Published in final edited form as:

Magn Reson Med. 2018 April ; 79(4): 2290–2296. doi:10.1002/mrm.26885.

***In vivo* whole-blood T_2 versus HbO_2 calibration by modulating blood oxygenation level in the femoral vein through intermittent cuff occlusion**

Michael C Langham¹, Ana E. Rodríguez-Soto¹, Nadav Schwartz², and Felix W Wehrli¹

¹Department of Radiology, University of Pennsylvania School of Medicine

²Department of Obstetrics and Gynecology, University of Pennsylvania School of Medicine

Structured Abstract

Purpose—To investigate the feasibility of estimating calibration constants (K and T_{20}) *in vivo* for converting whole-blood T_2 to blood hemoglobin oxygen saturation (HbO_2) according to the Luz-Meiboom model, $\frac{1}{T_2} = \frac{1}{T_{20}} + K(1 - HbO_2)^2$, where K and T_{20} are relaxivity and transverse relaxation time of fully saturated blood, respectively.

Methods—A range of HbO_2 values was achieved in the superficial femoral vein with intermittent cuff occlusion in seven healthy adults (four males) to establish a calibration curve between blood T_2 and HbO_2 at 1.5T. HbO_2 was derived via MR susceptibility, a technique previously validated, and the transverse relaxation time was quantified with an optimized T_2 -prepared bSSFP pulse sequence. Lastly, to evaluate the accuracy of the *in vivo* calibration method, T_2 and HbO_2 were quantified in the superior sagittal sinus (SSS) in six additional subjects and compared with susceptibility.

Results—Two sets of gender-specific calibration constants were derived, one for each gender corresponding to hematocrits (Hct) of 0.47 ± 0.02 for males and 0.38 ± 0.01 for females, yielding $K/T_{20} = 41 \text{ Hz}/260 \text{ ms}$ and $26 \text{ Hz}/280 \text{ ms}$, respectively. The *in vivo* calibration returned physiologically plausible SSS SvO_2 values ($65 \pm 5\% HbO_2$) and there was no significant difference between the results from the two methods (average difference $-0.3\% HbO_2$).

Conclusion—The results show feasibility of performing *in vivo* calibration for converting whole-blood T_2 to HbO_2 . The proposed approach bypasses the involved and cumbersome processes associated with *in vitro* calibration.

Keywords

T_2 oximetry; MR susceptibility; T_2 relaxometry

INTRODUCTION

The determination of oxygen saturation is of great importance in assessing a variety of clinical conditions, including congenital cardiac abnormalities causing mixing of arterial and venous blood, hypoxemias, and ischemic disease of various organs, including the brain, kidneys and liver. In 1991, Wright et al (1) conceived a T_2 -based approach based on the Luz-Meiboom model of transverse relaxation in the presence of chemical exchange between two sites (2). Blood is a heterogeneous system but the approach does not take diffusion into account, where local field inhomogeneity near erythrocytes is expected to contribute to T_2 shortening. It has been shown that at 1.5T the diffusion effect is minor compared to intra-to-extracellular chemical exchange (3), as evidenced by the excellent agreement between the data and Luz-Meiboom model (1). T_2 oximetry has demonstrated its clinical potential in a number of studies (1,4–8). More recent applications include estimation of oxygenation in the cardiac ventricles of fetal lambs (9) and oxygen consumption rate in human fetuses (10).

T_2 oximetry involves mapping the decay of the proton signal when spins are subjected to a train of refocusing pulses in a CPMG (11) or MLEV-4 type pattern (12) and relating T_2 to HbO_2 via simplified form of the Meiboom-Luz model, $\frac{1}{T_2} = \frac{1}{T_{2o}} + K(1 - HbO_2)^2$. The derived T_2 is a function of T_{2o} , the transverse relaxation time of fully oxygenated blood (which is itself a function of hematocrit (13)) and a contribution governed by deoxyhemoglobin fraction $(1 - HbO_2)$ in erythrocytes. K is the relaxivity, which is a function of inter-refocusing interval τ_{180} , magnetic field strength and various parameters that reflect underlying mechanisms, e.g. average exchange time τ_{ex} between two sites (intra- versus extracellular) and a parameter α accounting for red blood cell (RBC) shape (14). A limitation of the method is the extensive calibration that is needed with blood studied *ex vivo*. The complex procedure (13,15) includes preparing blood samples of varying oxygenation levels by exposing the blood to diffusing gases, O_2 or N_2 , while maintaining correct temperature and pH level under continuous agitation to prevent settling or foaming of RBCs. Once the desired blood oxygenation is achieved, verified by blood gas analysis (BGA), air exposure must be avoided during the transfer to MR sample tubes. Any remaining air spaces should be removed for optimal results. During the MR scan session the tubes must be maintained at 37°C (e.g. by blowing warm air and regulating via a thermocouple temperature feedback loop (13)) and periodically rotated to prevent settling of RBCs. Lastly, it is recommended that the HbO_2 and Hct be re-verified via BGA.

