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In vivo validation of T2- and susceptibility-based S_vO_2 measurements with jugular vein catheterization under hypoxia and hypercapnia

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Purpose: To investigate the mutual agreement of T2-based and susceptibility-based methods as well as their agreement with jugular catheterization, for quantifying venous oxygen saturation (S_vO_2) at a broad range of brain oxygenation levels.

Methods: S_vO_2 measurements using T2-relaxation-under-spin-tagging (TRUST) and susceptibility-based oximetry (SBO) were performed in 13 healthy subjects under room air, hypoxia, and hypercapnia conditions. Agreement between TRUST and SBO was quantitatively evaluated. In two of the subjects, TRUST and SBO were compared against the clinical gold standard, co-oximeter measurement via internal jugular vein catheterization.

Results: Absolute S_vO_2 measurements using TRUST and SBO were highly correlated across a range of saturations from 45% to 84% (Pearson $r = 0.91$, $P < .0001$). S_vO_2-TRUST was significantly lower than S_vO_2-SBO under hypoxia and room air conditions, but the two were comparable under hypercapnia. TRUST demonstrated a larger S_vO_2 increase under hypercapnia than SBO and had good agreement with jugular catheterization under hypercapnia but significantly underestimated S_vO_2 under room air and hypoxia. The agreement between S_vO_2-SBO and the reference did not depend on the physiological state.

Conclusion: A systematic bias was observed between T2-based and susceptibility-based methods that depended on the oxygenation state. In vivo validation with jugular catheterization indicated potential underestimation of TRUST under room air and hypoxia conditions. Our findings suggested that caution should be employed in comparison of absolute S_vO_2 measurements using either TRUST or SBO.

KEYWORDS
brain oxygenation, susceptometry-based oximetry, T2-relaxation-under-spin-tagging, venous oxygen saturation

1 | INTRODUCTION

Cerebral oxygen extraction fraction (OEF), defined as the difference between arterial and venous oxygen saturations (S_aO_2 and S_vO_2), is an important parameter for the assessment of brain oxygen consumption and tissue viability. Accurate OEF measurement is required to model the pathophysiology and optimize the treatment of neurological disorders with altered

cerebral hemodynamics, including stroke,[1] chronic anemia,[2,3] and neurodegenerative disorders such as multiple sclerosis.[4] While measurement of S_aO_2 can be easily performed with pulse oximetry, standard measurement of cerebral S_vO_2 is challenging because of the risks associated with invasive procedures. The clinical gold standard for global cerebral S_vO_2 measurement is co-oximeter measurement of blood periodically drawn from the internal jugular or superior vena cava through central venous catheters.[5] Although commonly used in the intensive care unit, the catheterization procedure is highly invasive, making it unsuitable for broad research use. Positron emission tomography with ^{15}O radiotracer is also considered gold standard for OEF measurement,[6] but its applicability is limited by radiation exposure, specialized facilities, and high cost. Therefore, there is an unmet clinical need for noninvasive and reliable measurement of cerebral OEF.

Magnetic resonance imaging (MRI) is a promising imaging surrogate for OEF assessment because it is noninvasive, safe, and easy to acquire.[7-11] There exist two types of MRI techniques for global cerebral S_vO_2 measurement: MR relaxometry and MR susceptometry. In the first category, TRUST[8,12] is the most widely applied technique; it measures the T2 relaxation of venous blood and converts T2 to S_vO_2 on the basis of an in vitro calibration model. Specifically, the TRUST sequence applies spin-tagging to separate the signal of venous blood from that of background tissue and uses a T2-preparation module to modulate the blood signal with T2 weighting. Monoexponential fitting of the signal decay produces the T2 relaxation of blood. The second category measures S_vO_2 on the basis of the magnetic susceptibility of venous blood. There is a simple linear relation between the concentration of deoxyhemoglobin and the magnetic susceptibility shift of blood.[13,14] The model is derived from physics with parameter constants readily known.[13] Therefore, no external calibration experiments are needed. Susceptometry-based oximetry (SBO)[7,9,10,15] is representative of this category; it measures the magnetic susceptibility shift of a vein that can be approximated as an infinitely long cylinder. For a straight vein that is nearly parallel to the main B_0 field, susceptibility of blood can be determined from the B_0 field shift of the vein relative to the surrounding tissue after correction of vessel tilt.

Despite the increasing applications of TRUST and SBO,[2-4,16-18] in vivo validation of these two techniques for global cerebral S_vO_2 measurement is still lacking. Prior validations of TRUST and SBO were based on cross-correlation with other physiological measurements[9,16-18] rather than on the clinical gold standards. In addition, the mutual agreement of TRUST and SBO in the same cohort and experimental setting has seldom been examined. Barhoum et al[19] compared TRUST and SBO at resting condition and reported slightly lower S_vO_2 values provided by TRUST. Rodgers et al[20] performed interleaved TRUST and SBO acquisition in one sequence and observed higher S_vO_2 response to hypercapnia indicated by TRUST than SBO. To our knowledge, there has been no comparison of these two methods under low saturation levels such as hypoxia. In order for these methods to be used clinically, their reliability needs to be tested more rigorously using the in vivo gold standard, and their mutual agreement needs to be tested under a broader range of oxygenation conditions.

The purpose of this study was to investigate the reliability and mutual agreement of TRUST and SBO for global S_vO_2 quantification at three different oxygenation levels. We performed TRUST and SBO measurements at the superior sagittal sinus (SSS) in healthy subjects during hypoxia, room air, and hypercapnia. In two of the subjects, validation of S_vO_2 measurements with internal jugular vein catheterization was performed. Repeatability of TRUST and SBO at resting condition was also evaluated.

2 | METHODS

2.1 | Study design

This study was approved by our Institutional Review Board (CCI-12-00338), and all subjects provided written informed consent prior to participation. Thirteen healthy subjects (7 males, 24 to 55 years) were studied. Blood hematocrit was measured in each subject on the same day as the MRI scans. The MRI was performed on a Philips 3T Achieva scanner with a 32-channel head receive coil. Subjects were imaged under three different oxygenation conditions: 1) hypoxia (12% O_2 and 88% N_2), 2) hypercapnia (5% CO_2 and room air), and 3) room air. During image acquisition, the subject was breathing through a mouthpiece with the nose sealed by medical tape and clip. The mouthpiece connected to a 2-L reservoir breathing circuit continuously supplied by gas tanks (Airgas Inc., Radnor, PA). The circuit included one-way valves to prevent partial gas mixture. The 2-L reservoir was sufficient to buffer instantaneous changes in minute ventilation so that subjects experienced resistance-free breathing. Gas flow was controlled at 15 L per minute for room air and hypoxia conditions and 25 L per minute for hypercapnia conditions. Tissue oxygenation was continuously monitored by near-infrared spectroscopy measurement (NIRO 200, Hamamatsu Photonics, Japan) with the probe placed on the skin of the right forehead.

