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T1 and T2 values of human neonatal blood at 3T: dependence on hematocrit, oxygenation and temperature

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Abstract

Purpose—Knowledge of blood T1 and T2 is of major importance in many applications of MRI in neonates. However, to date, there has not been a systematic study to examine neonatal blood T1/T2 relaxometry. This present study aims to investigate this topic.

Methods—Using freshly collected blood samples from human umbilical cord, we performed *in vitro* experiments under controlled physiological conditions to measure blood T1 and T2 at 3T and their dependence on several factors, including hematocrit (Hct), oxygenation (Y) and temperature.

Results—The arterial T1 in neonates was 1825±184ms (Hct=0.42±0.08), longer than that of adult blood. Neonatal blood T1 was strongly dependent on Hct ($p<0.001$) and Y ($p=0.005$), and the dependence of T1 on Y was more prominent at higher Hct. The arterial T2 of neonatal blood was 191ms at an Hct of 0.42, which was also longer than adult blood. Neonatal blood T2 was positively associated with blood oxygenation and negatively associated with hematocrit level, and can be characterized by an exchange model. Neonatal blood T1 was also positively associated with temperature ($p<0.001$).

Conclusion—The values provided in this report may provide important reference and calibration information for sequence optimization and quantification of *in vivo* neonatal MRI studies.

Keywords

umbilical cord blood; longitudinal relaxation time; transverse relaxation time; blood oxygenation; hematocrit; neonate

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INTRODUCTION

Neonatal Magnetic Resonance Imaging (MRI) is playing an increasingly important role in studies of early brain development and disease (1–9). Knowledge of the longitudinal relaxation time (T1) and transverse relaxation time (T2) of neonatal blood is of major importance in many applications of MRI in neonates. For instance, blood T1 is critical for perfusion imaging using arterial spin labeling (ASL) techniques (1,2,6–8). ASL techniques use magnetically inverted blood signal as endogenous tracer to measure cerebral perfusion. So the value of blood T1 determines the decay rate of this blood tracer, and is important for absolute quantification of cerebral perfusion (10). On the other hand, blood T2 is important for BOLD-based techniques such as quantification of venous oxygenation and metabolic rate of oxygen (4,9). Since T2 relaxation time of the blood has a well-known and calibratable relationship with oxygenation (11), one can measure venous blood T2 *in vivo* and then convert T2 to oxygenation using the relationship characterized in the present study.

While the T1 and T2 relaxometry of adult blood have been well established at 1.5T (12–15), 3T (16–19) and 7T (20–22), there has not been a systematic study to examine T1 and T2 relaxometry of neonatal blood. Consequently, most neonatal MRI studies have assumed blood T1 values and T2-Y relationships based on those measured in adults (1,2,4,7–9). However, these assumptions might not be valid due to the unique composition of fetal hemoglobin, which is the major type of hemoglobin present in fetal and neonatal blood. Fetal hemoglobin is the main oxygen transport protein in the fetus during the last 7 months of development in the uterus, and remains present in the newborn until approximately 6 months after birth (23,24). Because it has a different molecular structure from adult hemoglobin, the T1 and T2 relaxometry properties of neonatal blood might be different from that of adult blood.

This present study intends to characterize blood T1 and T2 properties in neonates by conducting *in vitro* experiments on neonatal blood samples. Using freshly collected blood samples from human umbilical cord, we measured blood T1 and T2 and their dependence on common physiological factors such as hematocrit, oxygenation and temperature at 3T. The values provided in this report may provide important reference and calibration information for sequence optimization and quantification of *in vivo* neonatal MRI studies.

METHODS

Collection of cord blood samples

Nine blood samples were collected from the umbilical cord in the delivery room from healthy controls who had no maternal or perinatal risk factors and did not require any resuscitation. All neonates were full-term born with gestational age of 39.7±0.9 weeks, and were healthy with a cord pH of 7.23±0.05. The blood samples were collected as part of a larger-scale neonatal study and followed institutional and ethical guidelines at UT Southwestern Medical Center. Informed written consent was obtained from the parents of each neonate before the delivery.

