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What is responsible for cochlear damage in patients with obstructive sleep apnea? Hypoxia or snoring noise?

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Abstract

Aim: Our aim in this study was to determine early cochlear changes caused by hypoxia and snoring noise in patients with Obstructive sleep apnea Syndrome and to examine the relationship of these changes with polysomnography parameters.

Materials and Methods: A total of 149 patients with symptoms of snoring and sleep apnea who underwent polysomnography were included in this study. We formed a patient and control group based on the apnea-hypopnea index. We compared the audiometric parameters and the Distortion Product Otoacoustic Emission amplitudes of the groups. We evaluated Polysomnography parameters such as snoring number, snoring index, oxygen desaturation index, minimum pO_2, mean pO_2, pO_2 $\leq$88%, which affect these results, by correlation.

Results: High frequency audiometry and high frequency Distortion Product Otoacoustic Emission amplitudes showed statistically significant differences in the Obstructive Sleep Apnea Syndrome group compared to the control group ($p<0.001$). PO_2 $\leq$88% affected high frequency audiometry and mean pO_2 affected high frequency Distortion Product Otoacoustic Emission amplitudes more than snoring number and snoring index ($p<0.001$).

Conclusion: In patients with OSAS, the inner ear is affected by hypoxia and snoring. However, the effect of hypoxia on cochlear dysfunction is greater than snoring noise. High-frequency audiometry and Distortion Product Otoacoustic Emission can guide in the early period to determine cochlear damage.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a chronic disease that occurs with partial or complete obstruction of the upper airways during sleep and progresses with recurrent apnea attacks. Patients experience hypoxic episodes during the night and excessive daytime sleepiness. OSAS is seen at a rate of 9% in middle-aged women and 24% in men [1]. These hypoxic attacks, which recur during the night in patients with OSAS, generate free oxygen radicals. This causes sympathetic activation, metabolic syndrome, and neurological-endocrine-cardiovascular diseases [2]. Polysomnography (PSG) should be performed in the sleep laboratory for the diagnosis of patients with OSAS.The most common symptom seen during the night in patients with OSAS is snoring.

Hearing loss is one of the important problems affecting the quality of life and is seen in %7-10 of society [3]. Ischemia caused by hypoxia is an important factor in sudden hearing loss. Cochlear functions are severely impaired when blood pO_2 decreases or blood flow to the cochlear decreases. In many studies, it has been stated that hypoxia reduces cochlear functions [4]. In addition, free oxygen radicals and nitric oxide formed during ischemia cause damage to cochlear outer hair cells [5]. Although many mechanisms have been stated to explain cochlear damage, fusion, synaptic-dendritic swelling, and sustained depolarization in outer hair cells of the cochlea and cilia are the most important consequences of hypoxia. Hypoxia causes apoptosis in outer hair cells by affecting the mitochondria of cochlear cells [6]. This causes an increase in pure tone hearing thresholds and a decrease in distortion product otoacoustic emission (DPOAE) amplitudes [7]. There are also studies showing that Pure tone audiometry (PTA) thresholds are elevated, and speech perception and speech discrimination scores are impaired in severe patients with OSAS [8]. However, these studies could not clearly explain

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the critical oxygen level that impairs hearing functions and which parameter in PSG affects hearing functions.
Otoacoustic emission (OAE); It is obtained as a result of measuring a kind of sound energy produced by the cochlea with a probe placed in the outer ear canal. It reflects the functional state of the outer hair cells in the cochlea. Therefore, hearing damage in patients can be detected using OAE. DPOAEs may deteriorate in the early stages of hypoxia because the outer hair cells of the cochlea are very sensitive to hypoxia [9]. Our aim in this study was to determine early cochlear changes caused by hypoxia and snoring noise in patients with OSAS and to examine the relationship of these changes with PSG parameters.

Materials and Methods

A total of 456 patients who applied to the Ear Nose and Throat Clinic of our hospital with complaints of snoring and sleep apnea were included in the study. Patients with normal otoscopic examination, no hearing loss, and PTA below 20 db were included in the study. One hundred eighty-two patients with PTA above 20 db were excluded from the study. 72 patients with acute and chronic otolaryngologic diseases that adversely affected the hearing mechanism (noise exposure, tinnitus, those with vertigo, those with perforation of the tympanic membrane, otitis media, and those who had undergone ear surgery), and patients with chronic diseases that caused hypoxia [ischemic heart disease, chronic lung disease, hypertension (HT), and diabetes mellitus (DM)] were excluded. 53 patients with missing PSG results and audiological tests were excluded from the study. One hundred forty-nine patients who met the study criteria were included in the study.
PSG results and audiological test results of the patients were evaluated by a double-blind specialist.
Our study complies with the Helsinki Declaration of Human Rights and signed consent forms were obtained from all participants. Ethics Committee Approval (Adana City Training and Research Hospital Medical Ethics Committee, Meeting Number: 60, Decision Number: 965, Date: 01/07/2020) was received.

