Cerebral blood flow and cognitive function in obstructive sleep apnea syndrome

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Abstract

Neuropsychological deficits are among the main symptoms of obstructive sleep apnea syndrome (OSAS), which could be related to impaired cerebral blood flow (CBF). *We conducted a study* in 20 subjects tested in our Sleep Laboratory, to assess regional CBF and cognitive function in OSAS. Our measurements included technetium-99m hexamethylamino propylenamine oxime brain perfusion scintigraphy in wakeful state, i.e. in the morning after polysomnography and also cognitive function tests after polysomnography, in 20 patients, 16 male and 4 female, aging between 30 and 60 years. *We found* that apnea-hypopnea index was greater than or equal to 5 in 16 (85%) subjects, consistent with OSAS. Mean arterial oxygen saturation during sleep was correlated with CBF in all regions. Cognitive function test scores in verbal memory were positively correlated with percentage of sleep duration with less than 90% of oxygen saturation during sleep. Cerebral blood flow was not uniform in OSAS patients, and was significantly lower in the left frontal and left temporal regions as compared to that of these regions on the right hemisphere. *In conclusion*, our findings indicated association of CBF and verbal memory with hypoxemia during sleep and decreased perfusion after apneic episodes in the left frontal and temporal lobes in OSAS patients, which could also indicate impairment of upper airway motor control.

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Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of breathing pause during sleep due to upper airway collapse. Definition of OSAS includes excessive day time sleepiness and apnea-hypopnea index (AHI) of at least 5 [1]. Obstructive sleep apnea syndrome is associated with increased mortality and morbidity due to cardiovascular and cerebrovascular diseases, including hypertension, stroke and arrhythmias [2-4]. Besides, OSAS disturbs normal sleep pattern and causes excessive daytime somnolence, memory impairment and lack of concentration [5]. Several studies in OSAS demonstrated the presence of cognitive deficits concerning memory, attention, executive functions and motor abilities [6, 7]. The obvious negative effect of cognitive dysfunction on daily life of these patients prompted an interest in their cognitive function evaluation [8]. It has been reported that decreased O_2 saturation and hypercapnia are common in OSAS due to changes in systemic hemodynamics [9].

There are few functional imaging studies in the literature on the assessment of brain function in OSAS patients. Doppler ultrasonography has been used and showed blood flow reduction during apneic episodes [10-12]. Brain perfusion scintigraphy reflects changes in brain metabolism; increased metabolism is coupled with increased cerebral blood flow (CBF) in that area and vice versa. Functional magnetic resonance imaging (fMRI) is based on the increase in blood flow to the local vasculature that accompanies neural activity in the brain, since deoxyhaemoglobin is paramagnetic, i.e. attracted to magnetic fields and thus demonstrates the increased cerebral metabolism in the scanning. Both imaging procedures are used to look at the change of regional CBF due to reduction of oxygen supply in OSAS patients. Our aim was to identify possible causes related to symptoms like memory loss, poor judgment, limited attention and personality changes in OSAS [13, 14].

To the best of our knowledge, there is no study present in the literature evaluating the relation between CBF and patients' cognitive status in OSAS therefore we conducted this study to assess CBF changes using technetium-99m hexa methyl amino propylenamine oxime (^{99m}Tc HMPAO) and investigate the association of polysomnographic findings with CBF and cognitive function in OSAS.

Material and methods

Twenty patients, referred to Hacettepe University Medical Center Sleep Laboratory for evaluation of snoring, witnessed apnea and day time hypersomnolence and underwent polysomnography testing. Patients were excluded from the study, if there they had: a) cardiovascular disease including hypertension; b) cerebrovascular disease; c) chronic obstructive pulmonary disease (COPD); d) previous diagnosis or treatment of OSAS.

All patients had complete physical examination and blood chemistry studies. All patients' blood heamatocrit levels were within normal limits (36%-54%) and awake O_2 saturation levels were 90% or above. All patients signed an informed consent form, and the study protocol was approved by the ethics committee of Hacettepe University.

Patients had an overnight polysomnographic study (Somnologica software), which included electro-encephalography (EEG), electromyelography (EMG), electrooculographic (EOG) and respiratory effort channels, pulse oximetry, airflow sensor, and microphone placed next to larynx to detect snoring. Sleep stages were scored in 30s epochs according to the standard criteria of Rechtschaffen and Kales, and as in the work by Grammaticos Ph et al (2005) [15, 16]. Obstructive apnea was defined by cessation of the airflow for a period of at least 10s, associated with respiratory movement. Hypopnea was defined by reductions in the baseline airflow amplitude of at least 30% for a period of at least 10s, associated with at least a 4% oxygen desaturation and/or arousal [17]. Arousals were defined as a noticeable change in EEG by the abrupt shift to higher frequency for at least 3sec [18]. Diagnosis of OSAS was based on symptoms related to excessive daytime sleepiness and polysomnographic findings (AHI ≥5).

