Proton NMR Relaxation Times of Human Blood Samples at 1.5 T and Implications for functional MRI

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Short title: Relaxation times of human blood at 1.5 T

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ABSTRACT

To further investigate the dependency of fMRI signal changes on echo time TE, we measured T_2 and T_2^* values, obtained from human blood samples at various oxygenation levels and used them in a simple model to calculate signal enhancement in fMRI. In addition, the longitudinal relaxation time T_1 of human blood was determined for reference. All measurements were performed at 23°C to reduce blood cell metabolism during the measurement procedure. At 23°C $\mathbf{T_1}$ values of **1434±53 ms** for venous and **1435±48 ms** for arterial human blood were obtained after correcting for hematocrit content, as hematocrit values ranged from 28% to 34% only. The $\mathbf{T_2}$ relaxation times obtained are **181±23 ms** for venous and **254±26 ms** for arterial human blood, $\mathbf{T_2^*}$ relaxation times corrected for inhomogeneities of the static magnetic field (B_0) are **42±2.8 ms** and **254±32 ms**, respectively. Furthermore, the absolute and relative signal changes in fMRI experiments are calculated. The results from the model calculations reveal that contrast in fMRI can be optimised by choosing an appropriate echo time.

Keywords: human blood, relaxation times, T_1,T_2,T_2^*, fMRI**,** model calculations

INTRODUCTION

Contrast in functional magnetic resonance imaging (fMRI) mainly relies on changes in regional cerebral blood flow and blood oxygenation level, however, the relative contributions of the respective effects to observed signal changes are still under debate. As they are not independent from each other, it has not been possible yet to separate flow and blood oxygenation level dependend (BOLD) effects in gradient-recalled echo fMRI quantitatively *in vivo*. However, the latter effect alters the transverse relaxation time (T_2) and the apparent transverse relaxation time (T_2^*) of human blood (throughout the paper relaxation times as well as relaxation rates ($R_X=1/T_X$) will be used depending on which are more instructive). Therefore, the dependence of human blood T_2 and T_2^* relaxation times on oxygen saturation is of some importance in functional brain mapping by fMRI. One possible approach for a better understanding of the BOLD effect in fMRI is to measure relaxation times of human blood *in vitro* (i.e. at the same field strength, and with a comparable shim and hardware performance many *in vivo* fMRI studies have been performed) and to extrapolate to *in vivo* conditions by means of a theoretical model without including the problems of movements artefacts. Furthermore, functional contrast depends on the echo time chosen in the actual fMRI experiment and may be used to differentiate (large) venous vessel "activation" from cortical activation (Kim et al, 1994).

MATERIALS AND METHODS

Blood Samples

Arterial and venous blood samples of a total of nine subjects (age: 30-70 years, both sexes) were taken into a heparin coated vacutainer with an inner diameter of 13 mm. The fraction of oxygenated red blood cells (blood oxygenation level Y or HbO_2 level) and hematocrit fraction were determined before and after the MRI-measurement with a clinical hemoximeter ABL 330 or ABL 912 (ABL LIST GesmbH, Austria) using the partial oxygen pressure and total hemoglobin value at 37°C. Immediately after the determination of the blood gas values the two tubes containing (arterial and venous) blood were placed in a test tube holder inside the MR-Imager.

Reference substances

Three reference tubes containing deionised water with various concentrations of manganese chloride (0.05mM and 0.08mM $MnCl_2$ solution) and/or an aqueous solution (0.072mM) of the contrast agent Magnevist®, a commonly used contrast agent in clinical MR-investigations, were put into the test tube holder together with the two blood sample tubes. The respective concentrations were chosen to obtain relaxation times very similar to those of human blood.

MRI experiments

All measurements were performed on a MAGNETOM SP4000 (SIEMENS Inc.,Germany) clinical whole body system operating at 1.5 Tesla using a standard circular polarized head coil. This setup is used in order to be closest to the one used for *in vivo* fMRI experiments (e.g. Gomiscek et al, 1993; Moser et al, 1995). It is especially important to use the same magnetic field strength as relaxation times of blood (T_1/T_2) measured at room temperature show a 4/10 fold variation with B_0 varying from 10-500 MHz (see Stadelmann et al, 1991). The sample holder standing in a bath of a 0.16 mM solution of $MnCl_2$ (to soften susceptibility differences at the blood-air surface and dephasing near the menisci of the tubes) was placed inside a cylindrical pipe which fit into the head coil. A transverse slice of 6 or 8 mm was selected along the axes of the tubes, in order to gain the maximum signal from the sample tubes. The $MnCl_2$ bath was kept at constant temperature of about 23±1°C throughout the whole measurement to reduce blood cell metabolism during the measurement procedure compared to 37°C.

T_1 was determined using a saturation recovery sequence with four different repetition times (TR=4000, 2000, 1000 and 500 ms) and a TE of 15 ms. T_2 was measured with a multiple spin echo sequence (TR=4000 ms; TE=25-495 ms, echo delay of 15 ms, n_{echo}=32). Matrix size was 128x128 and the FOV was 200 mm.