Eleven subjects were scanned without catheterization. The experiment consisted of two parts (Figure 1): a) S_vO_2 measurements using TRUST and SBO under three different oxygenation conditions and b) intersession repeatability evaluation of the two techniques at resting baseline. Pauses of 2 to 3 min were allotted after gas switching. When the subject reached steady oxygenation state (indicated by near-infrared spectroscopy), TRUST and SBO scans were

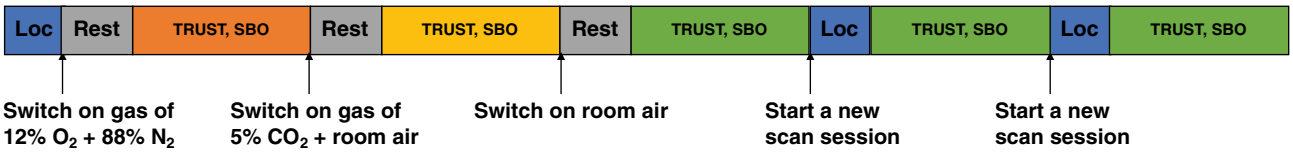

FIGURE 1 Protocol of scan without catheterization. Three scan sessions in the order of hypoxia (orange block), hypercapnia (yellow block) and room air (green block) were first performed. Pauses of 2 to 3 min were allotted (grey blocks), depending on the time needed for the subject to reach steady oxygenation state. Subsequently, two more scan sessions were conducted under room air, in which the subject was repositioned and new pre-scans were played. Order of MRI acquisitions under the same oxygenation state was counterbalanced to avoid bias. TRUST: T2-relaxation-under-spin-tagging; SBO: susceptometry-based oximetry

performed. Order of the MRI acquisitions under the same oxygenation state was counterbalanced to prevent bias. After the first room-air scan session, two more scan sessions, in which repositioning of the subject was followed by new localization and prescans, were performed. In this way, there were in total three scan sessions at baseline, which were used for the analysis of intersession variance. Intersession variance was calculated as $\frac{1}{11}\sum_{i=1}^{11} STD_i$, where STD_i is the standard deviation of baseline S_vO_2 measurements on the ith subject.

Two subjects were scanned after internal jugular vein catheterization with a three French tracker catheter. Subjects were put under different brain oxygenation conditions in the following order: room air, hypoxia, hypercapnia, room air, hypoxia, and hypercapnia. TRUST was continuously performed, while SBO was performed only when the subject reached steady oxygenation state (indicated by near-infrared spectroscopy). During the entire imaging session, 10 mL of blood was drawn from the catheter every 3 min by a cardiologist standing beside the patient table. The final milliliter was used for blood oxygen sampling and the rest of the blood returned to the patient or discarded. The blood sample was delivered out of the scanner room through the wave guide. Oxygen saturation of the blood sample was measured using a portable co-oximeter (Avoximeter 4000, Accriva Diagnostics, CA). The co-oximeter measurement was used as ground truth, against which the TRUST and SBO measurements were evaluated.

2.2 | Venous oxygen saturation measurement using TRUST

The TRUST sequence used in this study was analogous to that described by Lu et al.[8] Scan parameters: four effective echo times at 0, 40, 80, and 160 ms; CPMG $\tau = 10$ ms; voxel size = 3.44 × 3.44 mm^2; field of view = 220 × 220 mm^2; matrix size = 64 × 64; single-shot echo-planar imaging with SENSE rate of 3 and echo time of 3.77 ms; slice thickness = 5 mm; labeling thickness = 100 mm; distance between imaging slice and labeling slab center = 75 mm; inversion time = 1022 ms; repetition time = 3000 ms. We acquired three pairs of control and labeled images at each effective echo time. Total scan time was 1.2 min.

Magnitude difference between the control and labeled images was obtained at each effective echo time (Figure 2A). A region of interest (ROI) of four voxels with the largest difference signal at the location of SSS was manually selected. The T2 of blood was obtained by fitting the difference signal to an exponential decay (Figure 2B) and then correcting the T1 of blood.[8] Following a system upgrade in July 2018, the nonselective postsaturation module in the TRUST sequence as described by Xu et al[21] was inadvertently deactivated, forcing us to correct the resultant T2 underestimation retrospectively on the basis of Bloch simulation. The correction model is detailed in Supporting Information. The bovine blood model[12] was used to convert the T2 of blood to S_vO_2.

2.3 | Venous oxygen saturation measurement using SBO

In SBO, the magnetic field shift inside the vessel, ΔB_0, has a linear relationship with S_vO_2:

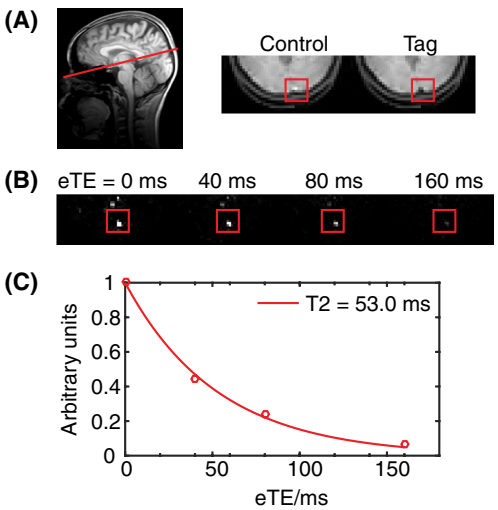

FIGURE 2 (A) Localization of the TRUST imaging plane (red line) at the superior sagittal sinus. (B) Difference images obtained upon subtraction of the control and labeled images at four effective echo times. Red boxes highlight the isolated blood signal at the sagittal sinus. (C) Mono-exponential fitting of the difference signal is performed to estimate T2 of blood

$$\Delta B_0 = \frac{1}{6}\mathrm{Hct}\cdot\Delta\chi_{do}\cdot\left(1-\mathrm{S_vO_2}\right)\cdot(3\cos^2\theta-1)\cdot B_0 \quad (1)$$

where Hct is hematocrit determined from the blood sample, $\Delta\chi_{do}=4\pi(0.27)$ ppm is the intrinsic susceptibility difference between fully deoxygenated and fully oxygenated hemoglobin (in SI units), and θ is the vessel tilt angle with respect to the main B_0 field.

