Assessing Reproducibility and Changes in Oxygenation with R2' during Clinical Hypercapnic and Hypoxic Gas Challenges

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Target audience: Neuroimaging clinicians and researchers interested in oxygenation mapping

Purpose: Oxygenation mapping provides invaluable information on brain physiology and pathology. One approach to validate such measurements is with gas challenges, where observed changes in MR parameters are attributed to oxygenation changes. In this study, we focused on changes in R2' (=R2*-R2), a direct measure of susceptibility, as modeled in the quantitative BOLD approach[1]. We performed hypercapnic and hypoxic challenges to demonstrate the sensitivity of R2' to changes in brain oxygenation, and assessed intra-scan reproducibility using repeated measurements

Methods: With IRB approval, 14 normal subjects (25-37y, 8 male) participated in hypercapnic and hypoxic studies (N = 8 and 6, respectively). The experimental setup utilized facemasks (Hi-Ox, Ceretec Inc.) for gas delivery, with oximetry and capnography monitoring (Medrad Veris 8600). During baseline, hypercapnic, and hypoxic epochs, subjects breathed medical air, 5% CO_2/21% O_2/84% N_2 gas mix, and 14% O_2/86% N_2 gas mix, respectively. Scanning was performed at 3T (MR750, GE Healthcare) using the paradigm in Fig 1. R2' mapping was performed with a modified GESFIDE sequence (Fig 2) with resolution 1.6×1.6×1.5 mm^3, TE_{SE}/TR 100/2000 ms, and 40 echoes at TE 5-130 ms [2]. After coregistration, we calculated $R2^*_A$, $R2^*_B$ and $R2^*_C$ using exponential fits for each segment (Fig 2). We then calculated two R2' measurements: $R2'_{AB}=(R2^*_A-R2^*_B)/2$ and $R2'_{BC}=(R2^*_C-R2^*_B)/2$. A 3D pseudo-continuous arterial spin labeling (ASL) sequence (resolution 3×3×4 mm^3, TL/PLD 1500/2025 ms) produced CBF maps. T1-weighted anatomic images were acquired with 3D IR-FSPGR to segment gray matter (GM) and white matter (WM). In 8 subjects, we obtained 2 separate CBF and oxygenation measurements during the initial medical air breathing epochs to evaluate reproducibility using Bland-Altman analysis (with reproducibility coefficient [RC] being 1.96 times SD). Statistical significance was assessed using Student's t-test at $p< 0.05$ (two-tailed and one-tailed).

Results: We first examined our control of the gaseous environment, by observing changes in CBF, peripheral oxygen saturation (S_pO_2), and end-tidal CO_2/O_2 in subjects receiving 2 measurements during medical air breathing. We observed a statistically significant etCO2 increase of 0.9±0.8 mmHg, but not in S_pO_2 or CBF. Between the first air epoch and the gas epoch, we found that we induced consistent hypercapnia ($\Delta etCO_2$ = +7.1±4.4 mmHg, $p<0.05$) and hypoxia (ΔS_pO_2 = -4.8±2.8%, $p<0.05$). Our R2' reproducibility results (Fig 3) found that whole brain $R2'_{AB}$ showed no significant change with RC of 0.47 s^{-1} (13% of mean). Whole brain $R2'_{BC}$ showed small significant change of -0.14±0.18 s^{-1}, with a RC of 0.36 s^{-1} (23%). For hypercapnia, $R2'_{AB}$ decreased significantly in both GM and WM (GM: -0.32±0.19 s^{-1} [-9±5%]; WM: -0.20±0.20 s^{-1} [-6±6%]) (Fig 4). Similarly, $R2'_{BC}$ also decreased in both GM and WM, with higher percent changes (GM: -0.34±0.17 s^{-1} [-16±8%]; WM: -0.18±0.16 s^{-1} [-15±14%]). In contrast, during hypoxia, both R2' measurements showed no significant changes by the two-tailed t-test, though the trend for both was to be positive. Right-sided one-tailed t-test found a significant increase in $R2'_{AB}$ in GM: 0.40±0.47 s^{-1} (11±13%). Finally, as expected, we observed a significant CBF increase in hypercapnia, but not in hypoxia. See Table 1 for complete results.