Polysomnography

PSG recordings of all patients using Comet-PLUS Grass® (Astro-Med Industrial Park, West Warwick, USA) PSG device examined. All parameters were performed according to the American Academy of Sleep Medicine (AASM) guidelines. Those with an apnea-hypopnea index (AHI) between 0 and 4.9 were taken as the control group, and those with AHI ≥5 as the OSAS group. The design of the study is a comparative case series.
AHI, oxygen desaturation index (ODI), minimum pO_2 value (min- pO_2), mean oxygen saturation (mean- pO_2) pO_2 ≤%88 snoring number, and snoring indexes were evaluated. Number of snoring; It is the number of snores that occur during sleep and the snoring index is determined by dividing this by the sleep time.

Audiologic test

Audiometry examination tests were performed by the same singe blind audiometrist. The external ear canal was checked for otitis, cerumen and external ear canal diseases. Timpanic membran integrity was found to be intact. Air and bone conduction hearing thresholds were recorded separately for the right and left ears at 250Hz, 500Hz, 1000Hz, 2000Hz, 4000Hz, 8000Hz, and 16000Hz, and the average of both ears was taken (clinical audiometry/otometrics) (Madsen Astrera). 250-500-1000-2000Hz frequency in PTA were evaluated as LFA (low frequency audiometry), 4000-8000Hz were HFA (high frequency audiometry), 16000Hz were EHFA(extended high frequency audiometry) [10].
Those with pure tone audiometry (PTA) 20 db and below were included in the study. In our study, the effects of hypoxia and snoring on the inner ear were examined in patients with normal hearing. It was checked at frequencies as high as 8000 Hz and 16000 Hz, which are not routinely checked.

DPOAEs, which are low-level acoustic signals from the outer ear canal, were measured using a Neuro-Audio/OAE device (version 2010, Neurosoft). It was set to 500 to 8000 Hz and recorded as a distortion product (DP-gram). DPOAE stimulus intensity was set to 55 for L1 and L2 levels. The f1 (65 dB SPL) and f2 frequency (55 dB SPL; f2/f1) ratios were set to 1.22. DPOAE amplitude values of 3dB higher than the noise threshold were considered significant. The measurement was carried out in a room where noise level did not exceed 50 dB. .DPOAE data were grouped as DPOAE 1kHz, 2kHz, 4kHz, 6kHz, 8kHz from low frequency to high frequency, respectively. Signal-to-noise ratio (SNR) values were recorded at different frequencies (1kHz, 2kHz, 4kHz, 6kHz, 8kHz) (10) In the control group and OSAS group LFA, HFA, EHFA, and DPOAE 1kHz, 2kHz, 4kHz, 6kHz, 8kHz values, and ODI, min- pO_2 , mean pO_2 , pO_2 ≤%88 snoring number, and snoring indexes were compared between the groups.

Statistical analysis

The normality of the distribution of continuous variables was evaluated using the Shapiro-Wilk test. The Mann-Whitney U test was used in the comparisons of the OSAS and control groups. Spearman Rho correlation coefficients were used to examine the linear relationship between individual variables in the OSAS and control groups. Sex distribution was checked using the Chi-square test. The level of statistical significance was taken as 0.05. The analysis of the data was evaluated using the SPSS 21 program.

Results

A total of 149 patients, 86 (57.7%) females and 63 (42.3%) males were included in the study. There were 52 (34.9%) patients in the control group and 97 (65.1%) patients in the OSAS group. There was no statistical difference between the patient and control groups in terms of age, gender and BMI (Table 1).

Sleep data

In the OSAS group, the number of snoring, snoring index, ODI and pO2 ≤%88 were significantly higher than in the control group, and the mean- pO_2, min- pO_2 were significantly lower ($p<0.001$) (Table 1).

Table 1. Demographic characteristics and polysomnography parameters of groups.

