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NMR Relaxation Times of Blood: Dependence on Field Strength, Oxidation State, and Cell Integrity

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Abstract: The variation with field strength or interecho interval of the T1 and T2 relaxation times of oxyhemoglobin (HbO_2), deoxyhemoglobin (Hb), and methemoglobin (MHb) in either intact or lysed red blood cells was studied with a variable field (0.19–1.4 T) nuclear magnetic resonance spectroscopy unit. The T2 relaxation time of intracellular HbO_2 decreased slightly with increasing field strength and interecho interval. The T2 relaxation times of intracellular Hb and MHb decreased markedly with increasing field strength and interecho interval. This T2 proton relaxation enhancement increased as the square of the applied field strength and was 1.6 times stronger for intracellular MHb than for intracellular Hb. The T2 relaxation enhancement is secondary to the loss of transverse phase coherence of water protons that diffuse across cellular magnetic field gradients. These field gradients occur when an external field is applied to a region with gradients of magnetic susceptibility. The heterogeneity of magnetic susceptibility is caused by the heterogeneous distribution (only intracellular) of the paramagnetic molecules (Hb or MHb). The T2 relaxation times of red cell lysates (homogeneous magnetic susceptibility) were independent of field strength or interecho interval. There was a decrease in the T1 relaxation times when the red cells were lysed. This may be due to an increase in the slow motional components of water molecules, because of the decrease in the average distance between water and hemoglobin molecules in the lysate. The T1 relaxation times of all the MHb samples were shortened because of proton-electron dipolar-dipolar relaxation enhancement. All the T1 relaxation times increased with increasing field strength. **Index Terms:** Blood—Hematoma—Magnetic resonance imaging, techniques.

Magnetic resonance (MR) has become an important imaging modality in the evaluation of many neurologic diseases. It has made it possible to visualize the evolution of hemorrhage because of its sensitivity to the physical and chemical changes that occur as oxygenated blood becomes deoxygenated, then is converted to methemoglobin (MHb) and finally to hemosiderin. Each of these changes is accompanied by a characteristic intensity pattern on spin-echo MR performed at high field (1.5 T) (1).

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Acute hematomas (0–7 days old) are isointense to gray matter on T1 weighted images and markedly hypointense on T2 weighted images. We hypothesized that the T2 shortening is due to a T2 proton relaxation enhancement (PRE) caused by the magnetic susceptibility heterogeneity of intracellular deoxyhemoglobin (Hb). Deoxyhemoglobin is paramagnetic (increased magnetic susceptibility) because it has four unpaired electrons. When exposed to a magnetic field, there will be magnetic gradients between the red cell interior and the surrounding plasma because of the difference in their magnetic susceptibility. Water protons in regions of different field strength precess at different rates (Larmor frequencies) and quickly lose their phase coherence. The usual spin-echo pulse sequence will correct the dephasing due to static field strength inhomogeneities. However, if the water molecules diffuse to regions of different field strengths during the interecho interval (the time between the 180°

pulses), the spin-echo pulse sequence will not allow a complete correction of the phase coherence loss.

After 1 week the hematoma periphery becomes hyperintense on T1 weighted images and subsequently on both T1 and T2 weighted images. We suspected that the initial hyperintensity on T1 weighted images (T1 shortening) of subacute hematomas is due to the known proton-electron dipolar-dipolar (PEDD) PRE of MHb. Methemoglobin is paramagnetic and has five unpaired electrons, which, unlike the four unpaired electrons of Hb, are accessible to water protons for the PEDD interaction. Because MHb is paramagnetic (increased magnetic susceptibility), it should also have a T2 relaxation enhancement when it is intracellular. This will cause an additional T2 shortening to that caused by the PEDD PRE, which shortens both T1 and T2 relaxation times.

The hyperintensity of subacute hematomas on T1 weighted images precedes that on T2 weighted images. We thought this may be due to red blood cell lysis that occurs after the formation of intracellular MHb. Red blood cell lysis will eliminate the T2 PRE of intracellular MHb. The free MHb of the lysate is diluted by protein resorption resulting in lower protein concentration, higher proton density (increased water concentration), and weaker PEDD PRE due to the lower MHb concentration. This dilute MHb solution will have slightly shortened T1 and T2 relaxation times as well as higher proton density and should appear hyperintense on both T1 and T2 weighted images. After ~1 week the cerebral parenchyma next to the hematoma becomes hypointense on T2 weighted images. This is due to the hemosiderin deposits in the reactive macrophages surrounding the hematoma.