A multiple gradient echo sequence applying 25 gradient echoes with two different repetition times was used to measure T_2*. The flip angle used was 40°. Echo times range from 4 ms to 119 ms (echo delay: 4.6 ms) for the shorter

repetition time (146 ms) and from 4 ms to 500 ms (the echo delay increases from 4.6 ms to 100 ms within one echo train) for the longer repetition time (507 ms), respectively. The two different repetition times are used in order to improve the fitting accuracy for the short (e.g. of blood sediment) as well as for the longer T_2^* relaxation times (e.g. of blood plasma). The other sequence parameters are: matrix size of 128x128 pixels, quadratic field of view of 200 mm, r.f. flip angle α of 40°, readout bandwidth of 300 Hz/pixel. The measurement time for the T_2^* measurement was 20 seconds for the short repetition time and 80 seconds for the longer one. Total measurement time for one blood sample set (= one experiment) was less than four hours including shimming.

Data evaluation

The MR images were evaluated with a fitting program based on the IDL software package (Research Systems Inc., Boulder, CO). The number of pixels included in a ROI exceeded 70 in order to obtain a reasonable mean signal intensity for the fitting procedure. The position of the ROI within the tubes was controlled for each echo time in order to eliminate partial volume effects of tube or fluid surfaces. The ROI was therefore always smaller than the inner tube diameter of 13 mm. The pixel intensities of this ROI were averaged over this area for each echo time and fitted using a single-exponential least square fitting procedure as Meyer et al (1995) reported that single-exponential fits perform much better than bi-exponential algorithms applied to blood data.

Magnetic field homogeneity

$\boldsymbol{B_0}$ inhomogeneities influence the accurate estimation of (blood) T_2^*. This is indicated by the following equation:

$$R_2^* = R_2 + R_2' \quad \text{with} \quad R_2' = R_2'_{shim} + R_2'_{cells} \tag{1}$$

R_2' reflects the influence of magnetic field variations, in this case either caused by B_0 inhomogeneities ($R_{2'shim}$) as well as by (deoxygenated) blood cells ($R_{2'cells}$). Fully oxygenated blood is only slightly diamagnetic (Weisskoff and Kiihne, 1992) and $R_{2'cells}$ for arterial blood is therefore small. The difference in R_2 and R_2^* relaxation times of arterial blood should therefore be dominated by $R_{2'shim}$. Thus, $R_{2'shim}$ may be obtained from R_2 and R_2^* of arterial blood using eq. 1. Subsequently, eq. 1 may then be used to calculate corrected R_2^* values of venous blood, i.e. without the influence of B_0 inhomogeneities.

Implications for fMRI at 1.5 Tesla

In order to demonstrate implications for fMRI of the brain, the data obtained during the *in vitro* study of human blood have been used in model calculations of fMRI signal enhancement. As the MR signal decays exponentially with time, the relaxation times of venous and arterial human blood can be used for calculating the remaining voxel signal as a function of echo time. The signal difference at a certain echo time is proportional to the fMRI signal enhancement between rest and stimulation, at least in voxels containing 100% blood. This simple BOLD-based model already described by Menon et al (1993) is used to describe absolute (ΔS, eq. 2) and relative signal enhancement ($\Delta S/S$, eq. 3), respectively:

$$\Delta S = S_0 \cdot (\exp(-TE / T_2^*_{stim}) - \exp(-TE / T_2^*_{rest})) \tag{2}$$

$$\begin{aligned} \Delta S / S &= \Delta S / (S_0 \cdot \exp(-TE / T_2{}^*_{rest})) = \\ &= \exp(-TE \cdot (R_2{}^*_{stim} - R_2{}^*_{rest})) - 1 \end{aligned} \tag{3}$$

S_0 is the voxel signal intensity at echo time TE=0. $T_2{}^*_{rest}$ is the $T_2{}^*$ value of human blood under resting conditions (i.e. no stimulation) and $T_2{}^*_{stim}$ is the $T_2{}^*$ value during stimulation ($R_2{}^*_{stim}$ and $R_2{}^*_{rest}$ are the inverse of $T_2{}^*_{stim}$ and $T_2{}^*_{rest}$).

The optimum echo time (TE_{opt}) for fMRI-contrast may be calculated via the maximum absolute signal, thus TE_{opt} is obtained by differentiation of Eq. 2:

$$TE_{opt} = (R_2{}^*_{rest} - R_2{}^*_{stim})^{-1} \cdot \ln(R_2{}^*_{rest} / R_2{}^*_{stim}) \tag{4}$$

RESULTS

Relaxation times

T_1 and T_2 relaxation times of human blood *in vitro* are given in the row 'whole blood' in Tab. 1. Measured T_2 relaxation times (Fig. 1; open circles) clearly increase with higher oxygen saturation, as expected, and show the same dependence on HbO_2 level as given by Wright et al (1991) (see Fig. 1; solid line shows the fit obtained by Wright et al, 1991).