MR susceptometry (16–18) is a calibration-free method for estimating HbO_2 where vessels are modeled as long paramagnetic cylinders. In this field-mapping method the intravascular field shift B relative to the surrounding tissue is proportional to the magnetic susceptibility of whole-blood, which in turn is a function of $(1 - HbO_2)$ (19). The main sources of error are static field inhomogeneity and vessel tortuosity, thus the method is limited to peripheral vessels in general, e.g. superficial femoral vein (SFV); an exception being the superior sagittal sinus (SSS), a major intracranial draining vein (20). However, there is compelling evidence for the accuracy of susceptometry to quantify intravascular oxygenation level if the necessary precautions to the method's limitations are taken (15,20,21). Thus we propose to calibrate T_2 -based oximetry against susceptometry as a reference standard.

Previously, T_2 -prepared bSSFP (T_2 -bSSFP) had been used for myocardial edema T_2 quantification (22), an appealing approach for T_2 -based MR oximetry given its high speed and SNR efficiency. However, the k-space center (which largely determines the signal intensity) is traversed after linear ramp-up catalyzation and acquisition of the reference lines, at which point the bSSFP signal is attenuated by modulation transfer function (MTF) and no longer represents the magnetization immediately following the T_{20} -prep. Further, because MTF varies with TE so does the fraction of signal attenuation. Consequently, the calibration curve for converting T_2 to HbO_2 based on the T_2 -prepared bSSFP pulse-sequence is expected to deviate from that derived in (1), where center-out spiral readout followed after a single RF excitation.

The purpose of this work was to derive the calibration curve for T_2 -bSSFP, i.e. to estimate K and T_{20} , based on the Luz-Meiboom model of chemical exchange. However, rather than oxygenating *ex vivo* blood to various HbO_2 levels we investigate the feasibility of modulating superficial femoral vein HbO_2 via intermittent cuff occlusions in order to perform the calibration *in vivo*. Lastly, we evaluated the relative agreement between HbO_2 levels measured independently *in vivo* via susceptometry and those predicted by the new T_2 -based method.

METHODS

T_2 Quantification

The semi-empirical Luz-Meiboom model relating to HbO_2 demands that τ_{180} be held constant for all T_2 -preparation durations (in contrast to T_2 -bSSFP of Giri et al (22) in which τ_{180} was stepped to vary TE).

In the present work the T_2 -preparation comprises integer multiples of MLEV-4 cycles as means to vary TE while keeping τ_{180} constant. The sequence was initiated with a magnetization reset to zero (saturation) and allowed to recover for T_{Sat} prior to T_2 -preparation, which consisted of a 90° RECT excitation pulse, MLEV-4 type refocusing pulses with $\tau_{180}=12\text{ms}$, ending with a composite 270_x360_{-x} tip-up pulse (Fig 1). The saturation ensures that the longitudinal magnetization is the same prior to each T_2 -preparation and allows the option to trade in SNR for shorter T_{Sat} , enabling T_2 quantification within a breath hold. bSSFP imaging parameters: FOV 144mm, 8mm thickness, TE/TR=1.8/3.6ms, flip angle 60° , in-plane resolution 1.0mm, bandwidth/pix 694Hz, half-Fourier with linear ramp-up signal stabilization (10 TRs) and 14 reference lines for reconstruction phase correction, $T_{Sat} = 2.5\text{s}$; acquisition time $\sim 15\text{s}$.

