Venous Oxygenation in Sickle Cell Patients and Controls using Quantitative Susceptibility Mapping versus T2-relaxation-under-spin-tagging

Hanna A. Stottbury1, Russell Murdoch2, Patrick Hales1, Janine M. Kawadler1, Melanie Kölbel1, David Carmichael3, Chris A. Clark1, Fenella Kirkham4, and Karin Struemer5

1Imaging and Biophysics, Developmental Neurosciences, UCL Great Ormond Street Institute of Child Health, London, United Kingdom, 2Department of Medical Physics and Biomedical Engineering, University College London, London, United Kingdom, 3Biomedical Engineering & Imaging Sciences, Kings College London, London, United Kingdom

Synopsis

In 15 homozygous sickle-cell disease patients (SCD; hemoglobin-SS) and 12 healthy controls (HC; 10 Hb-AA, 2 Hb-AS), we compared a quantitative susceptibility mapping (QSM)-based estimate of venous oxygen saturation (Yv) with T2-relaxation-under-spin-tagging (TRUST)-based estimates using bovine-hemoglobin (TRUST-HbBV), hemoglobin-S (TRUST-HbS), or hemoglobin-A (TRUST-HbA) calibrations. Agreement between methods varied, with QSM-Yv estimates in HC and SCD respectively on average 5-6% higher versus TRUST-HbBV, 5% higher and 9% lower versus TRUST-HbS, and 9% higher and 2% lower versus TRUST-HbA. Across all comparisons, the limits of agreement were wide (18-26%) underscoring the need for further studies comparing non-invasive methods with gold-standard jugular vein catheterization.

Introduction

Interest has grown in the potential for MRI estimates of venous oxygen saturation (Yv) to improve neurological risk prediction in sickle cell disease (SCD)1-3. However, many oxygen-sensitive MRI techniques rely on calibration models, which may be invalid in conditions such as SCD where alterations in blood rheology challenge assumptions.

T2-relaxation-under-spin-tagging (TRUST) is used widely for estimating Yv based on the principle that the transverse relaxation time (T2) of blood is dependent on its oxygenation saturation4. Whilst TRUST has revealed changes in Yv in SCD, Yv can appear either elevated or reduced depending on whether the calibration model is based on bovine-hemoglobin (HbBV)5-4, hemoglobin-A (HbA)5, or hemoglobin-S (HbS)5 blood.

Yv can also be measured using quantitative susceptibility mapping (QSM) which calculates the spatial distribution of magnetic susceptibility (χ) from gradient-echo phase images5. QSM assumes that χ measured in venous voxels (ve-water) is linearly related to Yv by:

\[ Y_v = 1 - \frac{\Delta \chi_{oxy-wat} - \Delta \chi_{deo-wat}}{\Delta \chi_{deo-wat}} \frac{Hc_t}{Hc} \]  

where hematocrit (Hct) is the percentage of erythrocytes in blood, \( \Delta \chi_{deo} \) is the χ shift between fully oxygenated and deoxygenated erythrocytes (0.27x4π ppm [SI]) and \( \Delta \chi_{oxy-water} \) is the χ shift between oxygenated erythrocytes and water (-0.03x4π ppm [SI]).

Previous work has demonstrated no significant χ difference between deoxygenated hemoglobin in sickle and normal erythrocytes5, suggesting that QSM may be valid in both SCD and healthy controls (HC). Moreover, whereas TRUST only provides an estimate of global Yv from the T2 relaxation within a few voxels, QSM provides estimates throughout the venous vasculature. Despite these potential advantages, there have been no QSM-Yv studies in SCD. Therefore, aiming to improve our understanding of Yv estimation in SCD, we compared agreement between QSM and TRUST estimates.