The sequence used for SBO is a 3D multiecho GRE with full flow compensation. Scan parameters are repetition time = 31 ms; four echoes at 4.2, 11.2, 18.2, 25.2 ms; voxel size = $1 \times 1 \times 1.3$ mm^3; FOV = $210 \times 189 \times 109$ mm^3; FA = 17°; BW = 293 Hz/pixel; SENSE rate of 2 in the right-left direction and 1.29 in the head-feet direction. Images were zero-padded to have reconstruction voxel size of $0.46 \times 0.46 \times 1.3$ mm^3. Flow was compensated for all echoes along all spatial axes.[22] Total scan time was 3.5 min.

In this study, SBO image processing was performed in a 3D manner (Figure 3). A B_0 field map was generated from the multiecho phase images using a nonlinear least square fitting algorithm.[23] The SSS was manually segmented on the B_0 field map (Figure 3A). There were four steps to determine the saturation of SSS. Step 1: In every eight continuous axial slices, the segment of SSS approximating a 10-mm-long cylinder was extracted as ROI candidate. For example, if SSS spans in 40 continuous slices, 33 segments (40 − 8 + 1) can be extracted. Step 2: Tilt angle was computed from the central line of each vessel segment. Segments with tilt angle larger than 30° were excluded. Step 3: To estimate the background field due to air-tissue interfaces, a 3D tissue region within 100-pixel distance from the vessel center was defined (Figure 3A). The background field was calculated by first performing a second-order polynomial fit to the B_0 field in the tissue region and then extrapolating the polynomial functions to the vessel region. The B_0 field shift of the vein was obtained by subtracting the background field from the total field (Figure 3B). Step 4: Among all ROI candidates, the one with the lowest intra-ROI variance of the local field was used for the final calculation of SSS S_vO_2 based on Equation (1).

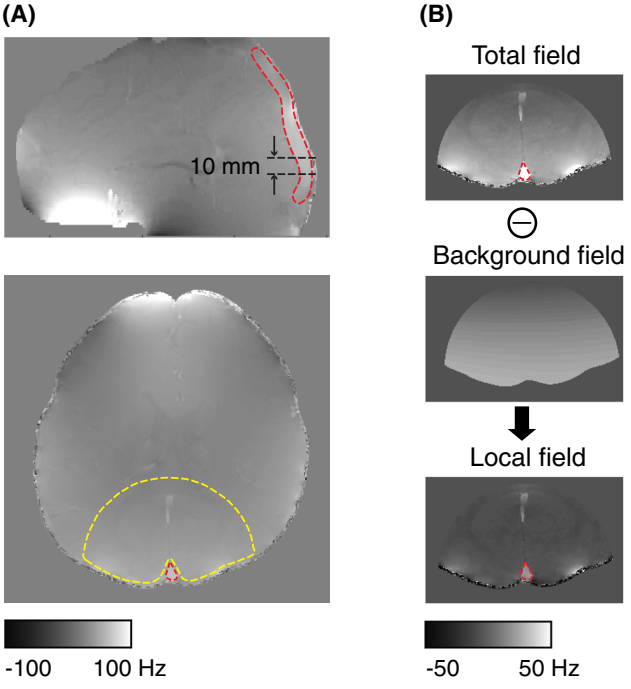

FIGURE 3 Background field removal in SBO. (A) Total B_0 field in sagittal and axial views. Segmentation of the superior sagittal sinus (SSS) is highlighted in red dashed line. Region of interest (ROI) was chosen as a cylindrical segment of SSS with vertical length of 10 mm. Background field was estimated by performing a second-order polynomial fit to the B_0 field in a tissue region within 100-pixel distance from the ROI center (yellow dashed line). (B) Local B_0 field is obtained by extrapolating the background field to the ROI and subtracting it from the total B_0 field

3 | RESULTS

Among the 11 volunteers scanned without catheterization, nine completed TRUST and SBO scans during both hypercapnia and hypoxia challenges. The remaining two volunteers experienced S_aO_2 drop below 80% and thus were not allowed to complete the hypoxia challenge. The two subjects scanned under jugular catheterization completed both the hypercapnia and hypoxia challenges. On average, the inter-session variances of baseline S_vO_2 measurements using TRUST and SBO were 1.7 ± 0.9% and 2.2 ± 1.4% in absolute saturation points, which suggested high repeatability.

3.1 | Comparison of S_vO_2 measurements using TRUST and SBO

S_vO_2 measurements using TRUST (noted as 'S_vO_2-TRUST' in the following) and S_vO_2 measurements using SBO ('S_vO_2-SBO') are compared in Figure 4. S_vO_2-TRUST averaged across the subjects were 74.2 ± 5.2%, 60.7 ± 5.2%, 48.8 ± 4.9% under hypercapnia, room air and hypoxia, and averaged S_vO_2-SBO were 77.5 ± 5.3%, 68.0 ± 5.5%, 59.4 ± 3.6%. One-way analysis of variance showed that S_vO_2-TRUST and S_vO_2-SBO measurements were significantly different under room air ($P < 0.001$) and hypoxia ($P < 0.001$) but comparable under hypercapnia ($P = 0.10$) (Figure 4A). TRUST indicated increased S_vO_2 by 13.5 ± 3.1% from room air to hypercapnia and decreased S_vO_2 by 11.6 ± 4.3% from room air to hypoxia. In comparison, the corresponding changes were considerably smaller measured with SBO: 9.5 ± 3.7% ($P = 0.003$) and 8.5 ± 3.8% ($P = 0.06$) (Figure 4B). A strong linear correlation was observed between S_vO_2-TRUST and S_vO_2-SBO (Pearson $r = 0.91$, $R^2 = 0.84$, Figure 4C). Bland-Altman analysis revealed a significant proportional bias ($P < 0.001$, Figure 4D).

