Modest Changes in Cerebral Glucose Metabolism in Patients with Sleep Apnea Syndrome after Continuous Positive Airway Pressure Treatment

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Key Words
Sleep apnea syndrome • Positron emission tomography • Continuous positive airway pressure

Abstract
Background: Decreased cerebral glucose metabolism has been reported in patients with sleep apnea syndrome (SAS), but it has yet to be decided whether cerebral glucose metabolism in SAS can be altered by continuous positive airway pressure (CPAP) treatment. Objective: The aim of this study was to evaluate cerebral glucose metabolism changes in patients with SAS after CPAP treatment. Methods: Thirteen middle-aged male patients with severe SAS [mean age 49.3 ± 7.2 years, mean apnea-hypopnea index (AHI) 60.4 ± 21.2] and 13 male controls (mean age 46.0 ± 9.4 years, mean AHI 4.1 ± 3.7) participated in the study. All 26 study subjects underwent fluorodeoxyglucose-positron emission tomography (FDG-PET), but SAS patients underwent FDG-PET twice, namely before and 3 months after acceptable CPAP usage. Results: Significant hypometabolism was observed in the bilateral prefrontal areas, left cuneus and left cingulate cortex of SAS patients before CPAP, and after CPAP, significant increases in cortical glucose metabolism were observed in the bilateral precentral gyri and left anterior cingulate cortex. However, these improvements in hypometabolism in both areas were insufficient to reach control levels, and hypometabolism in other regions persisted after CPAP treatment. Conclusions: Reduced cerebral glucose metabolism in the precentral gyrus and the cingulate cortex in patients with SAS was modestly improved by acceptable CPAP treatment. The findings of this study suggest that acceptable CPAP usage cannot completely reverse reduced cerebral glucose metabolism in SAS patients. Further studies are required to evaluate the long-term effects of CPAP treatment with total compliance.

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Introduction
Sleep apnea syndrome (SAS) is characterized by nocturnal hypoxemia and frequent arousals during sleep caused by repetitive respiratory pauses. The estimated prevalence of SAS among middle-aged adults is 9% for women and 24% for men [1]. Furthermore, SAS is associated with significant medical, cognitive and psychological sequelae, including excessive daytime sleepiness, an increased risk of cardiovascular disease and neurocognitive consequences [2–5]. Also, SAS-related intermittent
hypothesis and sleep fragmentation might result in structural and functional changes in the brain.

Investigations that have applied neuroimaging methodologies have made important contributions to our understanding of brain structure and function in individuals with SAS. Recent evidence suggests that SAS may lead to structural brain abnormalities [6, 7], and studies using functional neuroimaging techniques observe subtle cerebral changes associated with SAS. With regard to 18F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) studies, two preliminary, small-sample reports have been published [8, 9]. Recently, Yao et al. [10] reported that SAS with little cognitive impairment showed right-lateralized hypometabolism in the precuneus, middle and posterior cingulated gyri and the parieto-occipital cortex.

Continuous positive airway pressure (CPAP) is the first-line treatment in SAS and is effective at improving daytime sleepiness [11] and reducing the risks of cardiovascular complications [12]. However, the superiority of CPAP over placebo with respect to cognitive functioning has not been demonstrated in placebo-controlled studies, as impairments in executive function tend to persist despite CPAP, probably due to irreversible hypoxic damage [13, 14]. Tonon et al. [13] also showed in a study using magnetic resonance spectroscopy that decreased cortical N-acetylaspartate levels in SAS persisted after CPAP therapy. These studies show that some symptoms and complications of SAS are improved by CPAP, but that other abnormalities persist despite treatment.

However, it has not yet been shown whether CPAP treatment alters cerebral glucose metabolism in SAS patients. Thus, in this study, we undertook to evaluate brain glucose metabolism abnormalities in SAS patients using FDG-PET and to determine whether CPAP treatment alters glucose metabolism.

Methods

Subjects

Thirteen middle-aged, never-treated male SAS patients (mean age 49.3 ± 7.2 years) and 13 male controls (mean age 46.0 ± 9.4 years) participated in this study. All study subjects visited a sleep clinic for either snoring or suspected sleep apnea and were referred to the sleep laboratory in Seoul National University Bundang Hospital. No subject had a history of cerebrovascular or ischemic heart disease or central nervous system disorders. The 13 patients had severe SAS [apnea-hypopnea index (AHI) >30], whereas the healthy controls had an AHI of <5.