Thulborn et al. (2) studied Hb and oxyhemoglobin (HbO_2) in intact (IRBC) and lysed (LRBC) red blood cells at 1.9–11 T. They demonstrated that intracellular Hb had a T2 PRE that varied quadratically with field strength and Hb concentration. Its dependence on interecho interval (time between immediately adjacent echoes in a multiecho sequence) indicated a correlation time (τ_D) of 0.6 ms (the correlation time is the time it takes an entity to randomize a variable, such as its location or orientation, i.e., to "forget" its previous state) for the exchange of water protons across the cellular field gradients. They interpreted this correlation time to correspond to the transcellular diffusion of water. Extrapolation of their T2 PRE to 1.5 T yields an effect too weak to be observed, which is contrary to our clinical experience.

This study extends the work of Thulborn et al. to the lower fields used in MR imaging and to MHb. We also sought an explanation for the discrepancy between the clinical observation of a significant T2 PRE for intracellular Hb at 1.5 T, and measurements by Thulborn et al. that predicted a lack of such a T2 PRE at 1.5 T.

THEORY

In analyzing their data Thulborn et al. (2) applied the equation of Luz and Meiboom (3) for the T2 PRE (1/T2) due to the exchange of protons between regions of different magnetic field strength. Their equation is (3)

$$\frac{1}{T_2} = \delta^2\left[1 - \frac{\tau_D}{2\tau_{CPMG}}\tanh\left(\frac{2\tau_{CPMG}}{\tau_D}\right)\right]\tau_D \sum_i \rho_i(\Delta Hi)^2 \quad (1)$$

where δ is the gyromagnetic ratio of the proton, τ_D is the correlation time for the exchange, ΔH_i is the difference from the average of the field strength in the ith region, p_i is the probability of a proton being in the ith region, and $2\tau_{cpmg}$ is the interecho interval. If we define 1/T2(∞) as the limit of 1/T2 as $2\tau_{cpmg}$ approaches infinity, then

$$\frac{1}{T_{2(\infty)}} = \delta^2\tau_D \sum_i \rho_i(\Delta H_i)^2 \quad (2)$$

when $\tau_D/\tau_{CPMG} < 0.3$ (1) can be approximated by

$$\frac{1}{T_2} = \left(1 - \frac{\tau_D}{2\tau_{CPMG}}\right)\frac{1}{T_{2(\infty)}};\ \tau_{CPMG} > 3.3\ \tau_D \quad (3)$$

If we define the limit

$$S(\infty) \equiv \frac{d\left(\frac{1}{T_2}\right)}{d\left(\frac{1}{2\tau_{CPMG}}\right)}\ \tau_{CPMG} \to \infty$$

then we have

$$\tau_D = -S(\infty)T_2(\infty) \quad (4)$$

When the variation of 1/T2 versus $1/2\tau_{cpmg}$ is plotted, both S(∞) and 1/T2(∞) are easily obtained by linear extrapolation to $2\tau_{cpmg} \to \infty$ (i.e., $1/2\tau_{cpmg} \to 0$). These are then used to obtain a τ_D.

Thulborn et al. (2) demonstrated that the T2 PRE of intracellular Hb varies as the square of the magnetic field strength (1.9–11.0 T) and obtained a τ_D = 0.6 ms (τ_{cpmg} = 0.25–3.5 ms). Quadratic extrapolation of their graph data of the T2 PRE, attributable to the heterogeneity of magnetic susceptibility of intracellular Hb IRBC, to 1.4 T yields

$$\left\{\frac{1}{T_2(\text{Hb IRBC})} - \frac{1}{T_2(\text{HbO}_2\ \text{IRBC})}\right\}_{1.4T} \approx 0.59\ \text{s}^{-1}$$

$$2\tau_{CPMG} = 1.0\ \text{ms}$$

and

$$\frac{\frac{1}{T_2}(\text{Hb IRBC})}{\frac{1}{T_2}(\text{HbO}_2\ \text{IRBC})} \approx 1.12$$

i.e., only a 12% difference in relaxation rates between the paramagnetic intracellular Hb and the nonparamagnetic intracellular HbO_2 IRBC. With a $\tau_D = 0.6$ ms, this T2 PRE will increase by a factor of 5.7 on prolonging τ_{cpmg} from 0.5 ms to infinity (see Eq. 1). Thus

$$\left\{\frac{1}{T_2(\text{Hb IRBC})} - \frac{1}{T_2(\text{HbO}_2\ \text{IRBC})}\right\}_{1.4T} \approx 3.3\ \text{s}^{-1}$$

$$2\tau_{cpmg} = \infty$$

This is still insufficient to account for the T2 PRE at this field strength that has been attributed to intracellular Hb.