The umbilical cord was doubly clamped at the time of delivery to isolate blood from the placenta. The blood was drawn from the umbilical vein and arteries with uncoated syringes at 10±1 min after delivery of the neonates. According to previous studies (25), the 10 min sampling time and double clamped cords ensure reliable cord blood sampling. About 3–4 mL of the cord blood was put into a heparin-coated tube and transported to the imaging center for MRI scans. All MRI studies were performed within 6 hours of the blood collection.

Blood preparation

To ensure that the results are physiologically relevant, the temperature of the blood sample during the MRI scan was maintained at 37°C using a water bath. Blood T1 and T2 values were studied as a function of hematocrit (Hct) and oxygenation (Y). The Hct and Y levels of the blood samples, were measured with a blood gas analyzer (ABL830, Radiometer America Inc, Westlake, OH). Y of the blood was modulated by exposing the blood to either room air or N2 gas, to increase or decrease Y, respectively. For each blood sample, 3 to 6 oxygenation levels were examined ranging from 25% to 100%. Given the small volume of blood available, it was not feasible to use a centrifuge to accurately adjust the Hct value. Therefore, Hct of the blood was modulated by extracting from either the top portion (more serum contained) or the bottom portion (more red blood cells contained) of the precipitated (after >2 hours) blood, to increase or decrease Hct, respectively. At each combination of Hct and Y values, blood T1 and T2 values were determined. In one sample, we also studied the temperature dependence of blood T1, by varying the sample temperature from 20 to 40°C in 5°C steps.

MRI measurements

All experiments were performed on a 3T MRI system (Achieva, Philips Medical Systems, Best, The Netherlands). To minimize precipitation of the blood during the experiment period, we ensured that each scan session is less than 4 minutes and the sample was manually agitated between sessions. For similar reasons, T1 and T2 measurements were performed in separate sessions. An inversion recovery imaging sequence was used for T1 measurements(16), with inversion times (TI) of 10, 50, 100, 250, 500, 1000, 3000, and 10000 ms (in randomized order), and a constant recovery time (RT) of 5000 ms (~ 3 T1). A single slice of 2 mm thickness at the mid-sagittal plane of the blood container was imaged. Due to the small amount of cord blood available, a small field of view (FOV) of 50×50 mm^2 was used. Other imaging parameters were: matrix size=52×27, 3-shot EPI, non-slice-selective adiabatic inversion pulse, and scan duration=2.75 min. A Carr-Purcell-Meiboom-Gill (CPMG)-T2 sequence with inter-echo spacing τ_{CPMG} of 10ms was used to measure blood T2 (18). The images with four different T2-weightings were acquired by placing 0, 4, 8, or 16 non-slice-selective preparation pulses before the excitation pulse, yielding effective TE (eTE) of 0, 40, 80 and 160ms, respectively. Other imaging parameters of the T2 measurements were: FOV=50×50 mm^2, matrix size=52×30, TR=3000 ms, 4-shot EPI, and scan duration=2.5 min.

Data analysis

T1 values were calculated by fitting the blood signals to the model given by:

$$S=\left|S_0\cdot\left\{1-\left[1+\alpha\cdot\left(1-e^{-\frac{RT}{T1}}\right)\right]\cdot e^{-\frac{TI}{T1}}\right\}\right|, \quad \text{Eq. [1]}$$

in which three parameters were estimated from the fitting, S_0, the equilibrium signal, α, the inversion efficiency, and the blood T1. An example of the T1 fitting is shown in Figure 1a.

Regression analyses were used to examine the relationship between blood 1/T1 (also known as R1) and Y, Hct and temperature. We clarify that, consistent with the convention of relaxation theory, we used R1 (or R2) in the model fitting. For display and plotting, however, we used T1 (or T2) to follow the clinical nomenclature. A multivariate regression analysis was performed to evaluate the interaction between Y and Hct on blood T1, with 1/T1 as dependent variable, whereas Y, Hct, and the interaction term, Y×Hct, as independent variables. This multilinear model was also used to generate a 3-D surface plot for visualization purposes.