At baseline, patients and controls were evaluated for brain glucose metabolism by FDG-PET and completed questionnaires, including the Epworth Sleepiness Scale for daytime sleepiness, the Beck Depression Inventory for depressive mood and the Pittsburgh Sleep Quality Index for subjective sleep disturbances. After CPAP treatment for 3 months, patients were assessed again by FDG-PET and using the above-mentioned questionnaires. The study protocol was approved by the Institutional Review Board of the Seoul National University Bundang Hospital, and all subjects provided written informed consent.

Polysomnography

Overnight polysomnography (PSG) was performed using an Embla™ N7000 recording system (Embla, Reykjavik, Iceland) and standard electrodes and sensors. Every 30-second epoch of the PSG was scored based on the criteria of Rechtschaffen and Kales [15]. Apnea was defined as the complete cessation of airflow for at least 10 s. Hypopnea was defined as a substantial (≥50%) reduction in airflow for at least 10 s or a moderate reduction in airflow for at least 10 s associated with EEG arousal or oxygen desaturation (≥4%) [16]. AHI was defined as the number of apnea and hypopnea episodes per hour of sleep, and the oxygen desaturation index was defined as the number of oxygen desaturations (≥4%) per hour of sleep.

Positive Airway Pressure Treatment

After the baseline polysomnographic evaluation, a second-night PSG was performed for the titration of CPAP. The optimal pressure was the minimum pressure able to eliminate apneas and hypopneas in each patient [17]. After CPAP treatment for at least 3 months, data regarding CPAP usage and mean AHI during CPAP were obtained from data cards inside the CPAP machine. CPAP compliance was defined as days of CPAP use (for at least 4 h/day) expressed as a percentage of total study period days. Subjects with a CPAP compliance of 70% were defined as having acceptable compliance [18].

Image Acquisition

All patients underwent MRI and FDG-PET scan in the morning on the same days. A high-resolution T1-weighted volume MRI scan was conducted to exclude subjects with any cerebrovascular problem. A Philips Intera 1.5T MRI system was used to acquire high-resolution T1 anatomical brain images. Anatomical brain images were acquired using a 3-dimensional (3D) T1-weighted gradient echo (TITFE) sequence using the following parameters: TR = 8.0381 ms, TE = 3.6828 ms, flip angle = 8°, 175 slices, thickness = 1 mm, matrix size = 256 × 256.

FDG-PET images were acquired using a Philips Allegro PET scanner operating in 3D mode. All subjects fasted for at least 6 h before scanning. After being given an intravenous injection of 4.8 MBq/kg FDG in a dimly lit, quiet waiting room, each study subject was instructed to remain lying comfortably for 40 min for FDG equilibration. A 10-min emission scan and an attenuation map using a Cs-137 transmission source were then obtained. Attenuation-corrected images were reconstructed using the 3D row-action maximum likelihood algorithm and a 3D image filter of 128 × 128 × 90 matrices with a pixel size of 2 × 2 × 2 mm.

FDG-PET Analysis

Preprocessing and statistical analysis were performed using SPM5 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk).
uk/spm) implemented in Matlab 7.6 (The Mathworks, Mass., USA). FDG-PET images were normalized against a standard PET template, developed and distributed by the Montreal Neurological Institute, and then smoothed with a 12-mm full-width-at-half-maximum isotropic Gaussian kernel. Brain glucose metabolism at each voxel was proportionally scaled according to the mean FDG uptake value of the pons. The paired-sample t test was used to determine significant differences in brain regional metabolism after CPAP treatment. The difference was considered significant when a cluster consisting of at least 50 contiguous voxels exceeded a threshold height of p < 0.005 (uncorrected for multiple comparison).

Statistical Analysis
SPSS version 17 K for Windows (SPSS Inc., Chicago, Ill., USA) was used for the statistical analysis. Results are presented as means ± standard deviation. Differences between groups in terms of parametric clinical variables were assessed by using the two-sample paired t test or the independent t test. Furthermore, mean uptake in the brain regions which showed significant changes after CPAP on SPM analyses was extracted from pre- and posttreatment scans using MarsBaR (http://marsbar.sourceforge.net). Pearson’s or Spearman’s correlation coefficients were calculated to determine relationships between glucose metabolism changes and clinical or polysomnographic variables.

