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Empirical Model of Human Blood Transverse Relaxation at 3T Improves MRI T2 Oximetry

Adam Bush, MS^{1,2}, Matthew Borzage, Ph.D^{3,6}, John Detterich, MD¹, Roberta M Kato, MD⁵, Herbert J. Meiselman, Sc.D⁷, Thomas Coates, MD⁴, and John C Wood, MD, PhD^{1,2}

¹Division of Cardiology, Children's Hospital Los Angeles

²Department of Biomedical Engineering, University of Southern California

³Division of Neonatology, Children's Hospital Los Angeles

⁴Division of Hematology/Oncology, Children's Hospital Los Angeles

⁵Division of Pulmonary, Children's Hospital Los Angeles

⁶Department of Radiology, Children's Hospital Los Angeles

⁷Department of Physiology and Biophysics, Keck School of Medicine USC

Abstract

Purpose—We sought a human blood T₂-oximetry calibration curve over the wide range of hematocrits commonly found in anemic patients applicable with T₂ Relaxation Under Spin Tagging (TRUST).

Methods—Blood was drawn from 5 healthy control subjects. Ninety-three in vitro blood transverse relaxation (T_{2b}) measurements were performed at 37° C over a broad range of hematocrits (10–55%) and oxygen saturations (14–100%) at 3T. In vivo TRUST was performed on 35 healthy African American control subjects and 11 patients with chronic anemia syndromes.

Results—1/T₂ rose linearly with hematocrit ($r^2 = 0.96$), for fully saturated blood. Upon desaturation, 1/T₂ rose linearly with the square of the oxygen extraction, (1–Y)₂, and the slope was linearly proportional to hematocrit ($r^2 = 0.88$). The resulting bilinear model between 1/T₂, (1–Y)₂ and hematocrit had a combined r^2 of 0.96 and a coefficient of variation of 6.1%. Using the in-vivo data, the bilinear model had significantly lower bias and variability than existing calibrations, particularly for low hematocrits. In-vivo Bland Altman analysis demonstrated clinically relevant bias that was –6% (absolute saturation) for hematocrits near 30% and rose to +6% for hematocrits near 45%.

Conclusion—This work introduces a robust bilinear calibration model that should be used for MRI oximetry.

Introduction

T₂ Relaxation Under Spin Tagging (TRUST) MRI has emerged as a reliable and robust method for the non-invasive measurement of intravascular cerebral venous oxygen saturation^{1,2}. By magnetically labeling and isolating flowing spins in blood, TRUST avoids extraneous tissue partial volume effects and provides a quick and reproducible measure of the transverse relaxation time of blood, T_{2b}²⁻⁴.

Critical to TRUST and similar intravascular T_{2b} oximetry methods is the use of empirically derived calibration curves that covert T_{2b} into oxygen saturation. Wright et al was the first to devise a human blood T_{2b} calibration model by using a Luz Meiboom exchange model to describe oxygenation dependent spin-spin proton dephasing in blood⁵. Since then several groups have simplified that early model, included the influence of hematocrit and have studied T_{2b} dynamics over a wide range of magnetic field strengths⁶⁻¹². Continuing along those lines, the aim of this study was to further improve upon these foundational works by describing T_{2b} in hematocrits commonly found in thalassemia, sickle cell and other chronic anemia syndromes and reconciling some of the disparities observed between previously published empirical blood calibration studies across species¹³⁻¹⁵.