T_1 relaxation times of hematocrit and plasma (obtained from sedimented blood) were used in the two-compartment fast-exchange model proposed by Zimmerman and Brittin (1957), which can be adapted very well for blood (Fullerton and Cameron, 1988) to calculate "whole blood" relaxation times. These calculated relaxation times (see Tab. 1) are in reasonble agreement with measured whole blood values. This model is therefore used to correct hematocrit depending T_1 values in order to obtain data which may be compared quantitatively to similar studies (see Tab. 3; corrected T_1 values are indicated with an asterisk). T_1 and T_2 relaxation times obtained for reference solutions (also given in Tab. 1) show only small variations and are close to those for human blood. They are therefore used to control reproducibility between different experiments.

T_2^* relaxation times of human blood as well as of reference solutions are given in Tab. 2. As mentioned above, T_2^* values are very sensitive to $\boldsymbol{B}_0$ inhomogeneities. This may be seen from the short T_2^* relaxation times of the reference solutions, compared to corresponding T_2 values, and from the high standard deviations of T_2^* values, compared to those of T_1 and T_2 values.

In order to get a better estimate of T_2^* relaxation times of whole blood, three experiments were performed, where both T_2 and T_2^* values were measured and T_2^* values of whole blood were corrected with $R_{2'shim}$ as derived from arterial T_2^* values and eq. 1 (see Tab. 2). Corrected T_2^* values are significantly higher and show a much smaller standard deviation than the uncorrected ones (see also Fig.1; open squares = corrected T_2^* values for oxygenated and deoxygenated human blood).

From a particular experiment the dependence of relaxation time versus increasing oxygen saturation can be shown more clearly. T_2^* measurements were performed at the beginning and repeated after several hours when blood oxygenation already changed due to the slow continuation of blood cell metabolism (note: HbO_2 level was determined immediately before and after MRI measurements). T_2^* data (corrected as described above) are shown in Fig. 1 (open triangles). The dashed line shows the (least squares) fit using the model proposed by Wright (1991):

$$R_2^* = 3.9 + 351 \cdot (1 - Y)^2 \qquad (5)$$

DISCUSSION

Relaxation times

So far, only a few reports on human blood T_1 and T_2 at 1.5 T exist (Gomori et al, 1987; Wright et al, 1991; Stadelmann et al, 1991) and only one single study reports T_2*-values (Chien et al, 1994), with no T_2 reference values given.

We obtained highly reproducible T_1 values (relative SD ≤ 5%) from blood samples and reference solutions. In agreement with human blood data (Wright, 1991; Stadelmann, 1991) and rat blood measurements of Thulborn et al (1982), this parameter is not sensitive to different blood oxygenation levels. However, T_1 is depending on parameters like magnetic field strength (Stadelmann, 1991), temperature (Stadelmann, 1991) and hematocrit content (Fullerton and Cameron, 1988). Due to the use of anticoagulants blood hematocrit value is lower compared to average hematocrit values which normally range between 42% (female) and 47% (male) in large vessels (Miale, 1982). In order to obtain T_1 values which can be compared quantitatively with published data, it is necessary to correct for hematocrit content. This may be done by using an average hematocrit value of 45% in the two compartment fast exchange model mentioned above. The T_1 values are then in reasonable agreement with published data. A comparison of T_1 relaxation times obtained in this study (corrected T_1 data are indicated by an asterisk) with published data, measured under similar general conditions, is summarized in Tab. 3. However, Gomori et al. (1987) found a variation depending on the oxygenation level (T_1 (100% HbO_2) = 1180 ms and T_1 (0% HbO_2) = 1300 ms), which is not in agreement with

data obtained by us and others (Thulborn, 1982) and cannot be explained by them.

Highly reproducible T_2 values could be obtained from reference solutions (relative SD < 2%, except Magnevist®: relative SD = 7%; see Tab. 1). Due to different HbO_2 levels of blood samples, T_2 standard deviations are larger than that of reference solutions, but also show good reproducibility (relative SD ≤ 13%; see Tab. 1). As can also be seen from Tab. 1, T_2 relaxation times are shorter for venous than for arterial blood, which is due to the diffusion of hydrogen through magnetic field gradients generated by paramagnetic deoxyhemoglobin. This is true for whole blood as well as for blood sediment. Based on the data presented (see Tab. 3) and the fact that T_2 is not very sensitive to changes in hematocrit, temperature and field homogeneity, it is a perfect reference for data comparison. The temperature dependence found by Stadelmann (1991) at 42 MHz shows a T_2 increase of only 10% with temperature increasing from 23°C to 37°C.

T_2^* relaxation times show a stronger dependence on oxygenation level than T_2. This is due to dephasing of spins in regions of local magnetic field inhomogeneities caused by paramagnetic deoxyhemoglobin of venous blood. The reproducibility of T_2^* relaxation times is poor as they are very sensitive to B_0 inhomogeneity. This may be one reason why published T_2^* data of human blood are sparse and, furthermore, T_2^* data which depend on the actual shim-status are not very valuable. However, if T_2 values are measured in addition to T_2^* relaxation times, it is possible to account for deviations caused by B_0 inhomogeneities and it is shown here that the correction algorithm applied increases reproducibility dramatically. Recently, Chien et al (1994) obtained *in*

vitro T_2^* relaxation times of 70, 95, and 185 ms for oxygenation levels of 73.6%, 82.5%, and 98.4%, respectively (see also Tab. 3; corrected T_2^* values obtained in this study are indicated by an asterisk). *In vivo* they found T_2^* values of 142±30 ms and 241±6 ms for oxygenation levels of 70% and 100%, respectively. Obviously, their data are not very consistent. The differences between their and our findings can probably be explained by the huge time spacing they use between gradient echoes (20 ms seems to be rather long for the T_2^* expected) and by the, therefore, small number of echoes recorded. In addition, the measurement temperature was higher (37° C).

