MRI-based quantification of the $CMRO_2$ response to apnea in patients with obstructive sleep apnea

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TARGET AUDIENCE: Sleep disorders clinicians and scientists interested in MRI methods to quantify neuro-metabolism and cerebrovascular reactivity.

PURPOSE: Obstructive sleep apnea (OSA) is defined by structural and functional failure of the upper airways to maintain patency during sleep, resulting in periodic nocturnal apnea. Despite this well-defined structural etiology, OSA patients display numerous systemic comorbidities, including hypertension, stroke, and metabolic disorders, as well as neurologic comorbidities, most notably cognitive dysfunction. OSA has also been associated with neurologic lesions suggestive of hypoxic damage, including grey [1] and white [2] matter loss and focal white matter abnormalities [3]. However, the etiology of this OSA-associated neuropathology has not been established. While the normal physiologic response to apnea maintains cerebral oxygen delivery via reduced cardiac output, peripheral vasoconstriction, and central vasodilation, it is hypothesized that this response may become blunted in patients with OSA secondary to the chronic intermittent hypoxia they experience during repeated nocturnal apneic events [4,5]. Assessment of the neurometabolic response to apnea in OSA would provide a means for testing this hypothesis.

$CMRO_2$ – the cerebral metabolic rate of oxygen consumption – is believed to be a more specific metric of the brain's energy supply and demand than surrogate markers such as blood oxygen level dependent (BOLD) signal or arterial spin labeling (ASL)-based measurement of cerebral blood flow (CBF). In this work, we apply a recently developed $CMRO_2$ quantification technique utilizing rapid and simultaneous susceptometry-based oximetry and phase-contrast blood flow quantification – termed OxFlow – to study the $CMRO_2$ response to apnea in patients with OSA [6,7]. We hypothesize that patients with OSA will display reduced baseline $CMRO_2$, as well as a blunted $CMRO_2$ response to apnea in comparison to age- and weight-matched controls.

METHDOS: ***OxFlow Pulse Sequence*** **–** A dual-echo GRE with phase-contrast (PC) flow encoding (**Figure 1**) allows simultaneous acquisition of a field map for determination of intravascular blood venous oxygen saturation (SvO_2) and a velocity map for blood flow quantification. The method makes use of the fact that the superior sagittal sinus (SSS), the largest drainage vein of the brain, can be well approximated as an infinite paramagnetic cylinder, allowing quantification of SvO_2 directly from a field map, thus providing a simple, robust, and rapid approach to SvO_2 quantification. Application of view-sharing and SSS blood flow (*SSSBF*)-based estimation of *tCBF* allows $CMRO_2$ quantification in just 2 seconds [7] – an order of magnitude faster than previously reported methods – via the Fick equation: $CMRO_2=tCBF(SaO_2-SvO_2)$. Sequence parameters are: $TR/TE_1/TE_2$=19.2/5.5/12.5, VENC=50cm/s, matrix=208×208, resolution=0.8×0.8×5mm. MR studies were completed on a wide-bore 1.5 T system (Siemens *Espree*). ***Pilot Study*** – 6 OSA subjects and 8 age- and weight-matched controls without sleep disorders were recruited to complete an MRI protocol involving continuous, high-temporal resolution quantification of $CMRO_2$ at baseline and in response to three repeated 30 second volitional apneas. Following their initial study, subjects begin treatment with continuous positive airway pressure (CPAP), the mainstay of OSA treatment, to allow similar MRI assessment of treatment response at a future time point.

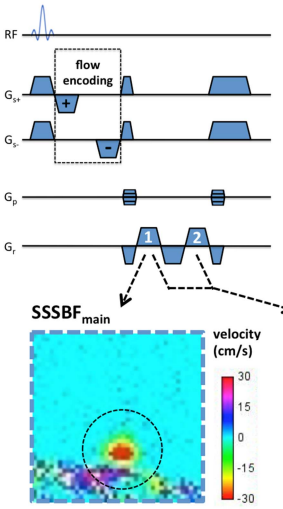

Figure 1: Sequence diagram of the flow-encoded dual-echo GRE (OxFlow) sequence used for $CMRO_2$ quantification with example phase contrast velocity map and phase difference field map images used for quantifying *SSSBF* and SvO_2, respectively. BRISK k-space sampling allows generation of one such image pair every 2 seconds.