Theory

Fundamentally, the oxygen carrying protein in blood, hemoglobin, is diamagnetic in the oxygen bound state, oxyhemoglobin, and paramagnetic in the unbound oxygen state, deoxyhemoglobin. The distinct magnetic susceptibility of these species produces local microscopic magnetic field inhomogeneities directly proportional to the oxygenation state of blood. As water protons move near these inhomogeneities, non-refocusable dephasing leads to T₂ shortening. Two theoretical constructs have been proposed to describe the biophysical spin behavior in a static magnetic environment, the fast exchange model¹⁶ and the diffusion model¹⁷⁻¹⁹. Although supporting data for both theories have been published, neither model perfectly describes observed transverse relaxation. Fortunately, T_{2b} calibration models are primarily focused on the practical model that can be used to convert T_{2b} into oxygen saturation. In this way, complex biophysical modeling of elusive microscopic red cell behavior is avoided for simple empirical coefficients. One of the earliest, most simple empirical equations used to model T_{2b} relaxation was first proposed by Wright⁵:

$$\frac{1}{T_{2b}} = \frac{1}{T_{2bo}} + K * (1 - Y)^2 \quad [1]$$

where T_{2bo} is the T₂ of fully oxygenated blood, Y is fractional blood oxygen saturation and K is a pulse sequence dependent, lumped constant. Several groups have extended this model in the form of:

$$\frac{1}{T_{2b}} = A + B * (1 - Y) + C * (1 - Y)^2 \quad [2]$$

where A, B and C are empirically determined constants.

The most widely used T_{2b} oximetry calibration model at 3T was proposed by Lu et al¹⁴ and introduced a hemoglobin dependence, breaking equation [1] into the following sub equations:

$$\begin{aligned} A &= a_1 + a_2 * HCT + a_3 * HCT^2 \\ B &= b_1 * HCT + b_2 * HCT^2 \\ C &= c_1 * HCT * (1 - HCT) \end{aligned} \quad [3]$$

where a_1 , a_2 , a_3 , b_1 , b_2 and c_1 are empirically determined coefficients¹⁴. Empirical T_{2b} calibration models were determined separately for both bovine blood and neonatal, infant cord blood¹⁵ using this method. Overall the resulting T_{2b} calibration models were very similar however subtle differences were observed particularly at the high oxygen saturation levels. In light of these discrepancy we acquired blood in healthy human adults and introduce a novel T_2 oximetry calibration model based on our empirical data.

Methods

In Vitro: All studies were performed at Children's Hospital Los Angeles. The study was approved by the Committee on Clinical Investigation (CCI#1200095) and informed consent was obtained from all subjects. Blood from five healthy human control subjects was studied (2 female, 35.4 ± 11.0 years old). Thirty milliliters of blood was drawn from the antecubital vein into heparinized vacuum tubes and stored at 4°C until analysis. Each study was conducted within 12 hours of phlebotomy. Oxygen saturation, hemoglobin, methemoglobin and carboxyhemoglobin were measured using a bench top co-oximeter (Radiometer, OSM3, Copenhagen, Denmark). Co-oximetry measurements were cross validated against a handheld point of care blood gas analyzer (Alere, Epoc, Waltham, USA) to insure that pH was controlled within a physiologic range (pH 7.30 ± 0.04). Specimen hematocrit was adjusted by recombining packed red cells or plasma and confirmed by spun microhematocrit.

MRI scans were performed on a 3T Achieva Philips Healthcare (Best, Netherlands) scanner with an eight channel phase array head coil. A custom blood imaging phantom was constructed consisting of a sealable, plastic reservoir encased within a heated water jacket. Water jacket temperature was controlled via connection to a continuously circulating, PID controlled waterbath outside the magnet room. Blood was injected and removed from jacketed reservoir by way of a stopcock and syringe. Blood temperature was measured directly and allowed to equilibrate at 37° C before imaging. Blood within the reservoir was agitated by repeatedly aspirating and reinjecting into the chamber prior to every scan to minimize blood sedimentation (supporting figures).