Radionuclide imaging

Scintigraphy was performed in all patients at the awake state, in the morning after tested in the Sleep Laboratory. Regional CBF images were obtained with ^{99m}Tc HMPAO. Patients were kept in a dim and silent room for 5 min, after ^{99m}Tc HMPAO injection, in order to minimize occipital cortex stimulation secondary to blood flow augmentation from visual and auditory stimuli [19]. Throughout the procedure a technician was with the patients to ensure their awake state. Single photon emission tomography (SPET) imaging was performed with a dual-headed rotating gamma camera (ECAM Siemens, USA) equipped with high-resolution, parallel-hole collimators. Visual interpretation of the SPET scans was performed independently by 2 nuclear medicine specialists (P.O.K. and B.V.S.), who had no knowledge of the clinical data. The distribution of radioactivity in the cerebral and cerebellar regions, focal or global blood flow differences, left to right and anterior-to posterior asymmetry, were evaluated. Perfusion deficits were considered only when the two observers agreed on the described evaluation criteria as above. Semi-quantitative analysis was also performed. Regions of interest (ROI) were drawn over frontal, parietal, temporal and occipital regions on 3 consecutive transaxial slices and mean counts (total counts/pixel size) for each ROI were calculated throughout the brain. At least 5 different slice sets were used for semi-quantitative analysis (in order to cover the whole brain). The analysis of CBF was carried out according to the guidelines [20] and the Talairach brain atlas was used in order to identify the areas of the brain lobes [21].

Cognitive function assessment

For the evaluation of cognitive function (CF) we used neuropsychological tests performed within the next 2 days after the polysomnographic recording. The physician conducted the tests without any information about the disease status of the patients. The CF battery comprised the following tests: Wisconsin Card Sorting Test (WCST), Verbal Fluency Test (VFT), Wechsler Memory Scale-Revised (WVMS) and Trail Making Test (TMT). The WCST examines the frontal lobe skills, as for the ability to form abstract concepts, planning and problem solving [22]. Patients were asked to match a series of cards according to sorting criteria. Performance was scored in a number of different ways. Achieved categories refer to the number of correct sorts, ranging from 0-6. Perseverative errors are calculated as they are the best measure of predicting the frontal involvement. The VFT examines verbal associative capacity [23]. Subjects were asked to produce as many words as possible with a given category during a 60s time period. The categories in the study were: name, animal and alternation. In the alternation phase, the subject was supposed to alternate between the name and animal categories while producing related words. The digit span, logical memory and visual reproduction subscales of WVMS was utilized to assess the verbal and visual compartments of memory [24]. The attention and working memory was measured by digit span subtests forward (DSFT) and backward (DSBT), respectively. During the DSFT the patients were asked to repeat immediately an increasing series of numbers read by the tester, while on the DSBT, patients were asked to repeat the numbers in a reverse order. In order to assess verbal and visual memory skills, Logical memory (LM) and visual reproduction (VR) subscales were given. We used the LM subtest of the scale to measure the ability to recall the number of ideas presented in two passages read to the patient, while the VR test required the subject to draw from memory simple geometric figures that were exposed briefly. The TMT tests were used for speed of visual search, attention, mental flexibility and motor function [25]. In this study both part A and B of the test were administered to the patients. Each patient was supposed to connect, in proper order by drawing lines, between 25 encircled numbers, randomly arranged on a page (Part A), and in alternating order between 25 encircled numbers and letters (Part B).

Statistical analysis

Association between CBF, CF test scores and polysomnography findings were investigated via Spearman (nonparametric) correlation coefficient. Chi square testing and where appropriate Fisher's exact tests were used for the comparison of frequencies. Mann-Whitney U test was used for the comparison of continuous variables. Distribution of the perfusion scores was compared via non-parametric Friedman test, to assess the uniformity of the perfusion. In the case of a significant difference between the perfusions, regions of interest (ROI) which had the lowest ranks were compared with the corresponding ROI in the contralateral side to assess impaired perfusion in a specific region. P values less than 0.05 were considered for statistical

significance. P values less than 0.01 and 0.001 were also denoted

Results

Evaluation of the patient's data

The group without OSAS (not OSAS group) consisted of 4 patients with an age range of 30 to 56 years (mean: 42.5, SD: 10.9). Of the 16 OSAS patients, 3 were female and their age ranged between 39 to 60 years (mean: 47.2, SD: 5.3 years). The age and education status of the OSAS vs the not OSAS patients did not differ (mean ±SD: 11.3 years ±4.9 vs 10.8 years ±4.0) (P>0.05). The BMI of the OSAS group was significantly higher than that of the not OSAS group (mean and ±SD in kg/m^2, OSAS: 28.5 ±1.8, not OSAS: 25.8 ±1.9, P<0.01).