	Control			OSAS			p
	Mean±SD	Median[IQR]	Min-Max	Mean±SD	Median[IQR]	Min-Max	
N	52	34.9%		97	65.1%		
Age	50.91±8.32	51[45.25-58]	31-64	51.37±7.91	52 [46-58]	31-64	0.798
Sex							
Female	28	53.8%		58	59.8%		0.484
Male	24	46.2%		39	40.2%		
BMI	26.31±5.71	25 [22-30.75]	18-40	26.21±5.76	25 [22-30]	18-40	0.877
Snoring number	9.08±3.18	9 [8-11]	0-15	20.53±17.23	15 [5-30.75]	0-68	<0.001
Snoring index	2.5±2.17	2 [0.93-3]	0-9	9.04±12.59	3 [0.53-12]	0-56	0.021
ODI	1.37±0.64	1.2 [0.8-1.8]	0,5-3	26.26±25.31	15.6 [7-43.7]	0.4-109.4	<0.001
Mean- pO_2	96.58±1.02	97 [96-97]	95-98	89.18±3.91	89 [86-92.9]	79.6-97	<0.001
Min-pO_2	94.12±2.52	95 [94-95]	78-96	76.26±11.59	80 [72-85]	50-93.7	<0.001
$pO_2 \leq$%88	0.14±0.39	0.05 [0-0.2]	0-2.8	13.97±20.42	4 [0.6-20.5]	0-93	<0.001

p:Mann Whitney U test *Chi-Square test OSAS:Obstructive Sleep Apnea,BMI:Body Mass İndex,ODI: Oxygen Desaturation Index,: pO2 Oxygen Saturations ,Min-SPO2:Minimum Oxygen saturations.

Table 2. Auditory Functions of groups.

	Control			OSAS			p
	Mean±SD	Median[IQR]	Min-Max	Mean±SD	Median[IQR]	Min-Max	
LFA	12.05±3.39	10.63 [10-14.38]	5-20	12.4±3.69	11.25 [10-15]	5-20	0.631
HFA	10.75±4.35	10 [6.25-16.88]	6.25-17.5	27.81±17.17	22.5 [15-35]	5-85	<0.001
EHFA	11.06±5.89	10 [5-20]	5-20	37.16±17.99	30 [30-50]	10-90	<0.001
DPOAE 1kHz	5±0.19	5 [4.85-5.19]	4.5-5.3	4.84±1.61	4.35 [4.1-5.45]	3.5-18.75	0.142
DPOAE 2kHz	8.43±0.17	8.35 [8.35-8.55]	8-8.75	8.66±2.68	8.2 [5.85-11.3]	4.4-11.6	0.946
DPOAE 4kHz	6.03±0.21	6.05 [5.95-6.23]	5.5-6.3	5.16±1.36	5.5 [3.9-6.1]	3.5-8.9	<0.001
DPOAE 6kHz	8.47±0.22	8.5 [8.3-8.64]	8-8.9	4.19±1.33	3.5 [3.05-5.48]	2.5-8.85	<0.001
DPOAE 8kHz	13.11±0.18	13.15 [12.95-13.25]	12.5-13.35	5.65±1.09	5.5 [5.05-5.88]	3.95-10.05	<0.001

p:Mann Whitney U test LFT: Low Freguency Audiometry. HFA: High Freguency Audiometry, EHFA: Extended High Freguency Audiometry, DPOAE: Distortion Product Otoacoustic emission.

Table 3. Analysis of OSAS group hearing functions and PSG parameters with Spearman Rho Correlation.

		HFA	EHFA	DPOAE 4kHz	DPOAE 6kHz	DPOAE 8kHz
Snoring number	r	.283**	.254*	,263**	-,242*	,332**
	p	.005	.014	,010	,017	,001
Snoring index	r	.213*	.163	,309**	-,339**	,394**
	p	.037	.116	,002	,001	,000
ODI	r	.418**	.363**	,288**	-,325**	,454**
	p	.000	.000	,004	,001	,000
Mean SPO_2	r	-.228*	-.208*	-,319**	,541**	-,488**
	p	.025	.043	,001	,000	,000
Min SPO_2	r	-.322**	-.322**	-,118	,390**	-,322**
	p	.001	.001	,252	,000	,001
$SPO_2 \leq$%88	r	.477**	.446**	,272**	-,416**	,352**
	p	.000	.000	,007	,000	,000

P: Spearman Rho Correlation OSAS:Obstructive Sleep Apnea,BMI:Body Mass İndex,ODI: Oxygen Desaturation Index, pO_2:Oxygen Saturations ,Min-pO_2:Minimum Oxygen saturations.

Audiometric and DPOAE data

The HFA of the control group and OSAS group was 10.75±4.35 and 27.81±17.17, respectively (p<0.001). The EHFA of the control group and OSAS group was 11.06±5.89 and 37.16±17.99, respectively (p<0.001). HFA

and EHFA hearing thresholds were significantly increased in the OSAS group.

