BOLD response to forepaw stimulation in rats exposed to chronic intermittent hypoxia

Bianca Gonzales Cerqueira¹, Shiliang Huang¹, Glenn M. Toney², and Timothy Q. Duong³
¹Research Imaging Institute, Univ. of Texas Health Science Center at San Antonio, San Antonio, TX, United States, ²Physiology, Univ. of Texas Health Science Center at San Antonio, San Antonio, TX, United States

Target Audience: Researchers in chronic intermittent hypoxia and sleep apnea

Purpose: Obstructive sleep apnea is a sleep related disorder in which an individual stops breathing periodically throughout the night. Hallmarks of sleep apnea include snoring, daytime sleepiness, and reduced cognitive function. Severe sleep apnea has been correlated with cardiovascular diseases including arterial hypertension, heart failure, and stroke, as well as pulmonary hypertension, endothelial dysfunction, vascular remodeling, reduced cerebral autoregulation, and increased sympathetic activity. Exposure to chronic intermittent hypoxia (CIH) is a model commonly used to model the hypoxia found in patients with obstructive sleep apnea, however it does not reproduce upper airway obstruction, intra-thoracic pressure swings, sleep time arousals, and hypercapnia. Despite these limitations, animals exposed to CIH do exhibit many of the pathologies associated with sleep apnea. CIH exposure of only 7 days raises mean arterial pressure in both dark and light phases by 7-10 mmHg. In this study, functional activation in response to electrical forepaw stimulation were evaluated for control animals and animals exposed to 14 and 28 days of CIH. CBF, BOLD, cerebral rate of oxygen consumption (CMRO₂), and basal cerebral blood flow (CBF) were measured.

Methods: Male SD rats exposed to chronic intermittent hypoxia were housed in chambers connected to a custom-built automated system in which ambient levels of oxygen were controlled. Oxygen cycled between 21% and 10% ten times an hour from 8:15am to 4:15pm, during the animals normal sleep time. Chambers were maintained at 21% oxygen from 4:15pm to 8:15am. Animals were exposed to CIH for either 14 days (n=9) or 28 days (n=4). Rats were intubated, and mechanically ventilated. Rectal temperature, oximetry and heart rates were monitored and maintained within normal physiological ranges.

MRI experiments were performed under 1.2% isoflurane at 7T. Combined CBF and BOLD measurements were made using continuous arterial spin labeling (cASL). Two needle electrodes were inserted into the palmar side of each forepaw. Bilateral forepaw stimulation used 4 epochs of 30 s stimulation, 96 s rest with an initial rest time of 96 s. Pulse parameters were 2 mA stimulation current, 8 Hz pulse frequency, and 3ms pulse duration. Five trials were repeated for each animal with breaks of at least 4 mins in between scans. Hypercapnic challenge was 2 mins air, 3 mins 5% CO₂ followed by 5 mins of air. Data analysis was performed using STIMULATE software (University of Minnesota). An ROI (6x6 pixels) was drawn over the somatosensory cortex. Cross correlation analysis was performed on the BOLD and CBF data sets to obtain percent change activation maps. CMRO₂ and M values were calculated. One-way ANOVA was used to compare groups with significance at p<0.05.

Results: Forepaw-evoked BOLD and CBF responses trended toward a reduction with increasing CIH exposure, although did not reach statistical significance. Basal CBF in the somatosensory cortex decreased with increasing CIH exposure, significantly when controls were compared to 28 day CIH animals. There were no changes in CMRO₂, M value, or CBF response to hypercapnia among the groups.

Discussion/Conclusion: Decreased BOLD and CBF fMRI responses found in animals exposed to CIH suggest that there is impairment in the hemodynamic-evoked responses. Studies on task positive network in patients with sleep apnea have shown decreased BOLD activation, however the area of activation increases in order to compensate. MR spectroscopy studies on patients with sleep apnea have shown metabolite changes suggestive of decreased frontal lobe neuronal viability and integrity. Decreased cerebral glucose metabolism has been found in patients with sleep apnea. We did not see any changes in CMRO₂, which could be due to the limitations of our CIH model (including the duration of CIH exposure) or a decoupling of glucose metabolism and CMRO₂. We predict that with larger sample sizes, basal CBF and fMRI responses to forepaw stimulation will reach statistical significance. Further studies will investigate varying durations of CIH exposure and evaluate novel treatment strategies.