For the T2 measurements, mono-exponential fitting of the blood signal to the four eTEs yields blood T2 values (Figure 1b), given by (26):

$$S=S_0\cdot e^{-\frac{eTE}{T2}}, \quad \text{Eq. [2]}$$

where S is the blood signal at a particular eTE, and S_0 is the equilibrium signal.

To establish an analytical relationship between T2, Y and Hct, the blood T2 was fitted to an spin-exchange model described by Golay et al.(13):

$$\frac{1}{T2}=A+B\cdot(1-Y)+C\cdot(1-Y)^2, \quad \text{Eq. [3]}$$

in which A, B and C are functions of Hct (18):

$$A=a_1+a_2\cdot Hct+a_2\cdot Hct^2, \quad \text{Eq. [4]}$$

$$B=b_1\cdot Hct+b_2\cdot Hct^2, \quad \text{Eq. [5]}$$

$$C=c_1\cdot Hct\cdot(1-Hct), \quad \text{Eq. [6]}$$

where the coefficients, a_1, a_2, a_3, b_1, b_2, c_1, are the outcomes of the model fitting that defines the relationship between T2, Y and Hct.

RESULTS

General results

The mean Hct level of our blood samples was 0.42±0.08, with a range of 0.25 to 0.51, which covers the typical range of neonatal Hct values (27).

Blood T1 and its dependence on Hct and Y

T1 of neonatal blood was strongly dependent ($p<0.001$) on Hct (see Figure 2a for the case of fully oxygenation blood, Y=0.97±0.03). Compared to adult blood, neonatal blood T1 was longer than that of adult blood (Figure 2a). Relevant for ASL quantification, at an Hct of 0.42, mean arterial T1 in neonate is 1825±184ms. Neonatal blood T1 was also found to be dependent on Y ($p=0.005$). Specifically, venous blood had a shorter T1 compared to arterial blood. There was also an interaction effect between Hct and Y ($p=0.04$). That is, the dependence of T1 on Y was more prominent in high hematocrit blood (Figure 2b) compared to plasma. Figure 2c shows the T1 measurements and the 3-D fitting using the multilinear model. According to the fitting, the relationship between neonatal blood T1, Y and Hct can be described by $\frac{1}{T1}=0.084\cdot Y+1.064\cdot Hct-0.490\cdot Y\cdot Hct+0.219$. We have also tested to use another nonlinear model, which is based on spin-exchange (20), but found that the fitting residual was greater than that using the multilinear model. The inversion efficiency, α, in the T1 measurements was 0.98±0.01.

Blood T2 and its dependence on Hct and Y

Figure 3a illustrates the relationship between neonatal blood T2, Y and Hct. The symbols indicate the experimental data points and the mesh shows the model-fitted surface described by Eqs [3–6]. The fitted coefficients in the model, a_1, a_2, a_3, b_1, b_2, c_1, are −1.1, 1.5, −21.4, −5.1, 29.4, and 242.9, respectively. These coefficients have no physiological meaning, but together they describe the relationship among blood T2, Y and Hct.

We report findings of T2 to be longer in arterial blood and in low hematocrit blood, which is expected since these types of samples contain low amounts of paramagnetic material. Furthermore, as can be seen in a 2D profile in Figure 3b, neonatal blood has a longer T2 than adult blood. At a typical Hct of 0.42, the arterial T2 of neonatal blood is 191ms, whereas the arterial T2 of adult blood is 147ms (18). Relevant for T2-based methods to estimate blood oxygenation (4,9), if one were to use the adult T2-Y relationship to calibrate in vivo neonatal T2 data, an overestimation in blood oxygenation is expected.

Temperature dependence of T1

Figure 4 shows that blood T1 is significantly correlated with temperature ($p<0.001$). Measurement of T1 at room temperature (20°C) resulted in an underestimation by 24% comparing to that measured at body temperature (37°C). Therefore, it is important to maintain the blood temperature at 37°C in *in vitro* experiments in order for the data to be applicable for *in vivo* studies.

