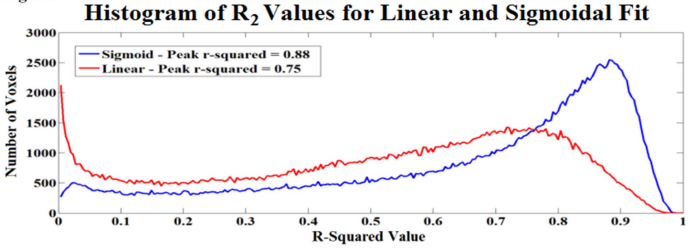
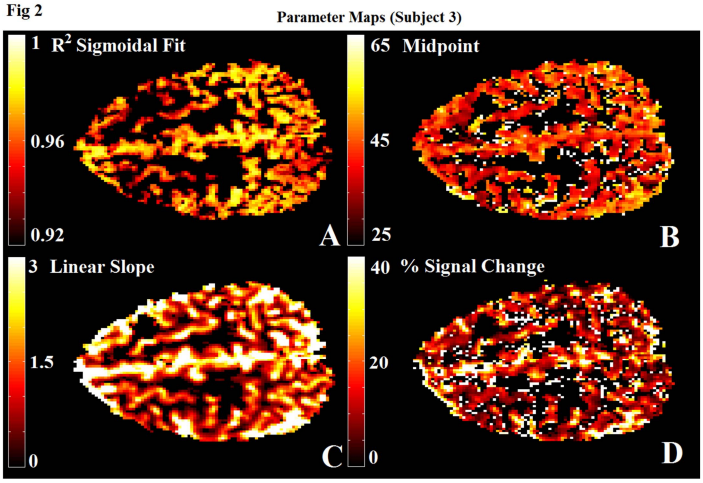


Fig 1-A: *Single subject whole-brain BOLD/PetCO₂ sigmoid fit - subject 2.*
Fig 1-B: *R^2 histograms derived from linear and sigmoidal fit - subject 2.*

Results: Fig 1-A show the result of a sigmoidal fit to BOLD vs. $PaCO_2$ for a single subject. Fig 1-B shows a whole brain histogram of fitted R^2 values derived from voxel-wise fitting to linear and sigmoidal models. Averaged over subjects, the peak R^2 values were 0.92 (+/-0.04) and 0.86 (+/- 0.09) for sigmoidal and linear fits respectively. On average, the number of voxels with R^2>0.9 was 3X greater for sigmoidal vs. linear fit. Figs 2A-D display sigmoidal fit parameters derived from a single slice. Fig 2-C displays slope values calculated from linear fitting. The peak whole brain %BOLD signal changes (including all brain voxels, (b/a)) based on sigmoid fit parameters for each of the 3 subjects were 4.9%, 6.2% and 12.1% corresponding to increases of $PaCO_2$ between 30-45, 35-50 and 25-65mmHg respectively. The changes observed using the block $PaCO_2$ stimulus (for 2 of 3 subjects) were 2.1% and 2.3% respectively. These represent average changes of 0.34 (ramp) 0.22 (block) %BOLD/mmHg $PaCO_2$ respectively.

Fig 2



CVR Parameters Derived from Sigmoidal and Linear Fitting of BOLD Data Acquired During Ramped CO_2 Challenge.

Fig 2-A*: Thresholded R^2 map (>0.92) showing response areas predominantly located in gray matter.* ***Fig 2-B****: Average sigmoid midpoint (c) value across all subjects was 46 mmHg CO_2 with a mean std. dev. of 17.6 mmHg.* ***Fig 2-C****: Slope magnitudes calculated from linear fitting. Slope steepness is indicative of reaction rate. Low values indicate more gradual CVR changes.* ***Fig 2-D****: %BOLD signal change derived by dividing the span of the sigmoid by the initial signal magnitude (b/a). R^2 thresholded mean %signal change was 17.2% with a mean std. dev. of 16.1%.**

**Fig 2B-D were masked to only include voxels having an R^2 threshold > 0.8*

Discussion/Conclusion: In comparison with a block stimulus, the %BOLD signal change per unit $PaCO_2$ was larger when calculated from ramp data. Large block stimuli may exceed CVR leading to a saturation of the BOLD signal in subjects with high resting baseline $PaCO_2$. Parametric analysis of ramped challenges described using a sigmoidal model provided more information on CVR than block challenges. Both in terms of fitting parameters and %BOLD/mmHg $PaCO_2$ signal change. Linear, rather than sigmoidal, descriptions of ramped data may be more robust; however, they tend to obscure information present in the data. A sigmoidal response model more accurately described the behavior of CVR with increasing $PaCO_2$; particularly in gray matter regions where highest response correlations were observed. White matter regions were predominantly excluded due to low SNR or a negative BOLD response. The high variation in midpoint (c), and thereby in timing of reactivity response, and %signal change parameters may be attributed to heterogeneous flow effects and regional variation in tissue composition. In conclusion, CVR measurements using ramped as opposed to block $PaCO_2$ protocols that are described by sigmoidal response functions provide more information with respect to CVR dynamics, and offer a more accurate way to calibrate signal changes attributable to vessel reactivity.

References: [1] Battisti-Charbonney A., et al. *J. Physiol* 2011; [2] Schwertfeger N., et al. *J. Neorol. Sci.* 2006; [3] Mandell DM., et al. *Stroke* 2008; [4] Webster WM., et al. *J. Vasc. Surg,* 1995; [5] Slessarev M., et al. *J. Physiol.* 2007; [6] Ito S., et al. *J Physiol*. 2008; **This study was part of the EU Artemis High Profile Study**