Discussion: Physiological and CBF measurements show that our experiment maintained stable and reproducible environments of hypercapnia and mild hypoxia. However, in results not shown here, we found that the actual inspired gas concentration was about half of that delivered. We believe this is related to entrainment of room air, leading us to achieve about half of the intended perturbation. Nevertheless, we observed significant and reproducible $R2'_{AB}$ and $R2'_{BC}$ responses to hypercapnia. On the other hand, the mild hypoxia we induced only increased $R2'_{AB}$ in GM. Given the RC values observed in our reproducibility study, it is important to induce a sufficiently high perturbation for single-subject measurement of ΔR2' to exceed the inherent measurement noise. Future improvements we envision are the use of more strongly hypercapnic and hypoxic gases and a longer transition period between gas states[3].

Conclusion: In this study, we evaluated reproducibility and induced changes in R2' measurements using the GESFIDE sequence with gas challenges. Based on our thorough characterization of physiological parameters during gas challenges, and the rich data afforded by the multi-echo GESFIDE imaging sequence, we believe such measurements have great potential for further research into clinical quantification and validation of regional brain tissue oxygenation.

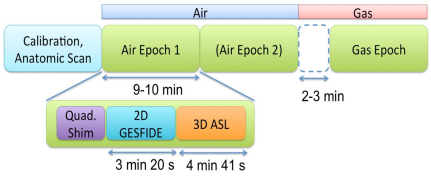

Fig 1: Imaging paradigm. 8 of 14 subjects were scanned with 2 air epochs to test reproducibility.

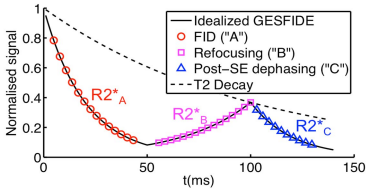

Fig 2: Idealized GESFIDE signal curve.

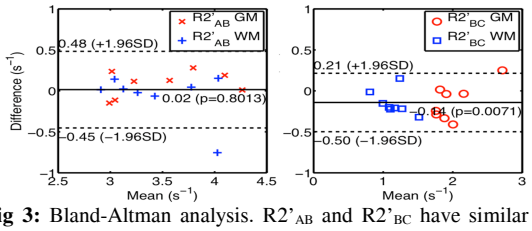

Fig 3: Bland-Altman analysis. $R2'_{AB}$ and $R2'_{BC}$ have similar absolute intra-scan reproducibility, though the higher SNR of $R2'_{AB}$ leads to higher reproducibility compared to the mean.

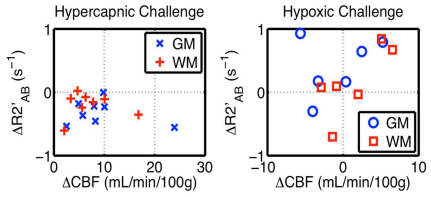

Fig 4: During hypercapnia, $R2'_{AB}$ (above) and $R2'_{BC}$ (not shown) experienced consistent decreases while CBF increased. No significant changes in either R2' or CBF were seen for hypoxia (with two-tailed t-test), though most subjects demonstrated an R2' increase.

		Mean ± St Dev (*p<0.05, 2-tailed; #p<0.05, 1-tailed)		
		Baseline Reproducibility (N=8)	Hypercapnic Challenge (N=8)	Hypoxic Challenge (N=6)
$\Delta R2'_{AB}$ (s^{-1})	GM	0.08±0.16	-0.32*#±0.19	0.40#±0.47
	WM	-0.06±0.29	-0.20*#±0.20	0.16±0.55
$\Delta R2'_{BC}$ (s^{-1})	GM	-0.14±0.22	-0.34*#±0.17	0.02±0.29
	WM	-0.15*#±0.15	-0.18*#±0.16	0.02±0.45
ΔCBF (mL/min/100g)	GM	-1.9±3.1	9.1*#±6.5	-0.8±4.2
	WM	-0.8±3.4	7.1*#±4.6	1.4±3.8

Table 1: Summary of R2' and CBF changes during reproducibility and gas challenge experiments.

References: 1. X He & DA Yablonskiy, MRM, 2007. 2. W Ni *et al.*, MRM, 2014. 3. F Xu *et al.*, JCBFM, 2012.

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