HbO_2 Quantification

In MR susceptometry (17,18) HbO_2 is quantified by modeling a vessel as a long cylinder and making use of the magnetic property of venous blood that scales with the fraction of deoxyhemoglobin, $(1 - HbO_2)$, which in turn determines the relative volume magnetic susceptibility, $\chi = \chi_{do}Hct(1 - HbO_2)$ of deoxygenated blood. Here, $\chi_{do} = 4\pi(0.27\text{ppm})$ (13,15) is the magnetic susceptibility between fully deoxygenated and fully oxygenated blood in SI units and Hct is the hematocrit, i.e. the volume fraction of red blood cells. The

relative susceptibility χ is obtained from the measured field shift,

$\Delta B - \frac{1}{6}\Delta\chi(3\cos^2\theta - 1)B_o$, relative to the surrounding diamagnetic tissue, where θ is the vessel tilt angle with respect to the main field, B_o . The field map B is obtained from the phase difference image, ϕ , computed from two gradient echoes separated by TE ,

$\phi = \gamma B TE$, where γ is the gyromagnetic ratio of water protons. Once hematocrit Hct is

determined from a blood draw HbO_2 can be computed as $HbO_2 = [1 - \frac{6\Delta\phi/\Delta TE}{\gamma\Delta\chi_{do}Hct \cdot B_o(3\cos^2\theta - 1)}]$. The following imaging parameters were used to estimate HbO_2 in the SFV at mid-thigh level: FOV 144mm, matrix size 144, 10 mm thickness, TE/TE/TR=5.7/8.88/38.5ms, FA=16°, bandwidth/pix 232Hz, partial-Fourier factor 0.83, acquisition time<5s.

Analysis

T_2 was quantified by fitting the average pixel intensities S of ROI from each of the five images to the three-parameter equation (23), i.e. $S = Ae^{-Bt} + C$, because the T_2 -prepared bSSFP signal approaches a steady-state instead of zero even at $t \rightarrow \infty$, and corrected TEs (0, 43.9, 87.7, 131.6, 175ms) were used in the fitting to reduce errors associated with T_1 decay while the magnetization is longitudinal during the composite pulses (24).

For HbO_2 quantification the effect of the static field inhomogeneity was first reduced by fitting the low spatial-frequency field variation to a second-order polynomial after masking out the vessels and weighting the phase difference image by the corresponding magnitude image (25).

Experiments

Preliminary evaluation of T_2 -bSSFP—The performance of the T_2 -bSSFP was first evaluated against the multi-spin echo pulse sequence in four homogeneous $MnCl_2$ solutions of different concentration (nominal T_2 values ranging from 105 to 200ms).

Since T_2 -bSSFP is designed to be used for quantifying whole-blood HbO_2 *in vivo* the bias in T_2 estimation in the presence of constant flow speed representative of venous flow (5 to 28cm/s) was assessed with one of the prepared $MnCl_2$ solutions (T_2 =135ms).

In Vivo calibration via intermittent cuff occlusions—Written informed consent was obtained prior to all examinations following an IRB-approved protocol. SFVs of four healthy males (38.8 ± 8 yrs old, Hct 0.47 ± 0.02) and three healthy females (28 ± 3 yrs old, Hct 0.38 ± 0.01) were imaged at 1.5T (Siemens Avanto) with a Siemens circularly polarized extremity Tx/Rx coil during the cuff paradigm (Fig 2a). Femoral arterial occlusion was achieved by application of super-systolic pressure (215mmHg) in a cuff secured around the thigh, inflated by a pneumatic tourniquet system (D.E. Hokanson, Inc; Bellevue, WA) capable of inflating and deflating in less than one sec. Fig 2b shows the range of venous oxygenation levels (%SvO₂) that can be observed in the SFV by inducing muscle ischemia achieved in transient occlusion of the feeding artery with a pressure cuff (26). The timing of the MRI protocol of RF-spoiled multi-echo GRE and T_2 -bSSFP pulse sequences was programmed using SequenceTree (27) to match the cuff paradigm of Fig 2a, whereas the intermittent cuff inflation/deflation was performed manually with a digital stopwatch.