Equation 1 quantitatively predicts an increase in T2 relaxation rate with increasing interecho interval. To visualize this we should remember that protons experiencing different field strengths will precess at different rates and thus lose their phase coherence. The spin-echo pulse sequence was devised to correct for static field inhomogeneities by reversing the phases with a 180° pulse after a time τ_{cpmg} and detecting the rephased (refocused) echo at $2\tau_{cpmg}$. As water protons move to regions of different field strength, this rephasing will be incomplete. The greater the difference in field strengths the greater will be the dephasing rate due to diffusion. The less frequent the echoes in the pulse sequence, the less effectively they will correct for this dephasing due to diffusion, and the dephasing rate will increase. However, after a certain time, the water protons will have sampled the full range of field strength variations. Tau_D is the technical term for this time. At interecho times $>10\tau_D$ there is no longer a significant increase in the dephasing rate with increasing interecho interval. Of course, the dephasing rate is another name for the T2 relaxation rate. Thus for interecho interval $<10\tau_D$ there will be a significant increase in T2 relaxation rate with increasing interecho interval. For example, if $\tau_D = 10$ ms, and we wish to image at echo time (TE) of 100 ms, there will be a significantly lower signal intensity if the TE of 100 ms is obtained as the first echo ($2\tau_{cpmg} = 100$ ms) than as the 10th echo ($2\tau_{cpmg} = 10$ ms). Thus the same sample with $\tau_D = 10$ ms will appear to have a faster T2 relaxation rate with $2\tau_{cpmg} = 100$ ms than with $2\tau_{cpmg} = 10$ ms. One must not confuse this with the lower intensity due to exponential decay that is observed as the TE is prolonged.

MATERIALS AND METHODS

Six samples were prepared from citrated whole human blood (hematocrit 45%). The samples consisted of three hemoglobin states; 100% HbO_2, 100% Hb, and 100% MHb with either IRBC or LRBC. Oxyhemoglobin was maintained by 100% O_2. Deoxyhemoglobin was obtained by the addition of a few grains of sodium dithionite (Fisher Scientific) and was maintained by 100% N_2. Methemoglobin was produced by replacing plasma with a few drops of a 2% solution of sodium nitrite (Sigma Chemical) in saline. The red cells were lysed by two freeze-thaw cycles.

Relaxation times of two samples of each blood state were measured at 20°C with a resistive variable-field (0.19–1.4 T) nuclear MR spectroscopy unit. The T1 relaxation time was measured by the null point of the inversion recovery sequence. The T1 relaxation time was measured twice for each sample. The T2 relaxation time was measured by fitting a single exponential decay rate to the spin-echo train. The interecho interval was varied from 2 to 64 ms. The T2 relaxation time was measured 10 times for each sample. The intact red cells were resuspended prior to each measurement. The T1 and T2 values were averaged for each blood state and standard deviations were calculated for the T2 values.

RESULTS

Figure 1 presents the variation of the T1 relaxation times with field strength for the blood samples and for plasma. The LRBC samples had shorter T1 relaxation times than the corresponding samples with IRBC, irrespective of field strength. There was a general prolongation of the T1 relaxation times with increasing field strength. All the MHb samples, either IRBC or LRBC, had significantly shorter T1 relaxation times than the corresponding HbO_2 or Hb samples.

Figure 2 presents the variation of the T2 relaxation times with field strength at various values of $2\tau_{cpmg}$. The T2 relaxation time of the LRBC samples did not vary with field strength or $2\tau_{cpmg}$. The T2 relaxation times of samples with IRBC decreased with increasing field strength and $2\tau_{cpmg}$. This was minimal for intracellular HbO_2 (essentially nonparamagnetic), marked for intracellular Hb, and most marked for intracellular MHb.