DISCUSSION

The present work represents the first *in vitro* quantification of blood T1 and T2 relaxometry for neonates. Using healthy cord blood samples, we evaluated the dependence of neonatal blood T1 and T2 on hematocrit, oxygenation and temperature. Key study findings were that neonatal blood has longer T1 and T2 values than adult blood.

The blood T1 values reported in this work can be utilized in ASL-CBF quantification as well as in other MRI techniques requiring knowledge of blood T1, such as black blood MR angiography (28) and vascular space occupancy (VASO)-dependent fMRI (29). In recent years, there is a surging interest in the field to measure CBF in neonates using ASL techniques (1,2,5–8). Abnormal ASL-CBF was found to be associated with cerebral ischemia (1,2,8) and a worse neurodevelopmental outcome in neonates with hypoxic-ischemic encephalopathy (HIE)(6). However, inaccurate assumption or estimation of blood T1 could largely affect the accuracy of CBF quantification in neonates. To give a quantitative example, if adult arterial T1 of 1664ms (16) were to be used in ASL quantification for neonates, it would lead to an overestimation of CBF by 16%, using the widely accepted ASL biophysical model (10). Therefore, neonatal blood T1 is needed for future ASL studies in neonates.

The T2-Y relationship can be used to estimate blood oxygenation *in vivo* (12,13,26,30,31), which is essential for the quantification of an important index, cerebral metabolic rate of oxygen (CMRO2), a key marker of the brain's energy state and functional integrity. It is known that normal development of the brain at early stage is heavily dependent on the oxygen metabolism to support the escalating cerebral energy demands for the complex structural and functional maturational processes (32). Consequently, many of the neonatal brain injuries such as hypoxic ischemic encephalopathy (HIE) have been linked to a disruption of oxygen supply and metabolism (33). Therefore, the ability to measure CMRO2 in neonates may provide an important tool to diagnose brain injuries, bring mechanistic insights into the disease course, and guide therapy on an individual basis (34). Non-invasive MRI techniques have been proposed to measure blood T2 *in vivo*, and then convert blood T2 to blood oxygenation via the T2-Y calibration plot (12,13,26,30,31). Previous studies have demonstrated successful implementation of this principle in neonates (4,9). But since a neonatal-specific T2-Y relationship was not available, the adult T2-Y calibration plot was used in those studies (4,9). Therefore, the comprehensive neonatal T2-Y-Hct calibration plot established in the present work should allow the refinement of those results.

Recently, a few attempts to measure neonatal blood T1 and T2 *in vivo* have been reported. Verela et al. reported venous T1 of 1799±206ms, ranging from 1393 to 2035ms, in 18 neonates (2 termed control, 11 preterm, and 5 with neonatal encephalopathy) aged between 22 to 46 gestational weeks (35). In another study using Look-Locker ASL and model fitting, Verela et al. reported blood T1 between 1861 and 2094ms in 7 infants (gestational age 31.5–77.5 weeks), where 4 of them had pathological conditions (5). De Vis et al used a "T2 prepared tissue relaxation inversion recovery" (T2-TRIR) sequence to fit for both T1 and T2 of blood in the sagittal sinus (4). They reported venous T1 of 1818±67, 2005±149, 1838±157 and 1837±228ms, and venous T2 of 93±9, 77±13, 89±19 and 80±14ms in 5 preterm, 17 term, 11 HIE and 9 neonates with other conditions, respectively (4). The blood T1 and T2 values reported in the present *in vitro* study are in general agreement with those literature values, but represent a more systematical characterization of these MR parameters in relationship to carefully controlled hematocrit and oxygenation.

The dependence of neonatal blood T1 and T2 on hematocrit, oxygenation and temperature reported in this study are in line with previous studies using adult blood at various field

strengths(13,15,20,21,29,36). It appears that regardless of blood type and field strength, blood T1 and T2 values are higher with lower Hct and higher oxygenation. Blood T1 is also positively correlated with temperature If MRI scans are performed during hypothermia, a lower blood T1 value should be considered.