T_2 relaxation was measured with a widely used TRUST sequence¹, slightly modified for in vitro imaging. The pulse sequence is outlined in Figure 1. For in vitro experiments arterial spin labeling was disabled because blood was not flowing. Head to head comparison with and without ASL enabled demonstrated no statistical difference in T_2 estimation (−1.2%

$\pm 5.1\%$). T_2 weighting was applied by using a Carr Purcell Meiboom Gill (CPMG) T_2 preparation (T_2 Prep) module with phase cycled MLEV composite refocusing hard pulses ($90^\circ 180^\circ 90^\circ$). The number of refocusing pulses were varied successively to achieve effective echo times of 0 40 80 and 160ms. Effective echo time weighting was performed with two different interecho spacing times, τ_{cpmg} , 10 ms and 20 ms corresponding to 0,4,8 and 16 inversion pulses and 0, 2, 4 and 8 inversion pulses. The nonselective pulses in the T_2 preparation module were order to acquire effective echo times of 0, 40, 80 and 160ms in an interleaved manner. This allowed T_2 to be generated every 12 repetition times (26 seconds) to capture rapid trends in T_2 . Six T_2 values were generated for each acquisition. Linear regression was used to fit T_2 drift during each acquisition and extrapolated to obtain an estimated T_{2b} at the time of blood agitation (30 seconds prior to imaging). Additional parameters included a repetition time of 1978 ms, field of view of 110 cm, slice thickness of 5mm, and inplane resolution of 1.7 by 1.7 mm. To reduce air susceptibility artifact, a three shot acquisition, using an echoplanar factor of 11 and sense factor of two was used instead of a single shot acquisition.

Following imaging, blood was removed from jacketed reservoir and deoxygenated in a temperature controlled gas chamber using a membrane oxygenator (Living System Instrumentation, Burlington, VT, USA). A gas mixture of 5% CO_2 and 95% N_2 was used for deoxygenation to maintain a physiologic pH during deoxygenation. Blood was returned to reservoir, sealed, saturation was measured on a hemoximeter and imaging was repeated. Blood saturation and temperature was measured again following imaging for stability assessment. Deoxygenation and imaging was repeated several times at various saturation levels. Hematocrit was adjusted by the addition of red cells or plasma. The sample was reoxygenated within temperature controlled gas chamber and membrane oxygenator using a 5% CO_2 , 20% O_2 and 75% N_2 gas mixture. Blood sample deoxygenation and imaging was repeated.

MATLAB (Mathworks, Natick, MA) scripts were written for data analysis. Manual regions of interest were drawn within the blood pool and fit to a monexponential using a Levenburg-Marquadt algorithm. Since arterial spin labeling was disabled, there was no need to adjust for blood T_1 . Data at each hematocrit were fit to equation 2 using a linear least squares method.

Three separate empirical calibration models were used to convert the measured T_{2b} into derived oxygen saturation. These models include the bovine and neonatal empirical models outlined above and a human bilinear model outlined below.

In vivo studies were performed at Children's Hospital Los Angeles on the same imaging platform and coil as the in vitro studies. The study was approved by the Committee on Clinical Investigation (CCI#11-00083). All patients provided informed consent or assent. Thirty-three healthy, African American control subjects and 11 healthy patients with chronic hemolytic anemia including thalassemia major (N=10) and dyserythropoietic anemia (N=1) were studied. Patients underwent vital signs measurement and phlebotomy. Complete blood count, reticulocytes, quantitative hemoglobin electrophoresis, and cell free hemoglobin levels were analyzed in the clinical laboratory. T_2 relaxation of the sagittal sinus was

measured using a TRUST sequence with parameters detailed in the in vitro experiments. Blood labeling was performed using transfer insensitive labeling technique (TILT)²⁰ with a label delay time of 1022ms. The average of pairwise subtraction was taken to obtain the isolated blood signal difference (Signal). The difference signal is proportional to the T₁ and T₂ decay of blood during the CMPG pulse module, described by the equation,

Signal=Signal₀e^{TE*C}, where C = R_{1b}-R_{2b} and Signal₀ is constant across effective TEs¹. Patient specific T₁ was corrected for using the Liu et al. calibration equation¹⁵, with the measured hematocrit and a presumed 60% saturation. Monoexponential fitting was used to derive C and T_{2b}. Peripheral arterial saturation was measured continuously throughout the study using a MRI compatible pulse oximeter (Nonin, Plymouth, MN, USA) and data acquisition system (BIOPAC, Goleta, CA, USA).