Figure 3a is a ln–ln (ln is the natural log) graph of the difference in T2 relaxation rates (1/T2) of intracellular Hb and intracellular HbO_2 versus field strength, at various values of $2\tau_{cpmg}$. The slope average over all $2\tau_{cpmg}$ was 1.90 ± 0.15. Figure 3b is a similar graph for intracellular MHb. Its average slope was 2.01 ± 0.19. These two slope averages

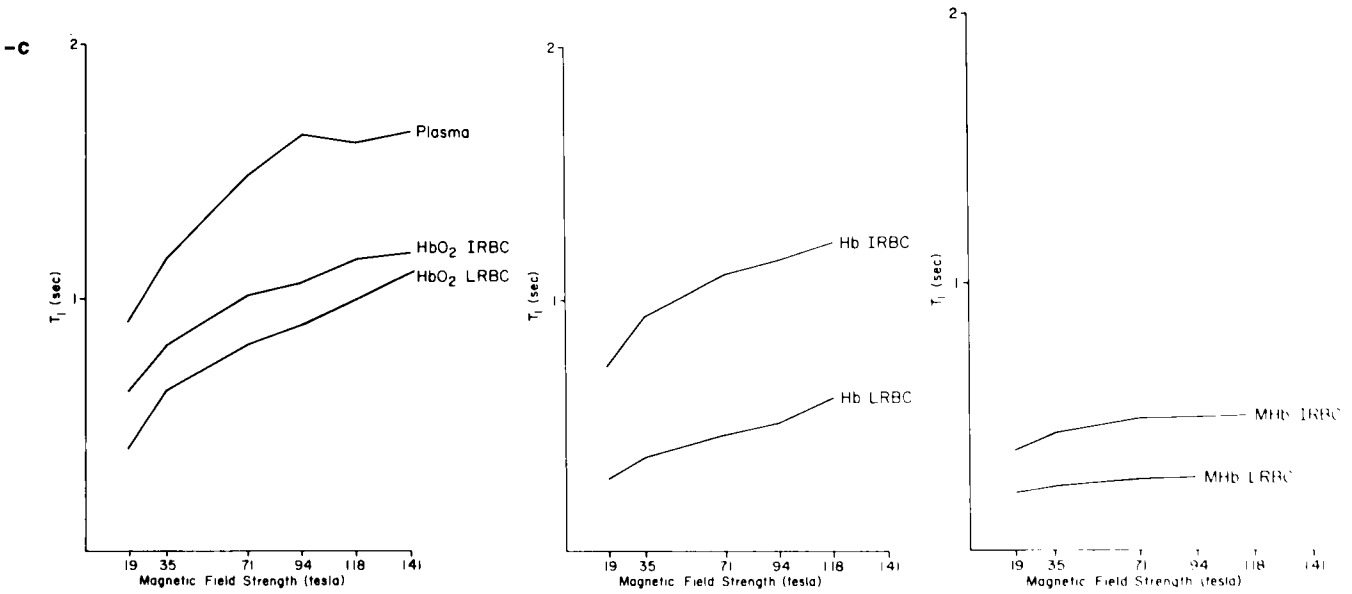

FIG. 1. Variation of T1 with magnetic field strength (two measurements for each sample). **a:** Plasma, oxyhemoglobin (HbO_2) intact red blood cells (IRBC), and HbO_2 lysed (LRBC) red blood cells. **b:** Deoxyhemoglobin (Hb) IRBC and Hb LRBC. **c:** Methemoglobin (MHb) IRBC and MHb LRBC.

indicate that the T2 PRE of intracellular Hb and intracellular MHb vary as the square of the magnetic field strength.

Figure 4a is a graph of the T2 PRE (1/T2) of intracellular Hb versus the echo rate ($1/2\tau_{cpmg}$) at various field strengths. Figure 4b is a similar graph for the T2 PRE of intracellular MHb. The equation Luz and Meiboom used for calculating the correlation time of the exchange of spins between environments of different local magnetic field strength, yields $\tau_D = 9.1 \pm 0.4$ ms for intracellular Hb ("asymptotic" slope obtained between $2\tau_{cpmg}$ of 32 and 64 ms and calculations performed at 0.71 and 0.94 T) Thulborn et al. (2) calculated their τ_D using $2\tau_{cpmg} < 7.1$ ms. When we used short $2\tau_{cpmg}$ at our field strengths, we did not find a significant T2 PRE for intracellular Hb for $2\tau_{cpmg} < 4$ ms. Unlike Hb, which has four unpaired electrons, MHb should have $(35/24)^2 = 2.1$ times the T2 PRE of intracellular Hb because this T2 PRE increases as the square of the intracellular magnetic susceptibility, which, all other things being equal, is approximately proportional to the number of unpaired electrons. Indeed we obtained a ratio of 1.7 at $2\tau_{cpmg} = 32$ ms. The T2 PRE of intracellular MHb was sufficiently strong to use in extending the calculation of Thulborn et al. to our range of field strengths (Fig. 4b) resulting similarly in a $\tau_D = 0.58 \pm 0.03$ ms ("asymptotic" slope obtained between $2\tau_{cpmg}$ of 2 and 4 ms and calculations performed at 0.94 and 1.18 T).