Calculated "whole blood" values from this study are in good agreement with the results of real whole human blood except when diffusion through large magnetic field gradients and $\boldsymbol{B_0}$ inhomogeneities play a role (i.e. venous T_2 and T_2^* values), which is not considered in the simple two compartment fast exchange model.

Implications for fMRI at 1.5 Tesla

Eq. 5 may be used to calculate T_2^* relaxation rates at HbO_2 levels estimated by *in vivo* fMRI experiments in large venous vessels (Haacke et al, 1995; Haacke, submitted). There, a Y of 0.55 has been found at resting conditions, which increases by 0.15 during stimulation, resulting in a $T_2^*_{rest}$ of 13.4 ms and a $T_2^*_{stim}$ of 28.2 ms. Taking these numbers into eqs. 2 and 3 we may estimate absolute and relative signal increase to be expected in fMRI at 1.5 T. Model calculations for a gradient echo sequence are given in Figs. 2 and 3, together with the results for a spin echo sequence, again using Wright's model and corresponding T_2 values (i.e. T_{2rest} of 112 ms and a T_{2stim} of 163 ms). The

optimum echo time (TE_{opt}) calculated via eq. 4 is 19 ms for the gradient echo sequence and 134 ms for the spin echo sequence, too long to be of practical use. As shown in Fig. 3, $\Delta S/S$ increases exponentially with increasing echo time in gradient echo fMRI, whereas $\Delta S/S$ contributions originating from a spin echo sequence can hardly be recorded at 1.5 T.

Fitting T_2^* values obtained from our *in vitro* study of human blood with the model of Wright et al (1991) we assume that T_2^* and T_2 values of fully oxygenated blood are equal. This assumption seems to be very reasonable as we observe a dramatic reduction of standard deviations of T_2^* values of venous blood (i.e. from 19% to 7%) after the correction applied. In addition, a quite large reduction of T_2 values of fully oxygenated blood (in case that the weak diamagnetism might reduce T_2^*) results in only minor changes of T_2^* values used in the calculation of fMRI signal changes.

A comparison of $\Delta S/S$ calculated with the model proposed here and fMRI data measured at various echo times with the same equipment, shows very reasonable agreement (Barth et al, 1996). $\Delta S/S$ at echo times frequently used in fMRI studies at 1.5 T (i.e. 40 to 60 ms) is about 5% to 10%, a range of signal enhancements which were also obtained in various systematic studies (e.g. Haacke et al, 1994; Moser et al, 1996). But at very long echo times ($\geq$ 130 ms) this simple model cannot account for mechanisms like signal dephasing due to partial volume effects (Haacke, 1996). This effect is one reason why the use of very long echo times does not automatically increase signal enhancement in fMRI (Barth, 1996). In addition, as the most relevant parameter in fMRI postprocessing is contrast to noise ($\Delta S/N$), it may be more important to optimize the echo time to maximum absolute signal (ΔS). The optimum echo

time at 1.5 Tesla (TE_{opt}) estimated with this model is 19 ms, but this accounts only for voxels with 100% blood. In case that other tissue, e.g. gray matter, is picked up within the same voxel, TE_{opt} should be longer. Thus, as empirically chosen in most gradient echo fMRI studies at 1.5 T, it is preferable to use echo times longer than 40 ms when fMRI signal changes from the small vessel network in the human cortex are the target.

On the other hand, only extremely long TE's may reveal cortical activation at 1.5 T. In a comparative study (Kim, 1994) it was shown that only "activated" vessels would be detected with short (TE = 10-20 ms) echo times at 4 T. Only if TE was increased to 30-60 ms, vessels and cortical activation could be detected. For gradient echo fMRI at 1.5 Tesla this would imply to chose TE's of about 70-140 ms. To our knowledge only one single study has been performed successfully at 1.5 T (Barth et al, 1997 in press) as SNR and magnetic field inhomogeneities are extremely critical.

In summary/conclusion we could show that (a) relaxation times of human blood at 1.5 T may be measured with reasonable accuracy in a clinical scanner, (b) after proper correction *in vitro* T_2^* relaxation times of human blood may be used to estimate fMRI signal enhancement at 1.5 T, and (c) very long echo times may be advantageous for detecting "cortical" activation at 1.5 T. In contrast to other published work so far we measured T_1, T_2 and T_2^* relaxation times of the same human blood sample at different oxygenation levels *in vitro* and, therefore, are able to estimate blood signal changes occurring in *in vivo* fMRI studies quantitatively.

Acknowledgments: The cooperation with the Department of Anaesthesia (Prof. M. Zimpfer), General Hospital Vienna, which provided the blood samples, is acknowledged. Mr. L. Schachinger has skillfully produced the sample holders. This study was financially supported by the Austrian Science Foundation (grant P10091-Med).