Results

A total of 93 T₂ measurements were performed at a τ_{cmpg} of ten milliseconds and 54 T₂ measurements were collected at a τ_{cmpg} of twenty milliseconds. Figure 2 demonstrates a tight linear relationship (r² = 0.956) between R₂ and hematocrit for fully saturated blood (saturation greater than 98%). R₂ was also linearly proportional to the square of oxygen extraction, (1-Y)₂, with r-squared values averaging 0.970 ± .045 (Figure 3a). However, the slope of this relationship (the empiric constant 'K' from equation 1) increased linearly with hematocrit, with an r² of 0.877 (Figure 3b).

Based on these observations, we modified the Wright⁵ model in equation 1 to include terms describing the linear HCT dependence of fully saturated blood, and a linear term reflecting the linear relationship between K and HCT. The resulting human blood bilinear transverse relaxation model was formed:

$$\frac{1}{T_{2b}} = R_{2b} = A_1 \text{Hct}(1 - Y)^2 + A_2 (1 - Y)^2 + A_3 \text{HCT} + A_4 \quad [4]$$

where (1-Y)₂ is the squared oxygen extraction, Hct is the fractional hematocrit and A₁, A₂, A₃ and A₄ are empirically determined constants. Figure 5a demonstrates the hyperplane fit to the bilinear model, illustrating the excellent agreement across the entire range of hematocrits and squared oxygen extractions. Model coefficients were A₁=77.5, A₂=27.8, A₃=6.95, A₄=2.34 for a τ_{cmpg} of 10ms and were A₁=167, A₂=20.8, A₃=10.3, A₄=2.15 for τ_{cmpg} of 20ms using [4] and the measured blood saturation and hematocrit. The overall model r² was 0.962; prediction error grew with measured R₂ value and was best described by a coefficient of variation (6.5%), with 95% confidence intervals of ± 12.7%. The bilinear model residual was regressed against additional variable used with previous models including HCT², HCT*(1-Y), and (1-Y) with no improved model accuracy.

This calibration compares favorably with the existing transverse relaxation models using bovine blood and neonatal cord blood^{14,15}. Figure 5 (left) (compares the bilinear, bovine and neonatal calibrations. Separate comparisons are shown for hematocrit greater and less than 30% respectively.

Figure 5 (right) demonstrates the oxygen saturation predicted by TRUST with the oxygen saturations measured by the co-oximeter for all three models. Table 1 summarizes error statistics across the models for both R_2 and oximetry estimates. The human bilinear calibration and the calibration from neonatal blood are unbiased and have equivalent accuracy for hematocrits greater than 30%, but the bilinear calibration is much more robust for hematocrits less than 30%. Both human models markedly outperform predictions from the bovine model at all hematocrits. The 95% confidence intervals for noninvasive oximetry can easily be derived from Table 1. For hematocrits greater than 30% they are $\pm 5.7\%$ (bilinear, neonatal) and $\pm 9.2\%$ (bovine) respectively. For anemic patients, the uncertainty increases to $\pm 8.1\%$ (bilinear), $\pm 16\%$ (neonatal) and $\pm 27.4\%$ (bovine) respectively; units are in absolute saturation differences.

In vivo TRUST measurements are summarized in Figure 6. The mean hematocrit was $39.8 \pm 3.6\%$ in healthy control subjects and $29.7 \pm 2.0\%$ in anemic patients. The mean derived venous saturation in healthy controls was $61 \pm 6\%$, $64 \pm 6\%$ and $62 \pm 6\%$ using the human bilinear, bovine and neonatal empirical models respectively. The mean venous saturation in anemic patients was $71 \pm 6\%$, $69 \pm 5\%$ and $71 \pm 5\%$ using the human bilinear, bovine and neonatal empirical models respectively (Figure 6). The bovine and neonatal models overestimated predicted saturations made by the bilinear model at high hematocrits and underestimated at low hematocrits (Figure 6). The bias was much worse for the bovine model, ranging from -6% to 6% (absolute saturation differences), while it ranged from -1% to $+3\%$ for the neonatal model.

