Assessment of R2* dependence on oxygenation across field strength.

Paula L Croal[1], Emma L Hall[1], Ian D Driver[1], Susan T Francis[1], and Penny A Gowland[1]
[1]*SPMMRC, School of Physics & Astronomy, University of Nottingham, Nottingham, Nottinghamshire, United Kingdom*

Introduction: The power law (β) relating blood oxygenation and tissue R2* is important in calibrated BOLD [1] and BOLD models. It has generally been predicted from Monte Carlo simulations or analytical models [2,3,4]. However there have only been few attempts to test these models experimentally, which is important since models generally do not fully include intravascular effects, which can be significant at low field and high oxygenations. Some studies have induced a change in R2* (ΔR2*) by neuronal activation or hypercapnia (HC) [5,6] (Fig. 1A), but these challenges cause confounding changes in CBV. Hyperoxia (HO) provides a method of independently modulating oxygenation without accompanying CBF, CBV and $CMRO_2$ changes. A recent study observed the effect of a HO-induced frequency shift (Δω) on ΔR2* without controlling for confounding changes in CO_2 levels [7]. **Aim:** To measure the relationship between blood oxygenation and tissue R2* using a graded HO stimulus at 1.5, 3 and 7T; to simulate the effect of a CBV change on this relationship.

Method: Scanning was performed on healthy subjects (6 subjects 3 f., 24-27 y.o.) using Philips 1.5/3/7T systems equipped with 8/32/32 channel receive coils respectively. A dual echo EPI was acquired (SENSE=2.5, TR=3s, 2x2x3mm^3) with TE1/TE2 =25/80, 22/60 and 16/47 ms and FOV=212x188x60, 212x184x60 and 192x192x15mm at 1.5/3/7T respectively. IR-EPI images (10 TI's, 0.1-3s) and multiple echo images (TEs from 25-80ms) were collected for R_2* mapping and vessel identification. The HO challenge was administered using a RespirAct system (Thornhill Research Inc., Toronto, CA), sequentially maintaining $P_{ET}O_2$ at the subject's baseline (3 min), before linearly increasing to 500mmHg (4 min), linear decreasing to baseline (4 min), then maintaining baseline (1 min) [8]. $P_{ET}CO_2$ was held constant throughout. Analysis: Motion correction was performed on the TE1 data and applied to the TE2 data (FLIRT, FSL), 3mm spatial smoothing was applied. R2* maps were calculated from the dual echo data**.** IR-EPI images were fitted for T1 from which a total GM mask was formed, and a mask of large vessels was created by thresholding the long TE images (1.5/3T: TE=80ms, 7T: TE=46ms) at each field to remove 14% of voxels from the total GM mask. This resulted in three ROI masks: Total GM, GM without large vessels and vessel dominated. Average R2* timecourses for each ROI were calculated for each subject at each B_0. $P_{ET}O_2$ was converted to Y [9] and realigned with the GM R2* timecourse [8], allowing the gradient between ΔR2* and (1-Y) to be calculated. Monte-Carlo (MC) simulations: (N=1000) were performed to assess the sensitivity of ΔR2* versus (1-Y) curves to β (0.7-2) over the range of Δω achievable using HO ((1-Y) = 0.3-0.4) and neuronal activation ((1-Y) = 0.2-0.4) as well as for (1-Y) = 0-1.

Results: Average $P_{ET}O_2$ peaked at 483 ± 6 mmHg (mean ±SE), ($P_{ET}CO_2$ varied <1.6%). For masked GM, baseline R2* was significantly higher for 7T than 3T and 3T than 1.5 T (Table 1; $p<0.05$, wilcoxon signed rank test). Removal of large vessel contribution significantly reduced the gradient of ΔR2*/(1-Y) at 1.5 and 3T (Table 1, $p<0.05$). Masked GM ΔR2* gradients (Fig. 1B) varied significantly with B_0 ($p = 0.009$, Friedman's 2-way ANOVA, Fig.1), with the ratio of these gradients 7:3:1.5 T of 1:0.31±0.05:0.37±0.06. Plots of R2* versus (1-Y) did not fit significantly better for β different to unity, but MC simulations showed limited sensitivity to β over the physiological range of Y (0.6-0.8) at all field strengths, for $\beta < 2$.

