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RESEARCH ARTICLE

Blood longitudinal (T_1) and transverse (T_2) relaxation time constants at 11.7 Tesla

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Abstract
Object The goal of the study was to determine blood T_1 and T_2 values as functions of oxygen saturation (Y), temperature (Temp) and hematocrit (Hct) at an ultrahigh MR field (11.7 T) and explore their impacts on physiological measurements, including cerebral blood flow (CBF), blood volume (CBV) and oxygenation determination.
Materials and methods T_1 and T_2 were simultaneously measured. Temperature was adjusted from 25 to 40°C to determine Temp dependence; Hct of 0.17–0.51 to evaluate Hct dependence at 25 and 37°C; and Y of 40–100% to evaluate Y dependence at 25 and 37°C. Comparisons were made with published data obtained at different magnetic field strengths (B_0).
Results T_1 was positively correlated with Temp, independent of Y, and negatively correlated with Hct. T_2 was negatively correlated with Temp and Hct, but positively correlated with Y, in a non-linear fashion. T_1 increased linearly with B_0, whereas T_2 decreased exponentially with B_0.
Conclusion This study reported blood T_1 and T_2 measurements at 11.7 T for the first time. These blood relaxation data could have implications in numerous functional and physiological MRI studies at 11.7 T.

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Introduction

The longitudinal relaxation time (T_1) and transverse relaxation time (T_2) of blood are important for a number of quantitative physiological and functional MRI measurements. For example, blood T_1 is used to quantify cerebral blood flow (CBF) using arterial spin labeling (ASL) techniques [1, 2]. The accuracy of blood T_1 is crucial for cerebral blood volume (CBV) determination using the vascular space occupancy (VASO) method [3]. Blood T_2 is important in differentiating between the extravascular and intravascular blood oxygenation level dependent (BOLD) contributions [4]. Blood T_2 has also been used for calibration in determining tissue oxygen extraction fractions (OEF) and the cerebral metabolic rate of oxygen ($CMRO_2$), including the $T2$-relaxation-under-spin-tagging (TRUST) techniques [5–8].

T_1 and T_2 values of blood are dependent on hematocrit content (Hct), oxygenation level (Y) and temperature (Temp). These relationships have been extensively studied at different magnetic field strengths from 1.5 to 7 T [1, 9–11]. With the rapid growth of functional studies on high field MRI scanners (>7 T) with animal models (especially with rodents), similar measurements are necessary for those high field systems in order to accurately determine CBF, CBV, OEF, and optimize BOLD contrast under various physiological conditions. To our knowledge, only blood T_1 and T_2 dependence on Y has been reported up to 9.4 T [12, 13]. The goal of the present study was to determine blood T_1 and T_2 values as functions of Hct, Y and Temp, and explore their impacts on CBF, CBV, OEF and

BOLD measurements at 11.7 T. Comparisons were also made with published data at different magnetic field strengths.

Materials and methods

Blood sample preparation

Fresh blood samples were taken from male Sprague–Dawley rats. Five rats (500–650 g body weight) were used for the study. Rats were anesthetized for surgical preparation with 4.0% isoflurane for induction, and maintained at a 2.0% isoflurane and air mixture using a face mask. Body temperature was kept at 37°C via a heating pad. PE-50 catheters were placed into the femoral artery and vein. For each measurement, a vial of 1.0 ml blood (with heparin) was taken from the rat (from either artery or vein, see details below). Blood gases, Y, total hemoglobin and temperature were measured with a blood gas analyzer (Radiometer ABL5, Copenhagen). Vials were then sealed. To minimize the error due to red blood cell precipitation, the samples were agitated immediately before measurement and the study time (preparation + scan) was accomplished within 30 min. In the middle of the experiment, blood samples were also taken out and agitated again to minimize settling. Blood oxygenation was also measured after the experiment.