Evaluation of the polysomnography data

Table 1 shows the polysomnography findings of the 16 patients with OSAS and 4 with not OSAS. The parameters: AHI, mean SaO_2 %, SaO_2 min % and SaO_2<90% were significantly different between the groups. Percentages of REM and of slow wave sleep (SWS) were not different between the groups.

Correlation of CBF and polysomnography findings

Table 2 shows the nonparametric correlation coefficients of the association between CBF % and polysomnography findings. Mean SaO_2 during sleep was positively correlated with regional CBF % in all brain areas. The correlation coefficient percentages ranged between 68% and 72%.

Table 1. *Polysomnography findings of the patients*

	Not OSAS (n: 4)		OSAS (n: 16)	
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
AHI	1.3 (0.9)	1.4 (0.3-2.3)	34.3 (20.3)**	31.5 (6.6-89.5)
SaO_2 mean %	95.9 (0.8)	95.8 (95-6.9)	93.0 (2.4)*	92.8 (86.2-97)
SaO_2 min %	90.0 (3.2)	90.5 (86-93)	74.1 (20.6)**	77 (50-84)
SaO_2 <90%	0.2 (0.3)	0.1 (0-0.6)	12.6 (15.2)**	8.6 (0.4-64.6)
REM %	13.4 (10.5)	12.7 (3-26)	12.9 (8.1)	13.6 (0-24)
SWS %	15.9 (5.7)	17 (8.4-20.9)	14.4 (7.9)	15.4 (1.4-29.2)

*:P<0.5, **:P<0.001, SaO_2<90%: <90% of arterial oxygen saturation, SaO_2 min %: minimum arterial oxygen saturation, SaO_2 mean %: mean arterial oxygen saturation, REM: Rapid eye movement, SWS: slow wave sleep

Correlation of the CF test scores and polysomnography findings

Table 3 shows the percentage of sleep with less than 90% of SaO_2 which was significantly correlated with verbal memory scores. The OSAS patients with lower 90% SaO2 levels, scored worse in WSMT digit span test and in verbal memory tests 1 and 2 (Table 3). No relation was found between CBF and CF tests results in OSAS patients. Table 4 shows that the distribution of regional CBF in the OSAS group was not uniform, where left frontal and left temporal lobes had decreased flow when compared to right frontal and temporal lobes and to the rest of the brain.

Discussion

Our study provided measurements of CBF in a group of OSAS patients and investigated the association of regional CBF with polysomnographic features of OSAS and CF. Inference was made to relate the CBF to the polysomnographic findings and CF test scores. Cross sectional design of the study and relatively small size of the study population were the main limitations. Study design did not allow us to detect the acute and temporary changes of CBF during sleep. Despite these difficulties in the interpretation of our findings, daytime CBF and impairment in verbal memory were associated with oxygen saturation during sleep. Our findings also suggested decreased CBF in the left frontal and temporal regions, which could play a role in the pathogenesis of OSAS.

CBF and nocturnal hypoxemia

It has been hypothesized that deficits in CF and motor abilities were related to hypoxemia [6]. There might be an apnea associated effect of local vascular autoregulation mechanism acting to compensate systemic blood flow alterations or blood gas changes, in OSAS [25]. Changes in cardiac and systemic hemodynamics during nocturnal episodes of OSAS are accompanied by decreased O_2 saturation and hypercapnia [9]. The arterial CO_2 tension

Table 2. *Nonparametric correlation coefficients of the association between polysomnography findings and cerebral perfusion percentages*