Discussion

This study is the first to validate T_{2b} oximetry measurements in adult human blood over a broad range of saturations and hemoglobin concentrations in multiple individuals. We demonstrate that more than 96% of the variability in blood R_2 can be described by a bilinear model using hematocrit and the squared oxygen extraction, even with hematocrit values into the teens. We further demonstrate that existing T_{2b} calibrations are highly inaccurate for hematocrits below 30% and should not be used in anemic patient populations²¹. In fact, the commonly used bovine calibration has sizable bias even for patients with normal hematocrit values. Lastly, we are the first to derive realistic 95% confidence intervals for T_{2b} oximetry calibration curves (Table 1) and demonstrate that the bilinear model is fundamentally more accurate than existing calibrations, with 2–3 fold tighter confidence intervals at hematocrits $<30\%$.

Despite the severe disagreement observed at lower hematocrits, our data showed considerable overlap with existing literature at higher hematocrits, increasing the overall confidence in the both T_{2b} oximetry calibration and TRUST. We replicated the linear relationship between R_2 and hematocrit in fully saturated blood that has been previously described⁵. R_2 was highly linear with the square of oxygen extraction, $(1-Y)^2$ ^{5,13}. The slope of this relationship, K , was proportional to hematocrit. Most importantly, our calibration was unbiased with respect to both the bovine and neonatal blood TRUST calibration for hematocrits greater than 30%^{14,15}. This implies that mean oximetry values and cerebral

metabolic rates previously published using these calibrations are reasonably accurate, despite errors in individual values.

Furthermore, the bilinear model facilitates a robust fit that can be generalized to most clinical situations. The bovine calibration was derived over a 35–55% hematocrit range. The neonatal calibration was derived over a broader hematocrit range (25%–52%) however there were very few samples at the lower hematocrits. Patients with chronic anemia often have hematocrits in the low twenties^{22,23}. Existing empirical models extrapolate poorly to this hematocrit range because they are highly nonlinear and have six degrees of freedom making them vulnerable to overfitting¹⁴. This precludes their use in anemic populations and also suggests that the underlying physical model assumptions may be incorrect. Not only did the proposed bilinear model fit hematocrits well below 30%, but it also outperformed the bovine model in the hematocrit range for which it was optimized (35%–55%).

Interestingly, our current results agree more closely with data from human cord blood than the bovine calibration. Lu and colleagues, noting differences between the neonatal and bovine calibrations, speculated that neonatal and adult blood were magnetically distinct¹⁵. The present work suggest an alternative hypothesis, namely that bovine blood is an imperfect surrogate for human blood. Several previous studies have implied that bovine blood is magnetically indistinguishable from human blood^{7,13,14,24}. Although diffusion characteristics of bovine blood may be similar to human blood,²⁵ bovine red blood cells have a mean corpuscular volume that is half that of human blood cell²⁶, have a slower sedimentation rate²⁷ and do not aggregate²⁸. All of these effects modify the length-scale of magnetic inhomogeneities that diffusing water protons encounter prior to echo formation¹⁷, potentially contributing to T_{2b} differences in cows and humans. Previous calibration studies using bovine blood did not observe significant T_2 drift or sedimentation over a six minute interval, in marked contrast to the present study, further emphasizing differences between bovine and human blood⁹. The Bland-Altman comparisons (Figure 6) demonstrate anticipated differences in oxygen saturation using the three models. Although the overall bias is modest, the human - bovine model bias systematically rises more than twelve absolute percentage points from a hematocrit of 25–40%. In contrast, the human model and neonatal model bias rises only four percentage points over the same range; a difference that could easily be explained by a model mismatch, rather than fundamental magnetic differences in neonatal and adult human blood.