The neonatal blood T1 and T2 are longer compared to those reported in adults at 3T. This difference could be due to the presence of fetal hemoglobin in neonatal blood. Fetal hemoglobin (2 α chains and 2 γ chains) is structurally different from adult hemoglobin (2 α chains and 2 β chains), resulting in a higher oxygen binding affinity for the fetus to extract oxygen from maternal blood in the placenta. The difference in hemoglobin structure could result in the difference of MR relaxation times, since T1 and T2 are sensitive to the spin's environment. A higher affinity of fetal hemoglobin would mean that, at the same oxygenation level, neonatal blood contains less free, dissolved oxygen, which could result in higher T1 and T2. In addition, the volume of neonatal red blood cells is 21% larger than that of adult red blood cells (37). This size difference of red blood cells between adult blood and neonatal blood may also contribute to their MR relaxometry differences.

The findings of this study should be interpreted in view of a few limitations. First, we only evaluated neonatal blood T1 and T2 at 3T. According to previous reports (14–22,38), one can expect higher blood T1 and lower blood T2 values at higher field strength. The arterial-venous difference in T1 and T2 has a quadratic dependence on magnetic field strength, and thus the neonatal-adult difference in T1 and T2 might also be more pronounced at higher field strength. Future experiments are needed for accurate quantification of neonatal blood relaxometry at other field strengths. Second, in some blood diseases such as the sickle cell disease, the shape of the red blood cells is changed (24), which may cause changes in their blood T1 and T2. So the neonatal blood T1 and T2 values we reported might not be applicable in those disease conditions.

In conclusion, we determined neonatal blood T1 and T2 at 3T using human cord blood samples measured under physiological conditions. We established the relationships between hematocrit, oxygenation, and neonatal blood T1 and T2 values. The neonatal blood relaxometry characteristics reported in this work may serve as a useful reference for future *in vivo* studies aiming to assess hemodynamic function in neonates.

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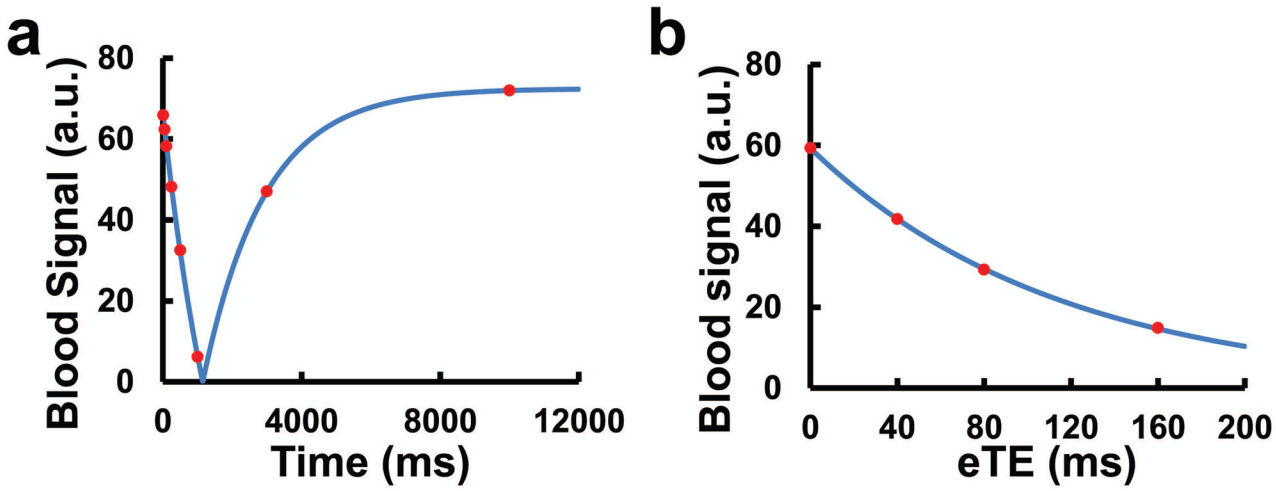

Figure 1.

Determination of blood T1 and T2. (a) Example of T1 fitting using Eq. [1]. (b) Example of T2 fitting using Eq. [2]. Red dots indicate measured value. Solid line indicates fitting curve.