DISCUSSION

The dependence of the T2 relaxation times of intracellular Hb and intracellular MHb on field strength is illustrated in Fig. 2f and i. We can appreciate the marked T2 shortening that occurs as the magnetic field is increased from 0.19 to 1.41 T. The T2 PRE increases as the square of the field strength (Fig. 3). The T2 relaxation times of intracellular Hb and intracellular MHb also markedly decrease as the $2\tau_{cpmg}$ (interecho interval) increases from 2 to 32 ms (Fig. 2e, f, h, and i).

The $\tau_D = 9.1 \pm 0.4$ ms derived from Fig. 4a is 15.2 times longer than the $\tau_D = 0.6$ ms calculated by Thulborn et al. and is probably due to the diffusion of water across the red cell (4). This slower exchange process was not appreciated at much higher field strengths (1.9–11.0 T) but is dominant at the clinical field strengths of the present study. It accounts for the T2 PRE of intracellular Hb and intracellular MHb observed at clinical field strengths. The dependence of this T2 PRE on $2\tau_{cpmg}$ means that a long TE is not sufficient to observe it on MR imaging; the long TE should be attained on the first echo rather than on the last of many echoes. For example, a TE of 120 ms can be obtained with the sixth echo of $2\tau_{cpmg} = 20$ ms, or as the first echo of $2\tau_{cpmg} = 120$ ms; a sixfold increase in $2\tau_{cpmg}$. Extrapolating from our in vitro measurements at 1.4 T and $2\tau_{cpmg} = 64$ ms to $2\tau_{cpmg} = \infty$ yields a T2 relaxation rate for intracellular Hb equal to 25.0 s^{-1}; i.e., eight times the effect expected by extrapolation from the measurement used by Thulborn et al. (2). This is due to the $\tau_D = 9.1 \pm 0.4$ ms; i.e., 15.2 times longer than the "τ_D" = 0.6 ms obtained by Thulborn et al. Interestingly, if we use the short $2\tau_{cpmg}$ (<4 ms) that Thulborn et al. used to obtain their τ_D we get a similar "τ_D" = 0.58 ± 0.03 ms.