The measurement of human blood in vitro under physiologic conditions was challenging. Temperature and pH need to be carefully controlled. While macroscopic blood sedimentation could be controlled by imaging quickly, red cell aggregation begins within seconds after agitation. The rapid T_2 increases were consistent with the time courses found in red cell aggregation and rouleaux formation²⁹. A flowing system could potentially reduce these effects, but would not eliminate T_2 drift unless the flow was fairly vigorous. Furthermore, flowing systems require unacceptably high blood volumes and are vulnerable to flow artifacts during image acquisition. In vivo, blood enters the sagittal sinus within seconds following complete disaggregation in the capillary vasculature. We chose to address aggregation and sedimentation by agitating the blood sample immediately preceding image acquisition, using a longitudinal imaging plane that conserved average hematocrit (in

contrast to a plane to the tube) and correcting T_2 drift by linear extrapolation (supporting figure S2).

Despite a closed system, there remained a small residual air volume in the upper portion of imaging phantom that produced local susceptibility gradients in the blood pool. These gradients may have caused us to slightly underestimate the true T_{2b} in vitro. We minimized the influence of this effect by reducing the EPI factor and manually avoiding these regions during segmentation. We were unable to demonstrate any T_2 gradient between the top and the bottom of the ROI, with an average difference equal to $0.5\% \pm 5.1\%$

Other in vitro confounders include red cell ex vivo age, pH, carboxyhemoglobin level and temperature. Red cell integrity and metabolic status are well preserved over twelve hours of storage in refrigerated conditions. Blood pH was maintained in the physiological range for venous samples by including 5% CO_2 in both the oxygenating and deoxygenating gases. Temperature was tightly controlled at $37^\circ C$ by heating the gases and the imaging chamber. Alterations in any of these parameters can influence red cell shape, permeability and or oxygen dissociation³⁰.

Despite the excellent empirical performance of the bilinear model, this study has several limitations. Firstly, the coefficients introduced by this work are specific to the T_2 preparation module and readout used in the aforementioned methods. The precise manner in which T_2 weighting is applied and data is readout will change the relative influences of T_2^* , contributing directly to pulse sequence specific model coefficients. In light of this fact, we used the most commonly reported TRUST sequence with and without blood tagging. Furthermore, we insured that the readout in our in vitro calibration curve generation matched the readout of the TRUST measurements performed in patients. Despite, limited applicability of the exact coefficients proposed in this work, the precision of this model suggest the underlying T_{2b} bilinear model structure will have utility in future works. Secondly, this study only examined the relaxation characteristics of subjects with AA hemoglobin. It remains possible that other hemoglobin variants, HgbS HgbF, HgbE etc have unique relaxation model coefficients and even model structures. Thirdly, we are presenting an in vitro calibration model that can be used predict in vivo saturation. This work does not address the absolute accuracy of TRUST measurements but rather the resulting bias arising from improper T_{2b} oximetry calibrations (Figure 6). In vivo measurements should be rigorously compare against a clinical gold standard. Despite controlling for several important physiological blood parameters including pH, temperature and aggregation, it remains possible that additional confounders including B1 inhomogeneity and eddy current formation could cause disparities between in vivo and in vitro measurement conditions. Fourthly, repeated aspiration and circulation of blood produced some sample hemolysis which will elongate T_{2b} relaxation¹⁸. We minimized hemolysis by limiting studies to three cycles through the membrane oxygenator and randomized the order that different hematocrits (lower or higher) were studied. Next, we cannot exclude nonlinear dependencies of R_2 on hematocrit and saturation even though we were unable to observe them in the present study. Lastly, this study makes no attempt to resolve the biophysical origin of the R_2 in whole blood. Future research should interrogate the theoretical and empirical effects of corpuscular volume, red cell aggregation and rouleaux formation effects on transverse

relaxation properties because these physical phenomena will cast insights into the relative merits of Luz Meiboom and diffusion models of red cell relaxation.

