

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

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7 **Abstract**

8 *Object* The goal of the study was to determine blood T_1
9 and T_2 values as functions of oxygen saturation (T), tem-
10 perature (Temp) and hematocrit (Hct) at an ultrahigh MR
11 field (11.7 T) and explore their impacts on physiological
12 measurements, including cerebral blood flow (CBF), blood
13 volume (CBV) and oxygenation determination.

14 *Materials and methods* T_1 and T_2 were simultaneously
15 measured with a RAREVTR sequence. Temperature was
16 adjusted from 25 to 40°C to determine Temp dependence;
17 Hct of 0.17–0.51 to evaluate Hct dependence at 25 and
18 37°C; and Y of 40–100% to evaluate Y dependence at 25
19 and 37°C. Comparisons were made with published data
20 obtained at different magnetic field strengths (B_0).

21 *Results* T_1 was positively correlated with Temp, inde-
22 pendent of Y , and negatively correlated with Hct. T_2 was
23 negatively correlated with Temp and Hct, but positively
24 correlated with Y , in a non-linear fashion. T_1 increased
25 linearly with B_0 , whereas T_2 decreased exponentially with
26 B_0 .

27 *Conclusion* The blood T_1 and T_2 values are important in
28 the determination of CBF and CBV, and the calibration of
29 the blood oxygenation level dependent (BOLD) signal.
30 These blood relaxation data could have implications in
31 numerous functional studies at 11.7 T.

Keywords BOLD fMRI · High fields · ASL · VASO · 32
TRUST 33

Introduction 34

The longitudinal relaxation time (T_1) and transverse relaxa- 35
tion time (T_2) of blood are important for a number of quan- 36
titative physiological and functional MRI measurements. For 37
example, blood T_1 is used to quantify cerebral blood flow 38
(CBF) using arterial spin labeling (ASL) techniques [1, 2]. 39
The accuracy of blood T_1 is crucial for cerebral blood volume 40
(CBV) determination using the vascular space occupancy 41
(VASO) method [3]. Blood T_2 is important in differentiating 42
between the extravascular and intravascular blood oxygen- 43
ation level dependent (BOLD) contributions [4]. Blood T_2 44
has also been used for calibration in determining tissue 45
oxygen extraction fractions (OEF) and the cerebral meta- 46
bolic rate of oxygen (CMRO₂), including the T_2 -relaxation- 47
under-spin-tagging (TRUST) techniques [5–8]. 48

T_1 and T_2 values of blood are dependent on hematocrit 49
content (Hct), oxygenation level (Y) and temperature 50
(Temp). These relationships have been extensively studied 51
at different magnetic field strengths from 1.5 to 7 T [1, 9– 52
11]. With the rapid growth of functional studies on high 53
field MRI scanners (>7 T) with animal models (especially 54
with rodents), similar measurements are necessary for 55
those high field systems in order to accurately determine 56
CBF, CBV, OEF, and optimize BOLD contrast under 57
various physiological conditions. To our knowledge, only 58
blood T_1 and T_2 dependence on Y has been reported up to 59
9.4 T [12, 13]. The goal of the present study was to 60
determine blood T_1 and T_2 values as functions of Hct, Y and 61
Temp, and explore their impacts on CBF, CBV, OEF and 62

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

66 Materials and methods

67 Blood sample preparation

68 Fresh blood samples were taken from male Sprague–
69 Dawley rats. Five rats (500–650 g body weight) were used
70 for the study. Rats were anesthetized for surgical prepara-
71 tion with 4.0% isoflurane for induction, and maintained
72 at a 2.0% isoflurane and air mixture using a face mask.
73 Body temperature was kept at 37°C via a heating pad. PE-
74 50 catheters were placed into the femoral artery and veins.
75 For each measurement, a vial of 1.0 ml blood (with heparin)
76 was taken from the rat (from either artery or vein, see
77 details in the following). Blood gases, Y , total hemoglobin
78 and temperature were measured with a blood gas analyzer
79 (Radiometer ABL5, Copenhagen). Vials were then sealed.
80 To minimize the error due to red blood cell precipitation,
81 the samples were agitated immediately before measure-
82 ment and the study time (preparation + scan) was
83 accomplished within 30 min. In the middle of the experi-
84 ment, blood samples were also taken out and agitated again
85 to minimize settling. Blood oxygenation was also measured
86 after the experiment.