Results
Table 1 shows the demographic and clinical characteristics of the study subjects. The mean age of the 13 SAS patients was 49.8 ± 7.0 years, and their mean AHI was 60.3 ± 21.2. The mean duration of CPAP treatment was 93.8 ± 19.8 days (range 90–119 days), and mean CPAP compliance was 78.9 ± 14.5%. Of the 13 SAS patients, 11 patients had acceptable compliance and the other 2 had compliance of 58.8 and 47%. Body mass index, oxygen desaturation index and education levels are also presented in table 1. During CPAP treatment, the mean AHI of the patients was significantly decreased from 60.3 ± 21.2 at baseline to 3.8 ± 2.2 (p < 0.05) after CPAP. Daytime sleepiness and quality of sleep were significantly improved after CPAP (p < 0.05). Controls and patients were similar for all demographic measures except body mass index.

SAS patients showed hypometabolism in the bilateral lateral prefrontal areas, bilateral precentral gyri, left cuneus, right angular gyrus, left superior parietal lobule and left cingulate cortex versus controls. After CPAP treatment, cerebral glucose metabolism increased in the bilateral precentral gyri and left anterior cingulate cortices (ACC; all p < 0.005; fig. 1). However, these improvements observed after CPAP treatment fell short of control levels (table 2). In addition, hypometabolism persisted after CPAP treatment in other regions that showed reduced metabolism before CPAP (table 2). Correlational analysis between changes in clinical variables such as AHI, Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index and changes in glucose metabolism in the bilateral precentral gyri and left ACC after CPAP treatment failed to reveal any relation.

Discussion
In the present study, significant hypometabolism was found in the bilateral prefrontal areas, precuneus and left ACC of SAS patients, which are known to be predominantly affected by hypoxia [19, 20]. This finding is largely consistent with previous PET studies, in which SAS patients with little cognitive dysfunction showed right-lateralized hypometabolism in the precuneus, middle and posterior cingulated gyri and the parieto-occipital...
CPAP Changes Cerebral Glucose Metabolism in Sleep Apnea Patients

Cortex [8–10]. These metabolic changes may precede future cognitive impairments in SAS, even if there are only minor cognitive deficits at the time of measurement [10, 13]. With regard to causes of the hypometabolism, apnea-associated microarousals may be correlated with the hypometabolism in SAS [10], but several experimental models of intermittent hypoxia [21, 22], as well as findings in SAS [13] and chronic obstructive pulmonary disease patients [23, 24], provide evidence that hypoxia can be the main cause of hypometabolism in SAS.

In the present study, it was found that cortical glucose metabolism in the bilateral precentral gyri and left ACC were modestly increased after acceptable CPAP treatment. This finding of a modest improvement in glucose metabolism after CPAP treatment partly concurs with the findings of Canessa et al. [25], who observed that cognitive impairments and gray matter volume deficits in SAS were recovered by CPAP. They reported significant improvements in memory, attention and executive function that paralleled gray matter volume increases in hippocampal and frontal structures. In addition, Castronovo et al. [20] suggested that an overrecruitment of brain regions by SAS patients was reduced by CPAP treatment in the ACC and hippocampus. These findings suggest that CPAP treatment induces neural compensation and reduces cerebral dysfunction.

**Fig. 1.** Changes in cerebral glucose metabolism after 3 months of CPAP treatment.

- A significant increase in cerebral metabolism after CPAP treatment was observed in the left ACC and bilateral precentral gyri (all p < 0.005; cluster size > 50). L = Left.
- Data points represent relative metabolism in these three regions of individual subjects before and after treatment. The y-axis denotes relative cerebral glucose metabolism, which was normalized against FDG uptake by the whole brain.

