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The effects of acute hypoxia on audition: An experimental study

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ABSTRACT

OBJECTIVE: Obstructive sleep apnea syndrome (OSAS) is a health problem that has increasing importance in society. In the literature, many studies about an audition in patients with OSAS are present. In this study, the effects of hypoxia on an audition that develop during the apnea attacks in OSAS were investigated experimentally.

METHODS: This study was conducted in Inonu University Audiology Laboratory after the approval of Inonu University Faculty of Medicine Experimental Animal Research Ethics Committee (Protocol Number: 2011/A-102). In this study, 15 Wistar albino rats with a weight of 250–300 g were used. Anesthesia was performed by 40 mg/kg Ketamine and 5 mg/kg Xylazine through intramuscular administration. The processes were applied in the silence. This study involved 15 rats with normal auditory functions. Only tracheotomy was performed in the control group. Auditory assays were administered with otoacoustic emission (DP gram) before and after the process. In hypoxia group, hypoxia was created by making apnea attacks that lasted at least 10 seconds after the tracheotomy process. Auditory assays using DP gram were performed before tracheotomy and during hypoxia in the hypoxia group.

RESULTS: In the control group, statistically significant values were not found. In the hypoxia group, statistically significant differences were detected in high frequencies.

CONCLUSION: In conclusion, cochlear reply decreased in high frequencies during hypoxia that was created by apnea attacks.

Keywords: Autoacoustic emission; hypoxia; obstructive sleep apnea.

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Obstructive sleep apnea syndrome (OSAS) is characterized as apneas due to the recurrent upper airway collapse during sleep, snoring and excessive daytime sleepiness [1]. Recurrent upper airway obstruction blocks the effective blood exchange in the lung alveolus. This blockage causes oxygen desaturation and increase in the carbon dioxide levels. Hypoxemia and carbon dioxide retention occurred during apnea induce sympathetic activation and vasoconstriction via chemoreflex cycle. Sympathetic activation increases during apnea and ends up by awakening. Heart rate volume and blood pressure increases with normal breathing function. Increased sympathetic activation continues in the day and causes permanent changes in the long term. Sympathetic activation ends up with the increased blood pressure and termination of apnea [2].

Hypoxia generally can be categorized as hypoxaemic hypoxia, anemic hypoxia, circulatory hypoxia, and histotoxic hypoxia. Hypoxia and ischemia are known as main factors that may cause hearing loss. Mazurek et al. [3] used an in vitro hypoxia and ischemia model of the

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newborn rat cochlea and showed the loss of both inner and outer hair cells. They showed this decrease especially on the inner hairy cells. Our aim was to evaluate hearing level during hypoxia caused by apnea attacks. There are some studies related to audition patients with obstructive sleep apnea syndrome in the literature [4].

Our aim was to evaluate auditory functions in rats after hypoxia that was created by apnea attacks with autoacoustic emission in our study.

MATERIALS AND METHODS

This study was conducted in Inonu University Audiology Laboratory after the approval of Inonu University Faculty of Medicine Experimental Animal Research Ethics Committee (Protocol Number: 2011/A-102). In this study, 15 Wistar albino rats with a weight of 250–300 g were used. Experimental rats were experimented with 12 hours of light, 12 hours of dark illumination, temperature (22±2°C) and humidity (45–50%) in automatically adjusted rooms. In the experimental process, all rats were fed with standard pellet feed in polycarbonate transparent lattices and fresh tap water was given every day. Anesthesia was performed by 40 mg/kg Ketamine and 5 mg/kg Xylazine through intramuscular administration. Then the processes were applied in the silence. Otoacoustic emission measurements were used to evaluate the hearing functions of all rats. Otoacoustic emission measurements were performed using Otoacoustic emission (DP Gram) values. This study involved 15 rats with normal auditory functions. Rats were randomly divided into two groups.

Grouping

Group 1 (control group)

Tracheotomy was performed on the five rats in this group after Distortion product otoacoustic emissions (DPOAE) measurements under general anesthesia. In this process, the rats were followed by an oxygen saturation probe (Mindray, MEC-1000, neonatal probe). DPOAE measurements were repeated without hypoxia after tracheotomy.

Group 2 (hypoxia group)

DPOAE measurements were performed under general anesthesia in 10 rats in this group, then, tracheotomy was performed. The tracheotomy cannula was closed for at least 10 seconds after the tracheotomy (an apnea attack was imitated). In this process, the rats were followed by an oxygen saturation probe (Mindray, MEC-1000, neonatal probe). At the moment when saturation decreased below 85% (hypoxia period), the measurements of distortion product otoacoustic emission were repeated. A single apnea was created that reduces oxygen saturation below 85%. Measurement was taken immediately after apnea.