87 MRI experiments and data analysis

88 Experiments were performed on an 11.7 T BioSpec MR
89 scanner (Bruker, Billerica, MA, USA). A quadrature vol-
90 ume coil (72 mm in diameter) was used for both RF
91 transmission and reception. T_1 and T_2 were simultaneously
92 measured using a RAREVTR sequence (RARE with vari-
93 able repetition time TR) sequence. The sequence used a
94 saturation scheme (i.e., varied TR) to acquire T_1 and used a
95 multi-echo CPMG scheme (i.e., varied TE) to acquire T_2 .
96 In the study, six TR values (208, 400, 800, 1,500, 3,000 and
97 3,500 ms) and five TE values (14, 42, 70, 98, and 126 ms)
98 were used. A single slice centered on the blood sample was
99 chosen. The region of interest (ROI) was chosen to cover
100 the blood sample area on the slice. Other imaging param-
101 eters were as follows: field-of-view (FOV) = 40 × 40 mm,
102 slice thickness = 1.0 mm, matrix size = 128 × 128 and
103 rare factor = 4. The total scan time was 3 min 46 s.

104 To evaluate temperature dependence, measurements
105 were made on arterial blood samples (Hct = 0.43 and
106 $Y = 98$ –99%) with temperature adjusted from 25 to 40°C
107 via a circulating water bath and monitored in real time by a
108 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%. Mea-
surements 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 $M(t) = M_0 [1 - c \times \exp(-TR/T_1)]$ and T_2 was cal-
culated by fitting $M(t) = M_0 \exp(-TE/T_2)$ using ParaVi-
sion 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 ($r = -0.95$, $P < 0.001$).

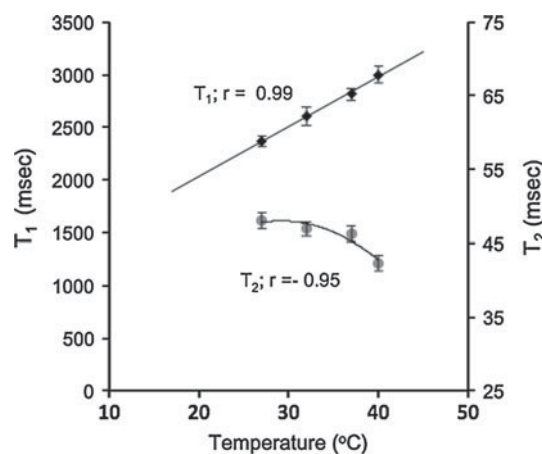


Fig. 1 Arterial blood T_1 and T_2 values as a function of temperature (25–40°C). T_1 was positively correlated with temperature ($r = 0.99$, $P < 0.001$). In contrast, T_2 was negatively, and non-linearly, correlated with temperature ($r = -0.95$, $P < 0.001$)

137 Study 2: Hematocrit level (Hct) dependency

138 A plot of arterial blood T_1 and T_2 ($Y = 99\%$ and
 139 Temp = 25 and 37°C) as a function of Hct is shown in
 140 Fig. 2. T_1 was negatively, and non-linearly, correlated with
 141 Hct at both temperature ($r = -0.99$, $P < 0.001$ at 25°C;
 142 $r = -0.94$, $P < 0.005$ at 37°C). Similar results were
 143 reported with bovine blood at 3 and 4.7 T [1, 9]. T_2 was
 144 also negatively correlated with Hct at the two temperatures
 145 ($r = -0.93$, $P < 0.001$, non-linearly, at 25°C; $r = -1.00$,
 146 $P < 0.0005$, linearly, at 37°C), consistent with that repor-
 147 ted at 3 T [14].

