Hyperoxia Modulated Evoked Cerebral Blood Flow in the Human motor Cortex: Measured with LL-FAIR ASL

Paula L. Croal[1], Emma L. Hall[1], Ian D. Driver[1], Penny A. Gowland[1], and Susan T. Francis[1]
[1]*Sir Peter Mansfield MR Centre, University of Nottingham, Nottingham, Nottinghamshire, United Kingdom*

Introduction: The mechanisms underlying control of local cerebral blood flow (LCBF) are complex and not yet fully understood. A widely held belief is that upon cortical activation LCBF increases to meet the increased metabolic demand (O_2) [1, 2], however $CMRO_2$ and LCBF may be decoupled [3]. More recently, it has been hypothesised that changes in evoked LCBF are proportional to neuronal activity, but not $CMRO_2$, with changes in the reactivity of the vasculature causing this [4,5,6]. If the evoked LCBF is mediated by the partial pressure of oxygen (PO2), it is expected that the functional hyperaemic response would be lower under hyperoxic compared to normoxia. However, LCBF Laser-Doppler flowmetry measurements have shown a reduction in baseline CBF on hyperoxia, but an increase in LCBF in response to electrical stimulation of the rat hind paw [4]. This study investigates the effect of hyperoxia on the evoked LCBF in the human motor cortex using a Look Locker (LL-) FAIR Arterial Spin Labelling method [8,9].

Methods: 5 healthy subjects participated in the study (24-28 years), which was approved by the local ethics committee. *Data Acquisition:* Data were acquired using a Philips Achieva 7.0 T system with head volume transmit and 32-channel SENSE receive coils. A BOLD localiser (30 s finger-tap/30 s rest for ~5 cycles) was used to identify the motor cortex for the subsequent LL-FAIR data acquisition: GE-EPI, SENSE factor 2, TE/TR=25/3000ms, 15 slices, 2x2x3mm^3 resolution, FOV=192x192mm^2. A LL-FAIR ASL scheme (FAIR labelling: 45mm selective (S), 250mm non-selective (NS) and in-plane pre-saturation) was used to measure LCBF: TI/TA/TR=300/200/300 and 8 GE-EPI phases (each of 5 slices) per TR, vascular crushing using bipolar gradients ($v_{cut\text{-}off}$=50mms^{-1}). In addition, an inversion recovery (IR) data with 10 TI's (100–2500ms) was acquired for T_1 mapping. *Functional Paradigm:* A feed-forward, low gas-flow system (RespirAct^{TM,} Thornhill Research Inc., Toronto, Canada) and sequential gas delivery circuit were used to deliver the respiratory challenge: 5 min of normoxic baseline (subject specific PET_{O2}), 5 min of isocapnic hyperoxia (targeted at 500mmHg PET_{O2},) and 2 min period of normoxic baseline. PET_{CO2} was targeted to remain at baseline throughout. Subjects performed a bilateral finger-tap task (30s tap (active), 30s rest) throughout the 12min respiratory challenge. *Data analysis:* Normoxic and hyperoxic PET_{O2} and PET_{CO2} values were calculated by averaging over each 5 minute period. A CBF motor ROI was formed by performing a GLM analysis on the LL-FAIR data using FEAT (FSL, FMRIB, Oxford).The LL-FAIR data was divided into active and rest data for both normoxia (NO) and hyperoxic (HO). LL-FAIR signal curves from the motor ROI were then fitted to a kinetic model [7] for arrival time (Δ_a) and exchange time (τ_{exc}) (from which arrival time at the tissue can be estimated (Δ_{tissue}= $\Delta_a+\tau_{exc}$)), in addition a region of global grey matter was also assessed. The T_1 of blood was assumed to be 2.1s at NO and 1.9s at HO [10,11], whilst the T_1 of grey matter (GM) was assumed to not change on HO (the change in $T_{1,GM}$ was <0.5% when fitting the NS-ASL data). M_o was estimated from the base EPI image and scaled to account for changes in R_2* due to HO and/or activation. The IR data were fitted to form a T_1 map from which to generate a global GM mask.

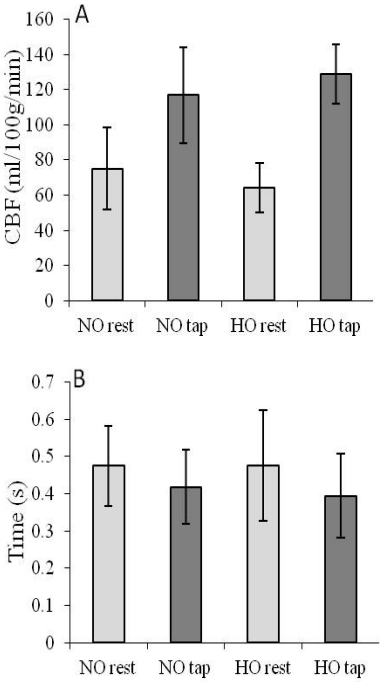

Figure 1: Absolute changes in A) LCBF (ml/100g/min) and B) arrival time, average across subjects for rest and activation (tap) on normoxia (NO) and hyperoxia (HO).

	Normoxia	Hyperoxia
Δ CBF (ml/100g/min)	42±9	65±5
Δ CBF (%)	32±4	40±11
change in Δ_a (ms)	-34±28	-62±83
change in τ_{exc} (ms)	-22±30	-20±40
change in Δ_{tissue} (ms)	-56±40	-82±92

Table 1: Evoked changes in LCBF and transit times for normoxia and hyperoxia, average across subjects

Results: PET_{O2} increased by 359 ± 14 mmHg (average ± std.err across subjects) while $PETCO_2$ changed < 1.5 mmHg. At rest, a small non-significant reduction in CBF was observed on hyperoxia compared to normoxia in the motor ROI (-11 ± 10 ml/100g/min (average ± std. err across subjects), p = 0.89, Wilcoxon signed rank test) and in the global GM mask (-6 ± 14 p = 0.893). For normoxia, the absolute change in LCBF on activation compared to normoxic baseline was 42 ± 9 ml/100g/min, for hyperoxia a change of 65 ± 5 ml/100g/min was found with respect to hyperoxic baseline (Fig 1). 4 of the 5 subjects show this larger absolute increase in LCBF on activation for hyperoxia. Δ_{tissue} reduced on activation for both normoxia (58 ± 44 ms, p=0.138) and hyperoxia (174 ±62 ms, p=0.345). Absolute and percentage changes in LCBF relative to their respective baseline levels, and absolute changes in transit times (Δ_a, τ_{exc}, and Δ_{tissue}) are shown in Table 1.

Discussion: The results suggest a general trend for increased evoked LCBF with hyperoxia, in agreement with [4,5,6] and this is further supported by a larger reduction in transit times on hyperoxia. However, data is currently limited by the small number of participants and further investigation with a larger sample size will be performed to provide adequate statistical power. These trends raise questions as to what extent the metabolic demand for oxygen drives the functional hyperaemic response to cortical activation. Animal literature suggests that hyperoxia may interfere with vasodilator products such as nitric oxide, potassium, hydrogen ions and potassium which are known to affect evoked LCBF [6, 12].

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