Highlight key points

- Acute hypoxia induced by tracheotomy.
- Cochlear reply decreased in high frequencies during hypoxia that was created by apnea attacks.

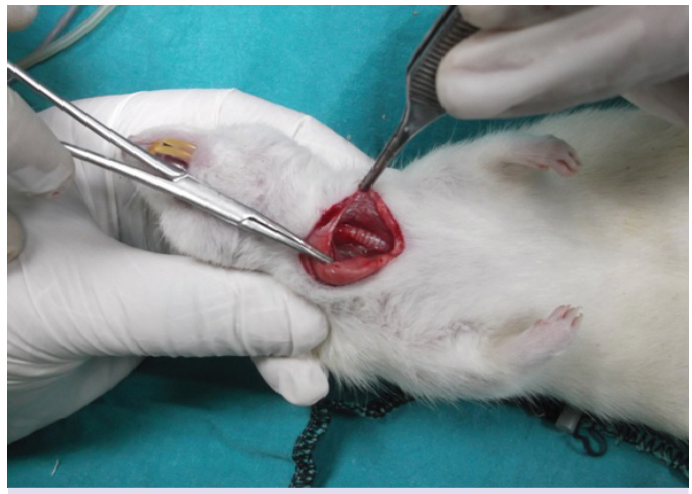

Figure 1. Tracheotomy incision.

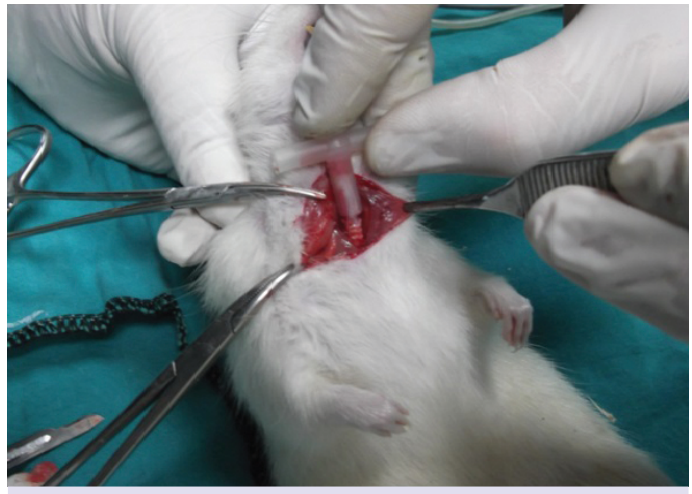

Figure 2. Tracheotomy cannula placement.

Tracheotomy Process

The experimental rat was fixed to the dissection table with warmer temperature and stable in the supine position. Surgical area was cleaned with 70% ethyl alcohol.

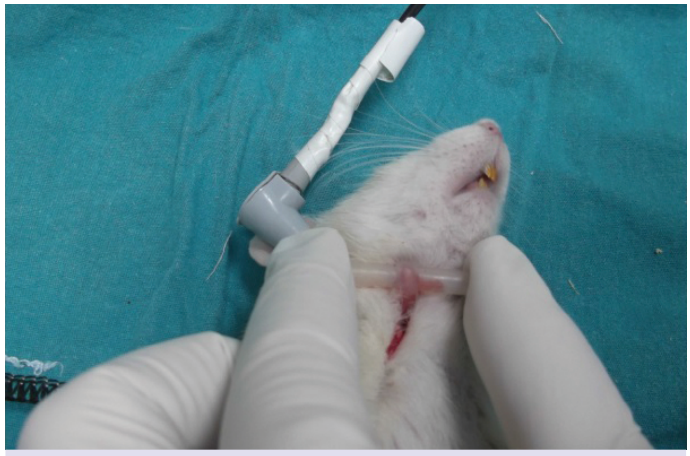

FIGURE 3. DPOAE Measurement during hypoxia.

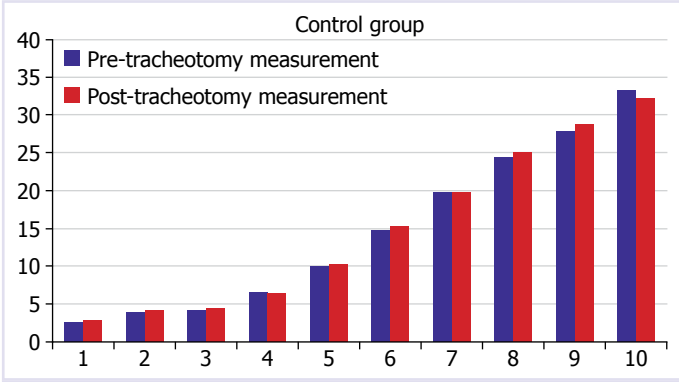

FIGURE 4. This graphic shows the change in DPOAE measurements made before and after tracheotomy in the control group. The vertical column represents the value of DPOAEs in SPL units, while the horizontal column represents the measured frequency numerically from small to large.