148 Study 3: Oxygenation level (Y) dependency

149 Figure 3 shows the plot of T_1 and T_2 versus Y with a normal
 150 hematocrit level (Hct = 0.43, Temp = 25°C and 37°C). T_1
 151 was not significantly correlated with Y ($r = 0.04$, $P > 0.5$
 152 at 25°C; $r = 0.02$, $P > 0.5$ at 37°C). This finding is con-
 153 sistent with those measured at lower fields [3, 12, 15, 16].
 154 T_2 was positively, and non-linearly, correlated with Y
 155 ($r = 0.95$, $P < 0.005$ at 25°C; $r = 0.97$; $P < 0.001$ at
 156 37°C). Arterial blood T_2 ($Y = 99\text{--}100\%$) was significantly
 157 longer than that of venous blood ($Y = 40\text{--}60\%$) at both
 158 temperatures (Table 1), in good agreement with literature
 159 [10, 13]. These findings indicate that there are strong T_2
 160 dependencies over the physiological Y ranges.

161 Study 4: Field strength (B_0) dependency

162 We compared our T_1 and T_2 results at 11.7 T to published
 163 data at other field strengths [3, 9–13, 15, 22, 23]. Figure 4a
 164 shows that both arterial and venous T_1 values ($T_{1(a)}$ and $T_{1(v)}$,
 165 respectively) are linearly dependent on B_0 ($T_{1(a)} = 133.98$
 166 T + 1,211.4, $r = 0.99$, $P < 0.001$, and $T_{1(v)} = 133.27$

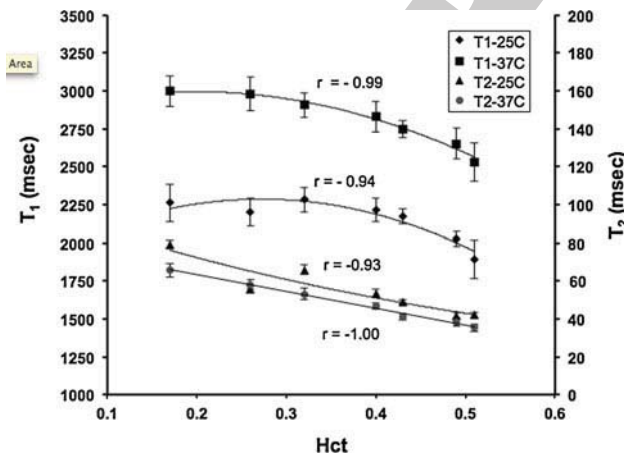


Fig. 2 Arterial blood T_1 and T_2 as a function of Hct (0.17–0.51) at 25 and 37°C. Both T_1 and T_2 decreased as Hct increased at both temperatures

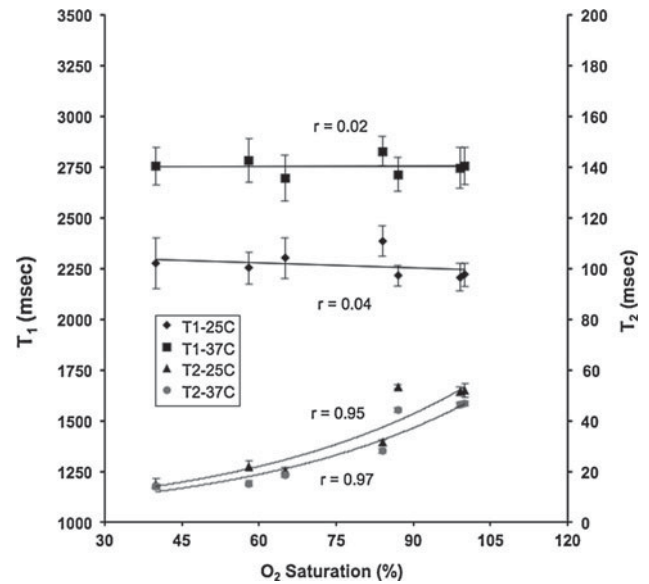


Fig. 3 Blood T_1 and T_2 values as a function of Y (40–100%) at 25 and 37°C. T_1 was independent of Y , while T_2 was positively, and non-linearly, dependent on Y at both temperatures