MRI experiments and data analysis

Experiments were performed on an 11.7 T BioSpec MR scanner (Bruker, Billerica, MA, USA). A quadrature volume coil (72 mm in diameter) was used for both RF transmission and reception. T_1 and T_2 were simultaneously measured using a RAREVTR sequence (RARE with variable repetition time TR) sequence. The sequence used a saturation scheme (i.e., varied TR) to acquire T_1 and used a multi-echo CPMG scheme (i.e., varied TE) to acquire T_2. In the study, six TR values (208, 400, 800, 1,500, 3,000 and 3,500 ms) and five TE values (14, 42, 70, 98, and 126 ms) were used. A single slice centered on the blood sample was chosen. The region of interest (ROI) was chosen to cover the blood sample area on the slice. Other imaging parameters were as follows: field-of-view (FOV) = 40 × 40 mm, slice thickness = 1.0 mm, matrix size = 128 × 128 and rare factor = 4. The total scan time was 3 min 46 s.

To evaluate temperature dependence, measurements were made on arterial blood samples (Hct = 0.43 and Y = 98–99%) with temperature adjusted from 25 to 40°C via a circulating water bath and monitored in real time by a temperature controller (Thermo Electron Co., Karlsruhe, Germany). This was done with a home-made acrylic tube (20 mm in diameter and 92 mm long) with a thermometer placed in the chamber but away from the imaging slice. To evaluate Hct dependence, plasma was added to arterial blood to achieve a Hct level of 0.17–0.51 with Y = 99% at room temperature (25°C) and body temperature (37°C). Hct was determined by a high-speed micro-hematocrit centrifuge (Model MB, International Equipment Company, MA, USA). To evaluate blood oxygenation dependence, oxygen concentration of the gas mixture that the animals inhaled was modulated to achieve Y = 40–100%. Measurements were also made at 25 and 37°C.

T_1 fitting was done with first echo (TE = 14 ms) and all the TRs; T_2 fitting was done with the 5th repetition time (TR = 3,000 ms) and all the echoes. T_1 was calculated by fitting $M(t) = M_0$ [1−c × exp (−TR/T_1)] and T_2 was calculated by fitting $M(t) = M_0$ exp (−TE/T_2) using ParaVision 5.0 software (Bruker) by fitting the absolute signals to a three-parameter model where $M(t)$ is the signal intensity at a particular TR or TE, M_0 is the equilibrium signal and C is a factor to account for incomplete inversion.

Results

Study 1: Temperature (Temp) dependency

Figure 1 shows the plot of arterial blood T_1 and T_2 as a function of temperature (Hct = 0.43 and Y = 99%). T_1 was positively correlated with temperature (r = 0.99, $P < 0.001$). T_2 was negatively correlated with temperature in a non-linear fashion ($r = -0.95$, $P < 0.001$).

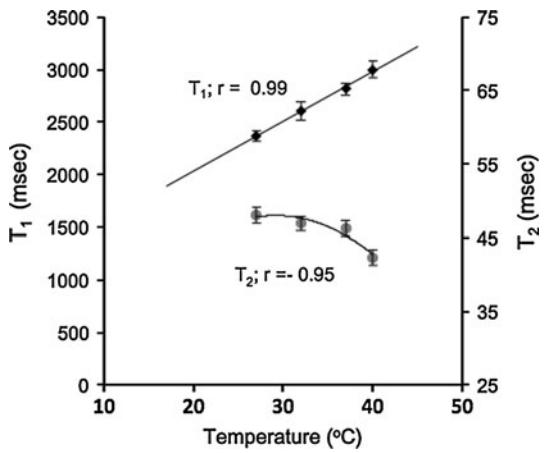

Fig. 1 Arterial blood T_1 and T_2 values as a function of temperature (25–40°C). T_1 was positively correlated with temperature (r = 0.99, $P < 0.001$). In contrast, T_2 was negatively, and non-linearly, correlated with temperature ($r = -0.95$, $P < 0.001$)

Study 2: Hematocrit level (Hct) dependency

A plot of arterial blood T_1 and T_2 ($Y = 99\%$ and Temp = 25 and 37°C) as a function of Hct is shown in Fig. 2. T_1 was negatively, and non-linearly, correlated with Hct at both temperature ($r = -0.99$, $P < 0.001$ at 25°C; $r = -0.94$, $P < 0.005$ at 37°C). Similar results were reported with bovine blood at 3 and 4.7 T [1, 9]. T_2 was also negatively correlated with Hct at the two temperatures ($r = -0.93$, $P < 0.001$, non-linearly, at 25°C; $r = -1.00$, $P < 0.0005$, linearly, at 37°C), consistent with that reported at 3 T [14].

