Altered Blood-Brain Barrier Function in Patients with Obstructive Sleep Apnea

Jose A Palomares[1], Danny JJ Wang[2,3], Bumhee Park[1], Sudhakar Tummala[1], Mary A Woo[4], Daniel W Kang[5], Keith S St Lawrence[6], Ronald M Harper[7], and Rajesh Kumar[1,3]

[1]Anesthesiology, University of California at Los Angeles, Los Angeles, CA, United States, [2]Neurology, University of California at Los Angeles, Los Angeles, CA, United States, [3]Radiological Sciences, University of California at Los Angeles, Los Angeles, CA, United States, [4]School of Nursing, University of California at Los Angeles, Los Angeles, CA, United States, [5]Medicine, University of California at Los Angeles, Los Angeles, CA, United States, [6]Lawson Health Research Institute, London, Canada, [7]Neurobiology, University of California at Los Angeles, Los Angeles, CA, United States

Introduction: Obstructive sleep apnea (OSA) subjects show significant brain damage (1,2), particularly in sites that control autonomic, cognitive, emotional, and breathing functions, deficient in the condition. Symptoms associated with these brain areas in OSA are linked to higher morbidity, mortality, and decreased quality of life in the syndrome. However, the underlying processes contributing to injury in these areas in OSA are unclear. Along with hypoxia, compromised blood-brain barrier (BBB) function is a potential cause of brain injury, which may exacerbate injury with time in OSA subjects. The BBB is located at the capillaries in the brain and restricts the diffusion of microscopic and large objects to protect neural tissue from harmful substances, such as bacteria and other infections or chemicals. Altered BBB function has been linked to significant brain damage in such conditions as meningitis, epilepsy, multiple sclerosis, and Alzheimer's disease. However, no reports of BBB changes are available in OSA subjects. Diffusion-weighted (DW) pseudo-continuous arterial spin labeling (pCASL) procedures are a non-invasive approach (3), without use of radiation or contrast agents, to examine BBB status, which is reflected by large artery integrity [indicated by arterial transient time (ATT)] and BBB function (shown by water exchange rates across the BBB), and may be useful to assess BBB in OSA subjects. Our aim was to examine global BBB function in OSA compared to control subjects using non-invasive diffusion-weighted pCASL procedures. We hypothesized that global BBB function would be altered in OSA compared to control subjects.

Materials and methods: Nine OSA [age, 46.7±10.5 years; body-mass-index (BMI), 24.7±3.3 kg/m^2; 5 female; apnea-hypopnea-index (n = 6), 23.8±10.2 events/hour] and 11 healthy control subjects (age, 36.7±7.6 years; BMI, 23.7±2.7 kg/m^2; 6 female) were studied. All OSA subjects were recently-diagnosed via overnight polysomnography, treatment-naïve, and recruited from the sleep disorders laboratory at the UCLA Medical Center. Control subjects were healthy, without any brain disorder that might alter brain tissue, and were recruited from the UCLA Medical Center and West Los Angeles region. All OSA and control subjects provided written and informed consent before the study, and the protocol was approved by the UCLA IRB. Brain imaging studies were performed using a 3.0-Tesla MRI scanner (Magnetom Tim-Trio; Siemens, Erlangen, Germany). High-resolution T1-weighted images were acquired using an MPRAGE pulse sequence. Two background suppressed diffusion-weighted pCASL scans (4) were collected with different imaging protocols for examination of ATT (TR = 3500 ms; TE = 43 ms; bandwidth = 3004 Hz/pixel; label offset = 90 mm; label-delay = 800 ms; matrix size = 64×64; FOV = 230×230 mm; slice thickness = 7.0 mm; distance factor = 20%; 17 axial slices; repeats = 40; b = 0 and 10 s/mm^2) and calculation of water exchange rates across the BBB (TR = 4300 ms; TE = 47 ms; label-delay = 1500 ms; repeats = 80; b = 0 and 50 s/mm^2), respectively. Using diffusion-weighted pCASL data, ATT maps (unit, ms) were calculated using the flow-encoding ASL regime by calculating the ratio of diffusion-weighted pCASL signals with b of 0 and 10 s/mm^2. With known ATT, Kw values, (Kw = Psw/Vc; Psw = capillary permeability surface area product of water, Vc = distribution volume of water tracer in capillary space; unit, min^{-1}), indices of BBB function, were further estimated by calculating the ratio of diffusion-weighted pCASL signals with b of 0 and 50 s/mm^2 at the long delay of 1500 ms. Demographic and biophysical data between groups were assessed with independent samples t-tests and Chi-square (IBM SPSS v22 software). Global ATT, DW pCASL, and Kw values were compared between groups using ANCOVA (covariate, age).

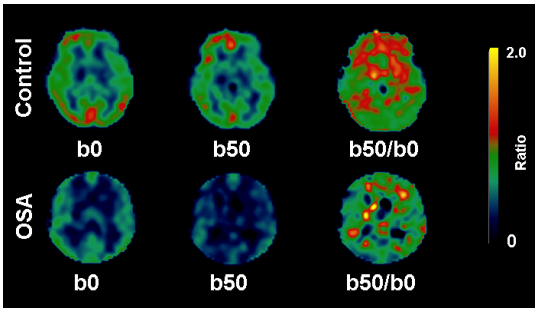

Fig. 1: *DW pCASL images and ratio maps from one control subject and one OSA patient. Multiple brain sites in OSA subject show global reduction in DW pCASL ratio over control subject (sites with hot vs. cool color).*

Results: No significant differences in BMI (p=0.45) or gender (p=0.96) appeared, but age (p=0.02) showed significant differences between OSA and control subjects. Global brain ATT values did not differ significantly between groups, while the global DW pCASL ratio (b50/b0) and Kw values were significantly reduced in OSA over control subjects (Table 1), controlling for age as a covariate. A set of DW pCASL images (b50 and b0) and their ratio maps from an OSA and a control subject are displayed (Figure 1) showing global reduction in the DW pCASL ratio in OSA over control subject. The DW pCASL ratio indicates the fraction of labeled water exchanging into tissue, which is directly linked to Kw (3).

Table 1: Global ATT, Kw, and Dw pCASL ratio values of OSA and controls.

Variables	OSA (n = 9; mean ±SE)	Controls (n = 11; mean ±SE)	p values
ATT (unit, s)	1.745±0.037	1.764±0.033	0.729
Kw (unit, min^{-1})	188.41±13.64	237.03±12.16	0.023
DW pCASL (b50/b0) ratio	0.749±0.023	0.835±0.021	0.019

Discussion: OSA subjects showed significantly lower Kw values over control subjects, with ATT values equivalent to controls, suggesting compromised BBB function, with intact integrity of large arteries. The altered BBB function in OSA can contribute to neural tissue injury in areas that control autonomic, cognitive, and affective functions abnormal in the condition. The findings suggest a need to repair BBB function in OSA, with strategies commonly-used in other fields **[**both in acute (e.g., stroke, traumatic brain injury, cardiac arrest, and multiple sclerosis) and chronic onsets (e.g., Alzheimer's disease, chronic hypoperfusion, mild cognitive impairment, cortical dysplasia, and autoimmune encephalomyelitis)**]** to protect neural tissue in the syndrome.

References:

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