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	T_1 [ms]		T_2 [ms]	
	venous	arterial	venous	arterial
whole blood	**1582±35 (n=6)**	**1585±69 (n=5)**	**181±23 (n=3)**	**254±26 (n=3)**
blood sediment	982±50 (n=5)	990±53 (n=5)	121±6 (n=5)	137±19 (n=5)
blood plasma	2308±89 (n=5)	2277±67 (n=5)	419±79 (n=5)	416±77 (n=5)
calculated values	1622±68 (n=4)	1622±68 (n=4)	235±15 (n=5)	253±31 (n=5)
$MnCl_2$ (0.05 mM/l)	1359±79 (n=7)		184±4 (n=7)	
$MnCl_2$ (0.08 mM/l)	1304±31 (n=5)		185±4 (n=7)	
Magnevist (0.072 mM/l)	1456±141 (n=7)		221±16 (n=8)	

Tab. 1: T_1 and T_2 Relaxation times of venous (HbO_2 = 71.9±2.6%) and arterial (HbO_2 = 96.7±1.6%) human blood samples (n = number of samples), as well as those of reference substances measured at 1.5 T and 23° C. Data presented are mean values ± one standard deviation.

	T_2*[ms]	
	venous	arterial
whole blood (n=5)	**26±6 (23%)**	**71±28 (39%)**
blood sediment (n=6)	21±8	37±18
blood plasma (n=6)	63±33	52±31
calculated values (n=6)	39±17	46±26
uncorrected whole blood (n=3)	28±5 (18%)	71±33 (46%)
corrected whole blood (n=3)	**42±3 (7%) ***	**254±32 (13%) ***
$MnCl_2$ (0.05 mM/l) (n=11)	60±35	
$MnCl_2$ (0.08 mM/l) (n=11)	58±31	
Magnevist® (0.072 mM/l) (n=7)	35±7	

Tab. 2: T_2* relaxation times of venous and arterial human blood samples at the same HbO_2 levels as indicated in Tab. 2, as well as those of reference substances measured at 1.5 T and 23° C. Corrected data are indicated by an asterisk. Data presented are mean values ± one standard deviation (n =number of samples).

	HbO_2 [%]	T [°C]	ω_0 [MHz]	T_1 [ms]	T_2 [ms]	ΔTE [ms]	T_2* [ms]	ΔTE [ms]	n
Gomori et al (1987)	0	20	60	1300	140	4	-	-	2
	100	20	60	1180	210	4	-	-	2
Wright et al (1991)	70	37	63.3	-	183	12	-	-	5
	96	37	63.3	-	252	12	-	-	5
Stadelmann et al (1991)	venous	20	63.3	1470	146	3	-	-	some
Chien et al (1994)	73.6	37	63.3	-	-	-	70	20	8
	98.4	37	63.3	-	-	-	185	20	8
This study	71.9	23	63.3	1434*	181	15	42	4.6	3-6
	96.7	23	63.3	1435*	254	15	254	4.6	3-6

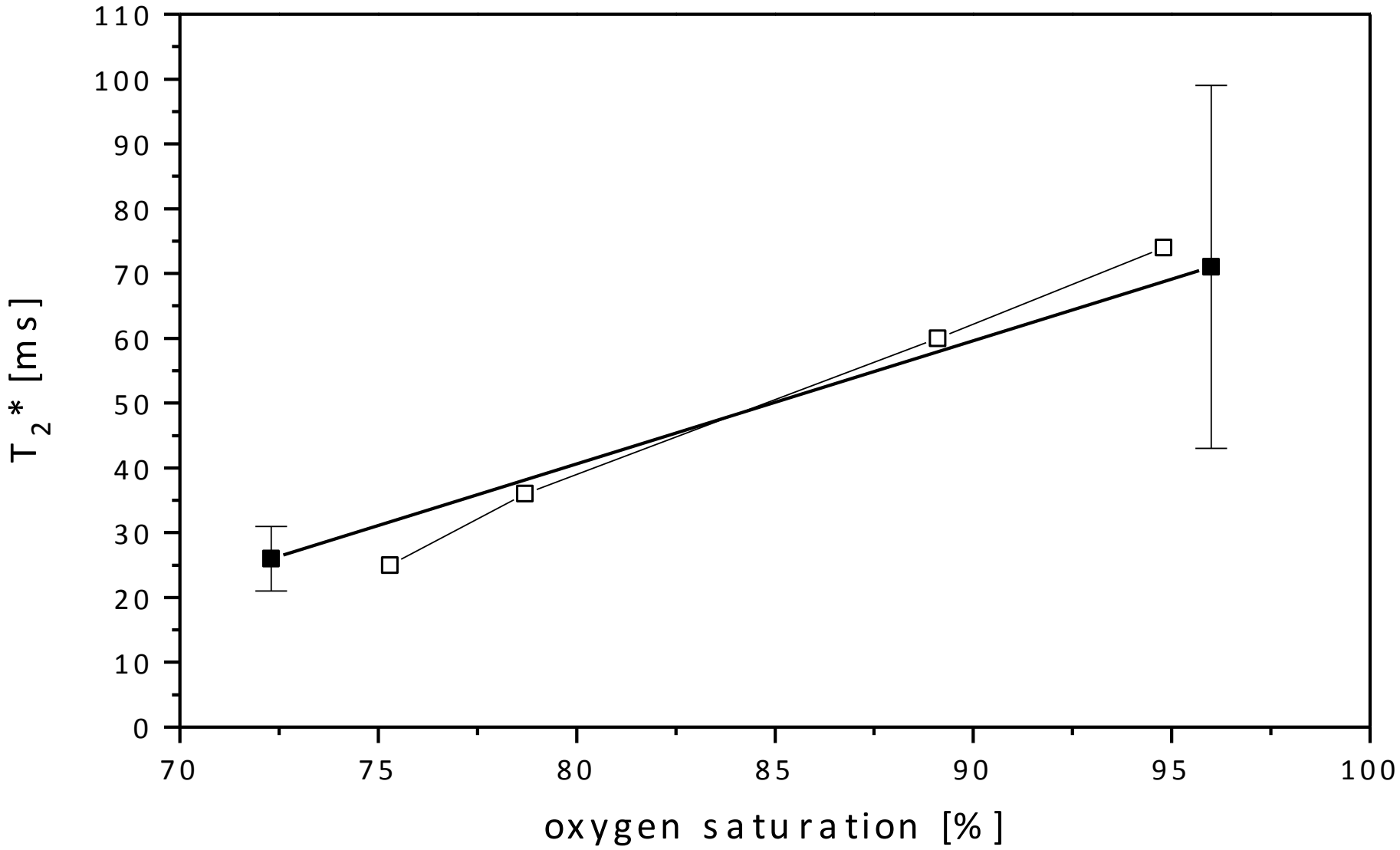
Tab. 3: Comparison of human blood relaxation times obtained at about 60 MHz. The asterisk denotes that T_1 values were corrected for normal *in vivo* hematocrit content as described in the text.