All surgical procedures were performed in a sterile environment and with sterile surgical instruments. Trachea was reached by dissecting tissues at the midline of the neck after a 1.5 cm incision in the vertical plane and an appropriately sized cannula was placed through the window opening in the trachea (Fig. 1, 2).

DPOAE Measurement Method

In the DPOAE test, GSI Audera DPOAE (Grason Stadler, Madison, USA) device was used. Otoacoustic emission probe was placed in the external ear canal in the measured ear (Fig. 3).

In the first measurements of the rats, the well hearing ears were determined and repeated measurements were continued in the same ear. The control and calibration of the probe were automatically performed by the measuring system before each test. Measurements were performed in an environment not exceeding 45 dB SPL. The primary stimulus levels for DP gram measurements were equalized at 65 dB. Two separate frequencies (f1 and f2) are arranged so that the most powerful responses can be obtained as f2 / f1 = 1.22. DP grams were measured at a frequency of 019.5 Hz, 1605.5 Hz, 2027.3 Hz, 2566.4 Hz, 3210.9 Hz, 4054.7 Hz, 5121.1 Hz, 6445.3 Hz at 8003.9 Hz and 10078.1 Hz. and results were recorded.

Statistical Analysis

In the statistical analysis, SPSS for Windows Version 17.00 program was used. The measurable variables were presented as mean±standard deviation. Wilcoxon two-sample paired test was used for the changes within the groups. $P<0.05$ was accepted as statistically significant.

RESULTS

Control Group

Tracheotomy was performed on the five rats in this group after DPOAE measurements under general anesthesia. In this process, the rat was followed by an oxygen saturation probe (Mindray, MEC-1000, neonatal probe). DPOAE measurements were repeated without hypoxia after tracheotomy. This group was used only for comparison with the other group concerning DPOAE responses. DP gram measurements before and after tracheotomy at 1019.5 Hz, 1605.5 Hz, 2027.3 Hz, 2566.4 Hz, 3210.9 Hz, 4054.7 Hz, 5121.1 Hz, 6445.3 Hz, 8003.9 Hz and 10078.1 frequencies were carried out and recorded.

The mean values in the pre-tracheotomy measurements of DPOAE were as follows: SPL, 3.88 SPL at 1605.5 Hz, 4.28 SPL at 2027.3 Hz, 6.54 SPL at 2566.4 Hz, 3210.9 9.98 SPL at Hz, 14.86 SPL at 4054.7 Hz, 19.76 SPL at 5121.1 Hz, 24.3 at 6445.3 Hz SPL was found as 27.84 SPL at 8003.9 Hz and 33.36 SPL at 10078.1 Hz (Table 1, Fig. 4).

Mean values of DPOAE post-tracheotomy measurements at 1019.5 Hz 2.86 SPL, 4.18 SPL at 1605.5 Hz, 4.52 SPL at 2027.3 Hz, 6.42 SPL at 2566.4 Hz, 10.38 SPL at 3210.9 Hz, 15.22 SPL at 4054.7 Hz, 19.8 SPL at 5121.1 Hz, 6445.3 25.06 SPL at Hz, 28.8 SPL at 8003.9 Hz and 32.18 SPL at 10078.1 Hz were found. In the control group, at the1019.5 Hz, 1605.5 Hz, 2027.3 Hz, 2566.4 Hz, 3210.9 Hz, 4054.7 Hz, 5121.1 Hz, 6445.3 Hz 8003.9 Hz ve 10078.1 frequencies. There

Table 1. DPOAE measurements before and after tracheotomy

	Fr 1 1019.5 Hz	Fr 2 1605.5 Hz	Fr 3 2027.3 Hz	Fr 4 2566.4 Hz	Fr 5 3210.9 Hz	Fr 6 4054.7 Hz	Fr 7 5121.1 Hz	Fr 8 6445.3 Hz	Fr 9 8003.9 Hz	Fr 10 10078.1
DPOAE before tracheotomy	2.68±0.87	3.88±1.57	4.28±3.03	6.54±2.41	9.98±2.5	14.86±2.52	19.76±4.47	24.3±3.79	27.84±5.97	33.18±4.89
DPOAE after tracheotomy	2.86±0.98	4.18±1.82	4.52±3.37	6.42±2.04	10.38±2.55	15.22±3.02	19.8±4.07	25.06±4.56	28.8±6.28	32.18±5.62

SEM: Standard error error of mean; DPOAE: Distortion-product otoacoustic emissions.