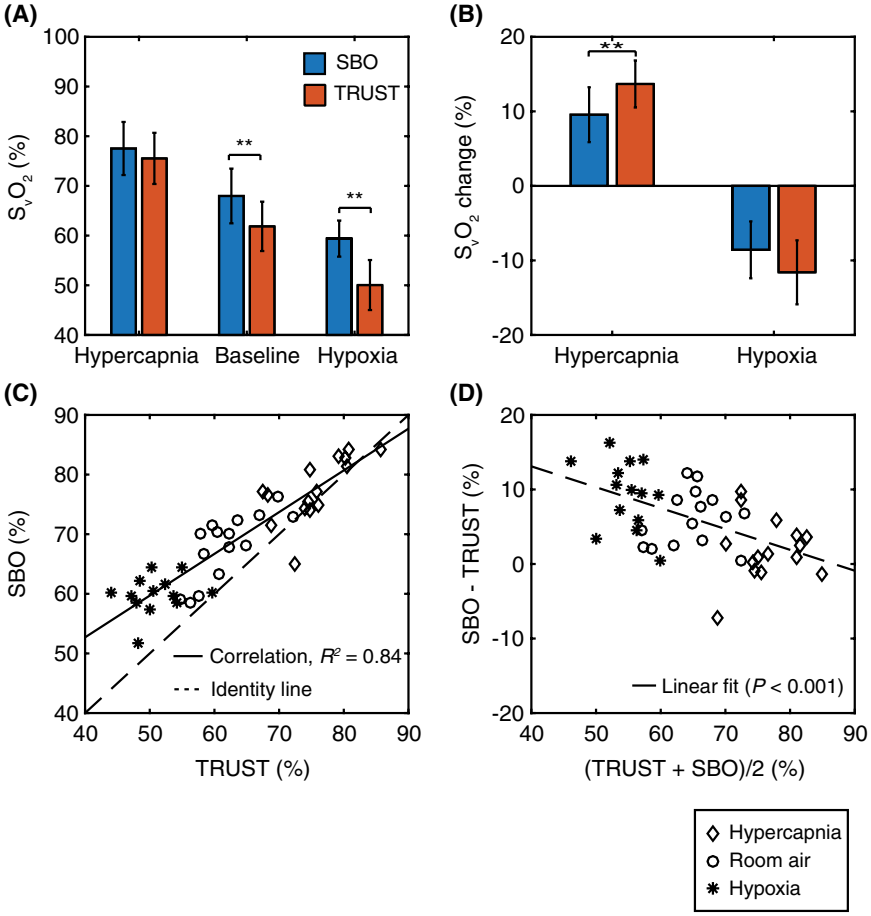

FIGURE 4 Comparison of S_vO_2-TRUST and S_vO_2-SBO measurements at the superior sagittal sinus. (A) S_vO_2-TRUST and S_vO_2-SBO measurements averaged across subjects under each condition. (B) Average change of S_vO_2 from room air to hypercapnia and to hypoxia. (C) Scatterplot of S_vO_2-TRUST and S_vO_2-SBO with the linear correlation regression line (solid) and identity line (dashed). (D) Bland-Altman plot with the average of the two measurements displayed in the horizontal axis and the difference between the two displayed in the vertical axis. **: $P < 0.01$

3.2 | Validation of S_vO_2 measurements with jugular vein catheterization

Figure 5 displays the time-course plots of S_vO_2 measurements under jugular catheterization. In both two subjects, S_vO_2-TRUST closely matched the jugular reference under hypercapnia but was lower than the reference under hypoxia and room air. In comparison, the difference between S_vO_2-SBO and the reference was independent of the physiological state.

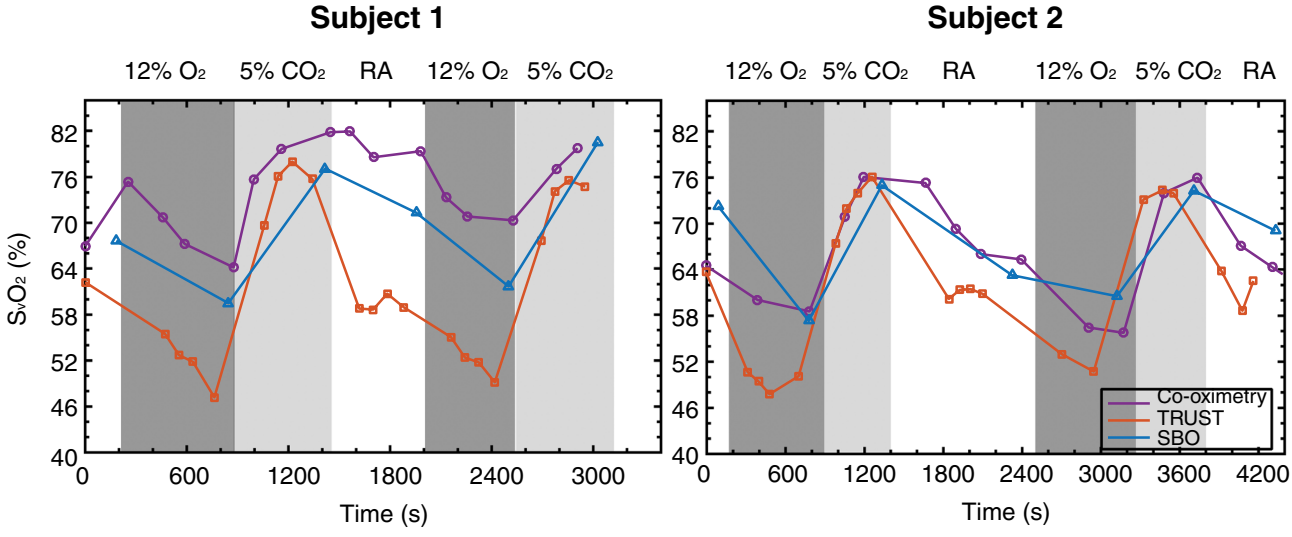

FIGURE 5 Time-course plots of S_vO_2 measurements in two subjects who underwent jugular catheterization. Co-oximeter measurement was repeated approximately every 3 min (purple circles), S_vO_2-TRUST measurement at the superior sagittal sinus was repeated approximately every 1.5 min (orange square), and S_vO_2-SBO measurement was only performed when steady state was achieved under each gas condition (blue triangle). Dark gray, light gray and white blocks indicate the duration of hypoxia ("12% O_2"), hypercapnia ("5% CO_2") and room air ("RA") conditions

All S_vO_2-TRUST measurements (28 in total) were compared with time-aligned co-oximetry reference. All SBO measurements (13 in total) were compared with co-oximetry reference during steady oxygenation states (Figure 6). On average, the bias between S_vO_2-TRUST and the co-oximetry reference was $-10.2 \pm 7.6\%$ in absolute saturation points ($P < 0.0001$), while the bias between S_vO_2-SBO and reference was $-1.0 \pm 4.9\%$ ($P = 0.45$). Another T2 calibration model based on healthy human blood ("human HbA model")[24] was also applied to convert the intravascular T2 into S_vO_2 (not shown). We observed that the bias between TRUST and the reference did not vary significantly with the choice of T2 calibration model (Supporting Information Figure S5).