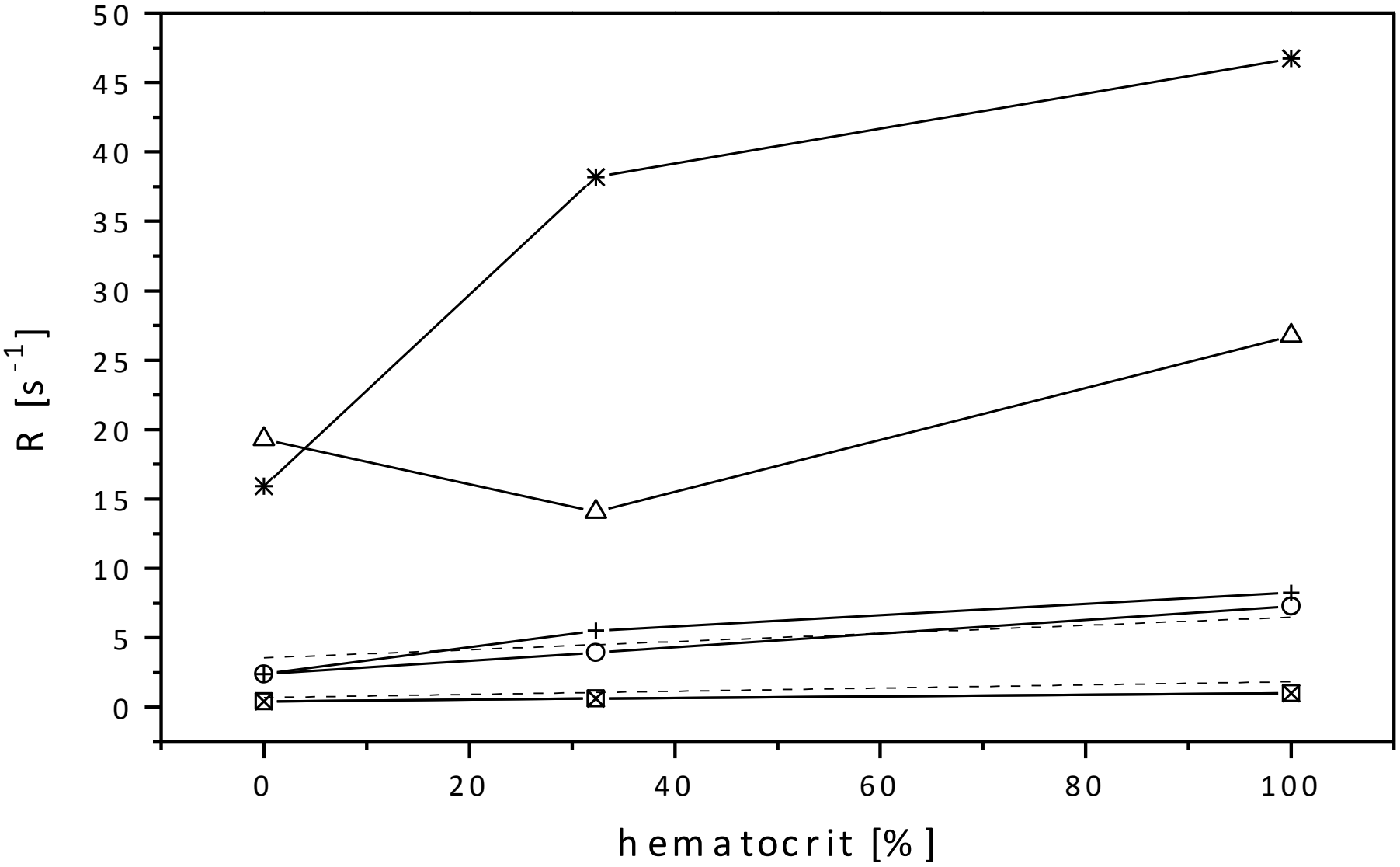
Figure Captions

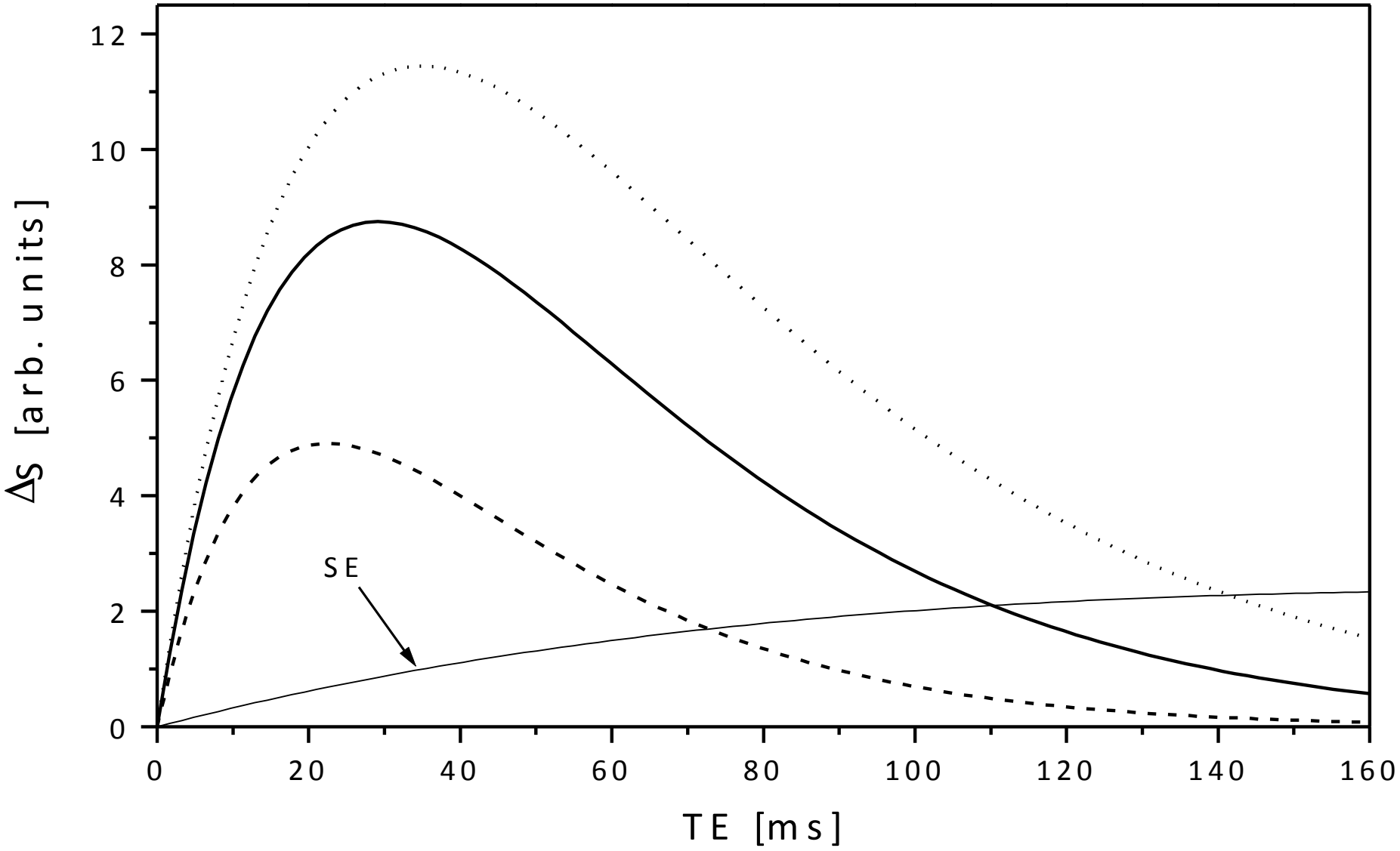
Fig. 1: Dependence of T_2 (open circles ± SD) and T_2^* relaxation times on oxygenation saturation of human blood *in vitro*. The solid line represents the fit to T_2 values obtained by Wright et al (1991). Data presented as open squares are average T_2^*-values (n=5) with error bars indicating one standard deviation. Open triangles show T_2^* data obtained from one single blood sample for comparison. Dashed line results from fitting the Wright model to the corrected *in vitro* blood T_2^* data obtained from this blood sample.