Table 1 T_1 and T_2 of arterial ($Y = 99\text{--}100\%$) and venous blood ($Y = 40\text{--}60\%$) 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

167 T + 1,187.4, $r = 1.0$, $P < 0.02$). Both arterial and venous
 168 T_1 values are linearly dependent on B_0 . Figure 4b shows $T_{2(a)}$
 169 and $T_{2(v)}$ decreased exponentially with B_0 ($r = -0.99$,
 170 $P < 0.001$ and $r = -0.90$, $P < 0.005$ for arterial and venous
 171 blood, respectively).

172 Discussion

173 Accurate blood T_1 is important for determining absolute
 174 CBF (with unit ml/g/min) with the following equation:
 175 $CBF = \lambda/T_1 [(SNL-SL)/(SL + (2\alpha-1)SNL)]$ (SNL and SL
 176 are signal intensities of the non-labeled and labeled images,
 177 respectively. α is the labeling efficiency, λ is the water
 178 tissue-blood partition coefficient) [17]. Based on the
 179 equation, one can estimate that quantitative CBF varies
 180 from -6 to 19% (-0.94–1.19 ml/g/min, respectively, with
 181 the assumed basal CBF of 1 ml/g/min at 37°C in rodents)
 182 across the four Temp points, and from -8 to 10% across
 183 the seven Hct levels at 37°C (assuming CBF baseline is
 184 Hct = 0.43).

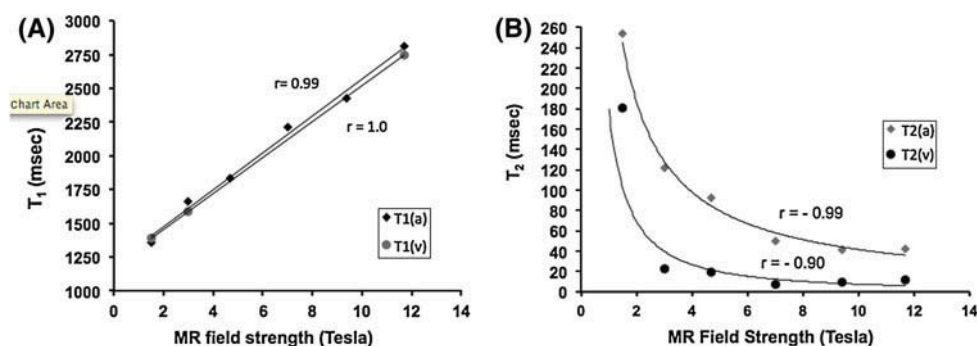


Fig. 4 **a** T_1 values of arterial and venous blood were both linearly dependent on B_0 . For arterial blood, $r = 0.99$, $P < 0.001$; data citation: 1.5 T [3]; 3 T [9]; 4.7 T [12]; 7 T [12]; 9.4 T [12]; 11.7 T [present study]. For venous blood, $r = 1.0$, $P < 0.02$; data citation: 1.5 T [3]; 3 T [9]; 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]