Table 2. Mean DPOAE measurement values before and after tracheotomy in hypoxia group

	Fr 1 1019.5 Hz	Fr 2 1605.5 Hz	Fr 3 2027.3 Hz	Fr 4 2566.4 Hz	Fr 5 3210.9 Hz	Fr 6 4054.7 Hz	Fr 7 5121.1 Hz	Fr 8 6445.3 Hz	Fr 9 8003.9 Hz	Fr 10 10078.1
Before tracheotomy	2.79±1.45	4.05±1.85	4.36±2.97	6.67±2.14	10.27±2.36	14.81±3.35	20.74±3.26	25.43±4.28	28.29±5.47	33.18±5.56
After hypoxia	2.53±1.59	3.80±1.43	4.26±2.79	6.37±2.11	9.89±2.19	14.37±3.20	20.05±3.61	24.5±4.04	27.14±4.97	31.65±5.45

SEM: Standard error error of mean.

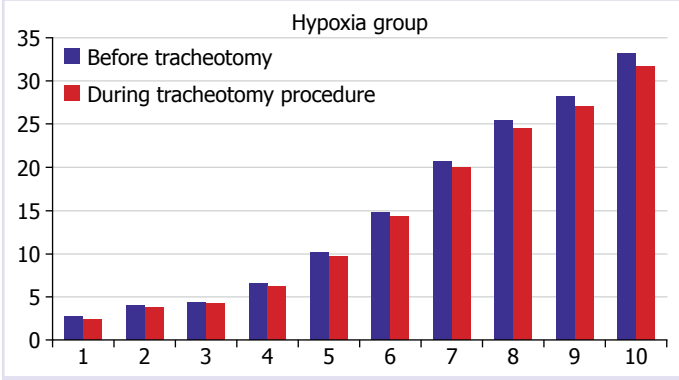

Figure 5. This graph shows the change in DPOAE measurements made before and after tracheotomy in the hypoxia group. The vertical column represents the value of DPOAEs in SPL units, while the horizontal column represents the measured frequency numerically from small to large.

were no statistically significant difference before and after the tracheotomy procedure (Table 1, Fig. 4).

Hypoxia Group

DPOAE measurements were performed under general anesthesia in 10 rats in this group. Then, tracheotomy was performed. The tracheotomy cannula was closed for at least 10 seconds after tracheotomy (an apnea attack was imitated). In this process, the rat was followed by oxygen saturation probe (Mindray, MEC-1000, neonatal probe). At the moment when saturation decreased below 85% (hypoxia period), the measurements of DPOAE were repeated. This group was used to compare pre- and post-hypoxia concerning DPOAE responses. DP gram measurements before tracheotomy and during hypoxia at 1019.5 Hz, 1605.5 Hz, 2027.3 Hz, 2566.4 Hz, 3210.9 Hz, 4054.7 Hz, 5121.1 Hz, 6445.3 Hz 8003, 9 Hz and 10078.1 Hz frequencies were carried out and results were recorded.

The mean values in the pre-tracheotomy measurements of DPOAE were as follows: SPL, 4.05 SPL at 1605.5 Hz, 4.36 SPL at 2027.3 Hz, 6.67 SPL at 2566.4 Hz, 3210.9 10.27 SPL in Hz, 40.87 Hz, 14.81 SPL, 512.72 SPL in 20.74 SPL, 6445.3 Hz 25.43 SPL 28.29 SPL at 8003.9 Hz and 33.18 SPL at 10078.1 Hz (Table 2, Fig. 5).

Mean values of DPOAE measurements during hypoxia were 2.55 at 1019.5 Hz. SPL, 3.80 SPL at 1605.5 Hz, 4.26 SPL at 2027.3 Hz, 6.37 SPL at 2566.4 Hz, 3210.9 9.89 SPL in Hz, 14.37 SPL in 4054.7 Hz, 20.05 SPL in 5121.1 Hz, 6445.3 Hz 24.53 SPL was 27.14 SPL at 8003.9 Hz and 31.65 SPL at 10078.1 Hz (Table 2, Fig. 5).