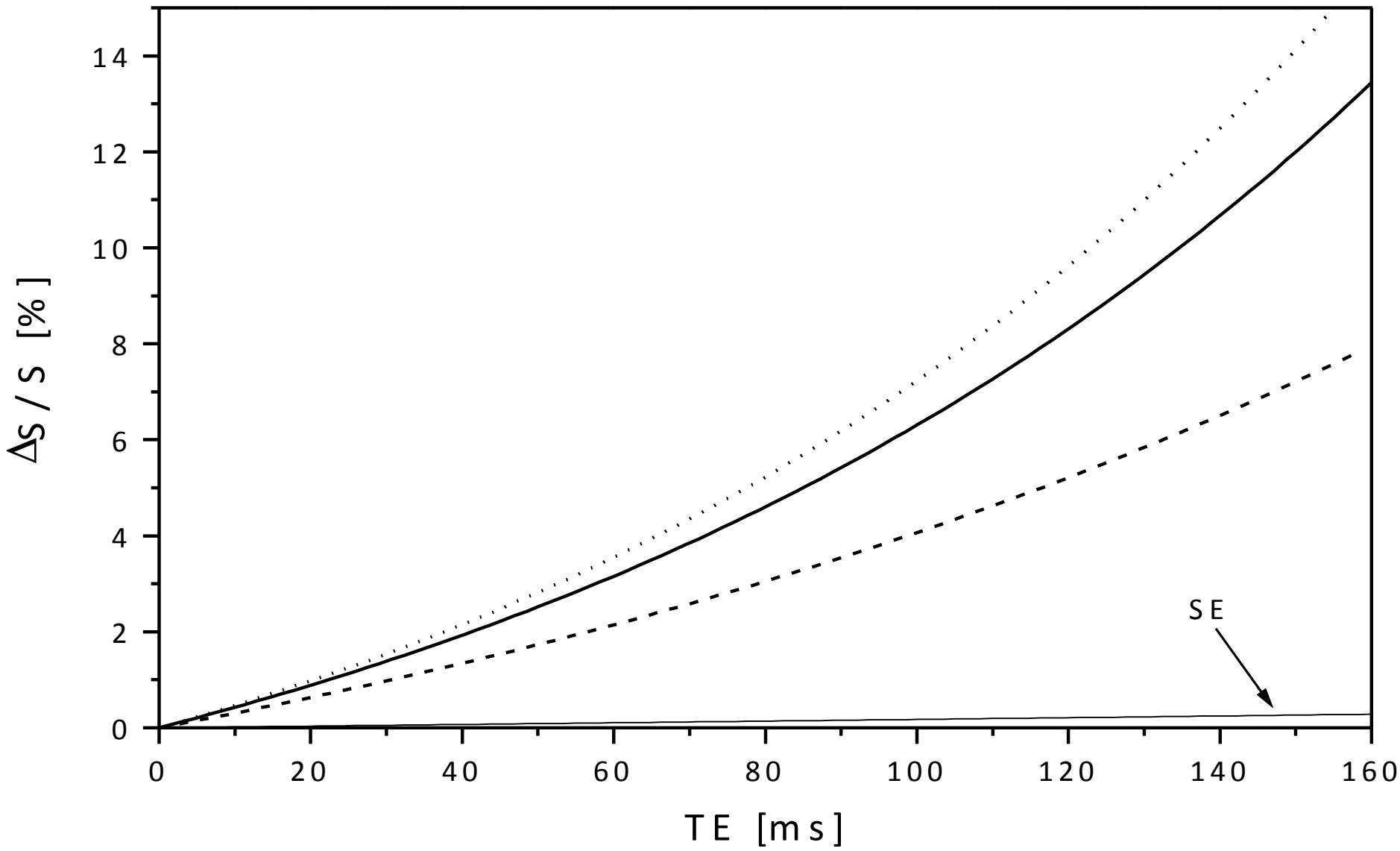
Fig. 2: Absolute signal increase (ΔS) expected from BOLD in fMRI experiments at 1.5 T. Data shown assume that the voxel is filled 100% with blood. ΔS was calculated using Eq. 2 with T_2^* values obtained from eq. 5. The solid line shows ΔS of gradient echo fMRI ($T_2^*_{rest}$= 13.4 ms, $T_2^*_{stim}$= 28.2 ms), whereas the dashed line shows ΔS of spin echo fMRI (T_{2rest} = 112 ms, T_{2stim} = 163 ms).

Fig. 3: Relative signal increase ($\Delta S/S$) expected from BOLD in fMRI-images at 1.5 T, calculated by using Eq. 2 with the same relaxation times values as for ΔS (Fig. 2). Again, the solid line indicates the expected signal increase obtained from a gradient echo experiment, whereas the dashed line shows $\Delta S/S$ obtained from a spin echo fMRI experiment.


110
100
90
80
70
60
50
40
30
20
10
0
T2* [ms]
70
75
80
85
90
95
100
oxygen saturation [%]


50
45
40
35
30
25
20
15
10
5
0
R [s-1]
0
20
40
60
80
100
hematocrit [%]


12
10
8
6
4
2
0
ΔS [arb. units]
SE
0
20
40
60
80
100
120
140
160
TE [ms]


14
12
10
8
6
4
2
0
ΔS / S [%]
0
20
40
60
80
100
120
140
160
TE [ms]
SE