The Dependency of Cerebral Blood Flow on End-tidal CO_2 Pressure

Eidrees Ghariq[1], Xingxing Zhang[1], Andrew G. Webb[1], Mark A. Van Buchem[1], Albert Dahan[2], and Matthias J.P. Van Osch[1]

[1]*C.J. Gorter Center for High Field MRI, Department of Radiology, Leiden University Medical Center (LUMC), Leiden, Zuid-Holland, Netherlands,* [2]*Deparment of Anesthesiology, Leiden University Medical Center (LUMC), Leiden, Zuid-Holland, Netherlands*

TARGET AUDIENCE – Neuroscientists using ASL/BOLD MRI for CO_2 cerebrovascular reactivity measurements or quantitative BOLD

PURPOSE – Cerebrovascular reactivity (CVR) due to CO_2 inhalation is believed to be a measure of the capacity of the cerebral blood vessels to match the cerebral blood flow (CBF) to the metabolic needs of the brain. CO_2 CVR has been shown to be disturbed in many neurological diseases, e.g. steno-occlusive diseases of the brain. ASL and BOLD MRI are increasingly used for the measurement of regional cerebrovascular reactivity to CO_2. The acquired data are often treated in the same way as fMRI data, i.e. a linear relationship is assumed between the end-tidal CO_2 pressure ($P_{Et}CO_2$) and the CBF or BOLD signal. However, already in 1964 Reivich showed that the CBF CO_2 reactivity curve in monkeys has a sigmoidal shape[1] and more recently the sigmoidal relationship between CO_2 and CBF velocity (CBFv), measured via transcranial doppler (TCD), has been reported in humans[2]. Furthermore, Bhogal et al. have recently showed that BOLD CO_2 reactivity curve has a sigmoidal shape. Thus the assumption of a linear relationship between $P_{Et}CO_2$ and CBF/BOLD could potentially confound any reported findings. The purpose of this study was to accurately measure the relationship between $P_{Et}CO_2$ and both CBF and BOLD reactivity. Additionally, it is tested whether these relationships differ between the anterior and posterior cerebral circulations.

METHODS – All the scans were performed on a Philips 3 Tesla Achieva scanner under a local IRB approved protocol. A dual-echo arterial spin labeling (DE-ASL) MRI sequence was used to acquire simultaneous BOLD and CBF data from ten healthy young adults. (Scan parameters: TR/TE1/TE2=4000/10/26 ms; labeling/post-label duration=1650/1525 ms; 2.75x2.75x6 mm^3; 17 slices; background suppressed). The stimulation was a 6 minute CO_2 'ramp' varying from hypocapnia to hypercapnia repeated 4 times (total scan duration = 24 min). To achieve hypocapnia the subjects were instructed to follow a respiratory cue with a predefined frequency (17 respirations per minute) while breathing room air (O_2/CO_2=21/0 %). This pace was also followed during the hypercapnic episodes. During the hypercapnic episodes the fraction of inhaled CO_2 was increased stepwise from 0 to 7.5 % via a gas mixer, causing a corresponding increase in $P_{Et}CO_2$ (Figure 1). The partial pressures of the gasses in the inhaled/exhaled air was continuously measured with a Datex Capnomac Ultima capnograph monitor situated outside the MRI scanner. In addition to the DE-ASL scans, M_0 scans were acquired for the quantification of the ASL data and regional perfusion maps to separate the perfusion territories of the three feeding arteries of the brain (left and right internal carotids and basilar arteries).

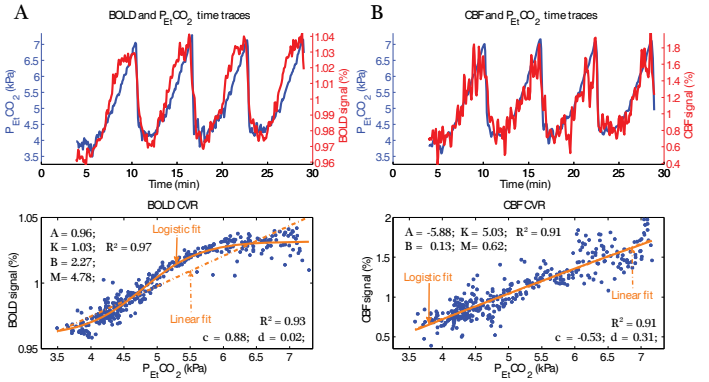

Figure 1. $P_{Et}CO_2$ values and BOLD and CBF signals are plotted as functions of time (upper parts of the figure). The lower panels are plots of BOLD and CBF signals as a function of $P_{Et}CO_2$. The orange lines are the linear and logistic (sigmoidal) fits of the data.

The BOLD data were calculated from the second echo images and the ASL data from the first echo images of the DE-ASL scans. The ASL data were quantified to CBF values using the M_0 scans based on the quantification model proposed in the recently submitted ASL white paper. Both CBF and BOLD data were averaged for each of the three perfusion territories and then normalized to their respective mean values and plotted as a function of $P_{Et}CO_2$. These time traces were then fitted using both a linear model [y(x)=c+d*x] as well as a general logistic model [y(x)=A+(K-A)/(1+exp(-B*(x-M)))] describing the sigmoidal curve. For both models the adjusted R^2 of the fit was calculated for every subject. Alternatively, to minimize any bias due to the fitting of a sigmoidal function with four degrees of freedom to CBF vs. $P_{Et}CO_2$ data, cross-correlation coefficients were calculated between the CBF and $P_{Et}CO_2$ traces, and the CBF trace and a sigmoidal transformation of the trace of $P_{Et}CO_2$ based on the BOLD reactivity curves. These cross-correlation coefficients were then used as an unbiased measure of a sigmoidal versus linear relationship between CBF reactivity and $P_{Et}CO_2$ in the measured $P_{Et}CO_2$ range.

