

## Detection of Changes in $T_1$ Values in Normal Brain During Normobaric Hyperoxia

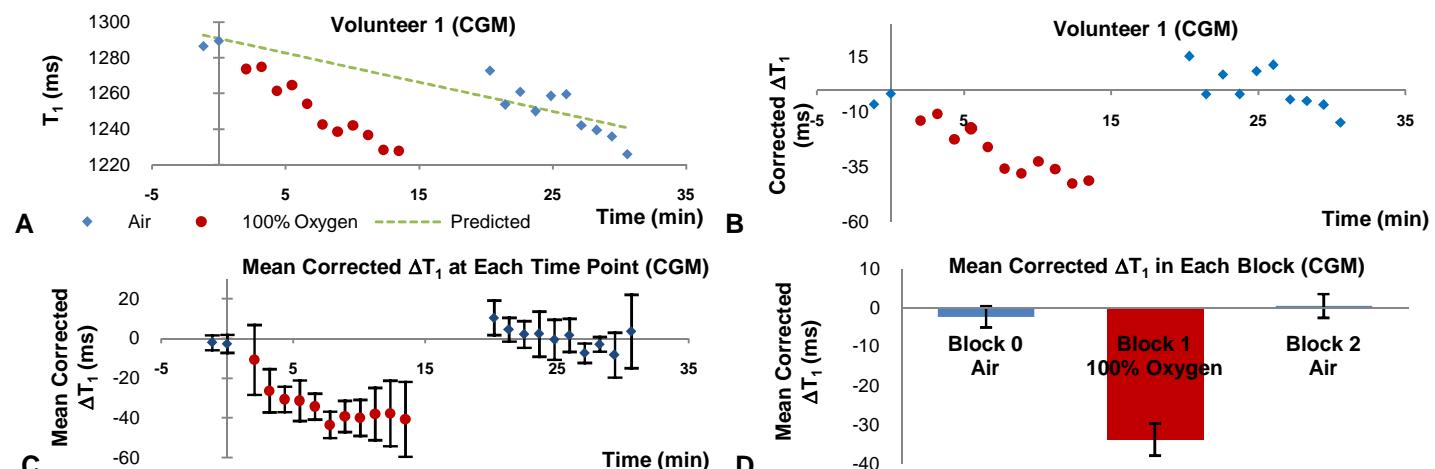
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**Introduction:** Dissolved oxygen is paramagnetic and therefore reduces the  $T_1$  value of tissue and blood[1]. The use of oxygen as a longitudinal relaxivity contrast agent has been investigated in a variety of tissues outside the brain[2]. With increasing interest in the oxygenation status of tumours and in the potential significance of changes during standard chemo-radiotherapy and anti-angiogenic therapy, change in oxygenation status is increasingly being investigated as a tumour and tissue response biomarker[2]. To the best of our knowledge no evidence has yet been reported indicating that the paramagnetic effects of dissolved molecular oxygen can be observed in the healthy brain. Our intention was to perform experiments to test the null hypothesis that no significant reduction in the  $T_1$  of cerebral tissues is detected during normobaric hyperoxia in healthy volunteers.

**Methods:** Ethical approval was granted. Five young, healthy volunteers were imaged. Volume  $T_1$  maps were acquired using variable flip angle spoiled gradient echo sequences (TE=1.1ms, TR=3.5ms;  $\alpha=2^\circ, 5^\circ, 10^\circ, 16^\circ$ ; matrix 128x128x25, 1.8mmx1.8mmx4.2mm, 4 signal averages) on a Philips Achieva 3T MRI scanner with an 8 channel SENSE head coil (Philips Medical Systems BV, Best, Netherlands). A block design was used with 3 acquisitions on medical air (block 0), 11 on 100%  $O_2$  (block 1), and 11 on medical air (block 2), with a temporal resolution of approximately 1.2 min. Prior to block 0 and between blocks 1 and 2 a phase contrast angiography (PCA) sequence was acquired for a separate investigation. A non-rebreathing mask was used for gas delivery at 15l.min<sup>-1</sup>. Mean  $T_1$  values were determined at each time point for each volunteer in 5 tissue types: splenium of corpus callosum (CC), deep white matter (DWM – left forceps minor), cortical grey matter (CGM – left paracentral lobule), thalamus (BG), and skeletal muscle (SkM - trapezius). VOIs were delineated on the initial acquisition and applied to the time series with an assumption of minimal volunteer movement (one volunteer was rejected due to significant movement). Data from each tissue VOI were averaged across the remaining volunteers and plotted against time.

