REVISITING THE ^{129}XE RELAXATION RATE IN HUMAN BLOOD AND QUANTIFYING THE RELAXIVITY OF DEOXYHAEMOGLOBIN IN THE PRESENCE OF ^{129}XE

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Target Audience: MR spectroscopists; hyperpolarised media MR community

Purpose: Integral to the design and feasibility of hyperpolarised (HP) ^{129}Xe MR perfusion experiments is an accurate knowledge of the spin-lattice relaxation rate, R_1, of ^{129}Xe in blood. This is necessary for accurate modelling of the ^{129}Xe signal evolution while xenon is carried in the blood to the target tissues and organs of interest [1]. Previous work has shown the R_1 to be dependent upon blood oxygenation [2,3]. In this study, ^{129}Xe-RBC relaxation was examined over the widest yet range of blood oxygenations (sO_2 values from 0.02–1.00) and a value for the relaxivity of deoxyhaemoglobin in the presence of ^{129}Xe nuclei has been estimated for the first time.

Methods: ***HP ^{129}Xe samples*****:** for the generation of all HP ^{129}Xe samples, a home-built spin-exchange optical pumping ^{129}Xe polariser was used. ^{129}Xe polarisations were typically 10 to 15 % [3]. ***Blood sample preparation and analysis*****:** whole blood was withdrawn from three self-consenting volunteers by venipuncture and transferred into lithium heparin vacuum containers approximately 2-3 hours prior to the start of the NMR experiments. To create xenon-saturated blood samples, xenon and blood were passed through an exchange module (Contactor 680, Membrana, USA) – see Fig. 1. To analyse the blood samples for pH, sO_2, pO_2 and haemoglobin concentration, a clinical blood gas analyser (Radiometer, ABL80, UK) was used. To increase the blood oxygenation, O_2 was passed through the exchange module, resulting in an sO_2 increase of ~ 0.05 per 3 ml of O_2. To decrease the blood oxygen saturation to values lower than 0.70, a saline suspension of sodium dithionite ($Na_2O_4S_2$) was mixed with blood external to the exchange module. Finally, a single blood sample was equilibrated with carbon monoxide, using the same mixing procedure as described above for oxygen, to provide a non-paramagnetic reference blood sample. ***NMR spectroscopy*****:** for all ^{129}Xe-blood NMR spectroscopy experiments, a 1.5 T MR scanner (GE Signa HDx, Milwaukee, WI) was used with a home-built, 8-turn solenoid RF coil (2cm diameter, 4 cm length) resonating at 17.66 MHz. For ^{129}Xe relaxation measurements, the sequences employed consisted of n = 15–20 pulses with inter-pulse delay times (TR) of 150 ms and 500 ms for blood sO_2 ranges of 0.02–0.4 and 0.4–1, respectively. ^{129}Xe-red blood cell (RBC) relaxation times and rates were calculated by fitting the decay in the ^{129}Xe-RBC NMR signal to the relationship $S_n = S_0\sin(\alpha)\cos(\alpha)\exp-[(n-1)TR/T_1]$, where S_0 is the initial signal intensity and α is the excitation flip angle (12° throughout all NMR acquisitions).

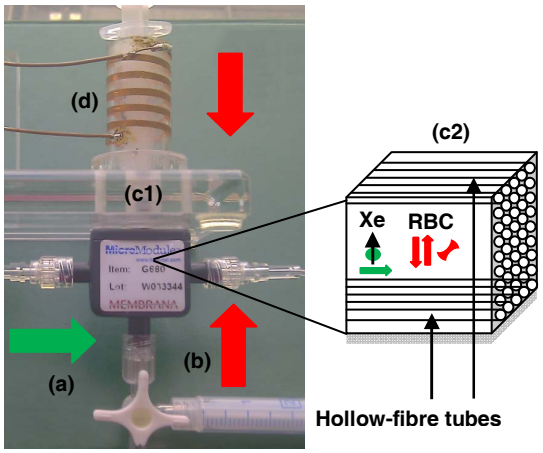

Figure 1: (left) Photograph of xenon-blood exchange apparatus and (right) cross section of exchange module. Xenon, (a), is pushed through the hollow-fibre tubes of the exchange module, (c1) and (c2), unidirectionally at a rate of ~ 1 ml/s, while the blood, (b), is passed into and out of the membrane and the sample volume (3 ml syringe enclosed within a custom-built solenoid RF coil, (d)

