Chemical Shift of ^{129}Xe is dependent on Red Blood Cell Oxygenation

General Leung[1], Graham Norquay[1], Jan Wolber[2], and Jim M Wild[1]
[1]*Department of Cardiovascular Science, University of Sheffield, Sheffield, South Yorkshire, United Kingdom,* [2]*GE Healthcare, Chalfont St Giles, Buckinghamshire, United Kingdom*

Target Audience Hyperpolarized Xenon community

Purpose Evaluate the chemical shift relationship between hyperpolarized ^{129}Xe and Red blood cell oxygenation (sO_2)

Introduction Owing to its large highly polarizable electron cloud, ^{129}Xe is sensitive to its chemical environment and undergoes changes in its resonance frequency when dissolved in various biological tissues. Using this dissolved ^{129}Xe resonance, physiologically important parameters such as gas exchange and uptake can be evaluated. Furthermore, the ^{129}Xe resonance in RBCs has been shown to be sensitive to blood oxygen saturation (sO_2), possibly due to the conformational change of hemoglobin as it binds and releases oxygen[1]. Using exogenous agents as a probe for *in-vivo* oximetry is appealing as endogenous contrast suffers from physiological variations that confound measurements of oxygenation. However, for ^{129}Xe to be a useful probe of blood oxygenation, a robust, quantitative relationship between the oxygen saturation and the chemical shift must be established.

Methods NMR spectroscopy was performed after mixing freshly extracted blood and hyperpolarized (HP) ^{129}Xe. An exchange module (Contactor 680, Membrana, USA) was used to increase surface area for gas exchange[2] and positioned near the coil to minimize T_1 relaxation. 15mL of hyperpolarized ^{129}Xe, prepared in a home built spin exchange optical pumping system, was infused by hand into the membrane at a rate of approximately 0.5 mL per second. 3 mL of blood was passed through the membrane twice at a flow rate of approximately 1 mL / second. Data were acquired on both a 1.5 T (GE, USA software 14M4) and 3 T (Philips, Netherlands, Achieva) MRI. 512 points were acquired with a 2.5 kHz receiver bandwidth and a calibrated 90 degree excitation pulse. Blood was extracted from the imaging volume after each spectral measurement and analyzed in a blood gas analyzer (ABL80 FLEX, Radiometer UK) within minutes of NMR acquisition. Blood oxygenation was increased progressively by adding pure O_2 to increase oxygenation and sodium dithionite to deoxygenate the RBC. Data were imported into MATLAB (R2011b) and spectra were fit to the spectral model using

$$S(t) = a \cdot e^{-i(\omega_a t+\phi_a)-t/T_2^{*}{}_a} + b \cdot e^{-i(\omega_b t+\phi_b)-t/T_2^{*}{}_b}.$$

Results Figure 1 shows a change in the resonance frequency of ^{129}Xe dissolved in RBCs with increasing oxygenation. The resonance frequency shifts from approximately 21 ppm in a deoxygenated state to approximately 24 ppm when fully oxygenated. The resonance frequency of the ^{129}Xe dissolved in the plasma compartment (0 ppm) does not vary significantly as a function of blood oxygenation. The extracted peak positions are plot as a function of sO_2 in Fig 2. The chemical shift of ^{129}Xe in RBCs appears to be linearly dependent on the measured sO_2. Linear regression on the data collected at 1.5T produces a relationship of $\Delta\omega = 0.0338 sO_2 - 20.58$ with a calculated Pearson's correlation coefficient of $R^2 = 0.87$. Similarly, data at 3T show a relationship of $\Delta\omega = 0.0318 sO_2 - 20.46$ with a calculated Pearson's correlation coefficient of $R^2 = 0.97$. Student's t-test shows no significant difference between the value of the ($p>0.3$) suggesting the effect is field strength independent.