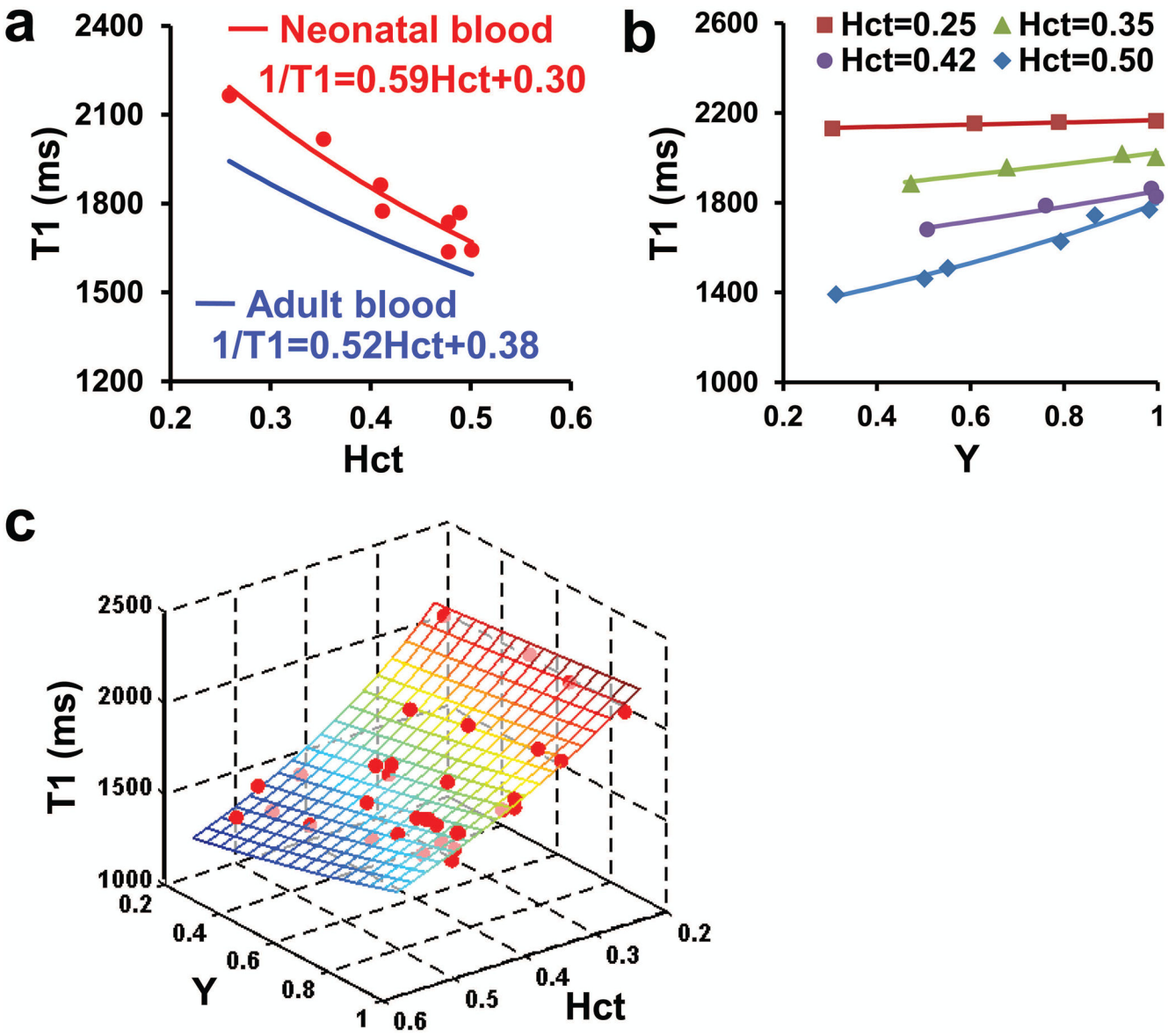

Figure 2.