![Pre-CPAP < post-CPAP](image)
Frontal lobe plasticity might explain the improved glucose metabolism observed in the present study. In human and animal studies, frontal regions are known to be vulnerable to hypoxia, which generates cellular and biochemical stresses, resulting in the disruption of functional homeostasis and reductions in neuronal and glial viability [26]. Brain structural plasticity (especially in the frontal area and hippocampus) caused by environmental enrichment has been demonstrated in animal models [27], and there is evidence that cognitive training can cause plasticity in the frontal area [28]. Interestingly, structural reversibility was also found in a transcranial magnetic stimulation study [29], in which it was suggested that these changes simply reflect vascularization effects. It is widely known that recurrent hypoxia and reoxygenation can induce oxidative stress, increase the production of oxygen free radicals, activate inflammatory pathways and cause vascular endothelial dysfunction [30]. Furthermore, they can induce changes in metabolism. On the other hand, CPAP treatment can reduce the risk of hypoxia, induce revascularization and improve brain metabolism [31]. Thus, CPAP treatment may reinforce brain plasticity that facilitates metabolic recovery in the frontal and connected brain areas.

These findings might also be compatible with previous cognitive function studies, although we did not assess cognitive function in this study. The ACC theory states that the ACC is related to error detection and that part of the circuit is involved in a form of attention that serves to regulate both cognitive and emotional processing [32]. Several placebo-controlled studies conducted on SAS patients have demonstrated the superiority of CPAP over placebo with regard to attention [33, 34], which is related to the function of the ACC. The precentral gyrus, as an area of the premotor cortex, plays a role in planning movements, and impaired motor functions in patients with SAS [14, 35, 36] have been reported to be improved by CPAP [14, 36, 37].

Unfortunately, the results of this study do not allow us to conclude that brain functional damage caused by hypoxic insults in SAS may be improved by acceptable CPAP treatment. In our patients, hypometabolism in the ACC and precentral gyrus was not fully recovered, and hypometabolism persisted in other regions. Also, Tonon et al. [13] reported that CPAP treatment in SAS subjects had little impact on lowered cortical metabolism measured by magnetic resonance spectroscopy, and they concluded that hypoxic damage in SAS might result in neuronal loss rather than neuronal dysfunction, and this cannot be reversed by CPAP. Some authors have suggested that nocturnal hypoxemia can cause irreversible cerebral damage in SAS. Furthermore, the finding that CPAP can improve deficits related to somnolence, but not those related to hypoxemia, supports this suggestion [8, 14]. However, hypoxemia could also interfere with the synthesis of neurotransmitters to produce functional revers-

<table>
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<tr>
<th>Region</th>
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<th>Brodmann area</th>
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<tr>
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<tr>
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Impaired glucose metabolism in patients with severe SAS persisted after CPAP treatment (p < 0.005, k = 50). MNI = Montreal Neurological Institute; L = left; R = right.
ible damage. In particular, the cholinergic neurotransmitter system is implicated in many cerebral functions [38] and is sensitive to cerebral hypoxemia of short duration [21]. Therefore, the reduction of hypoxic events induced by CPAP could normalize the synthesis of neurotransmitters and consequently improve cerebral function. Studies on the impact of long-term CPAP treatment with higher compliance are needed to clarify whether hypoxic cerebral damage in SAS is reversible or irreversible.

This study has several limitations that require consideration. Sham CPAP treatment with subtherapeutic pressure or observation without any treatment could have addressed the placebo effect of CPAP treatment, although it appears unlikely that sham CPAP or observation only could impact on severe SAS with marked hypoxia. In addition, the correction of hypoxia by CPAP was indirectly evaluated using AHI values obtained from the CPAP machine. However, in the clinical setting we routinely evaluated using AHI values from the CPAP machine. Mulgrew et al. [39] showed that there were no differences in the AHI between measurements on the CPAP machine and PSG. Measurements of cognitive function could have provided a more comprehensive understanding of hypoxic cerebral damage and its reversibility by CPAP in SAS patients. Nonetheless, this is the first study to examine the impact of CPAP on cerebral glucose metabolism using an homogenous group of severe SAS patients who complied with the treatment protocol.

In conclusion, reduced glucose metabolism was observed in severe SAS patients in regions susceptible to hypoxemia, and these abnormalities were found to be modestly corrected by acceptable CPAP treatment. Our results suggest that acceptable CPAP usage cannot completely reverse reduced cerebral glucose metabolism in SAS patients. Further studies are needed to evaluate long-term effects of CPAP treatment with total compliance.

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Financial Disclosure and Conflicts of Interest

The authors have no conflicts of interest to declare in relation to this work.

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