Methods

15 SCD patients (median age=19.80 years, 7 male) and 12 HC (race- and age-matched, median age=20.30 years, 4 male, 2 HbAS) underwent MRI and pulse oximetry for estimation of peripheral oxygen saturation (SpO2). We used literature values of 0.47 for hematocrit in HC males6, 0.41 in HC females6, 0.27 in SCD males7, and 0.25 in SCD females7.

Magnetic resonance imaging (MRI) was acquired using a 3T Siemens Prisma system with 80 mT/m gradients and a 64-channel receiver coil. The protocol included established TRUST sequences (Fig. 1). MRI Processing

Figures

<table>
<thead>
<tr>
<th>Method</th>
<th>MPM PD-w</th>
<th>MPM T1-w</th>
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As described previously\textsuperscript{12}, to isolate signal from the superior sagittal sinus (SSS), labelled TRUST images were subtracted from unlabelled images, providing difference images for each of the eTEs. A region of interest (ROI) was then manually drawn around the SSS, within which the four voxels with the highest signal intensities were selected (Fig. 2). The average intensity for each eTE was then used to fit blood $T_2$ over eTE, with blood $T_1$ estimated from hematocrit and $SpO_2$\textsuperscript{13}. Calibration models based on HbBV\textsuperscript{4}, HbS\textsuperscript{2}, and HbA\textsuperscript{2} blood were then used to convert $T_2$ to $Y_v$.

QSM were calculated from the three MPM sequences via the following pipeline: B0 field maps were obtained from a nonlinear fit of the complex images\textsuperscript{14} and underwent phase unwrapping with SEGUE\textsuperscript{15} and background field removal using Projection onto Dipole Fields\textsuperscript{16}. Field-to-$\chi$ inversion was performed using Tikhonov regularization\textsuperscript{17} with regularization parameter $\lambda=0.06$, selected using L-Curve methods. Brain masks were calculated from the final-echo PD-w magnitude image using FSL BET\textsuperscript{18}. $\chi$ maps from the three MPM sequences were then averaged. A single ROI was segmented from the SSS using a semi-automated approach in ITK-SNAP\textsuperscript{19}, based on thresholding the average $\chi$ map. The average $\chi$ within the ROI was then substituted into equation 1 to estimate $Y_v$ (Fig. 2).

**Results**

Whereas QSM and TRUST-HbBV estimates of $Y_v$ were significantly lower in SCD compared to HC, TRUST-HbS estimates were significantly higher (Fig. 3). There were no significant between-group differences in TRUST-HbA estimates.

QSM and TRUST methods were moderately correlated in HC, but not in SCD (Fig. 4). Although no proportional bias between methods was observed, agreement varied with QSM-$Y_v$ estimates on average 5-6\% higher in both HC and SCD compared to TRUST-HbBV, 5\% higher in HC and 9\% lower in SCD compared to TRUST-HbS, and 9\% higher in HC and 2\% lower in SCD compared to TRUST-HbA (Fig. 5).

**Discussion**

The directions of the estimated mean difference in $Y_v$ between SCD and HC for different TRUST calibration models were similar to those described in prior literature\textsuperscript{1,2,8,20}. In this regard, QSM-based estimates were most closely aligned with TRUST estimates with HbBV calibration. Strengthening the argument for their potential validity in SCD, the QSM and TRUST-HbBV results were also in line with those from prior MRP\textsuperscript{21} and PET studies\textsuperscript{22}.

Aside from one outlier, the range for $Y_v$ in HC was narrower using QSM. Moreover, QSM- and TRUST-based estimates of $Y_v$ were only moderately correlated in HC. The small sample size, along with our reliance on literature averages for hematocrit may, in part, account for the poor concordance observed in patients. At the individual level, agreement between methods varied substantially, with wide limits of agreement (18-26\%) observed in both SCD and HC.

**Conclusion**

These findings indicate variable agreement between QSM and TRUST estimates of $Y_v$ in SCD and HC, underscoring the need for work comparing non-invasive MRI methods with gold-standard jugular vein catheterization.

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**References**