Further, the MRI protocol was programmed so as to delay launching of the pulse sequence by two sec following cuff inflation to ensure suspension of blood flow during the data acquisition. As indicated in Fig 2a 13 pairs of susceptometry-based HbO_2 values and T_2 were measured in each subject.

The imaging plane was prescribed perpendicular to the superficial femoral vessels based on 3D rendering of multi-slice 2D time-of-flight acquisition to minimize partial volume effect. Lastly, Hct was determined via a blood sample obtained from the fingertip (Hb 201+, Hemocue, Angelholm, Sweden).

Evaluation of Agreement with Susceptometry—In order to determine whether the *in vivo* calibration equation returns physiologically plausible SvO_2 values and to test agreement with susceptometry, six additional subjects were recruited (three males). Males and females had Hct values ranging from 0.45 to 0.47 and 0.38 to 0.40, respectively. Measurements with the two methods were conducted in the SSS, a location previously evaluated by susceptometry at 1.5T (28). The field and T_2 maps were acquired successively with RF-spoiled multi-echo GRE and T_2 -bSSFP pulse sequences, respectively, using a 12-channel head coil. Imaging parameters: 1) bSSFP – FOV 192mm, voxel size $1 \times 1 \times 8 \text{ mm}^3$, TE/TR=2/4ms, 60° flip angle and bandwidth/pixel 694Hz. 2) GRE – same FOV and voxel size, TE/TR=5.4/7.92/50ms, 16° flip angle and bandwidth/pixel 260Hz.

RESULTS

Phantom evaluation of T_2 -bSSFP

Sample T_2 -bSSFP images of $MnCl_2$ solutions and the corresponding three-parameter fits are shown in Figs 3a and b. The extracted T_2 values are less than 5% compared to those values quantified with multi-spin echo. In the presence of constant flow rate the bias in T_2 quantification was less than or equal to 4% (Fig 3c) relative to the static solution.

In Vivo calibration via intermittent cuff occlusions

Examples of phase difference and T_2 -prepared bSSFP images are shown in Figs 4a and b, respectively. The vein exhibits strong phase contrast relative to the surrounding muscle tissue (Fig 4a), unlike the adjacent artery, whose phase is indistinguishable relative to the tissue. The magnified view of the vessels in Fig 4c highlights large difference in T_2 decays rates between arterial and venous blood, paralleling the differences in signal decay plots in Fig 4d. The distribution of Hct of males and females were bimodal (0.47 ± 0.02 and 0.38 ± 0.01) consequently two separate calibration curves involving two sets of K and T_{20} constants are derived (Fig 5).

Evaluation of Agreement with Susceptometry

The results are tabulated and included as Supporting Information. There was no difference between two oximetry methods (average difference in $SvO_2 = -0.3\% HbO_2$ paired t-test, $p=0.8$) and all values of SSS SvO_2 were within physiological range ($65 \pm 5\% HbO_2$).

DISCUSSION

The work shows the feasibility of performing an *in vivo* calibration for conversion of whole-blood T_2 to HbO_2 . The proposed calibration technique obviates many of the precautions necessary and difficulties to be overcome for *in vitro* calibration. Among the latter are settling of red blood cells occurring on the order of minutes (13,15). The intermittent cuff occlusions and short acquisition time (20s) ensure that blood is refreshed, therefore precluding settling during the short periods (20s) of transient occlusions and, of course, temperature stability is ensured, nor can there be changes in O_2 saturation during the experiment. Calibration could therefore easily be replicated and performed at other field strengths and arbitrary experimental conditions for T_{20} mapping.

A limitation of the *in vivo* calibration method presented here is the reduced range of HbO_2 values available for measurement as for 3–5 min arterial occlusion venous oxygenation was found to rarely fall below 40% HbO_2 . In contrast, the full range of HbO_2 values can be achieved *ex vivo*. Further, it is not possible to exogenously vary Hct *in vivo* considering that the derived constants are hematocrit dependent. The refinement of the calibration requires increase in the sample size to cover the range of naturally occurring Hct values. The range is actually quite small (35–40% for females, 45–50% for males) (29). The accuracy of the proposed method, of course, critically hinges on the accuracy of MR susceptometry. Some of the authors had previously validated MR susceptometry at 3T on freshly drawn blood samples across the entire range of saturation values from 6 to 98% HbO_2 against blood gas analysis (15) showing excellent agreement. Additional studies on the accuracy of susceptometry have included investigations on flow bias (18) and errors associated with vessel tilt and non-circularity as well as *in vivo* reproducibility, via quantification of HbO_2 at multiple locations along the same vein (30). Prior investigations also addressed potential errors due to substantial deviations from cylindrical geometry, e.g. bifurcations, tapering, noncircular cross-section and curvature (21).