Conclusion

This work introduces an empirical bilinear model of transverse relaxation of human blood. This model has superior statistical performance over existing empirical models utilizing bovine and cord blood over a wider range of hematocrits. This bilinear model should supplant existing calibration curve models for TRUST oximetry. This framework is also relevant to several other T_2 based oximetry approaches including TRUPC³¹, QUIXOTIC³² and VSEAN³³, although the coefficients could vary with technique.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Modified TRUST pulse sequence used for T_{2b} oximetry calibration. The sequence consists of a TILT labeling pulse followed, by a Carr Pucell Meiboom Gill T_2 preparation module and Echo Planar Imaging readout. Experiments were performed with two distinct T_2 prep modules, with an interecho spacing, τ_{cpmg} , of 10 ms and other 20 ms. Radiofrequency spoiling and gradient crushing following G_z crusher was performed in G_x and G_y (not shown for visual simplicity). For in vitro imaging, the label was turned off to shorten scan time. T_{2b} estimates with and without TILT label were not statistically different.

Figure 2.

R_2 dependence on hematocrit for fully oxygenated blood. Tight linear fit ($r^2=0.956$) was observed across 5 healthy hemoglobin AA subjects. Shapes correspond to separate subjects.

Figure 3.

Hemoglobin saturation influence on R_2 . Left panel demonstrates linear dependence of R_2 on the squared oxygen extraction, $(1-Y)_2$, for five different hematocrit values. The slope of this relationship, K , was linearly proportional to hematocrit (right panel).

Figure 4.

Hyperplane resulting from the bilinear model fit of the experimental data. R_2 is plotted with respect to the squared oxygen extraction, $(1-Y)_2$ and hematocrit. The experimental data are displayed as black circles and the bilinear model is represented by the mesh.

Figure 5.

Human bilinear model comparison with existing bovine and neonatal hemoglobin calibrations. Top and bottom panels correspond to model accuracy at hematocrits above and below 30%, respectively. The left and right panels correspond to predicted R_2 and saturation respectively. At hematocrits above 30% the three models are unbiased, although the bovine model has greater scatter. However, at hematocrits below 30% the bovine and neonatal empirical relaxation models underestimate oxygen saturation and demonstrate unacceptable variance.

Figure 6.

Bland-Altman analysis of in- vivo TRUST measurements. Left panel is oxygen saturation measured in healthy controls and anemic patients using human bilinear, bovine and neonatal models. The saturation in healthy controls was $60.6 \pm 6.3\%$, $63.8 \pm 6.7\%$ and $62.4 \pm 6.2\%$ using the human bilinear, bovine and neonatal empirical models respectively. The mean saturation in anemic patients was $69.8 \pm 6.0\%$, $68.2 \pm 4.8\%$ and $70.1 \pm 5.3\%$, respectively. There was a statistical difference between healthy controls and anemic patients ($P < .05$), using all models. The right panel depicts the difference between the human bilinear model and the bovine and neonatal models with respect to hematocrit. There is a positive saturation bias introduced by both models at higher hematocrits and a negative saturation bias at low hematocrits. The neonatal model performance is more similar to the human bilinear model than the bovine model.

Table 1

Error statistics of measured vs predicted R_2 and O_2 saturation. The bilinear and neonatal models predict O_2 saturation similarly well with comparable standard deviation and mean squared error at hematocrits above 30%. The bovine model demonstrates a slight bias in O_2 saturation and has 50% larger confidence intervals compared with the other two calibrations. At hematocrits below 30% both the bovine and neonatal models have large negative bias and considerable variance in model predictions. The proposed bilinear model maintains accuracy across this range.

		R_2 Relaxation (1/s)			O_2 Saturation (%)		
		Mean Error	Standard Deviation	Mean Squared Error	Mean Error	Standard Deviation	Mean Squared Error
Hematocrit	Human	-0.165	0.975	0.958	0.037	2.86	8.00
	Bovine	0.522	1.26	1.83	1.78	4.56	23.5
	Neonatal	0.146	0.984	0.968	0.537	2.84	8.19
Hematocrit < 30%	Human	0.153	1.64	2.68	0.424	4.40	19.1
	Bovine	-6.01	3.91	51.1	-24.0	13.7	759
	Neonatal	-1.92	2.58	10.2	-9.93	8.069	162