Investigating BOLD signal properties under targeted hyperoxic combined with progressive hypercapnia at 7T

Alex Bhogal[1], Esben Petersen[1], Manus J Donahue[2], Marielle Philippens[3], Peter Luijten[1], Hans Hoogduin[1], and Jeroen C.W. Siero[1]

[1]Radiology, University Medical Center, Utrecht, Netherlands, [2]Radiology and Radiological Sciences, Vanderbilt University, TN, United States, [3]Radiotherapy, University Medical Center, Utrecht, Netherlands

TARGET AUDIENCE: Researchers interested in mechanistic studies of BOLD contrast and related cerebrovascular reactivity measurements.

PURPOSE: To investigate whether vascular and BOLD mechanistic signal properties can be separated using a targeted progressive hypercapnic ramp in combination with targeted hyperoxia.

INTRODUCTION: Calibrated BOLD techniques, using both hypercapnic and hyperoxic stimuli, aim to estimate the scaling parameter 'M' [1] which defines the maximum theoretical BOLD signal change in a voxel for a given baseline condition [2]. Hypercapnia is a primarily isometabolic vasoactive stimulus which increases cerebral blood flow (CBF), thus washing out venous de-oxyhemoglobin (dHb) which results in an increase of the BOLD signal relative to normocapnic-normoxic baseline. By contrast, hyperoxia increases venous oxygen saturation via increases [HbO_2] and O_2 dissolved in plasma [3]. Here, we examine the non-linearity of the BOLD-CVR response to increasing $PaCO_2$ under targeted normoxia and hyperoxia at 7T to evince the maximum vasodilatory capacities of the brain vasculature and understand the corresponding influence on the BOLD signal.

METHODS: Healthy volunteers (n=2) were scanned on a Philips 7T scanner using a 32 ch. receive coil. Single-shot GE-EPI BOLD images (α= 90°, TR/TE= 3000/25ms, EPI/SENSE factor= 47/3, spatial resolution= 1.5x1.5x1.6mm^3, slices= 43, volumes= 240) were acquired throughout two (normoxic and hyperoxic) 720s targeted hypo- to hypercapnic breathing challenges delivered by a RespirAct^{tm} (Thornhill Research Inc, Toronto, Can). Challenge timing is provided on the x-axis of Fig A. Hypercapnic ramps were targeted up to 20 mmHg above baseline $PaCO_2$. During the hyperoxic ramp, PaO_2 was targeted at 350 mmHg. BOLD images were processed in FSL: Brain extraction (BET), re-alignment (MCFLIRT), ROI segmentation of mean image to GM-WM ROIs (FAST). BOLD data was linearly detrended using the normoxic/normocapnic baseline points, then normalized to baseline ROI signal. For the hyperoxic challenge, normalization to normoxic and hyperoxic baselines was performed to examine the signal effects of increasing O_2 and CO_2 independently. The ramped stimulus was temporally matched to measured $PaCO_2$ values to create BOLD-CVR curves. Eroded ROIs (inset Fig B) were used to calculate average timeseries for GM and WM. ROI signal timeseries' were temporally smoothed (Loess filter, 6% regression window) and a sigmoidal model was fit to the resulting data:

$$\%\Delta S=[S_o+(S_{span}/(1+\exp(-(x\text{-midpoint}_{mmhg})/\text{linear span}_{mmhg})))].$$

RESULTS & DISCUSSION: The range of targeted $PaCO_2$ values was consistent between both normoxic and hyperoxic $PaCO_2$ ramps (Fig A). Although PaO_2 was targeted at 350mmHg, it displayed a ramping behavior in both subjects (subj. 1: 320-360mmHg, subj. 2: 300-350 mmHg). Hyperoxia in subject 1 elicited an obvious initial increase in %ΔBOLD in WB and GM (Fig B), however WM appeared less sensitive to this effect. Subject 1 WB and GM response curves are as expected assuming that signal plateau are solely the result of BOLD signal saturation. In this case the hyperoxic and normoxic BOLD CVR curves should converge at a similar plateau value due the complete removal of venous dHb. The effect of increasing $PaCO_2$ under norm- and hyperoxic conditions is shown by normalizing to the hyperoxic baseline signal (Fig B bottom row/Fig C). In subject 1, the point at which the %ΔBOLD under hyperoxia levels off decreases relative to the normoxic condition (Fig B, blue curve). This was not the case in subject 2 whose hyperoxic and normoxic BOLD-CVR curves diverged at increasing $PaCO_2$. These results highlight two possible situations which could be due to the previously described inter-subject variability in measured 'M' values [4]. Reduced hyperoxic %ΔBOLD under hypercapnia of subject 1 suggests that the increased PaO_2 may have enhanced dHb washout to the point where the maximum %ΔBOLD has been reached (BOLD ceiling effect). The progressive increases in PaO_2 likely accelerated this effect. The plateau in subject 2, on the other hand, may be the result of maximum vasodilatation. Here, increasing PaO_2 raises the baseline BOLD signal, however sufficient signal headroom likely remains before the onset of the BOLD ceiling effect. It follows then that increasing PaO_2 causes a progressive signal increase leading to divergent response curves. It is unclear how changing of the baseline vascular tone/dilation affects these response curves since potential O_2 induced vasoconstriction may compete against the vasoactive effect of increasing $PaCO_2$, thus modulating the BOLD signal response. Accompanying ASL measurements for baseline CBF information seem warranted.