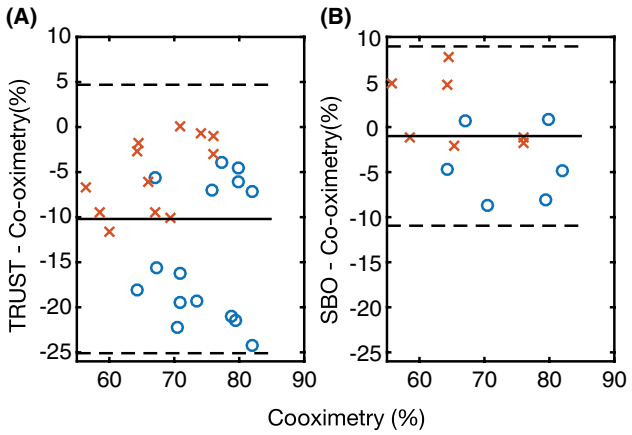

FIGURE 6 Comparison of TRUST and SBO measurements against the co-oximeter reference. (A) 15 S_vO_2-TRUST measurements from Subject 1 (blue circle) and 13 from Subject 2 (red cross) are compared against the time-aligned co-oximeter reference. Taken all data points, the mean bias of SvO_2-TRUST is -10.2% ($P < 0.0001$). (B) Six S_vO_2-SBO measurements from Subject 1 and seven from Subject 2 are compared against the co-oximeter reference during steady oxygenation states. Taken all data points, the mean bias of S_vO_2-SBO is -1.0% ($P = 0.45$)

4 | DISCUSSION

Although previous studies have demonstrated the accuracy and repeatability of T2-based[16,17,25] and susceptibility-based[9,18] S_vO_2 quantification, this is the first validation of MRI-based S_vO_2 measurements with internal jugular catheterization. Furthermore, this study performed the comparison of the two categories of techniques across a broad range of saturation levels (from 45% to 84%) in three different oxygenation states. The mean S_vO_2 values obtained at room air, hypoxia and hypercapnia conditions were comparable to those reported in previous TRUST and SBO studies (Table 1). The inter-subject and inter-session variances of S_vO_2 measurement were also in line with literature values,[19,25] supporting the validity of our results.

4.1 | Validation with jugular vein catheterization

In both of the two subjects scanned with jugular catheterization, S_vO_2-TRUST measurements were close to the reference

TABLE 1 Literature values of venous oxygen saturation measurement at the superior sagittal sinus under different physiological conditions

Physiological State	Method	S_vO_2 (%)	S_vO_2 Change (%)[a]	Reference
Hypercapnia	TRUST	78.2 ± 1.4	15.8	Xu et al., 2011[16]
	TRUST	78.4 ± 3.5	16.1	Rodgers et al., 2015[20]
	TRUST	74.2 ± 5.2	13.5	This study
	SBO	77.2 ± 4.8	10.5	Rodgers et al., 2015[20]
	SBO	78 ± 5	13	Jain et al., 2011[18]
	SBO	77.5 ± 5.3	9.5	This study
Hypoxia	TRUST	54.6 ± 1.1[b]	10.5	Xu et al., 2012[17]
	TRUST	48.8 ± 4.9	11.6	This study
	SBO	59.4 ± 3.6	8.5	This study
Room air	TRUST	61 to 65		Xu et al., 2011;[16] Xu et al., 2012;[17] Liu et al., 2013[25]
	TRUST	60.7 ± 5.2		This study
	SBO	64.0 to 68.6		Jain et al., 2010,[9] 2011;[18] Barhoum et al., 2015;[19] Rodgers et al., 2015[20]
	SBO	68.0 ± 5.5		This study

[a] S_vO_2 change from room air is presented in absolute saturation points.
[b] Hypoxia challenge was induced by inhalation of 14% O_2 and 86% N_2.

under hypercapnia. However, TRUST yielded lower S_vO_2 values under hypoxia and room air than the reference. Compared to TRUST, SBO provided closer agreement with the jugular reference (Figure 6).

SSS drains the cerebral cortex, while the internal jugular vein (IJV) combines the drainage from not only SSS but also the straight sinus (SS), which is a major vein draining deep brain regions. One could logically question whether IJV is an adequate reference. In fact, the saturation difference between SSS and IJV has been well characterized (1-2% under resting conditions),[26,27] which is much smaller than the discrepancy we observed between the TRUST measurement and the jugular reference. Furthermore, previous studies have showed that SSS and SS contributed about 60% and 20% of the blood flow in IJV, and this blood flow distribution remained the same regardless of oxygenation conditions.[26] As a supplemental part of the study, we have also measured the saturation of SS using TRUST in the 11 subjects scanned without jugular catheterization (Supporting Information). S_vO_2-TRUST of SS was systematically higher than that of SSS under all three conditions (hypoxia 5.7 ± 5.1%, $P = 0.02$; room air 4.5 ± 3.0%, $P = 0.08$; hypercapnia 2.3 ± 3.0%, $P = 0.37$), in line with previous studies.[26-28] Using these saturation differences and the previously published flow distribution ratios, we estimated a worst-case 2.0% deviation between SSS and IJV saturations, which is much smaller than our observation (Figure 6).

Flow through an inhomogeneous magnetic field can cause intravoxel dephasing,[29,30] which has not been accounted for in conventional TRUST quantification. If the B_0 field variation is approximated as a gradient field of 1500 Hz/m concurrently playing with the T2-preparation module (Supporting Information Figure S3), intravoxel dephasing due to flow at 20 cm/s can induce signal loss of 2%, 9% and 34% at effective echo time of 40 ms, 80 ms and 160 ms respectively (Supporting Information Figure S4). Such signal loss can cause T2 underestimation and further translate to saturation underestimation. At true saturation of 55% (representative of hypoxia saturation) and 85% (representative of hypercapnia saturation), saturation can be underestimated by 2% and 7% respectively (Supporting Information Figure S4C). The pattern of estimation error (small during hypoxia, large during hypercapnia) was opposite to our observation. Therefore, although flow-induced intravoxel dephasing might exist, the factor alone can hardly explain the observed discrepancy between TRUST and the reference. Related simulation is detailed in Supporting Information.