RESULTS: **Figure 2** displays an example apneic response data set from an OSA patient, with measured parameters shown in **Figure 2a** (MRI-derived *tCBF* and SvO_2, as well as pulse oximetry derived SaO_2) and computed parameters in **Figure 2b** (AVO_2D, equal to SaO_2-SvO_2, *tCBF*, and their normalized product, the $CMRO_2$). The table below displays group average baseline $CMRO_2$ and relative change in $CMRO_2$ during the end-apnea period. OSA subjects display both lower baseline $CMRO_2$ (p=0.11) and apneic $CMRO_2$ response (p=0.24).

	Baseline $CMRO_2$ (μMol/100g/min)	Apneic $CMRO_2$ Response (%)
Controls (N=8)	140 ± 10	-6 ± 3
OSA (N=6)	127 ± 18	-11 ± 11

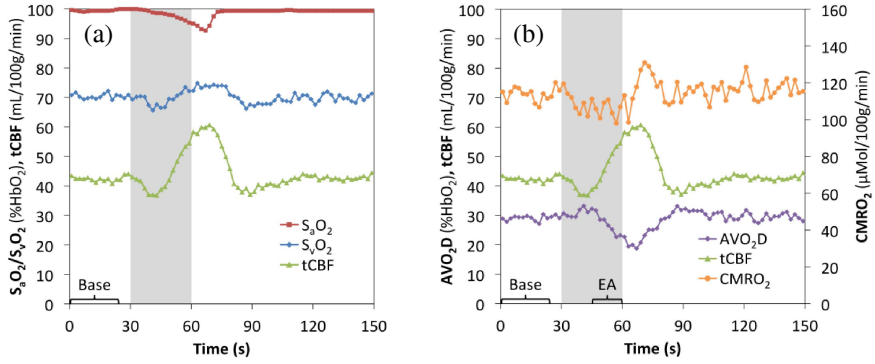

Figure 2: Example data set from an OSA patient (male, age 42, BMI 31.2). Gray bars indicate the apnea period. Values are averaged across the three repeats of the paradigm and bracketed sections indicate data used for computing average baseline ('Base') and end-apnea ('EA') parameter values.

DISCUSSION: The preliminary data in this study suggest feasibility of applying this apnea paradigm in a clinical population at 1.5 T field strength on a wide-bore scanner. This is significant, as virtually all susceptometic work has been done at 3 T field strength, where the induced field is twice that of 1.5 T and the bulk magnetization is greater. Although preliminary results support the hypothesis of decreased $CMRO_2$ at baseline and a blunted $CMRO_2$ response to apnea in OSA patients, these results do not meet statistical significance. A previous study of young healthy subjects using an equivalent technique demonstrated a small (6.0±3.5%) but highly significant (p=0.00044) increase in $CMRO_2$ in response to apnea at 3.0 T [7]. The control subject apneic response in this study appears to be at variance with this prior result, however, it is noted that the controls in this study are older, largely obese, and although free of diagnosed sleep disorders, were recruited because of symptoms suggestive of a sleep disorder, and are thus not equivalent to the young healthy subject group.

CONCLUSION: This study demonstrates feasibility of dynamic assessment of $CMRO_2$ in response to apnea at 1.5 T in an OSA patient population. Results are suggestive of reduced baseline $CMRO_2$ and abnormal $CMRO_2$ response to volitional apnea in OSA. Of particular interest is the question of whether CPAP treatment has an impact on $CMRO_2$ and apneic $CMRO_2$ response, which is being assessed in ongoing studies.

REFERNCES: [1] Macey et al., *AJRCCM* **31** (2002); [2] Macey et al., *Sleep* **65** (2008); [3] Morrell et al., Thorax **95** (2010); [4] Gora et al., *AJRCCM* **166** (2002); [5] Urbano et al., *J. Appl. Physiol.* **105** (2008); [6] Jain et al., *JCBFM* **30** (2010); [7] Rodgers et al., *JCBFM* **33** (2013). **GRANT SUPPROT:** NIH R21-HD069390.