Study 3: Oxygenation level (Y) dependency

Figure 3 shows the plot of T_1 and T_2 versus Y with a normal hematocrit level (Hct = 0.43, Temp = 25°C and 37°C). T_1 was not significantly correlated with Y ($r = 0.04$, $P > 0.5$ at 25°C; $r = 0.02$, $P > 0.5$ at 37°C). This finding is consistent with those measured at lower fields [3, 12, 15, 16]. T_2 was positively, and non-linearly, correlated with Y ($r = 0.95$, $P < 0.005$ at 25°C; $r = 0.97$; $P < 0.001$ at 37°C). Arterial blood T_2 ($Y = 99$–100%) was significantly longer than that of venous blood ($Y = 40$–60%) at both temperatures (Table 1), in good agreement with literature [10, 13]. These findings indicate that there are strong T_2 dependencies over the physiological Y ranges.

Study 4: Field strength (B_0) dependency

We compared our T_1 and T_2 results at 11.7 T to published data at other field strengths [3, 9–13, 15, 22, 23]. Figure 4a shows that both arterial and venous T_1 values ($T_{1(a)}$ and $T_{1(v)}$, respectively) are linearly dependent on B_o ($T_{1(a)} = 133.98$ T + 1,211.4, $r = 0.99$, $P < 0.001$, and $T_1(v) = 133.27$ T + 1,187.4, $r = 1.0$, $P < 0.02$). Both arterial and venous T_1 values are linearly dependent on B_0. Figure 4b shows $T_{2(a)}$ and $T_{2(v)}$ decreased exponentially with B_0 ($r = -0.99$, $P < 0.001$ and $r = -0.90$, $P < 0.005$ for arterial and venous blood, respectively).

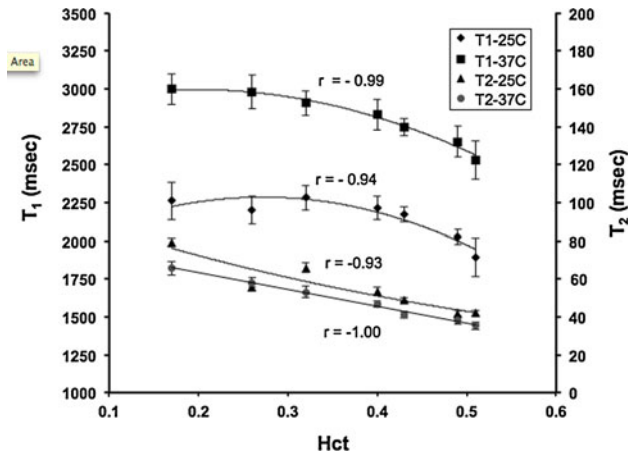

Fig. 2 Arterial blood T_1 and T_2 as a function of Hct (0.17–0.51) at 25 and 37°C. Both T_1 and T_2 decreased as Hct increased at both temperatures

