Dependence of blood R_2 relaxation rate on echo spacing using a CPMG sequence at 7T

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INTRODUCTION: Functional MRI studies use the BOLD effect to identify activity within the brain. This uses blood deoxyhaemoglobin level as an intrinsic contrast mechanism. As such it is important to understand how sequence parameters and physiological factors effect measured MR signal and relaxation rates, e.g.: transverse relaxation R_2 / R_2^* for spin-echo / gradient-echo respectively. The dependence of the experimentally measured R_2 on the oxygenation state of blood has been demonstrated in previous studies of *in-vitro* blood samples [1-4]. Further, the dependence of the R_2 relaxation rate on inter-echo spacing of a multi-echo Carr-Purcell Meiboom-Gill (CPMG) SE sequence has also been reported, showing an increase in apparent R_2 as inter-echo spacing, τ_{cp}, is increased. The effect of inter-echo spacing effect is more pronounced at lower oxygenation (Y) and high haematocrit (Hct), due to increased levels of paramagnetic deoxyhaemoglobin in the sample. This study investigates these effects at ultra-high field, 7T, and compares results with previous literature in the range of 1.5 – 4.7T.

THEORY: Blood can be considered to be a two-pool system comprising plasma and erythrocytes, with rapid exchange of water protons between the erythrocytes and the plasma (which have an associated frequency shift between them dependent on Y and Hct [5]). This leads to a dephasing of the MR signal which is not refocused by a spin-echo, causing an enhancement of measured R_2 rate, as described by equation 1 below:

Eq. 1) $R_2 = R_{2,0} + R_{2,ex}$ *where*

Eq. 2) $R_{2,0} = R_{2,plas} + Hct * ([R_{2,dia} + R_{2,oxy}] + (1-Y)[R_{2,deoxy} - R_{2,oxy}])$

$R_{2,0}$ is relaxation in the absence of exchange and $R_{2,ex}$ the enhanced exchange contribution.

The subscripts plas, dia, oxy and deoxy refer to different blood R_2 components, for plasma, diamagnetic, oxygenated and deoxygenated haemoglobin [3].

At short τ_{cp} the measured R_2 should tend towards $R_{2,0}$, whilst with relatively long τ_{cp} effectively protons can exchange many times between the two sites, eventually leading to maximal dephasing, as the 180^0 pulses in a CPMG sequence will only refocus the dephasing experienced by the protons due to static inhomogeneities. The rate of dephasing increases with low Y, as the high level of paramagnetic deoxyhaemoglobin pushes the frequency shift towards its maximum. The frequency shift between plasma and erythrocytes also scales with field strength, so that the inter-echo time at which maximal dephasing occurs should reduce with field.

METHOD: Fresh blood samples were taken by venepuncture from healthy adult volunteers, who gave informed consent. Lithium heparin was used as the anti-coagulant. Sample Y and Hct values were then manipulated within 24 hours of drawing, by altering plasma content from settled samples (drawing off plasma to increase Hct and adding plasma from same volunteer sample to reduce Hct). Samples were gently bubbled in a fume cupboard with either O_2 or CO_2 (5%) / N (95%) to raise / lower Y respectively. Sample parameters were measured using an ABL710 Blood Gas Analyser (Radiometer). Scanning was performed in spectroscopic mode on a 7T small-bore magnet (Bruker), using a CPMG sequence with a series of τ_{cp} from 4 to 40ms, in order to obtain the respective apparent R_2 rates. Two to sixteen 180^0 hard pulses sequentially formed the echo train, with four-shot phase cycling employed and data acquired following each pulse pair. TR of 12s was used between acquisitions. Samples were kept at 37^0C using a water bath outside the scanner, and a warm air blower within the magnet bore, which was monitored continuously with a digital thermometer placed on the sample holder. Samples were rotated at 60rpm during TR period to prevent plasma-erythrocyte settling, with a TTL control switching off rotation during data acquisition. Samples remained in the scanner for a maximum of 120 minutes. Following scanning sample Y and Hct were again measured. To validate the results, a Gd-doped water phantom (nominal R_2 4.5 s^{-1}) was first scanned and analysed and showed no variation in R_2 across τ_{cp}, proving that R_2 enhancement seen in blood as τ_{cp} increased is due to sample exchange effects.