RESULTS – Figure 1A and B show time traces of the BOLD and CBF data (red) and the trace of $P_{Et}CO_2$ (blue) for the basilar artery territory of a representative subject. The lower parts of the figures show plots of the corresponding BOLD and CBF data as functions of $P_{Et}CO_2$. As can be seen from the images, the BOLD CO_2 reactivity curve shows a clear sigmoidal shape, while the CBF data is more noisy, preventing a clear conclusion about the shape of the curve to be drawn. This was confirmed from a comparison between the adjusted R^2 values from the two models. Fitting the BOLD data with a sigmoidal function resulted in significantly higher R^2 values for all the perfusion territories, while this was not the case for the CBF data (Table 1). The non-superiority of a sigmoidal fit of the CBF-$P_{Et}CO_2$ curve was further confirmed by the high correlation coefficients of the CBF traces with their corresponding $P_{Et}CO_2$ traces compared to the coefficients between CBF traces and the sigmoidal transformed $P_{Et}CO_2$ (Table 2). All the aforementioned findings were similar for all three perfusion territories.

		ICA1	ICA2	BA
BOLD	Sigmoidal	0.952	0.952	0.967
	Linear	0.931	0.927	0.945
	p-values	0.010	0.021	0.022
CBF	Sigmoidal	0.713	0.731	0.843
	Linear	0.712	0.727	0.842
	p-values	0.648	0.243	0.517

Table 1: Mean adjusted R^2 values for the two models (linear and sigmoidal) for the different perfusion territories. The p-values correspond to a paired t-test between the two fits.

	ICA1	ICA2	BA
$P_{Et}CO_2$	0.974	0.976	0.981
Sigmoid $P_{Et}CO_2$	0.955	0.957	0.955
p-values	<0.0001	<0.0001	<0.0001

Table 2: Mean cross-correlation coefficients between the CBF signal and the $P_{Et}CO_2$ signal and sigmoidal transformed $P_{Et}CO_2$. The lower row is a list of the p-values from a paired t-test.

DISCUSSION – Our results confirmed that BOLD-$P_{Et}CO_2$ relationship is best described by a sigmoidal function. However, CBF reactivity curve was better fitted by a linear function compared to a sigmoidal function. One possible explanation could be that the CBF data had a considerably lower SNR compared to the BOLD data. However, this was less probable considering the results of the alternative analysis which were also in favor of a linear relationship. An alternative explanation is that the non-linear part of the sigmoidal CBF reactivity curve is not reached in this range of $P_{Et}CO_2$ values. Reivich for example reported that in monkeys the maximum CBF values were only achieved at arterial CO_2 values above 20 kPa[1]. This contradicts the sigmoidal relationship observed between CBFv and $P_{Et}CO_2$ in ref 2 in the 3-8 kPa $P_{Et}CO_2$ range. This contradiction could be explained by the fact that the authors used TCD to measure CBFv in the medial cerebral artery (MCA), which is known to be unreliable due to changing MCA diameter at higher $P_{Et}CO_2$ values (> 6kPa) (results submitted in a separate abstract), but warrants further study. Furthermore, it is not unexpected that the BOLD signal changes reach their maximum at lower $P_{Et}CO_2$ values than CBF signal changes, because as CBF increases the concentration of deoxyhemoglobin (dHb) at the venous blood compartment keeps falling until all the deoxy-Hb is washed out. At that moment the BOLD signal flattens while CBF signal continues to increase; an assumption often made in the quantitative BOLD literature[4]. Finally, based on these results it is confirmed that the assumption of a linear BOLD-$P_{Et}CO_2$ relationship is incorrect and can lead to biased findings, especially because the sigmoidal BOLD reactivity curves are not centered around the same $P_{Et}CO_2$ value in every subject. But unlike BOLD data, the analysis of the CBF data could safely be done on the assumption of a linear relationship with $P_{Et}CO_2$ within the 3-8 kPa range. This advantage potentially makes CBF a more robust measure of regional CO_2 cerebrovascular reactivity.

CONCLUSION – The analysis of the BOLD CO_2 reactivity should be performed with caution because of the sigmoidal shape of the BOLD reactivity curve in the range of 3-8 kPa $P_{Et}CO_2$ as most often used for CVR measurements. CBF is more robust for CO_2 CVR measurements, because in 3-8 kPa $P_{Et}CO_2$ range CBF is linearly associated with $P_{Et}CO_2$.

REFERENCES – [1] Reivich M., *Am. J. Physiol.* **206,** 1964; [2] Battisti-Charbonney A. et al., *J. Physiol.* **589,** 2011; [3] Bhogal A. et al., *ISMRM 2013* **0852,** 2013; [4] Simon A. B. et al., *PLoS One* **8,** 2013.