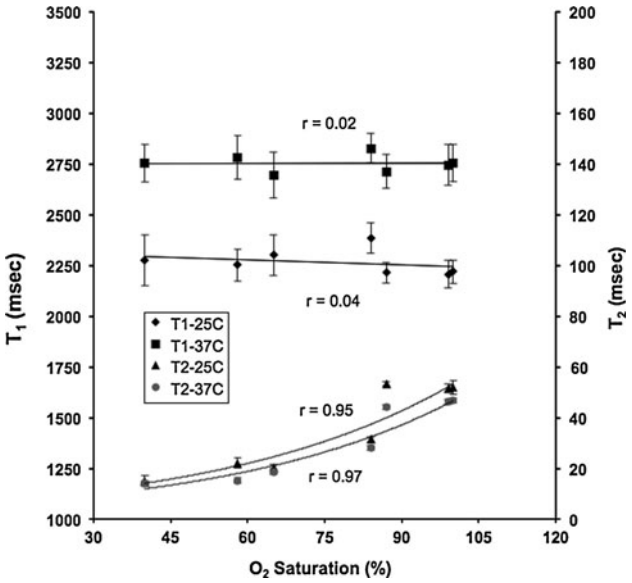

Fig. 3 Blood T_1 and T_2 values as a function of Y (40–100%) at 25 and 37°C. T_1 was independent of Y, while T_2 was positively, and non-linearly, dependent on Y at both temperatures

Table 1 T_1 and T_2 of arterial ($Y = 99$–100%) and venous blood ($Y = 40$–60%) under normal physiological conditions (Hct = 0.43) measured at room temperature (25°C) and body temperature (37°C)

	T_1 (ms)		T_2 (ms)	
	Arterial	Venous	Arterial	Venous
25°C	2,249 ± 106	2,272 ± 79	48.5 ± 1.9	20.1 ± 1.1
37°C	2,813 ± 56	2,768 ± 69	46.3 ± 0.8	14.7 ± 1.3

Discussion

Accurate blood T_1 is important for determining absolute CBF (with unit ml/g/min) with the following equation: $CBF = \lambda/T1\ [(SNL–SL)/(SL + (2\alpha\text{-}1)SNL)]$ (SNL and SL are signal intensities of the non-labeled and labeled images, respectively. α is the labeling efficiency, λ is the water tissue-blood partition coefficient) [17]. Based on the equation, one can estimate that quantitative CBF varies from −6 to 19% (0.94–1.19 ml/g/min, respectively, with the assumed basal CBF of 1 ml/g/min at 37°C in rodents) across the four Temp points, and from −8 to 10% across the seven Hct levels at 37°C (assuming CBF baseline is Hct = 0.43).

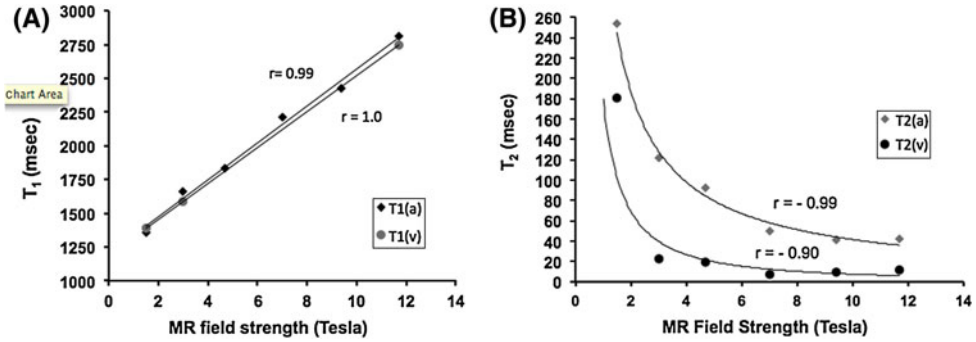

Fig. 4 **a** T_1 values of arterial and venous blood were both linearly dependent on B_0. For arterial blood, $r = 0.99$, $P < 0.001$; data citation: 1.5 T [3]; 3 T [9]; 4.7 T [12]; 7 T [12]; 9.4 T [12]; 11.7 T [present study]. For venous blood, $r = 1.0$, $P < 0.02$; data citation: 1.5 T [3]; 3 T [9]; 11.7 T [present study]. **b** T_2 values of arterial and venous blood as a function of magnetic field. For $T_{2(a)}$: 1.5 T [23]; 3 T ([11], Hct = 0.44, $Y = 0.99$); 4.7 T ([15], $Y = 0.9$–1.0); 7 T [present study]; 9.4 T [13]; 11.7 T [present study]; for $T_{2(v)}$: 1.5 T [23]; 3 T ([10], Hct = 0.44, $Y = 0.44$); 4.7 T ([15], $Y = 0.4$); 7 T [22]; 9.4 T [13]; 11.7 T [present study]