	Age yr	Edu-cati-on, yr	AHI	SaO_2 mean	SaO_2 min	SaO_2 <90	RE M%	SW S%
RtT	-0.11	0.23	-0.18	0.70* (P: 0.001)	0.29	-0.31	0.06	0.21
LtT	-0.04	0.19	-0.19	0.71.** (P: 0.0001)	0.30	-0.33	0.10	0.21
RtF	--0.06	0.17	-0.20	0.701* (P: 0.001)	0.27	-0.32	0.09	0.20
LtF	-0.06	0.18	-0.19	0.70* (P: 0.001)	0.25	-0.30	0.14	0.19
RtO	-0.02	0.18	-0.20	0.71.** (P: 0.0001)	0.28	-0.32	0.11	0.19
LtO	-0.07	0.18	-0.23	0.72** (P: 0.0001)	0.30	-0.35	0.12	0.18
RtBG	-0.02	0.19	-0.20	0.72** (P: 0.0001)	0.27	-0.31	0.16	0.15
LtBG	-0.002	0.18	-0.18	0.72** (P: 0.0001)	0.27	-0.32	0.14	0.15
RtC	-0.001	0.24	-0.12	0.69* (P: 0.001)	0.26	-0.28	0.12	0.15
LtC	-0.004	0.24	-0.16	0.71.** (P: 0.0001)	0.27	-0.31	0.17	0.13
RtP	-0.07	0.21	-0.20	0.70* (P: 0.001)	0.26	-0.30	0.14	0.18
LtP	-0.07	0.18	-0.24	0.72** (P: 0.0001)	0.28	-0.33	0.17	0.18

*: P<0.001, Rt: right, Lt: left, F: frontal lobe, T: temporal lobe, O: occipital lobe, P: parietal lobe, BG: basal ganglion, C: caudate lobe, SaO_2<90% : <90% of arterial oxygen saturation, SaO_2 min %: minimum arterial oxygen saturation, SaO_2 mean %: mean arterial oxygen saturation, REM: rapid eye movement, SWS: slow wave sleep, AHI: apnea hypopnea index

Table 4. *Distribution of CBF scores within the brain in the OSAS group*

	OSAS (n:16) Rank *		
	Right	Left	P
Temporal lobe	6.75	4.25	0.011
Frontal lobe	6.5	4.56**	0.003
Parietal lobe	6.75	5.06	NS
Occipital lobe	6.44	6.19	NS
Basal ganglion	6.44	6.56	NS
Caudate	9.56	8.94	NS

Friedman related samples nonparametric test ranks are given in this Table for the comparison of CBF scores OSAS group. NS: P>0.05

and the perivascular pH constitute a major regulatory parameter for the control of rCBF [26]. Doppler measurements of rCBF suggest that obstructive apneas are associated with blood flow reduction due to individual apneic episodes, impairment of cerebrovascular autoregulation and diminished cerebral vasodilatator reserve [10-12]. Ischemic effects of decreased CBF are further potentiated by hypoxemia secondary to apnea. Indeed cerebral tissue hypoxia has been recorded during episodes of OSAS [27]. We could not measure the acute effect of breathing impairment on CBF or the cerebral tissue oxygenation in our study. Impairment of CBF changes has been reported in healthy subjects after experimental exposure to isocapnic intermittent hypoxia. It was also reported that the changes of CBF persisted for 12 days, which suggests the sustained effect of chronic intermittent hypoxia on the CBF [28]. Patients in our study did not have daytime hypoxemia, but the strong association between SaO_2 means during sleep and the rCBF scores suggest that nocturnal hypoxemia and other blood gas changes in OSAS, like hypercapnia and

Table 3. *Nonparametric correlation coefficients of the association between polysomnography findings and cognitive function test scores*

	Age, yr	Education, yr	AHI	SaO_2 mean%	SaO_2 min%	SaO_2 <90%	REM%	SWS %
WVMS-ds	0.22	-0.22	-0.37	0.18	0.43	-0.49* (P:0.04)	-0.13	-0.22
WVMS-lm1	0.48*(P:0.05)	0.007	-0.11	-0.20	-0.15	0.09	-0.17	-0.27
WVMS-lm2	0.25	-0.17	-0.23	0.20	0.20	-0.25	0.10	-0.24
WVMS-vr1	0.32	-0.41	-0.07	0.27	0.38	-0.49* (P:0.04)	-0.20	-0.30
WVMS-vr2	0.23	-0.39	-0.21	0.34	0.49*(P: 0.04)	-0.59* (P:0.01)	-0.25	-0.18
TMTA	-0.05	-0.07	0.19	-0.12	-0.10	0.14	0.25	0.30
TMTB	-0.18	-0.06	0.21	-0.30	-0.36	0.32	0.32	-0.06
VFT-n	0.16	0.06	-0.19	0.13	0.16	-0.24	-0.32	-0.29
VFT-a	0.41	0.42	0.39	0.17	-0.17	0.19	-0.44	-0.21
VFT-al	0.29	0.15	0.44	0.04	-0.24	0.20	-0.46	-0.30
WCST-cc	-0.03	-0.30	-0.12	-0.07	-0.10	-0.02	-0.27	-0.39
WCST-pr	-0.30	-0.02	-0.12	-0.20	0.07	-0.04	0.24	0.16
WCST-pd	-0.27	-0.22	-0.11	-0.19	0.06	-0.04	0.26	0.24
WCST-npd	-0.28	0.01	-0.13	-0.11	0.13	-0.07	0.14	0.32
WCST-t	-0.12	-0.17	0.25	-0.22	-0.23	0.24	-0.09	0.28
WCST-cr	0.24	-0.41	0.11	0.10	-0.15	0.10	-0.25	-0.23

