Structural and vascular changes in rats exposed to chronic intermittent hypoxia

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Target Audience: Researchers interested in chronic intermittent hypoxia or sleep apnea

Purpose: Sleep apnea is a sleep related disorder in which an individual stops breathing periodically throughout the night, resulting in intermittent brain hypoxia. Chronic sleep apnea could lead to long-lasting cardiovascular effects, including remodeling of cerebrovascular tones.[1,2] We modeled the sleep apnea by using chronic intermittent hypoxia (CIH) exposure in rats and used it to investigate the effects of CIH on basal cerebral blood flow (CBF) and CBF fMRI of cerebrovascular reactivity in responses to hypercapnic and hyperoxic challenges. Comparisons were also made with diffusion measurements.

Methods: Male Sprague Dawley rats (Charles River) 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. Basal CBF, CBF changes due to 5% CO_2 or O_2 challenge and ADC/FA were measured using standard protocols.[3,4] Combined CBF and BOLD measurements were made using the continuous arterial spin labeling (cASL) Hypercapnic and O_2 challenges were 2 mins air, 3 mins 5% CO_2 or 100% O_2 in balance of air, followed by 5 mins of air. Cross correlation analysis was performed on the CBF data sets to obtain percent change activation maps. All data is presented as mean ± S.E.M. One-way ANOVA was used to compare groups with significance at $p<0.05$. Five ROI were generating including the hippocampus, cingulate, somatosensory cortex, thalamus, and whole brain.

Results: Exposure to CIH reduced basal blood flow for all ROIs analyzed, although only significantly when controls were compared to 28 day CIH in the somatosensory cortex (Fig. 1). Exposure to CIH did not affect the CBF response to hypercapnia significantly, although a decreasing trend was observed in the hippocampus (Fig. 2). Exposure to CIH did not significantly change the CBF response to an oxygen challenge in any brain region (Fig. 3). CIH exposure had no significant change to ADC for all ROIs. For FA values (Fig. 4), there was a significant decrease in the somatosensory cortex (control vs. 14 day CIH, control vs. 28 day CIH) and the thalamus (14 day CIH vs. 28 day CIH).

Discussion/Conclusion: Reduced basal blood flow seen in CIH exposed animals is consistent with studies on patients with sleep apnea.[5,6] CIH did not affect CBF responses to hypercapnia significantly, consistent with findings in patients with sleep apnea.[7] However, some studies suggest that cerebral vasoreactivity may be impaired in sleep apnea patients due to endothelial dysfunction.[8]. This may explain our downward trend of CBF response in the hippocampus. Decreased FA values have been found in sleep apnea patients in multiple regions including the cingulate cortex, anterior corpus callosum, and frontal cortex consistent with our findings of decreased FA values in the somatosensory cortex and the thalamus.[9] We concluded that 14-day or 28-day of CIH exposure resulted in some structural and cerebrovascular changes, consistent with results found in patients with sleep apnea. Future studies will investigate varying CIH durations as well as explore additional MRI measures.

References: 1. Dempsey et al. Physiol Rev. 2010; 90(1):47-112. **2.** Knight et al. Am J Physiol Regul Integr Comp Physiol. 2011; 301(1):R131-9. **3.** Duong et al. Magn Reson Med. 2000; 43:383-92. **4.** Shen et al. J Cereb Blood Flow and Metab. 2003; 23:1479-88. **5.** Joo et al. Sleep Apnea. 2007; 30(11):1515-20. **6.** Kiratli et al. Hel Jour of Nucl Med. 2010; May-Aug;13(2):138-43. **7.** Urbano et al. J Appl Physiol. 2008; 105:1852-7. **8.** Jones et al. Sleep Med. 2013;14:428-32. **9**. Macey et al. Sleep. 2008;31(7):967-77.

Figure 1. Basal blood flow measurements

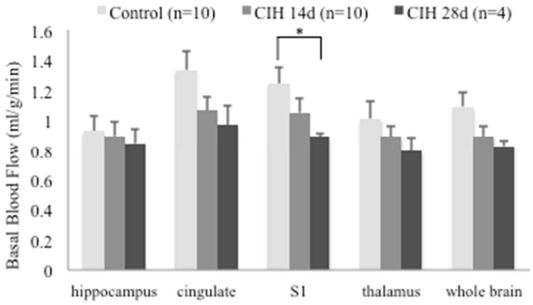


Figure 2. CBF percent change from baseline in response to hypercapnic challenge

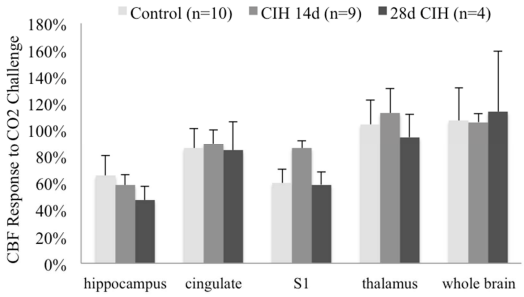


Figure 3: CBF percent change from baseline in response to O_2 challenge

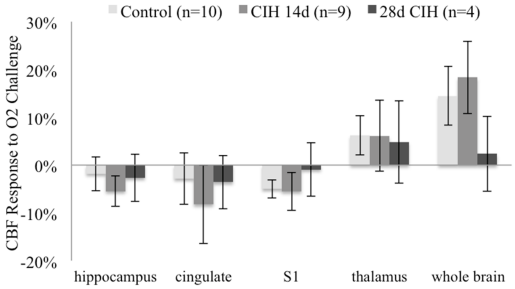
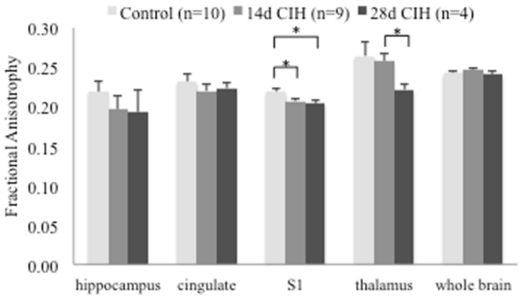


Figure 4: Fractional anisotropy values



* $p<0.05$