CONCLUSION: The results presented here suggest that the BOLD signal plateau observed at high $PaCO_2$ is likely the result of mixture of vascular and BOLD signal saturation effects. Baseline conditions are known to be variable between subjects, thus inclusion of more subjects (ongoing work) is required to examine which signal components can be attributed to vascular behavior or BOLD-related mechanisms. Nevertheless, BOLD imaging at 7T using high spatio and temporal resolution, in combination with targeted respiratory waveforms show promising preliminary results and may shed light on vascular and BOLD mechanistic signal components.

REFERENCES & ACKNOWLEDGEMENTS: [1] Krieger et. Al, Neuroimage 2013, [2] Davis et. Al, PNAS, [3] Blockley et al. NMR Biomed, 2012, [4] Hoge RD, Neuroimage 2012 **This study was part of the EU Artemis high profile project**
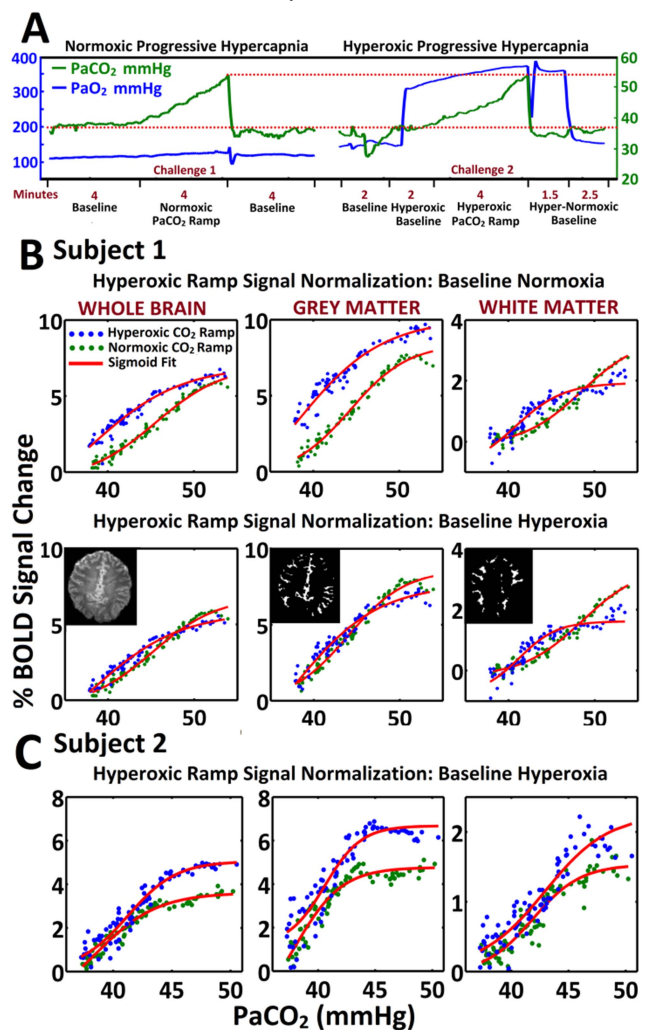
Fig A: Subject 1 $PaCO_2$ and PaO_2 values for normoxic and hyperoxic breathing challenges respectively. Challenge timing is provided on the x-axis. Dotted red lines define the $PaCO_2$ span, illustrating target $PaCO_2$ reproducibility. *Fig B (top row)*: BOLD-CVR curves normalized to the normoxic (initial 120s) baseline BOLD signal illustrating the effect of increasing PaO_2. *Fig B (bottom row)*: Subject 1 hyperoxic BOLD-CVR curve normalized to hyperoxic baseline. The effect of increasing $PaCO_2$ under norm- and hyperoxic conditions is illustrated. *Inset left:* single slice GE-EPI image used to create WM mask *Inset center/right*: representative GM/WM masks *Fig C:* Same as Fig B (bottom) for Subject 2