Systematic errors of susceptometric oximetry have been discussed in detail (25,30). The most significant possible source of error, unless retrospectively corrected, is static field inhomogeneity. Additional 3D shimming improves the suppression of the inter-muscular fat signal that can confound the field correction since the inter-echo phase difference due to the intra- to extravascular susceptibility difference cannot be distinguished from a chemical shift difference between water and fat. The femoral vein's tilt angle exceeding 25° with respect to B_0 leads to increased contribution of the non-local field in the surrounding reference tissue and partial volume effects. Prescribing the imaging slice perpendicular to the vein can alleviate the latter.

The difference in K is larger than expected between male and female cohorts given that the two groups differ in Hct by less than 10 percentage points (39% versus 47%). The water dynamics across the RBC and the geometry of RBCs are characterized by the exchange lifetime τ_{ex} and RBC shape parameter α , respectively, typically lumped into K along with Hct in the Luz-Meiboom model. The mean value of τ_{ex} has been reported to be about 12 ms and it is also a function of Hct (31). Consequently, it can be shown that the Luz-Meiboom model

predicts about 11% increase in K for $Hct=0.47$ relative to $Hct=0.39$. Similarly, Spees et al (13) reported about a 10% increase in K in blood samples upon increase in Hct by 0.1.

The recent results of Nemeth et al (32) may provide a rationale for future investigation on possible gender differences in α that could impact K . The authors of ref. (32) reported hemo-rheological gender differences in two mammalian animal species in terms of RBC deformability and aggregation. This is potentially relevant to α parameter since RBC aggregation depends on the cell's shape, cell surface's glycocalyx and deformability, with the latter being determined by RBC's surface to volume ratio, viscosity and morphology. Future work could involve comparison of blood T_2 between female and male blood at the same Hct to probe the dependence on α .

On the other hand, the results for T_{20} are in good agreement compared to (1) as expected if we approximate oxygenated blood as a magnetically homogenous medium. The shorter T_{20} in the male sub-group is consistent with the well-known linear dependence of the water proton relaxivity of protein solutions and suspensions and has previously been reported by Thulborn et al who studied T_2^{-1} as a function of hematocrit in fully oxygenated blood (33). The results of additional six subjects (Supporting Information) further support the validity of the derived calibration constants in terms of providing physiologically plausible SSS SvO_2 values as well as agreement with susceptometry.

The impact of flow on *in vivo* T_2 quantification with T_2 -bSSFP was assessed by comparing the T_2 values in the SSS (i.e. quantified in the presence of flow on the order of 15–20cm/s (34)) and femoral vein where T_2 was measured during flow suspension. The male subject's T_2 in the femoral vein was 128ms at 71% SvO_2 while T_2 at the SSS was 132ms. For the female, T_2 differed by 10ms between femoral vein and SSS at $SvO_2 \sim 60\% HbO_2$. Therefore, in the presence of flow, the difference in estimated SvO_2 based on Fig 5 was 2% HbO_2 in both subjects.

In conclusion the results suggest that calibration of T_2 -based oximetry can be performed *in vivo*, thereby obviating the need for blood draws and blood gas analysis, along with the experimental complexities of handling blood samples.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

NIH Grants K25 HL111422, U01 HD087180 and R01 HL109545.

References

1. Wright GA, Hu BS, Macovski A. 1991 I.I. Rabi Award. Estimating oxygen saturation of blood in vivo with MR imaging at 1.5 T. J Magn Reson Imaging. 1991; 1(3):275–283. [PubMed: 1802140]
2. Luz Z, Meiboom S. Nuclear magnetic resonance study of the protolysis of trimethylammonium ion in aqueous solution--order of the reaction with respect to solvent. The Journal of Chemical Physics. 1963; 39(2):366–370.

