Relaxation of blood at high field: another exchange regime

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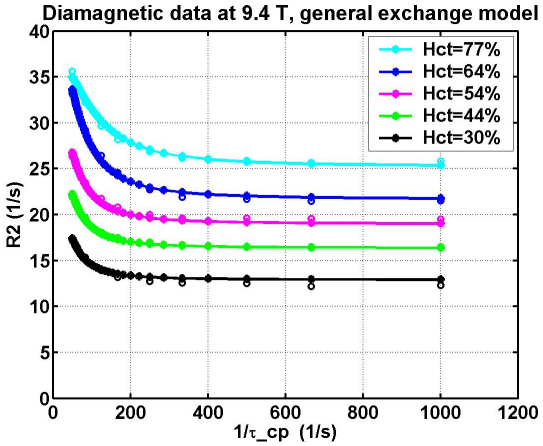
Introduction Changes in oxygenation of red blood cells in blood during brain activation result in local changes in magnetic susceptibility and BOLD fMRI signal variations. After almost 20 years, there is still no complete quantitative description of this complex effect with contributions coming from a multi-component system containing blood (intravascular BOLD) and tissue (extravascular BOLD). The BOLD effect is spatially heterogeneous and depends on voxel size and voxel location. It also depends on magnetic field strength, and physiological parameters such as hematocrit (Hct), cerebral blood flow (CBF), cerebral metabolic rate of oxygen (CMRO2) and, for extravascular BOLD, on cerebral blood volume. In a basic attempt to better understand the relationship between MR transverse relaxation rates (R_2) and oxygenation, hematocrit, and intravascular BOLD effects, a first step has been to study physiologically controlled blood perfusion systems that are more homogeneous in that they can be described using two compartments (erythrocytes and plasma), and in which Hct and oxygenation can be varied [1-5]. Even then, the interpretation of experiments is still up for discussion, in particular whether R_2 should be explained based on exchange between two compartments with different magnetic susceptibilities or on diffusion of water molecules through field gradients caused by these two compartments [6,7]. The data can be fit well using either description, but one indication that fast exchange is not a good approximation comes from the result that the life time of water in the erythrocyte (τ_{ery}) compartment reduces with field strength [1,2,8]. This is not surprising in view of the fact that, with susceptibility differences between the compartments on the order of 0.05-0.1 ppm for venous blood, and a life time of about 10ms (k = 1/ τ_{ery} = 100Hz), the exchange range determined by the relationship between $\Delta\omega = 2\pi\Delta f$ and k varies from fast exchange at 1T ($\Delta\omega$ = 13-26Hz) to intermediate exchange at higher fields, e.g. 4T and up. We realized that, to really investigate the effect of exchange, it is needed to use the general exchange equations, including the intermediate and slow exchange ranges. As a first application, we applied this to oxygenated blood at multiple Hct values at 9.4T, for blood relaxation rates acquired at multiple inter-echo spacings in a Carr-Purcell-Meiboom-Gill (CPMG) sequence.

Methods Bovine blood was used in the experiments with 25 mM sodium citrate added to prevent coagulation. Blood samples of different hematocrits were prepared by separating red blood cells and plasma by centrifugation, and mixing the fractions of each to achieve blood hematocrit values from 30-77 %. Samples of lysed blood were prepared by disruption of red blood cells using sonication, while cell debris was removed by centrifugation. The concentration of the hemoglobin in lysed blood was prepared to be equal to the concentration of the hemoglobin in an erythrocyte. A homemade perfusion apparatus was used to provide a continuous flow of blood through an NMR sample tube, thereby mimicking physiological conditions in a perfused tissue. The temperature was maintained at 37°C with a circulating water bath. Blood samples were taken before and after each experiment for measurement of hemoglobin oxygen saturation (Y), hematocrit (Hct), methemoglobin and pH, by using a blood gas analyzer. Transverse relaxation rates of water spins in whole blood were determined using a CPMG sequence at 9.4 T, with inter-echo spacings (τ_{cp}) varying from 1-20 ms. Data was acquired as a function of hematocrit (30, 44, 54, 64, 77%) at full oxygenation (Y=1). This diamagnetic data was fitted to the general model for the relaxation rate constant for two-site system from Carver and Richards [9] that covers the range of fast, intermediate and slow chemical exchange, with physiological and blood parameters substituted for the rates and compartments. In order to verify the fitting model, we performed R_2 measurements of water spins in lysed blood with no influence of outer plasma environment. R_2 measured from lysed blood was compared to the fitted erythrocyte transverse relaxation rate (R_{2ery}) from the general exchange model. Data fitting to the general exchange model was performed using multivariate nonlinear least squares curve fitting method across five different hematocrit values, while assuming the same R_{2ery} and τ_{ery}, but possible different susceptibility values for each Hct (overdetermined system with 7 unknowns for 5 curves at multiple τ_{cp}).

Results The figure shows the diamagnetic data (97-100% oxygenation range) for the five Hct values used. The resulting parameters were τ_{ery} = 12.2 ms (95% confidence interval 8.5-15.9 ms), R_{2ery} = 31.3 s^{-1} (95% confidence interval of 30.1-32.5 s^{-1}), and $\Delta\omega$ of -0.063, -0.055, -0.043, -0.039 and -0.041 ppm, for Hct = 77, 64, 54, 44 and 30 % respectively, with $\Delta\omega$ values assumed negative for diamagnetic hemoglobin. The erythrocyte lifetime falls into the range of previously determined values of 9.8-14 ms by other methods [10]. The R_2 value obtained from the lysed blood experiment was 31.9 s^{-1} ± 1.17 (mean ± SD) which corresponds very well to the R_{2ery} value obtained from the data fitting. Literature values for the diamagnetic susceptibility difference between erythrocyte and plasma are -0.014 ppm [11], -0.023 ppm [12,13], and -0.030 ppm [14], in good agreement with our fitted $\Delta\omega$ for lower Hcts. The increase in absolute values of $\Delta\omega$ between erythrocytes and plasma at higher Hct values may indicate a breakdown of the general exchange model, indicating a need to extend it with diffusion through field gradients.



Conclusions The results show that a reasonable lifetime can be fitted for water in erythrocytes and that the inner erythrocyte transverse relaxation rate (R_{2ery}) compared well to that determined from a solution of lysed erythrocytes with hemoglobin concentrations ($[Hb_{tot}]$) equivalent to those in the erythrocyte. In addition, the fitted diamagnetic $\Delta\omega$ was in good agreement with estimates reported in the literature. These results confirm that the general exchange model for two-site system works well for diamagnetic blood at high magnetic field.

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