Results and Discussion: The ^{129}Xe-RBC T_1 was found to be non-linearly dependent on blood oxygen saturation, over an sO_2 range of 0.02–1.00, whereas the ^{129}Xe-RBC R_1 exhibits a linear dependence on sO_2. The calculated values of ^{129}Xe-RBC T_1 range from 2.5 s in fully deoxygenated blood to ~ 8 s in fully oxygenated blood. Typical ^{129}Xe-RBC T_1 values in blood corresponding to venous and arterial conditions were measured to be ~ 5 s and ~ 7.5 s respectively. Blood equilibrated with CO was found to have a ^{129}Xe-RBC T_1 of 10.7 s, 34 % greater than the ^{129}Xe-RBC T_1 in fully oxygenated blood samples. In light of this newly observed linear dependence of ^{129}Xe R_1 on blood oxygenation, we can express the relationship between R_1 and the concentration of paramagnetic deoxyhaemoglobin as

$$(R_1)_{obs} = r[\text{dHb}] + (R_1)_0, \quad (1)$$

where [dHb] is the concentration in mmol l^{-1} (mM) of paramagnetic deoxyhaemoglobin present in the blood, r is the ^{129}Xe-dHb relaxivity with units mM^{-1}s^{-1}, $(R_1)_{obs}$ is the observed ^{129}Xe relaxation rate and $(R_1)_0$ is the ^{129}Xe relaxation rate in the absence of any paramagnetic molecules. A linear fit of ^{129}Xe-RBC R_1 versus [dHb] was evaluated (Fig. 2), yielding the relationship R_1 ([dHb]) = 0.035[dHb] + 0.12. Comparison with Eq. (1) gives a relaxivity of 0.035 mM^{-1}s^{-1} and a ^{129}Xe-RBC relaxation rate in the absence of paramagnetic dHb, $(R_1)_0$, of 0.12 s^{-1} (relaxation time, $(T_1)_0$, of ~ 8 s). The longer ^{129}Xe-RBC T_1 of 10.7 s measured for blood equilibrated with CO may be attributed to the total absence of dissolved paramagnetic oxygen molecules in the CO-equilibrated sample when compared with oxygenated blood samples, suggesting dissolved oxygen may have a non-negligible contribution to ^{129}Xe relaxation in blood.

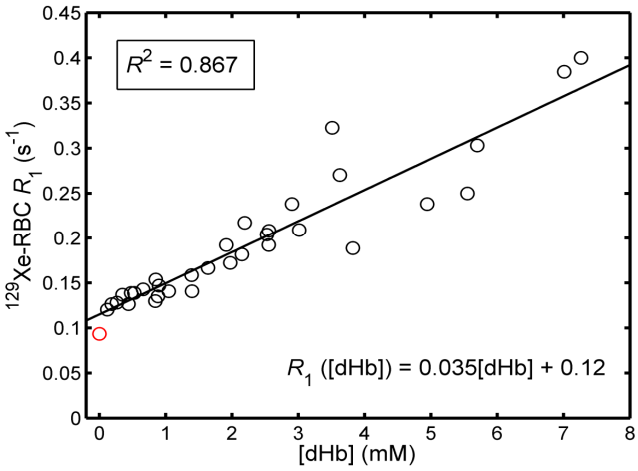

Figure 2: ^{129}Xe-RBC relaxation rate, R_1, vs. deoxyhaemoglobin concentration, [dHb]. Red circle represents a blood sample equilibrated with CO.

Conclusions: A linear dependence of the ^{129}Xe-RBC longitudinal relaxation rate on blood oxygenation has been observed over a large range of blood oxygenations. In light of this observation, we believe that the principal mechanism responsible for the change in ^{129}Xe relaxation with blood oxygenation is ^{129}Xe interactions with red blood cells that have different oxygenation-dependent net paramagnetic susceptibilities. It has been reported for the first time, therefore, a value for the relaxivity of deoxyhaemoglobin in the presence of ^{129}Xe nuclei in RBCs. This linear relationship and the relatively long measured relaxation times have positive implications for future studies of xenon transport from the lungs to distal tissues, organs and tumours and should provide a sound experimental basis upon which to design novel MR experiments for these purposes.

References: [1] Kilian, W. F., *et al*. MRM, 2004. 51(4): p. 843-7. [2] Wolber, J., *et al*. NMR Biomed, 2000. 13(4): p. 234-237. [3] Norquay, G., *et al* Proceedings ISMRM, p2520, 2013. [4] Norquay, G., *et al*. J Appl Phys, 2013. 113(4): p. 044908.