3. Matwyloff NA, Gasparovic C, Mazurchuk R, Matwyloff G. The line shapes of the water proton resonances of red blood cells containing carbonyl hemoglobin, deoxyhemoglobin, and methemoglobin: implications for the interpretation of proton MRI at fields of 1.5 T and below. *Magn Reson Imaging*. 1990; 8(3):295–301. [PubMed: 2366641]
4. Nield LE, Qi XL, Valsangiacomo ER, Macgowan CK, Wright GA, Hornberger LK, Yoo SJ. In vivo MRI measurement of blood oxygen saturation in children with congenital heart disease. *Pediatr Radiol*. 2005; 35(2):179–185. [PubMed: 15490150]
5. Nield LE, Qi X, Yoo SJ, Valsangiacomo ER, Hornberger LK, Wright GA. MRI-based blood oxygen saturation measurements in infants and children with congenital heart disease. *Pediatr Radiol*. 2002; 32(7):518–522. [PubMed: 12107586]
6. Li KC, Wright GA, Pelc LR, Dalman RL, Brittain JH, Wegmueller H, Lin DT, Song CK. Oxygen saturation of blood in the superior mesenteric vein: in vivo verification of MR imaging measurements in a canine model. *Work in progress Radiology*. 1995; 194(2):321–325. [PubMed: 7824705]
7. Li KC, Pelc LR, Dalman RL, Wright GA, Hollett MD, Ch'en I, Song CK, Porath TS. In vivo magnetic resonance evaluation of blood oxygen saturation in the superior mesenteric vein as a measure of the degree of acute flow reduction in the superior mesenteric artery: findings in a canine model. *Acad Radiol*. 1997; 4(1):21–25. [PubMed: 9040866]
8. Li KC, Dalman RL, Wright GA. In vivo flow-independent T2 measurements of superior mesenteric vein blood in diagnosis of chronic mesenteric ischemia: a preliminary evaluation. *Acad Radiol*. 1999; 6(9):530–534. [PubMed: 10894061]
9. Wedegartner U, Kooijman H, Yamamura J, Frisch M, Weber C, Buchert R, Huff A, Hecher K, Adam G. In vivo MRI measurement of fetal blood oxygen saturation in cardiac ventricles of fetal sheep: a feasibility study. *Magn Reson Med*. 2010; 64(1):32–41. [PubMed: 20572133]
10. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, Grosse-Wortmann L, Jaeggi E, McCrindle BW, Kingdom J, Hickey E, Miller S, Seed M. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. *Circulation*. 2015; 131(15):1313–1323. [PubMed: 25762062]
11. Meiboom S, Gill D. Modified Spin-Echo Method for Measuring Nuclear Relaxation Times. *The Review of Scientific Instruments*. 1958; 29(8):668–691.
12. Levitt M, Freeman R. Composite Pulse Decoupling. *Journal of Magnetic Resonance*. 1981; 43(3):502–507.
13. Spees WM, Yablonskiy DA, Oswood MC, Ackerman JJ. Water proton MR properties of human blood at 1.5 Tesla: magnetic susceptibility, T(1), T(2), T*(2), and non-Lorentzian signal behavior. *Magn Reson Med*. 2001; 45(4):533–542. [PubMed: 11283978]
14. Luz Z, Meiboom S. Nuclear Magnetic Resonance Study of the Protolysis of Trimethylammonium Ion in Aqueous Solution -- Order of the Reaction with Respect to Solvent. *The Journal of Chemical Physics*. 1963; 39(2):5.
15. Jain V, Abdulmalik O, Probert KJ, Wehrli FW. Investigating the magnetic susceptibility properties of fresh human blood for noninvasive oxygen saturation quantification. *Magn Reson Med*. 2012; 68(3):863–867. [PubMed: 22162033]
16. Ogawa S, Lee TM, Nayak AS, Glynn P. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med*. 1990; 14(1):68–78. [PubMed: 2161986]
17. Haacke EM, Lai S, Reichenbach JR, Kuppusamy K, Hoogenraad FGC, Takeichi H, Lin W. In Vivo Measurement of Blood Oxygen Saturation Using Magnetic Resonance Imaging: A Direct Validation of the Blood Oxygen Level-Dependent Concept in Functional Brain Imaging. *Human Brain Mapping*. 1997; 5:341–346. [PubMed: 20408238]
18. Fernández-Seara M, Detre JA, Techawiboonwong A, Wehrli FW. MR susceptometry for measuring global brain oxygen extraction. *Magn Reson Med*. 2006; 55(5):967–973. [PubMed: 16598726]
19. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A*. 1990; 87(24):9868–9872. [PubMed: 2124706]
20. Jain V, Langham MC, Wehrli FW. MRI estimation of global brain oxygen consumption rate. *J Cereb Blood Flow Metab*. 2010; 30(9):1598–1607. [PubMed: 20407465]