Results of neonatal blood T1 measures. (a) Arterial T1 decreases with Hct level. Blood T1 is higher in neonates than in adults (16). (b) Neonatal T1 decreases with Y, and this decrease is more pronounced at lower Hct level. Symbols indicate measured T1 values. Solid lines are linear fitting curves. (c) 3-D fitting of the T1 results showing the dependence of T1 on Y and Hct.

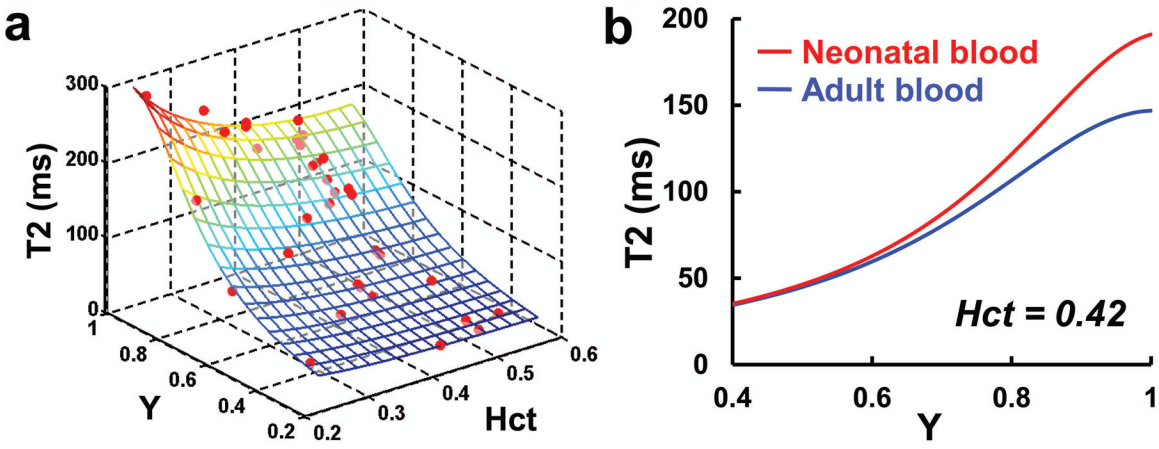

Figure 3.

Results of neonatal blood T2 measures. (a) 3D calibration plot showing the dependence of blood T2 on Y, and Hct at 3T, with τ_{CPMG}=10ms. (b) Neonatal blood T2 is different from adult blood T2 at Hct of 0.42 (18).

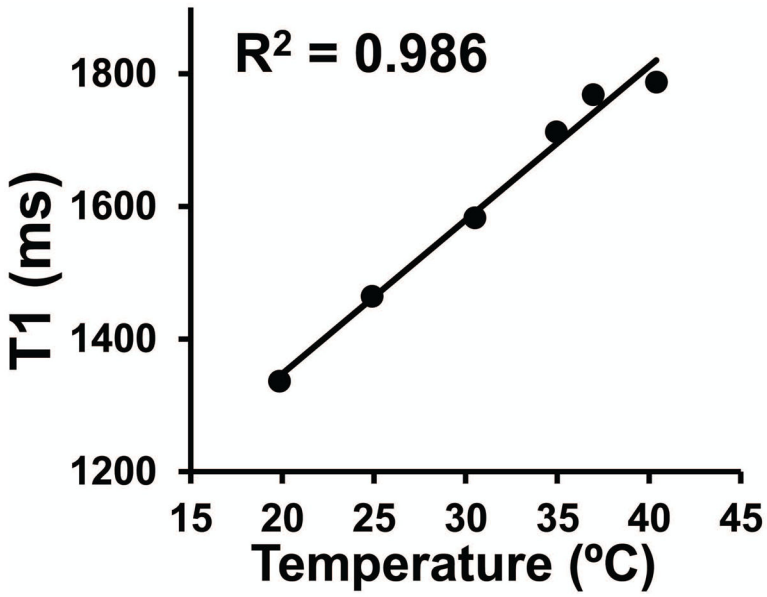

Figure 4.
Neonatal blood T1 increases with temperature. Symbols indicate measured T1 values. Solid line indicates linear fitting curve, given by y=23x+881.