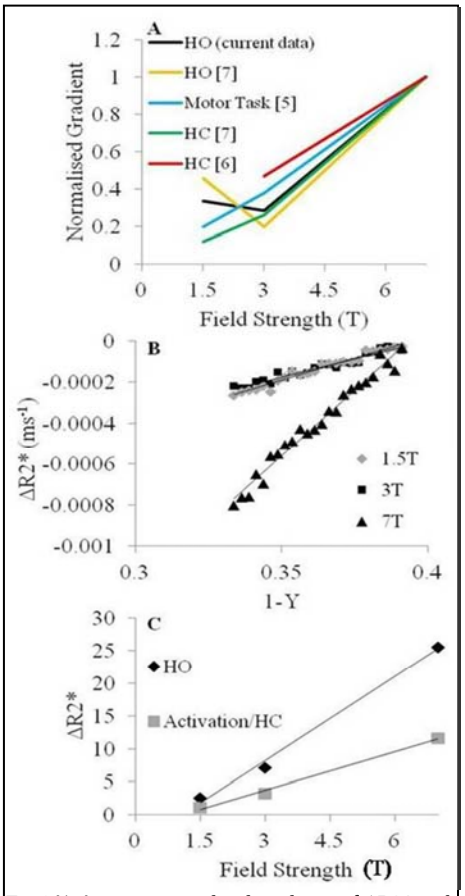

Fig.1A) Average normalised gradients of ΔR2* with Δω across B_0 compared to literature [6,7,8]. B) ΔR2* dependence on (1-Y) for 1.5, 3 and 7T. C) Simulated ΔR2*across B_0 for HO (1-Y) = 0.3-0.4) assuming a constant CBV of 0.1, and functional activation assuming an increase in CBV to 0.2), assuming β = 1.5 at all field strengths.

Discussion: At a given field, the relationship between R2* and (1-Y) appeared linear (Fig.1B), in agreement with MC simulations which suggest limited sensitivity to β over this physiological range of Δω. However, by changing B_0, a larger Δω is induced, and so β can be explored. Empirically, the relationship between blood oxygenation and tissue R2* is described by $R2^*=k.V\Delta\omega^{\beta}TE^{1-\beta}+k'$ (**Eq. 1**). Here $\Delta\omega=k''\gamma B_0\chi(1-Y)$ where Y is the fractional blood oxygenation and χ is the susceptibility of fully deoxygenated blood; V is blood volume, the constants k, k' and k'' depend on vessel geometry, diffusion and tissue and blood T2. TE is included to make the equation dimensionally correct [4] and is consistent with simulation results that imply that the variation of β with Δω depends on TE [10]. By differentiating Eq. 1 with respect to (1-Y) the ratio of gradients at different field strengths can be predicted. Based on this the ratios of the gradients measured here are not consistent with β =1 at 3 and 7T, and can only be explained by a reduction in β between 1.5 and 3T, and β > 1 at 3 and 7T. These results are in reasonable agreement with previous simulations suggesting β =1.5 for l.5T, falling to ~1 at higher field [2,3,5,6]. It is likely that the larger value of β measured here at high field is due to intravascular effects and this could be investigated by use of vascular crushing. Titration of Gd-DTPA rather than HO would increase the accessible dynamic range at a given field. Previous cross field studies use neuronal activation or hypercapnia tasks that induce a change in CBV as well as Y, these cannot be used to estimate β because of the interacting effects of Δω and CBV (Fig 1A). This is shown in Fig.1C, which shows the simulation of ΔR2* (assuming β = 1.5 at all field strengths) for constant V (HO) and V varying from 0.1 at baseline to 0.2 on activation/HC. **Conclusion:** β is somewhat greater than unity at 3 and 7T but MC simulations suggest that for an activation task, the effects of such a change in β on $CMRO_2$ estimation will be within noise.

ROI	B0	R2* (s^{-1})	ΔR2*/(1-Y) s^{-1}
Total GM	1	13.3±0.2	5.3±0.8
	3	20.6±0.4	4.4±0.3
	7	34.8±0.8	12.4±1.5
Masked GM	1	12.7±0.2	4.3±0.5
	3	19.7±0.4	3.6±0.3
	7	33.9±1.0	12.7±2
Vessel Dominated	1	17.2±0.4	11.7±3.5
	3	26.3±0.9	9.3±2.6
	7	40.8±1.2	10.3±3.7

Table1: Baseline R2* and gradient of ΔR2* versus oxygenation (1-Y) for Total GM, masked GM and vessel dominated ROI.

References: [1] Davis et al., PNAS., 95:1834-1839(1998); [2] Boxerman et al., MRM, 34:555-566(1995); [3] Ogawa et al., Biophys.J. 64:803-812 (1993); [4] Yablonskiy et al., MRM,32:749-763(1994) [5] Van Der Zwaag., NeuroImage 47:1425-1434 (2009) [6] Driver et al., NeuroImage, 51:274-279 (2010); [7] Rossi et al., NMR Biomed. 25:1007-1014 (2012); [8] Croal et al. Int.Proc ISMRM (2012); [9] Chiarelli et al., NeuroImage, 37:808-820 (2007). [10] Martindale et al., MRM. 59(3):607-18 (2008);

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