We postulate that the discrepancy between TRUST and the jugular reference under hypoxia and room air may originate from the calibration models used in TRUST. Experiment by Lu et al showed that arterial saturation measured by TRUST matched closely with pulse-oximeter measurement under hypoxia.[12] However, it should be noted that the pH and pCO_2 of arterial blood were relatively tightly controlled in the previous experiment. In fact, previous in-vitro TRUST calibrations (both bovine and human blood) have been performed under controlled gas conditions, all approximating those found in arterial blood (pH ~ 7.4 and pCO_2 ~ 40 torr). In this study, co-oximeter measurement of the jugular blood sample reported pH of 7.37 and pCO_2 of 50 torr under room air condition. Hypoxia can stimulate increased minute ventilation, leading to hypocapnia (decreased blood pCO_2) and respiratory alkalosis (increased blood pH). Under hypoxia, pH and pCO_2 were measured 7.40 and 35 torr respectively. In contrast, hypercapnia can increase pCO_2 (55 torr measured in this study) and produce mild acidosis (pH measured 7.32). Conceivable fluctuations in pCO_2 and pH might modulate the membrane properties of red blood cells, which in turn can alter the T2-saturation relationship.[31,32] However, this hypothesis requires further investigation.

4.2 | Comparison of T2- and susceptibility-based S_vO_2 measurements

The proportional bias between TRUST and SBO has been suggested by several prior studies,[19,20] but we demonstrated it in the broad oxygenation range produced. Compared to SBO, TRUST presented significantly lower S_vO_2 values under room air and hypoxia conditions but comparable S_vO_2 values under hypercapnia. Previous study by Barhoum et al[19] also reported lower S_vO_2-TRUST than S_vO_2-SBO under room air condition, although the difference is smaller than our observation. TRUST indicated a significantly bigger increase of S_vO_2 induced by hypercapnia challenge than SBO, which agrees with the previous findings by Rodgers et al.[20] Such bias between the two techniques can be big enough to produce conflicting interpretation on the change of cerebral metabolic rate of oxygen consumption ($CMRO_2$), as suggested by Rodgers et al.[20] The comparison of TRUST and SBO based on datasets acquired without catheterization was in line with the observation in the jugular validation experiment. Therefore, we believe the difference between TRUST and SBO measurements could essentially be a state-dependent S_vO_2 underestimation by TRUST.

4.3 | Variance in SBO measurement

Although validation with the jugular catheterization suggested smaller bias of SBO than TRUST, SBO has major challenges for use in the SSS. In the conventional 2D implementation of SBO, location of an axial slice intersecting the SSS is usually determined by visual inspection on a survey or venography scan.[9] In this study, we acquired 3D whole-brain GRE datasets. The purpose was to investigate the variance of SBO measurement along the slice direction (i.e. the

head-feet direction), an issue overlooked in previous SBO studies. We measured S_vO_2 at each viable axial slice (vessel tilt < 30°)[15,33] using a processing approach similar to Ref 9. A variation range of 22% (absolute saturation points) was observed for S_vO_2 measurements across slices (Supporting Information Figure S6). Such high variance along the slice direction will lessen the confidence of using 2D acquisition for absolute S_vO_2 quantification and $CMRO_2$ assessment.

Numerical simulations based on realistic 3D models of SSS showed that the error of S_vO_2-SBO measurement was within 5% for vessels whose tilt angles were less than 30°.[15,33] Phantom experiments by Langham et al[15] revealed errors less than 2% resulting from non-circular vessel cross section. These data supported the validity of the long cylinder approximation. However, the variance of S_vO_2-SBO measurement can be contributed by other factors, including incomplete background field removal and blood flow. In this study, background field was estimated by fitting the B_0 field variation to a second-order polynomial after masking out the SSS, but accuracy of this approach has only been verified in phantoms and the femoral veins.[34] SSS is near the brain tissue boundary, where the background field arising from air-tissue interfaces can have higher orders of spatial variation. In the future, modeling the background field with subject-specific susceptibility models[35] and prior knowledge of scanner shimming may improve the accuracy of SBO. Moreover, spins flowing through an inhomogeneous magnetic field can cause quadratic phase evolution in gradient echo acquisition. Xu et al[22] demonstrated that using linear phase fitting to obtain the B_0 field shift of veins could cause susceptibility estimation error, the size of which depended on both the blood velocity and the B_0 field variation. Future studies are needed to investigate whether quadratic phase fitting can reduce the measurement variance of SBO.

4.4 | Practical considerations of TRUST and SBO

TRUST has been used to measure brain oxygenation changes in response to hypercapnia,[16] hyperoxia,[17] hypoxia,[17] and caffeine challenges[28] and in disease states such as multiple sclerosis[4] and sickle cell anemia.[3] The wide application of TRUST is motivated by its high reproducibility and ease of use. TRUST has been shown with test-retest probability < 2% (absolute saturation points)[25] and comparable variability across five major imaging centers.[36] The blood isolation feature also exempts the operator dependence of ROI selection. However, before the previously discussed biases are confirmed and corrected, caution should be placed when TRUST is used or compared under different physiological conditions. For diseases that provide drastically different blood properties from existing in-vitro calibration materials, like sickle cell anemia, calibration models should also be reconsidered.[3]

Previous studies have demonstrated the utility of SBO for quantifying S_vO_2 in the internal jugular,[37] SSS,[9] and femoral veins.[15] One advantage of SBO is that it does not require calibration experiments, making it robust to derangements of red blood cell shape and permeability. SBO with single axial slice acquisition, combined with phase-contrast CBF measurement, has been applied to study the change of $CMRO_2$ at high temporal resolution.[18,20,38] However, absolute S_vO_2 measurement in boundary veins such as the SSS requires caution due to inadequate compensation of background fields. Despite uncertainly in absolute S_vO_2 quantification, S_vO_2 changes measured by SBO are likely to be robust to background field errors and may serve to track responses to physiological perturbations.

4.5 | Limitations

This study has limitations. First, internal jugular vein data was only obtained in two subjects, because it was challenging to recruit subjects to this study arm. We do not fully understand the inter-subject variability in the difference between TRUST and co-oximetry reference (average difference was −14.1% in Subject 1 and −5.2% in Subject 2). Subject 1 was older, born prematurely, and had mild restrictive lung disease. He may have needed to raise his minute ventilation to a greater extent in response to 12% oxygen to maintain adequate saturation, which could have lowered his blood pCO_2 moreso than Subject 2 and potentially impacted the TRUST calibration. Despite the noticeable difference between the two subjects, all TRUST measurements acquired under room air and hypoxic conditions (19 samples) were lower than their corresponding co-oximetry references, suggesting that the TRUST bias was larger than measurement variability. To design a more complete validation study with jugular catheterization, a rough power analysis could be performed using the variances of the paired difference between TRUST and jugular reference observed within Subject 1 and 2 (7.4% and 4.2% respectively). For example, to detect a 5% saturation measurement bias between TRUST and jugular catheterization, one would need 9 to 21 subjects, assuming the standard deviation of the difference to be 4.2% to 7.4%. To detect a systemic bias of 5% between SBO and jugular catheterization, 11 subjects would be needed assuming the standard deviation of the difference to be 4.9%.