185 VASO signal changes are acquired at blood null point
186 (T_{1null}), which is determined based on the blood T_1 . VASO
187 signals will have blood signal contamination with inaccurate
188 T_1 values. Because changes in CBV are determined
189 from VASO signal [3], slightly changes in VASO signal
190 changes could result in dramatic difference in CBV changes.
191 For example, VASO changes from -1.2 to -3.7%
192 could result in CBV changes from 21 to 38%, respectively,
193 based on the model presented in [3]. Because CBV change
194 is an important parameter in determining cerebral $CMRO_2$
195 via the fMRI BOLD biophysical model [18–20], accurate
196 determination of CBV changes is important. A CBV
197 change from 21 to 38% would cause an error in $CMRO_2$
198 changes of 5–10%. Therefore, caution must be taken to
199 determine VASO changes when applying blood T_1 values
200 at various physiological conditions. Oxygenation level
201 does not significantly affect blood T_1 , suggesting that the
202 utilization of arterial or venous blood T_1 should not cause
203 significant differences for VASO determination.

204 Blood T_2 values, on the other hand, are highly dependent
205 on oxygenation level. This makes T_2 particularly useful for
206 quantitatively estimating Y . Several groups have used this
207 T_2 MRI approach to determine quantitative OEF ($=1-Y$)
208 and $CMRO_2$ ($=CBF \times OEF \times CaO_2$; where CaO_2 is the
209 oxygen content), including the TRUST techniques [5–8,
210 14]. MRI OEF and $CMRO_2$ data have been shown to be
211 consistent with those obtained by O-15 positron emission
212 tomography (PET), which is considered the gold standard
213 [21]. MRI OEF and $CMRO_2$ will likely have widespread
214 utility because they are totally non-invasive.

215 In addition to Y , blood T_2 values are also dependent on
216 Temp and Hct. It is interesting to see from Table 1 that
217 venous blood T_2 has a much lower T_2 at higher tempera-
218 tures, opposite to the trend of blood T_1 , and is more nega-
219 tively correlated with temperature than is arterial blood T_2
220 (Table 1). The Hct-dependent T_2 is an important factor for

221 calibrating OEF measurement since Hct could vary slightly
222 across individuals. All three parameters (Y , Temp and Hct)
223 are thus crucial for OEF and $CMRO_2$ determinations.

224 Blood T_2 also can be used to dissect the BOLD signal
225 contributions. The BOLD signal consists of an intravas-
226 cular (IV) and an extravascular (EV) component. The IV
227 BOLD component exists because blood deoxyhemoglobin
228 content strongly influences blood T_2 , as well as the sus-
229 ceptibility-induced frequency difference between blood
230 and surrounding tissue. At the same field strength (B_0), as
231 demonstrated in the study, the IV contribution to BOLD
232 signal should increase as Y increases, and decrease as Hct
233 and Temp increase. At different B_0 , T_2 decreases as B_0
234 increases. One can expect, therefore, that the IV contri-
235 bution to the BOLD signal decreases with the increase of
236 B_0 . However, it is clear from previous and present studies
237 that T_2 did not decrease as steeply at high fields (>7 T) [4,
238 13, 22]. This has strong implications in BOLD fMRI.
239 Signals can be improved at high fields by using spin-echo
240 acquisition because the intravascular venous signal is not
241 visible at high field values [4]. Our finding suggests that
242 going to higher field values may not result in further
243 reduction of the intravascular venous signal per se,
244 although BOLD contrast also increases overall.

245 Conclusion

246 This study analyzed the T_1 and T_2 values as a function of Y ,
247 Temp, and Hct of rat blood at 11.7 T. Over the ranges of
248 physiological conditions investigated, change of arterial
249 blood T_1 was negatively correlated with Hct (-883.7 ms
250 per unit of Hct change), but positively correlated with
251 temperature (51.8 ms/ $^{\circ}C$). T_2 change was negatively cor-
252 related with temperature (arterial T_{2a} , -0.36 ms/ $^{\circ}C$), and
253 was non-linearly correlated with Y and Hct. These results

254 could have implications in many physiological studies at
 255 11.7 T, including CBF using ASL, CBV using VASO, OEF
 256 using TRUST, and high spatial specificity BOLD fMRI.

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