RESULTS: The area under the blood sample peak was measured and for each τ_{cp} a single R_2 value was obtained by fitting the natural log of the decay of the echo train to time, using a linear, weighted, least-squares fit.

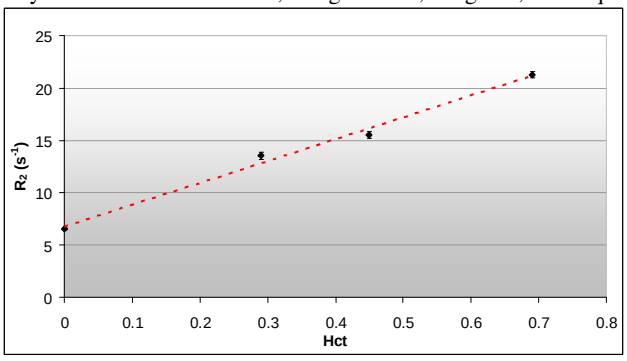

Figure 1: High oxygenation samples (Y > 0.95); Hct vs. R_2..

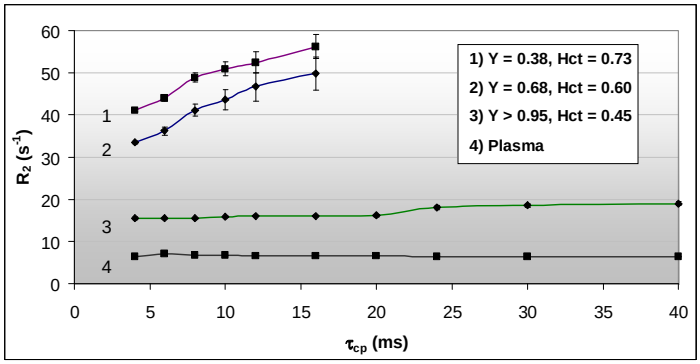

Figure 2: Measured R_2 vs. τ_{cp} for four samples; various Y and Hct.

Figure 1 shows a strong linear increase in $R_{2,0}$ with increasing Hct, for highly oxygenated blood samples (Y > 0.95). Figure 2 shows the increase in measured R_2 with τ_{cp} for different blood samples, with low Y samples showing both high R_2 rates, and the largest rate of increase as τ_{cp} was increased, as predicted. Plasma showed little change. There was insufficient SNR to fit for samples 1 and 2 at τ_{cp} later than 16 ms.

The Y>0.95 samples were fitted to Eq. 2 (simplified to $R_{2,0} = R_{2,plas} + Hct * [R_{2,dia} + R_{2,oxy}]$ when $Y \approx 1$) to give first two terms. The remaining samples of various Y and Hct were fitted to the full Eq. 2, and parameter results presented in Table 1 (shown compared to previous literature). The values found in this study are in reasonable agreement to the literature. Of note is the R_2 rate of plasma, which corresponds to a T_2 of 153 ± 2 ms and is not effected by τ_{cp} increase.

Field (T)	$R_{2,plas}$ (s^{-1})	$R_{2,dia}+R_{2,oxy}$ (s^{-1})	$R_{2,deoxy}-R_{2,oxy}$ (s^{-1})	Ref
1.5	1.6	5.5	8.1	3
2.35	1.5 ±0.3	7.0 ±0.7	9.0 ±0.9	4
4.7	4.6	9.3	42	2
7.0	6.8 ±0.6	20.9 ±1.4	68.4 ±7.0	-

Table 1: $R_{2,0}$ parameters fitted to Eq. 2; comparison to literature.

DISCUSSION: The dependence of blood R_2 rate on sample Y and Hct has been demonstrated at ultra-high field. This is important for quantifying venous and arterial oxygenation in vivo. Using Eq. 2, $R_{2,0}$ blood component values have been found which correspond well to previous studies at lower field strengths. The R_2 of plasma has also been directly measured at 7T and was insensitive to τ_{cp}.

REFERENCES: 1 – Thulborn, BBA, 1982; 2 – van Zijl, Nat Med, 1998; 3 – Golay, MRM, 2001; 4 – Gardener, ISMRM, 2004; 5 – Spees, MRM, 2001.