There was no statistically significant difference between DPOAE 1kHz and DPOAE 2 kHz between the groups. DPOAE 4kHz DPOAE 6kHz, DPOAE 8kHz amplitudes were significantly decreased in the OSAS group (Table 2).

Spearman Rho correlation between sleep data, audiometric data, and DPOAE in OSAS group

pO_2 ≤%88; It affected HFA and EHFA more than other PSG parameters ($p<0.001$, r=477 and r=446, respectively).

The mean- pO_2 ; It affected DPOAE 4kHz, DPOAE 6kHz, DPOAE 8kHz more than other PSG parameters ($p<0.001$, r=319, r=541, and r=488, respectively) (Table 3).

Discussion

OSAS is a chronic disease that progresses with recurrent hypoxic attacks and affects all systems. The cochlea vestibular system is adversely affected by this hypoxic state and subsequent metabolic events. Snoring is the most common symptom that causes patients with sleep disorders to come to the doctor. In some studies, it has been shown that high-frequency hearing loss in patients with OSAS is caused by snoring [10]. In our study, we examined the effects of both hypoxia and snoring sound on cochlear functions in patients with OSAS without hearing loss in daily life.

In their study with 58 patients with OSAS and 20 controls, Li et al. compared the control group with patients with OSAS and showed that 4000 and 8000 Hz hearing thresholds were increased in PTA, and DPOAE amplitudes decreased significantly even if there was no hearing loss [11]. However, they did not evaluate hearing thresholds at higher frequencies such as 16,000 Hz in PTA. In our study, we determined that it could be affected at high frequencies such as 16,000 Hz. Even without hearing loss, chronic hypoxia in patients with OSAS affects hearing thresholds and DPOAE amplitudes, especially at high frequencies. DPOAE is an objective marker of cochlear functions in patients with OSAS.

Yilmaz et al. investigated the effects of hypoxia on the inner ear in their study of 30 patients with chronic obstructive pulmonary disease (COPD) according to spirometry and SPO_2, 30 patients with normal otoscopic examinations, and 30 controls [7]. PTA was high in the patient group, and Speech Discrimination (SD) was low. They averaged DPOAE 1, 2, 4, and 8 kHz and found the SNR value to be low in the patient group. However, they did not specify which frequencies were more affected. Prolonged hypoxia in COPD affected DPOAE values and increased hearing thresholds. In the 15 minutes following cochlear hypoxia, swelling and deterioration of the outer hair cells begin. When examined closely with an electron microscope, swelling and deterioration are observed, especially in mitochondria, endoplasmic reticulum, and nucleic acids The decrease in the oxygen level decreases the activity of the Na/K ion pump. Ischemic symptoms caused by acute hypoxia may not improve during the reperfusion period 5. In an animal study, Morawski et al. found a significant decrease in DPOAE levels, especially at high frequencies, compared with the preischemic period after 5 minutes of hypoxia followed by 60 minutes of reperfusion. PO_2 values were found to be between 55 and 70 in hypoxic conditions, which caused a decrease in DPOAE values, and the free oxygen radicals formed were held responsible for this damage [12]. However, Yılmaz et al. could not reach a clear conclusion about the critical pO_2 causing cochlear damage. Because patients with COPD did not want to enter the audiometry test room if their pO_2 was <60 without oxygen support due to increased respiratory distress and anxiety. Determining the critical pO_2 level that causes cochlear damage is therefore difficult in humans. However, more accurate results can be obtained by conducting animal studies [13]. In our study, we included patients with OSAS, not patients with COPD, to examine the effect of hypoxia on the inner ear, and examined 149 patients. We determined that hearing thresholds increased at 4000, 8000, and 16,000 Hz, and DPOAE amplitudes decreased at 4000-6000-8000 Hz. Even if hearing thresholds are normal, we found that min -pO_2, pO_2 ≤%88 levels, and mean-pO_2 were more responsible for cochlear damage than other PSG parameters. Reducing the min -pO_2 and pO_2 ≤%88 and increasing the mean- pO_2 value in patients with OSAS may reduce the cochlear damage caused by hypoxia and minimize the high-frequency hearing loss.