Another limitation lies in the long data acquisition time (3.5 min) for SBO, mainly due to the 3D whole-brain spatial coverage. The purpose of choosing a large FOV was to investigate the sensitivity of SBO measurement to ROI slice position. We obtained relatively stable S_vO_2-SBO measurements by extracting a pool of viable SSS segments and then selecting the one with the smallest intra-segment variance for the final determination of vessel susceptibility. However, optimal ROI selection criteria and suitable spatial coverage need to

be determined in future studies. Acceleration schemes such as sparse sampling or non-Cartesian acquisition[39,40] may also be incorporated to shorten the scan time. Thirdly, end-tidal gases were not monitored or controlled in the experiments. There could be inter-subject variability in achieved hypoxia and hypercapnia levels. In the future, we plan to overcome this limitation by using breathing apparatus that can independently record and manipulate end-tidal gas levels.[41]

Lastly, our implementation of the TRUST sequence (Supporting Information Figure S1) did not include the post-saturation module proposed by Xu et al[21] to reset the longitudinal magnetization of blood spins every TR. T2 underestimation due to spin history was modeled and retrospectively corrected based on Bloch simulation. Assuming bovine calibration model, such T2 underestimation translated to saturation underestimation that was relatively constant (3.3% to 4.5%) across the achieved saturation range (Supporting Information Figure S2). Although the T2 underestimation correction needs further in-vivo validation, its relatively constant effect on saturation values can hardly explain the observed proportional bias between S_vO_2-TRUST and S_vO_2-SBO. In fact, when TRUST was compared with the other two methods (SBO and jugular catheterization), the same trends remained whether with or without the T2 correction.

5 | CONCLUSIONS

We have performed a systematic comparison of T2- and susceptibility-based S_vO_2 quantification at a broad range of physiological states; validation with internal jugular catheterization was also performed in two subjects. Under hypoxia and room air conditions, TRUST yielded systematically lower saturation values than SBO and jugular catheterization. While TRUST and SBO responded concordantly with gas challenges, the magnitude of S_vO_2 change was higher for TRUST than SBO and jugular catheterization. Taken together, these data suggest the need to validate the calibration models used by TRUST under realistic blood gas and flow conditions. While S_vO_2 measurement by SBO was unbiased with respect to the jugular reference across physiological states, we found the measurements highly sensitive to imaging slice position. The results suggested that caution should be taken for comparison of absolute S_vO_2 measurements using either TRUST or SBO.

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CONFLICT OF INTEREST

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REFERENCES

1. Geisler BS, Brandhoff F, Fiehler J, et al. Blood oxygen level-dependent MRI allows metabolic description of tissue at risk in acute stroke patients. *Stroke*. 2006;37:1778–1784.
2. Jordan LC, Gindville MC, Scott AO, et al. Non-invasive imaging of oxygen extraction fraction in adults with sickle cell anaemia. *Brain*. 2016;139:738–750.
3. Bush AM, Coates TD, Wood JC. Diminished cerebral oxygen extraction and metabolic rate in sickle cell disease using T2 relaxation under spin tagging MRI. *Magn Reson Med*. 2018;80:294–303.
4. Ge Y, Zhang Z, Lu H, et al. Characterizing brain oxygen metabolism in patients with multiple sclerosis with T2-relaxation-under-spin-tagging MRI. *J Cereb Blood Flow Metab*. 2012;32:403–412.
5. Schell RM, Cole DJ. Cerebral monitoring: jugular venous oximetry. *Anesth Analg*. 2000;90:559–566.
6. Mintun MA, Raichle ME, Martin WR, Herscovitch P. Brain oxygen utilization measured with O-15 radiotracers and positron emission tomography. *J Nucl Med*. 1984;25:177–187.
7. Haacke EM, Lai S, Reichenbach JR, et al. 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. *Hum Brain Mapp*. 1997;5:341–346.
8. Lu H, Ge Y. Quantitative evaluation of oxygenation in venous vessels using T2-Relaxation-Under-Spin-Tagging MRI. *Magn Reson Med*. 2008;60:357–363.
9. Jain V, Langham MC, Wehrli FW. MRI estimation of global brain oxygen consumption rate. *J Cereb Blood Flow Metab*. 2010;30:1598–1607.
10. Fan AP, Benner T, Bolar DS, Rosen BR, Adalsteinsson E. Phase-based regional oxygen metabolism (PROM) using MRI. *Magn Reson Med*. 2012;67:669–678.
11. Fan AP, Bilgic B, Gagnon L, et al. Quantitative oxygenation venography from MRI phase. *Magn Reson Med*. 2014;72:149–159.
12. Lu H, Xu F, Grgac K, Liu P, Qin Q, van Zijl P. Calibration and validation of TRUST MRI for the estimation of cerebral blood oxygenation. *Magn Reson Med*. 2012;67:42–49.
13. Spees WM, Yablonskiy DA, Oswood MC, Ackerman JJH. Water proton MR properties of human blood at 1.5 Tesla: Magnetic susceptibility, T1,T2,T*2, and non-Lorentzian signal behavior. *Magn Reson Med*. 2001;45:533–542.