21. Li C, Langham MC, Epstein CL, Magland JF, Wu J, Gee J, Wehrli FW. Accuracy of the cylinder approximation for susceptometric measurement of intravascular oxygen saturation. *Magn Reson Med*. 2012; 67(3):808–813. [PubMed: 21858859]
22. Giri S, Chung YC, Merchant A, Mihai G, Rajagopalan S, Raman SV, Simonetti OP. T2 quantification for improved detection of myocardial edema. *J Cardiovasc Magn Reson*. 2009; 11:56. [PubMed: 20042111]
23. Akcakaya M, Basha TA, Weingartner S, Roujol S, Berg S, Nezafat R. Improved quantitative myocardial T2 mapping: Impact of the fitting model. *Magn Reson Med*. 2014
24. Foltz WD, Stainsby JA, Wright GA. T2 accuracy on a whole-body imager. *Magn Reson Med*. 1997; 38(5):759–768. [PubMed: 9358450]
25. Langham MC, Magland JF, Floyd TF, Wehrli FW. Retrospective correction for induced magnetic field inhomogeneity in measurements of large-vessel hemoglobin oxygen saturation by MR susceptometry. *Magn Reson Med*. 2009; 61(3):626–633. [PubMed: 19107914]
26. Langham MC, Zhou Y, Chirico EN, Magland JF, Sehgal CM, Englund EK, Mohler ER, Guo W, Barhoum S, Wehrli FW. Effects of age and smoking on endothelial function assessed by quantitative cardiovascular magnetic resonance in the peripheral and central vasculature. *Journal of Cardiovascular Magnetic Resonance*. 2015; 17(1):19. [PubMed: 25884943]
27. Magland JF, Li C, Langham MC, Wehrli FW. Pulse sequence programming in a dynamic visual environment: SequenceTree. *Magn Reson Med*. 2016; 75(1):257–265. [PubMed: 25754837]
28. Jain V, Buckley EM, Licht DJ, Lynch JM, Schwab PJ, Naim MY, Lavin NA, Nicolson SC, Montenegro LM, Yodh AG, Wehrli FW. Cerebral oxygen metabolism in neonates with congenital heart disease quantified by MRI and optics. *J Cereb Blood Flow Metab*. 2014; 34(3):380–388. [PubMed: 24326385]
29. Gagnon DR, Zhang TJ, Brand FN, Kannel WB. Hematocrit and the risk of cardiovascular disease--the Framingham study: a 34-year follow-up. *Am Heart J*. 1994; 127(3):674–682. [PubMed: 8122618]
30. Langham MC, Magland JF, Epstein CL, Floyd TF, Wehrli FW. Accuracy and precision of MR blood oximetry based on the long paramagnetic cylinder approximation of large vessels. *Magn Reson Med*. 2009; 62(2):333–340. [PubMed: 19526517]
31. Golay X, Silvennoinen MJ, Zhou J, Clingman CS, Kauppinen RA, Pekar JJ, van Zijl PC. Measurement of tissue oxygen extraction ratios from venous blood T(2): increased precision and validation of principle. *Magn Reson Med*. 2001; 46(2):282–291. [PubMed: 11477631]
32. Nemeth N, Kiss F, Furka I, Miko I. Gender differences of blood rheological parameters in laboratory animals. *Clin Hemorheol Microcirc*. 2010; 45(2–4):263–272. [PubMed: 20675908]
33. Thulborn KR, Waterton JC, Matthews PM, Radda GK. Oxygenation dependence of the transverse relaxation time of the water protons in whole blood at high field. *Biochim Biophys Acta*. 1982; 714:265–270. [PubMed: 6275909]
34. Jain V, Magland J, Langham M, Wehrli FW. High temporal resolution in vivo blood oximetry via projection-based T2 measurement. *Magn Reson Med*. 2013; 70(3):785–790. [PubMed: 23081759]

Fig. 1.