In a study in which patients with OSAS examined the audiological parameters, as in our study, Mahmut and Deniz et al. took AHI<5 as the control group, but they divided the patients with OSAS into mild, moderate, and severe according to AHI. They concluded that if the AHI was above 15 and BMI was above 30, the hearing functions are impaired and that weight control can improve hearing functions [14]. Hypoxia caused by OSAS negatively affects hearing functions. There are 2 types of hypoxic states in patients with OSAS. The first is low-frequency and continuous hypoxemia. The second is short-term high-frequency hypoxemia (episodic) observed during sleep and the condition continues cyclically throughout the night. Episodic hypoxemia is followed by reoxygenation and reperfusion. Hypoxia induces chemoreflexia and vasoconstriction occurs, vascular functions are impaired and tissue oxygenation is affected [15]. In OSAS, the oxygen level is within normal limits during daytime wakefulness. According to Xu et al., if the AHI is greater than 10 in OSAS, cochlear damage begins [16]. According to another study, hearing functions are impaired in severe OSAS [17]. In our study, we compared patients with OSAS with a control group and determined that the hearing thresholds increased at high frequencies and at the DPOAE amplitudes decreased (4000-8000-16000 Hz).

Kayabaşı et al. evaluated 120 patients with OSAS and compared PSG parameters and hearing functions [8]. Similar to our study, those with AHI <5 were included in the control group. Hearing functions were affected at high frequencies in the moderate OSAS group and affected at all frequencies in the severe OSAS group. AHI, ODI, and min-pO_2; while it showed positive correlation with PTA and SRT, it showed negative correlation with SD. In our study, we did not divide patients with OSAS into groups, but we determined that hearing loss especially at high frequencies decreased. Seo et al. stated that the cause of inner ear

dysfunction, which increases with the severity of OSAS, was damage to the cochlear sensory epithelium [18,19]. In some previous human studies, temporal bone dissections were performed to determine cochlear and nerve damage in various diseases [20].

In severe OSAS, acoustic trauma due to snoring may affect hearing [21]. Clinical studies indicate that after noise exposure, cochlear oxygen levels decrease and ischemia occurs in noise-induced hearing loss. Anoxia and reperfusion impair cochlear functions by causing inflammation; especially nitric oxide affects the outer hair cells of the cochlea [22]. Ekin et al., in their study with 21 controls, 18 simple snorers, and 27 patients with OSAS, both ears were evaluated with low (250, 500, 1000, 2000), high (4000, 6000, 8000 Hz), and very high (10,000, 12,000, 14,000, 16,000 Hz) looked at frequencies of PTA [10] .They stated that hearing loss in patients with simple snoring may be due to snoring noise While they did not see low and high-frequency hearing loss in patients with OSAS, they found very high-frequency hearing loss and stated the reason for this as continuous noise exposure. In hearing physiology, it is noted that frequency coding across the basilar membrane progresses from high frequencies to low frequencies as it moves away from the basal portion to apex. The basal part is first affected by hypoxia, and thus high-frequencies are lost first. Some studies mentioned hypoxia in high-frequency hearing loss in patients with OSAS and others described noise-induced hearing loss caused by snoring [23]. In some studies, it has been shown that snoring causes acoustic trauma in bed partners and causes hearing loss in unilateral high frequencies at snores side [23]. However, when we performed Spearman Rho correlation analysis, we found that min - pO_2, pO_2 $\leq$%88 and mean-pO_2 affect the inner ear more than snoring, and are more responsible for high-frequency hearing loss in patients with OSAS.

Of course, in cochlear damage, both the damage of the vascular walls, the deterioration of the blood flow to that area and the decrease in the oxygen level in the blood are very important. Since our patients consist of patients without diabetes, hypertension and chronic disease, we only evaluated hypoxia due to sleep apnea. While we determined how important the oxygen value was in our study, we found that snoring, which may cause acoustic trauma, was not as effective as hypoxia and did not affect audiometric data as much. In studies, we know that hypoxia causes cochlear damage at the symptomatic and cellular level. It is obvious that acoustic trauma also causes cochlear deterioration. However, we could not reach the study comparing these two conditions as a result of our literature review. Our work compares these two data.

Conclusion

As a result, in patients with OSAS, the inner ear is affected by hypoxia and snoring. However, the effect of hypoxia on cochlear dysfunction is greater than snoring noise. High-frequency audiometry and DPOAE can guide in the early period to determine cochlear damage.

Limitation

Although we measured the number and index of snoring in polysomnography, we did not measure snoring severity in decibels. If we had, we could have evaluated the effect of snoring severity on cochlear damage. We conducted our study in a single center and with a limited number of patients. In the future, more detailed studies can be conducted in multiple centers, with a larger number of patients, in which lower pO_2 levels can be measured with more advanced PSG devices, more parameters can be examined with correlation analysis, and temporal bone dissections of patients with OSAS can be performed.

Ethics approval

This study was approved by the Adana City Training and Research Hospital Medical Ethics Committee with the decision no. 695 dated 01.07.2020.

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