Discussion/ Conclusion This finding differs from prior work using ^{129}Xe[1] that reported the same range of chemical shift, however a non-linear relationship between the ^{129}Xe chemical shift and sO_2. It was hypothesized that this effect was due to the co-operative binding mechanism of hemoglobin[3]; conformational changes of the hemoglobin molecule with oxygenation would alter the accessibility of ^{129}Xe docking sites. Work on the magnetic properties of hemoglobin[4] suggest that the magnetic susceptibility of a bulk solution of hemoglobin changes linearly as a function of sO_2 despite the conformational changes in the protein caused by co-operative binding. This is due in part to the observation that the hemoglobin is predominantly in either extreme of oxygenation (0 or 4 bound O_2 molecules). The co-operative binding mechanism in this case would be unobservable macroscopically and instead the source of chemical shift would be sampled as an ensemble average. This hypothesis is corroborated by experiments in proton NMR[5] where a linear dependence between the proton resonance frequency and sO_2 was also found. These observations taken in conjunction suggest that the mechanism of this ^{129}Xe chemical shift is dominated by this fast exchange mechanism between the oxy and deoxygenated states of hemoglobin and exhibits a linear dependence with paramagnetic deoxyhemoglobin concentration.

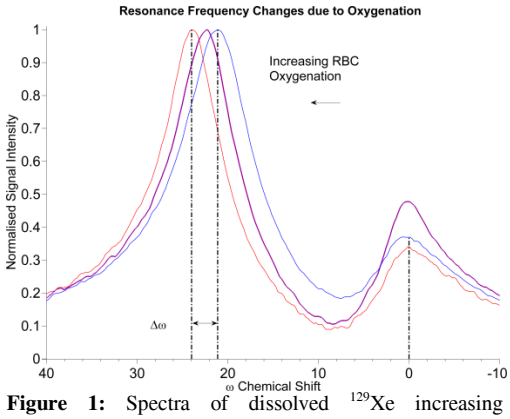

Figure 1: Spectra of dissolved ^{129}Xe increasing oxygenation

Figure 1 (left) are spectra from ^{129}Xe dissolved into freshly extracted human blood. Two distinct peaks are seen, centered at 0 ppm is a peak associated with ^{129}Xe dissolved in plasma, and peaks at higher frequency are ^{129}Xe dissolved in red blood cells (RBCs). With increasing oxygenation, a chemical shift to higher frequency, denoted by Δω, is detected in the peak associated with ^{129}Xe RBC peak.

Figure 2 (right) Chemical shift is plotted as a function of measured blood oxygenation. Data are plotted from acquisitions at two field strengths, 1.5 T (denoted by o's), and 3 T (denoted in +'s). The line of best fit has a regression equation and Pearson's Correlation Coefficient of $R^2 = 0.87$

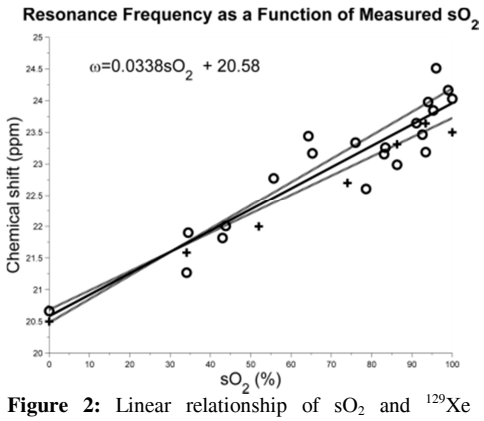

Figure 2: Linear relationship of sO_2 and ^{129}Xe chemical shift

References 1. Wolber *Magnetic Resonance in Medicine*. 2000;43(4):491–496. 2. Cleveland *PLoS ONE*. 2010;5(8):e12192.3. Perutz *Nature*. 1970;228(5273):726–739.4. Coryell CD, *Journal of Physical Chemistry*. 1939;43(7):825–839.5. Zhernovoi *Biomedical Engineering*. 2000;34(1):1–4.