These findings suggest that at the high fields used

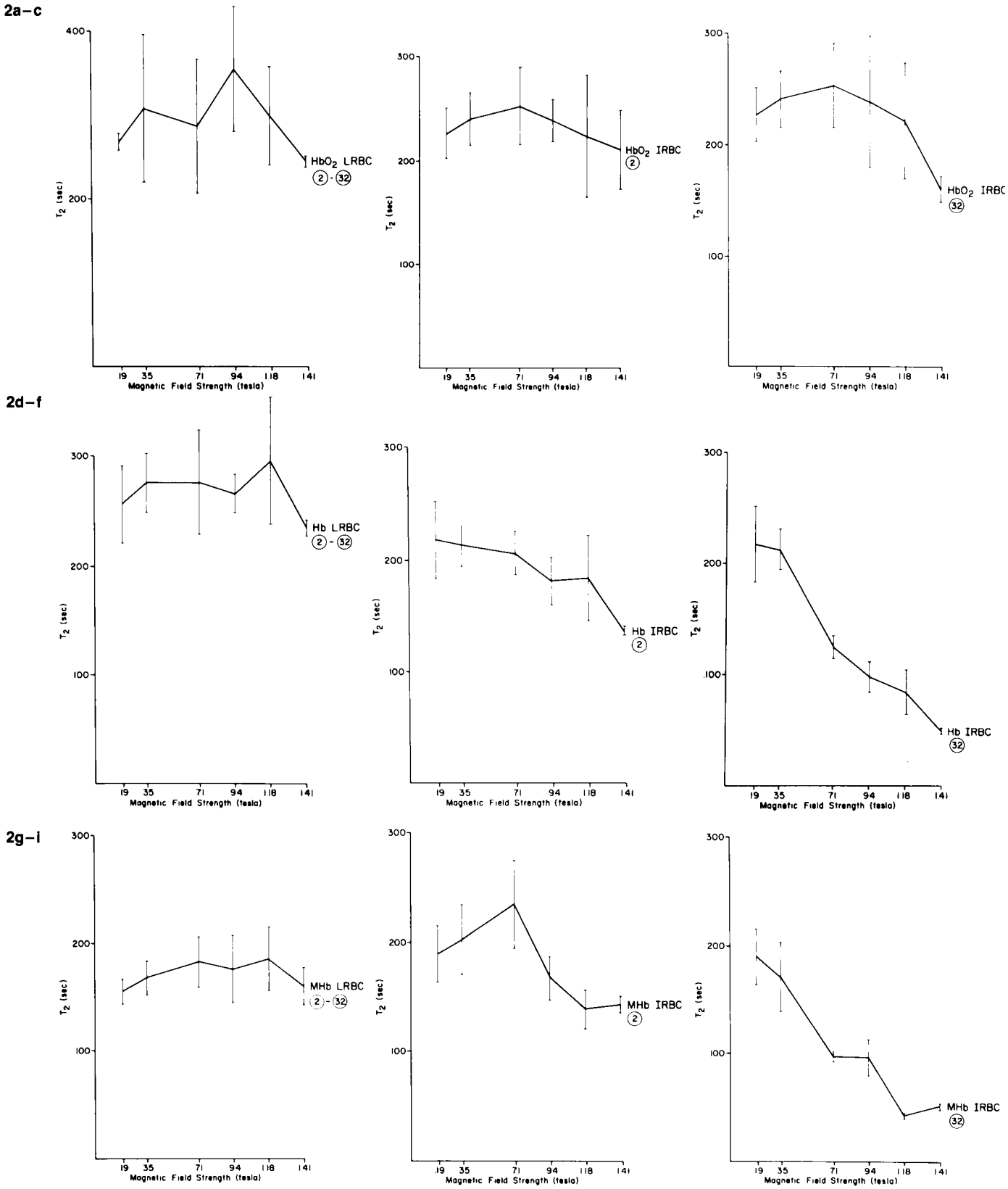

FIG. 2. Variation of T2 with field strength and interecho interval ($2\tau_{cpmg}$). Bars indicate the standard deviation of the T2 measurement (10 measurements for each sample). The following list gives the samples and $2\tau_{cpmg}$ (ms) for each figure: **(a)** oxyhemoglobin (HbO_2) lysed red blood cells (LRBC), 2–32; **(b)** HbO_2 intact red blood cells (IRBC), 2; **(c)** HbO_2 IRBC, 32; **(d)** deoxyhemoglobin (Hb) LRBC, 2–32; **(e)** Hb IRBC, 2; **(f)** Hb IRBC, 32; **(g)** methemoglobin (MHb) LRBC, 2–32; **(h)** MHb IRBC, 2; **(i)** MHb IRBC, 32.