14. Weisskoff RM, Kiihne S. MRI susceptometry: Image-based measurement of absolute susceptibility of MR contrast agents and human blood. *Magn Reson Med*. 1992;24:375–383.
15. 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;62:333–340.
16. Xu F, Uh J, Brier MR, et al. The influence of carbon dioxide on brain activity and metabolism in conscious humans. *J Cereb Blood Flow Metab*. 2011;31:58–67.
17. Xu F, Liu P, Pascual JM, Xiao G, Lu H. Effect of hypoxia and hyperoxia on cerebral blood flow, blood oxygenation, and oxidative metabolism. *J Cereb Blood Flow Metab*. 2012;32:1909–1918.
18. Jain V, Langham MC, Floyd TF, Jain G, Magland JF, Wehrli FW. Rapid magnetic resonance measurement of global cerebral metabolic rate of oxygen consumption in humans during rest and hypercapnia. *J Cereb Blood Flow Metab*. 2011;31:1504–1512.
19. Barhoum S, Rodgers ZB, Langham M, Magland JF, Li C, Wehrli FW. Comparison of MRI methods for measuring whole-brain venous oxygen saturation. *Magn Reson Med*. 2015;73:2122–2128.
20. Rodgers ZB, Englund EK, Langham MC, Magland JF, Wehrli FW. Rapid T2- and susceptometry-based CMRO2 quantification with interleaved TRUST (iTRUST). *NeuroImage*. 2015;106:441–450.
21. Xu F, Uh J, Liu P, Lu H. On improving the speed and reliability of T2-relaxation-under-spin-tagging (TRUST) MRI. *Magn Reson Med*. 2012;68:198–204.
22. Xu B, Liu T, Spincemaille P, Prince M, Wang Y. Flow compensated quantitative susceptibility mapping for venous oxygenation imaging. *Magn Reson Med*. 2014;72:438–445.
23. Liu T, Wisnieff C, Lou M, Chen W, Spincemaille P, Wang Y. Nonlinear formulation of the magnetic field to source relationship for robust quantitative susceptibility mapping. *Magn Reson Med*. 2013;69:467–476.
24. Bush A, Borzage M, Detterich J, et al. Empirical model of human blood transverse relaxation at 3 T improves MRI T2 oximetry. *Magn Reson Med*. 2017;77:2364–2371.
25. Liu P, Xu F, Lu H. Test-retest reproducibility of a rapid method to measure brain oxygen metabolism. *Magn Reson Med*. 2013;69:675–681.
26. De Vis JB, Lu H, Ravi H, Hendrikse J, Liu P. Spatial distribution of flow and oxygenation in the cerebral venous drainage system. *J Magn Reson Imaging*. 2018;47:1091–1098.
27. Jain V, Magland J, Langham M, Wehrli FW. High temporal resolution in vivo blood oximetry via projection-based T 2 measurement. *Magn Reson Med*. 2013;70:785–790.
28. Krishnamurthy LC, Liu P, Ge Y, Lu H. Vessel-specific quantification of blood oxygenation with T 2-relaxation-under-phase-contrast MRI. *Magn Reson Med*. 2014;71:978–989.
29. Fan Z, Sheehan J, Bi X, Liu X, Carr J, Li D. 3D noncontrast MR angiography of the distal lower extremities using flow-sensitive dephasing (FSD)-prepared balanced SSFP. *Magn Reson Med*. 2009;62:1523–1532.
30. Brown RW, Haacke EM, Cheng YC, Thompson MR, Venkatesan R. *Magnetic Resonance Imaging: Physical Principles and Sequence Design*. New York, NY: John Wiley & Sons; 1999:673–675.
31. Morariu VV, Pop VI, Popescu O, Benga G. Effects of temperature and pH on the water exchange through erythrocyte membranes: nuclear magnetic resonance studies. *J Membr Biol*. 1981;62:1–5.
32. Wright GA, Hu BS, Macovski A. Estimating oxygen saturation of blood in vivo with MR imaging at 1.5 T. *J Magn Reson Imaging*. 1991;1:275–283.
33. Li C, Langham MC, Epstein CL, et al. Accuracy of the cylinder approximation for susceptometric measurement of intravascular oxygen saturation. *Magn Reson Med*. 2012;67:808–813.
34. 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;61:626–633.
35. Liu J, de Zwart JA, van Gelderen P, Murphy-Boesch J, Duyn JH. Effect of head motion on MRI B0 field distribution. *Magn Reson Med*. 2018;80:2538–2548.
36. Liu P, Dimitrov I, Andrews T, et al. Multisite evaluations of a T 2 - relaxation-under-spin-tagging (TRUST) MRI technique to measure brain oxygenation. *Magn Reson Med*. 2016;75:680–687.
37. Fernández-Seara MA, Techawiboonwong A, Detre JA, Wehrli FW. MR susceptometry for measuring global brain oxygen extraction. *Magn Reson Med*. 2006;55:967–973.
38. Barhoum S, Langham MC, Magland JF, et al. Method for rapid MRI quantification of global cerebral metabolic rate of oxygen. *J Cereb Blood Flow Metab*. 2015;35:1616–1622.
39. Rodgers ZB, Jain V, Englund EK, Langham MC, Wehrli FW. High temporal resolution MRI quantification of global cerebral metabolic rate of oxygen consumption in response to apneic challenge. *J Cereb Blood Flow Metab*. 2013;33:1514–1522.
40. Cao W, Chang YV, Englund EK, et al. High-speed whole-brain oximetry by golden-angle radial MRI. *Magn Reson Med*. 2018;79:217–223.
41. Fan AP, Evans KC, Stout JN, Rosen BR, Adalsteinsson E. Regional quantification of cerebral venous oxygenation from MRI susceptibility during hypercapnia. *NeuroImage*. 2015;104:146–155.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

FIGURE S1 Pulse sequences experienced by blood spins in two consecutive TRs. The TRUST sequence acquires control and labeled images in an interleaved manner. Blood spins are assumed to locate in the labeling slab during the previous TR and stay in the imaging slice during the current TR. (top) Illustration of control imaging, in which blood spins have experienced an inversion RF pulse and a T2-preparation module in the previous TR. (bottom) Illustration of tag imaging, in which blood spins have only experienced a T2-preparation module in the previous TR

FIGURE S2 Simulation of T2 underestimation caused by short TR. A. T2 estimated from mono-exponential fitting is plotted against the true T2 (ms) in cases of different TRs (s). B. Assuming Hct = 0.42, T2 underestimation is converted into saturation underestimation using the bovine blood calibration model

FIGURE S3 Comparison of the T2-preparation module without (A) and with (B) B_0 field inhomogeneity (approximated as a gradient field, $G_{\Delta B0}$)

FIGURE S4 Effect of intra-voxel dephasing on T2 estimation, assuming the B_0 field variation as a gradient field of 1500 Hz/m. A. Signal loss ratio (%) depends on both the spin velocity (cm/s) and the duration of the CPMG T2-prep module (ms). B. T2 estimated from single-exponential fitting is plotted against the true T2 (ms) in cases of different spin velocities. C. Using the bovine blood model and assuming Hct of 0.42, simulated saturation error increases with spin velocity (cm/s) and the true saturation

FIGURE S5 Time-course plots of S_vO_2 measurements using co-oximeter (purple), TRUST with bovine blood model (orange) and TRUST with HbA model (blue) in two subjects who underwent jugular catheterization

FIGURE S6 Large variation of S_vO_2-SBO measurement along the head-feet direction. Each subplot represents one subject. The 2D S_vO_2-SBO measurement (horizontal axis) is plotted as a function of slice index (vertical axis). Measurements under hypercapnia, hypoxia and room air are represented as red, yellow and blue lines. Susceptibility of SSS measured under room air condition is converted to S_vO_2 values and plotted in sagittal view aligning with the vertical axis of the S_vO_2 plot. Orientation of the main B_0 field is labeled

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