*: P<0.05 WVMS-ds: Wechlers Visual Memory Test (ds: digit span, lm: logical memory, vr: visual reproduction), TMT-A, B: Trail Making Test A and B, VFT: Verbal Fluency Test (n: name, a: animal, al: alternation, WCST: Wisconsin Card Sorting Test (cc:completed category, pr:perseverative reaction, pd: perseverative defects, npd: nonperseverative defects, t: trial, cr:cognitive reaction) SaO_2<90%: <90% of arterial oxygen saturation, SaO_2 min %: minimum arterial oxygen saturation, SaO_2 mean %: mean arterial oxygen saturation, REM: rapid eye movements, SWS: slow wave sleep, AHI: apnea hypopnea index

respiratory acidosis during sleep could have an influence on daytime CBF

CBF and OSAS

Changes in rCBF in OSAS patients could lead to critical cerebrovascular disorders. An early study by others, using ^{133}Xe inhalation method reported reduced CBF during wakefulness and sleep in patients with OSAS [29]. The same authors reported reduced CBF in the cerebellum and the brainstem at the wakeful state and enhanced of blood flow in the right temporoparietal regions during REM sleep in both narcoleptics and sleep apnea patients [29].

Despite the difficulties in the aetiological interpretation of the CBF changes in OSAS patients, findings of previous studies suggest that primary central neural dysfunction contributes to the genesis, maintenance and progression of OSAS [9]. In our study, among the OSAS patients distribution of CBF was not uniform and comparison of the ROI suggested decreased CBF in the left frontal and left temporal regions. Others found gray matter loss in these regions, which could reflect impairment in upper airway function (left frontal region) and in the CF (frontal region and left temporal regions) [30]. Others demonstrated reduced CBF in the left parietal region and speculated that these changes might be a result of apnea associated local vascular

auto-regulation in the brain [31]. However, the above findings were not validated by other colleagues who indicated that these findings could be due to a more rigorous definition of study subjects and age matching in the study [32]. Our findings could be regarded as an evidence against the other potential explanation (ie. blood flow loss is the consequence of OSAS). Otherwise, CBF would be more likely uniform in the OSAS patients.

CF and OSAS

Severe psychological and neurological complications such as CF impairment and high vascular morbidity have been demonstrated in patients with OSAS [33]. Others in 29 OSAS patients performed multiple regression analysis and found frequency of apneas plus hypopneas and of arousal with extent of nocturnal hypoxemia as the variables most strongly associated with CF deficits [34]. It has been hypothesized that deficits in CF and motor abilities were related to hypoxemia [6]. Irreversible, chronic hypoxemic damage, particularly affecting the frontal lobes, were considered as the crucial substrate of executive functions [35]. In our study Digit Span subtest of the WMS-R, which assesses the "frontal lobe skills" such as verbal and visual memory, was associated with hypoxemia during sleep [24]. Decreased CBF in left frontal and left temporal regions in our study was not associated with CF test sores. This could imply the causative association between decreased blood flow and impaired function related to these regions and OSAS. As CF tests were performed in the morning after polysomnography, this time interval might have affected the association between other polysomnography findings related to sleep disruption, and decreased CBF. However, hypoxemia during sleep in OSAS patients is not likely to change to a great extent over a short time interval.

In conclusion, our study findings suggest OSAS group: a) A positive association between SaO_2 during sleep and CBF in all regions during the awake period. b) Negative correlation between visual memory and SaO_2 during sleep. c) Decreased CBF in the left frontal and left temporal lobes in OSAS patients. The positive association of CBF and verbal memory with hypoxemia and decreased CBF after apneic episodes could indicate impairment of upper airway motor control in OSAS patients. Further studies, testing the effect of positive pressure treatment on these changes would help to elicit these findings.

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