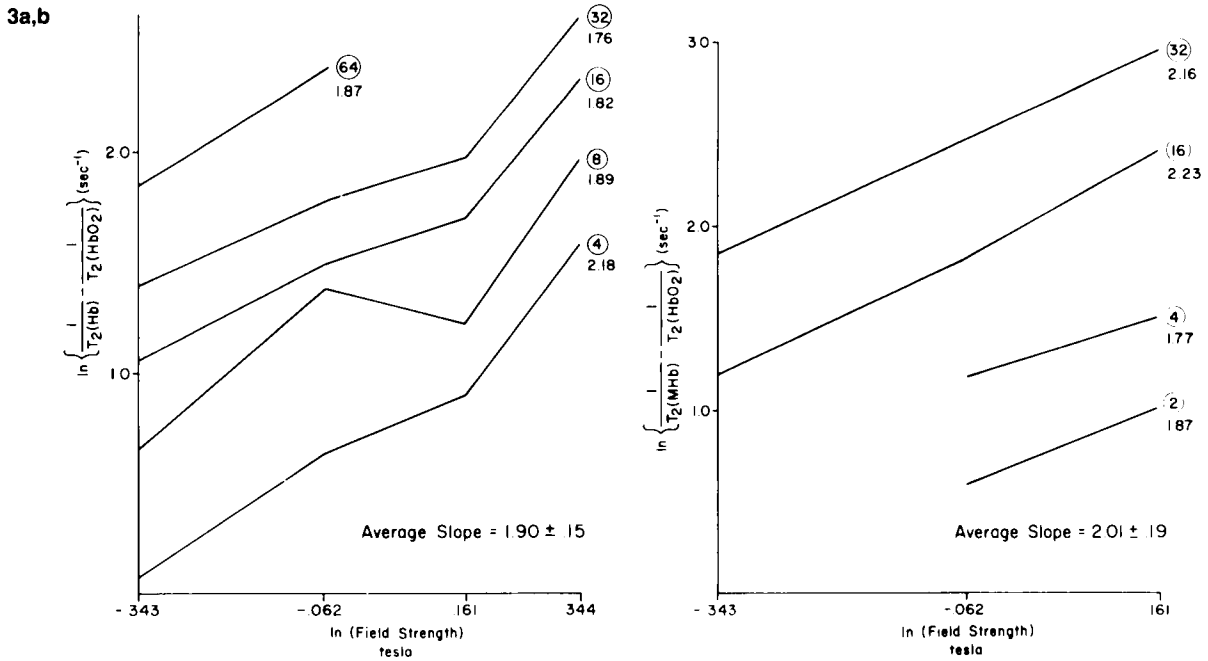

FIG. 3. a: The ln–ln (ln is the natural log) graph of the difference in T2 relaxation rates (1/T2) between deoxyhemoglobin (Hb), intact red blood cells (IRBC) and oxyhemoglobin (HbO_2) IRBC; i.e., {(1/T2(Hb IRBC)) − (1/T2(HbO_2 IRBC))} versus field strength at various $2\tau_{cpmg}$ (4, 8, 16, 32, and 64 ms). Average slope of each curve is indicated alongside it. The average slope of all curves is indicated at bottom right. **b:** Same as (a) except that methemoglobin (MHb) IRBC replaces Hb IRBC. These two figures indicate a quadratic relation between T2 proton relaxation enhancement of intracellular paramagnetic form of hemoglobin and field strength.

by Thulborn et al. there was almost complete dephasing of the water protons before they had a chance to sample the full range of field strength variations. Since the water protons sampled only a fraction of the full range of field strength variations, it took them less time to do it, resulting in the observation of a shorter τ_D. At lower field strengths this limited sampling of field strength variations was insufficient to cause complete dephasing. Therefore, we were able to observe the longer correlation time τ_D necessary to sample the full range of field strength variation, i.e., the correlation time for cellular diffusion. One would expect that the limited range of field strengths sampled in the "τ_D" = 0.6 ms observed by Thulborn et al. should be in the region having most rapid variation (gradient) of field strength. This should correspond to the region near the red cell surface where the gradient varies inversely as the fourth power of the distance (5). The time required to diffuse a distance is proportional to the square of the distance. If 9.1 ms is the time required to diffuse across one red cell (4), then in 0.6 ms, diffusion will cover $\sqrt{0.6/9.1}$ (7 μm) = 1.8 μm. Thus, at the high fields studied by Thulborn et al., diffusion over 1.8 μm (~1/4 of the red cell diameter) through the high field gradients near the red cell surface appears to have caused a sufficient T2 PRE to prevent observation of the full range of field variations about the red blood cell and the surrounding plasma.

Our data confirm and extend to clinical field strengths the work of Thulborn et al., who demonstrated that the T2 PRE of intracellular Hb varies as the square of the magnetic field strength increases (Fig. 3a). This effect is due to the dephasing of water protons by diffusion across cellular magnetic field gradients which are due to the application of an external magnetic field to regions containing gradients of magnetic susceptibility. The heterogeneity of susceptibility is caused by the heterogeneity in distribution (only intracellular) of the paramagnetic molecules (Hb or MHb). The T2 shortening of intracellular MHb is greater than that of intracellular Hb by a factor of $(35/24)^2 = 2.1$ because MHb has five unpaired electrons whereas HbO_2 has four, effectively increasing the concentration of paramagnetic substance by 35/24.

The T2 PRE ceases when cells containing intracellular Hb or MHb are lysed (Fig. 2d and g). With red cell lysis the heterogeneous distribution of paramagnetic substance is no longer present, and the rapid dephasing of water protons by the local field gradients does not occur. The T2 PRE enhancement of intracellular HbO_2 is minimal even at 1.4 T and long $2\tau_{cpmg}$ (Fig. 2c). This is due to the presence of a single unpaired electron in HbO_2 resulting in $(3/24)^2 = 1/64$ the T2 PRE of intracellular Hb.