**Results:** Example data in CGM are shown in figure 1. Baseline drift of unknown origin was noted in the  $T_1$  values in all tissue types across all volunteers. As a first approximation it was assumed to be linear and unrelated to oxygen administration effects. This was therefore corrected by linear regression analysis on data from air-breathing blocks (0 and 2) (fig 1A). Residual values representing corrected  $\Delta T_1$  were calculated for each time point in comparison with the predicted baseline (fig 1B) and averaged across subjects (fig 1C). Mean values of corrected  $\Delta T_1$  in CGM across each block are shown in figure 1D. Following correction, significant  $\Delta T_1$  values were observed in each tissue during inhalation of 100%  $O_2$ . Table 1 shows the mean reduction in  $T_1$  for each tissue during the normobaric hyperoxic phase (block 1) with 95% confidence intervals (CI), and the results of t-test analysis comparing the pre-hyperoxic and hyperoxic phases (block 0 vs block 1), the hyperoxic and post-hyperoxic phases (block 1 vs block 2), and the pre- and post-hyperoxic phases (block 0 vs block 2).



**Figure 1:** A) An example of the absolute  $T_1$  value over time in a healthy volunteer in cortical grey matter showing normoxia (blue), hyperoxia (red) and a predicted baseline (green). B) Residuals of the observed minus the predicted  $T_1$  to correct for baseline variation in the same volunteer. C) Mean  $\Delta T_1$  versus time in cortical grey matter for all included volunteers (n=4) showing 95% CI. D) Mean corrected  $\Delta T_1$  in each block showing 95% CI.

Tissue Type	CC	DWM	CGM	BG	SkM
Mean Baseline $T_1 \pm sd$ (ms)	1199 $\pm$ 57	832 $\pm$ 53	1176 $\pm$ 120	1553 $\pm$ 57	962 $\pm$ 82
100% $O_2$ $\Delta T_1$ (ms) $\pm$ 95%CI	-8.0 $\pm$ 5.0	-8.5 $\pm$ 2.3	-33.8 $\pm$ 4.1	-16.4 $\pm$ 6.5	-10.1 $\pm$ 3.3
unpaired t-test	Block 0 vs 1	0.062	<b>0.0025</b>	<b>&lt;0.0001</b>	<b>0.040</b>
one tail	Block 1 vs 2	<b>0.008</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
equal variance	Block 0 vs 2	0.290	0.465	0.244	0.251

**Table 1:** Mean corrected  $\Delta T_1$  during hyperoxia with t-test comparison of  $T_1$  before, during and after hyperoxia

between pre-hyperoxic and hyperoxic states in CC ( $p=0.062$ ) although there was a significant change following the switch back to air ( $p=0.008$ ). It is not clear whether the dominant effect reducing VOI  $T_1$  values is an increase in dissolved tissue oxygen[3], an increase in dissolved blood plasma oxygen[4], or reduction in fractional blood volume[5]. Further investigation with a longer block 0 and randomisation to a control block 1 will allow testing of the assumption of baseline collinearity and further characterisation of the  $T_1$  drift. Obtaining rCBV maps during plateau phase may clarify the relative contribution of underlying physiological changes to the  $T_1$  change.

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### References:

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**Discussion:** The method described here shows significant ( $p<0.05$ ) decreases in longitudinal tissue relaxivity during normobaric hyperoxia in DWM, CGM, BG and SkM in healthy volunteers, following correction for baseline drift. No significant difference was seen

switch back to air ( $p=0.008$ ). It is not clear whether the dominant effect reducing VOI  $T_1$  values is an increase in dissolved tissue oxygen[3], an increase in dissolved blood plasma oxygen[4], or reduction in fractional blood volume[5].