VASO signal changes are acquired at blood null point (TI_{null}), which is determined based on the blood T_1. VASO signals will have blood signal contamination with inaccurate T_1 values. Because changes in CBV are determined from VASO signal [3], slightly changes in VASO signal changes could result in dramatic difference in CBV changes. For example, VASO changes from −1.2 to −3.7% could result in CBV changes from 21 to 38%, respectively, based on the model presented in [3]. Because CBV change is an important parameter in determining cerebral $CMRO_2$ via the fMRI BOLD biophysical model [18–20], accurate determination of CBV changes is important. A CBV change from 21 to 38% would cause an error in $CMRO_2$ changes of 5–10%. Therefore, caution must be taken to determine VASO changes when applying blood T_1 values at various physiological conditions. Oxygenation level does not significantly affect blood T_1, suggesting that the utilization of arterial or venous blood T_1 should not cause significant differences for VASO determination.

Blood T_2 values, on the other hand, are highly dependent on oxygenation level. This makes T_2 particularly useful for quantitatively estimating Y. Several groups have used this T_2 MRI approach to determine quantitative OEF (=1−Y) and $CMRO_2$ (=CBF × OEF × CaO_2; where CaO_2 is the oxygen content), including the TRUST techniques [5–8, 14]. MRI OEF and $CMRO_2$ data have been shown to be consistent with those obtained by O-15 positron emission tomography (PET), which is considered the gold standard [21]. MRI OEF and $CMRO_2$ will likely have widespread utility because they are totally non-invasive.

In addition to Y, blood T_2 values are also dependent on Temp and Hct. It is interesting to see from Table 1 that venous blood T_2 has a much lower T_2 at higher temperatures, opposite to the trend of blood T_1, and is more negatively correlated with temperature than is arterial blood T_2 (Table 1). The Hct-dependent T_2 is an important factor for calibrating OEF measurement since Hct could vary slightly across individuals. All three parameters (Y, Temp and Hct) are thus crucial for OEF and $CMRO_2$ determinations.

Blood T_2 also can be used to dissect the BOLD signal contributions. The BOLD signal consists of and intravascular (IV) and an extravascular (EV) component. The IV BOLD component exists because blood deoxyhemoglobin content strongly influences blood T_2, as well as the susceptibility-induced frequency difference between blood and surrounding tissue. At the same field strength (B_0), as demonstrated in the study, the IV contribution to BOLD signal should increase as Y increases, and decrease as Hct and Temp increase. At different B_0, T_2 decreases as B_0 increases. One can expect, therefore, that the IV contribution to the BOLD signal decreases with the increase of B_0. However, it is clear from previous and present studies that T_2 did not decrease as steeply at high fields (>7 T) [4, 13, 22]. This has strong implications in BOLD fMRI. Signals can be improved at high fields by using spin-echo acquisition because the intravascular venous signal is not visible at high field values [4]. Our finding suggests that going to higher field values may not result in further reduction of the intravascular venous signal per se, although BOLD contrast also increases overall.

Conclusion

This study analyzed the T_1 and T_2 values as a function of Y, Temp, and Hct of rat blood at 11.7 T. Over the ranges of physiological conditions investigated, change of arterial blood T_1 was negatively correlated with Hct (−883.7 ms per unit of Hct change), but positively correlated with temperature (51.8 ms/°C). T_2 change was negatively correlated with temperature (arterial T_2, −0.36 ms/°C), and was non-linearly correlated with Y and Hct. These results could have

implications in many physiological studies at 11.7 T [24–26], including CBF using ASL, CBV using VASO, OEF using TRUST, and high spatial specificity BOLD fMRI [4, 22].

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