We observed shortening of the T1 relaxation times with red cell lysis (Fig. 1) due to an increase

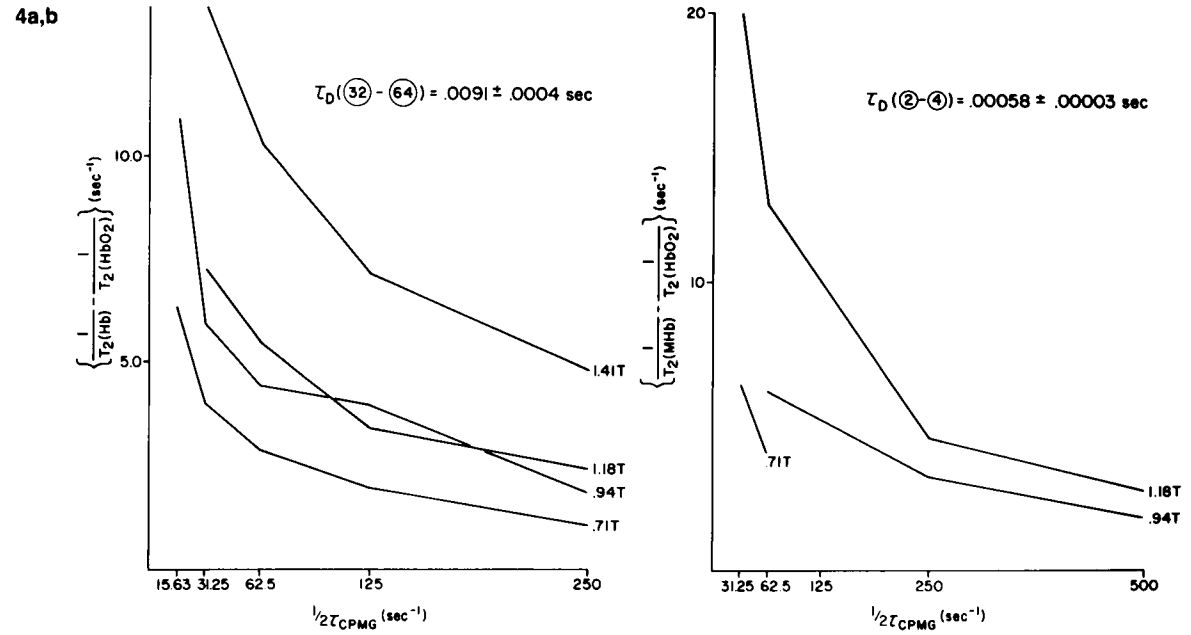

FIG. 4. a: Graph of $1/2\tau_{cpmg}$ versus the difference in T2 relaxation rate (1/T2) between deoxyhemoglobin (Hb) and oxyhemoglobin (HbO_2) intact red blood cells (IRBC); i.e., {(1/T2 (Hb IRBC)) − (1/T2 (HbO_2 IRBC))} at various field strengths. **b:** Same as (a) except that methemoglobin (MHb) IRBC replaces Hb IRBC. Note the marked increase in the T2 proton relaxation enhancement with long $2\tau_{cpmg}$ (short $1/2\tau_{cpmg}$).

in the slow motional components of water molecules. This may be secondary to the decrease in the average distance between water and hemoglobin molecules in the lysate enhancing the protein–water molecule interactions. The shorter T1 relaxation time of the MHb samples is due to the familiar PEDD PRE (6,7). The general increase in the T1 relaxation time with field strength has been previously observed (8) and is incompletely understood (8,9). The field invariance of the T2 relaxation times of the lysed samples has also been previously described (8,9). We do not have an explanation for the difference in T1 relaxation times of corresponding HbO_2 and Hb samples, which is in disagreement with previous reports (11,12). It may be due to differences in field strength, hematocrit, or methods for preparing Hb.

In conclusion, our in vitro experiments validate the hypothesis that intracellular Hb and MHb produce T2 PRE that varies as the square of the magnetic field. Our findings explain the discrepancy between observations of Thulborn et al. at very high field strengths and the findings at lower field strengths on clinical imaging. Significantly, the T2 PRE increases with $2\tau_{cpmg}$. Our experiments also confirm that MHb has a PEDD PRE, that T1 relaxation times increase with field strength, and that the T2 relaxation times of red cell lysates are field strength independent.

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