T_2 -prepared bSSFP. The pulse sequence is initiated with magnetization reset to zero, saturation recovery time T_{sat} , T_2 -preparation, ramp-up signal stabilization (10 TRs), acquisition of reference 14 lines and half-Fourier bSSFP readout, i.e. k-space center is collected on the 25th pulse cycle. The duration of MLEV-4 is 48ms comprising four composite refocusing pulses, each consisting of 90° - 180° - 90° RECT pulses separated by $150 \mu\text{sec}$. The amplitude of all RECT pulses was fixed and the duration was $500 \mu\text{sec}/90^\circ$, i.e. the 180° pulse lasted $1000 \mu\text{sec}$. Thus, $TE=0, 48, 96, 144$ and 192ms corresponded to 0, 1, 2, 3 and 4 MLEV-4 cycles, respectively. The RF and gradient pulses are represented by rectangles and solid trapezoids, respectively. Color scheme is used to indicate the directions of the pulses, i.e. $+x$, $+y$, $+z$, $-y$ and $-x$ directions are denoted by black, blue, gray, green and red, respectively.

Fig. 2.

a) Cuff paradigm and MRI protocol for *in vivo* calibration of T_2 vs HbO_2 . The cuff occlusion and cuff release are represented by red and green, respectively. The durations of cuff release immediately after the 3 min long cuff occlusions were 10s and 20s to image venous blood with the lowest HbO_2 and highest HbO_2 , respectively. The thinner green bars denote brief period (5s) of cuff deflations to allow blood with different HbO_2 to enter the imaging slice. HbO_2 and T_2 quantifications, denoted by black/gray bars (20s in duration total), are performed during cuff occlusions; white space/bars represent absence of MRI events. Because T_2 -bSSFP is initiated with a saturation recovery the acquisition with RF-spoiled multi-echo GRE sequence or HbO_2 quantification was performed first. **b)** Modulation of venous oxygen saturation by cuff-induced ischemia. Femoral vein SvO_2 time-course in a healthy young subject after 5 min occlusion illustrates kinetics of the oxygen-depleted blood in the capillary bed upon cuff release ($t=0$). Note desaturation to about 40% followed by transient rise to 90% during the reperfusion phase before approaching venous equilibrium values.

Fig. 3. Four MnCl_2 solutions differing in T_2 . **a)** Magnitude images acquired using T_2 -prepared bSSFP with $\tau_{180} = 12$ ms. The reference T_2 values (clockwise from upper left) quantified with multi-spin echoes are 200, 150, 135 and 105 ms. **b)** Sample three-parameter fit and extracted T_2 values. **c)** In the presence of constant flow rate the bias in T_2 quantification relative to the static solution was 4% or less.

Fig. 4.

Whole-blood T_2 -to- HbO_2 *in vivo* calibration with T_2 -bSSFP and MR susceptometry in 29 year old female with $Hct = 0.39$. **a)** Phase difference image between two RF-spoiled GREs 10s after the 3 min cuff occlusion corresponding to $SvO_2 = 40$ %HbO₂. There is significant phase accumulation in the vein relative to surrounding muscle tissue and femoral artery. **b)** Representative bSSFP image (TE = 0 ms) acquired during the same intermittent cuff occlusion. **c)** Magnified view of the superficial femoral vein and artery (white rectangle in **b**) at different TEs (left to right): 0, 48, 96, 144 and 192 ms. **d)** Three-parameter fit of T_2 -bSSFP signal intensities in SFV (blue) and SFA (red).

Fig. 5.

In vivo calibration enabling conversion of whole-blood T_2 to HbO_2 . **a)** Regression analysis of data from four male subjects, each represented by distinct marker shape and color. There are twice as many red markers because the subject had venous duplication. **b)** Corresponding plot comprising data from three females.