In the hypoxic group at the following frequencies: 1019.5 Hz, 1605.5 Hz, 2027.3 Hz, 2566.4 Hz, 3210.9 Hz, 4054.7 Hz, 5121.1 Hz, 6445.3 Hz before and after hypoxia. There were no statistically significant differences between the measurements ($p>0.05$). In the hypoxia group, there were statistically significant differences between 8003.9 Hz and 10078.1 Hz frequencies before the tracheotomy and after hypoxia ($p<0.05$).

DISCUSSION

Blood pressure and heart rate decreases in the early phase of apnea [5]. In the second phase of apnea, oxygen saturation decreases, blood pressure and heart rate increases [6]. It has been shown that hypoxemia, even a short-term and mild, may affect hearing levels and cochlear functions [7]. Hypoxia and ischemia are thought to be important factors that cause hearing loss. Mazurek et al. [3] used an in vitro hypoxia and ischemia model of the newborn rat cochlea and showed the loss of both inner and outer hair cells. They showed this decrease especially on the inner hairy cells.

Our aim was to evaluate audition during the hypoxic period created by apnea attacks. Tracheotomy was performed under general anesthesia in the control group (consisting of five rats) after auditory assays were made with DPOAE. Rat was monitored with oxygen saturation probe during the process. Auditory assays were repeated by DPOAE gram after tracheotomy process without creating hypoxia. This group was only used to compare DPOAE responses with the other group.

DPOAE gram measurements were carried out at 1019.5 Hz, 1605.5 Hz, 2027.3 Hz, 2566.4 Hz, 3210.9 Hz, 4054.7 Hz, 5121.1 Hz, 6445.3 Hz 8003.9 Hz ve 10078.1 Hz frequencies before and after tracheotomy processes and results were recorded. Tracheotomy was performed under general anesthesia in the second group (consisting of ten rats) after auditory assays were made with DPOAE. Rat was monitored with oxygen saturation probe during the process. After the tracheotomy procedure, the cannula is closed for at least 10 seconds and it was observed that saturation fell below 85 percent (hypoxia was created by mimicking an apnea attack). This group was used to compare DPOAE responses before and after hypoxia.

DPOAE gram measurements were carried out at 1019.5 Hz, 1605.5 Hz, 2027.3 Hz, 2566.4 Hz, 3210.9 Hz, 4054.7 Hz, 5121.1 Hz, 6445.3 Hz 8003.9 Hz ve 10078.1 Hz frequencies before tracheotomy process and during the hypoxia and results were recorded. Otoacoustic emission (OAE) measurements have significant advantages in clinical use. It is a painless, sensitive process, suitable for children, does not require anesthesia and presents objective data. It is especially useful for evaluating cochlear functions in infants [8–11]. DPOAE can be easily measured even in small experimental animals [12–14]. The distortion created by the same stimulus, under proper sedation and placement of the probe, may make a difference of ±5 dB in records made at different times [15]. A normal middle ear is required for the measurement of otoacoustic emissions. Energy reflected from the cochlea is about 12 dB even if there is a normal middle ear structure [11]. Therefore, rats were evaluated with DPOAE before starting our study. Rats with normal emission values were included in our study group. Arnold et al. [16] investigated the relationship between ultra-high frequency (UHF) hearing and DPOAE in their study in which they tested the the ability of DPOAE to detect a reduction in cochlear function. They revealed that the 4-to 8-kHz DPOAE levels were significantly correlated with the pure-tone average (PTA); they also found that the PTA for 4–8 kHz account for about 14% of the changes in DPOAE levels. Eventually, it was determined that UHF hearing influences DPOAEs and in this region, emissions are sensitive to minor changes in outer hair cells not yet detected by pure-tone thresholds.

Kim et al. [17] compared the level of DPOAE at the tested frequency with the pure tone sensing threshold of the ear. They reported that DPOAE could be used as an objective test with useful frequency features in testing the function of the cochlea. We used DPOAE to investigate the effects of hypoxia on the inner ear and hearing in our study due to this feature. OAEs are the energy that is derived from the cochlea and is transmitted by the bone chain, eardrum and external auditory canal. OAEs show the normal movement of all middle ear ossicular chain, oval window and stapes together with eardrum movement [18, 19].

Significant changes occur in the measurement results in the negative and positive pressure changes in the middle ear. Therefore, the middle ear should be evaluated when OAE measurement is performed [20].

In our study, we performed an otoscopic examination of rats before performing OAE measurements and included rats with normal membrane structure. The most important problem in the application of otoacoustic emission measurement in rats is the difficulty of the narrow external ear canal and inserting the probe. Khvoles et al. [21] placed the tube in the outer ear canal after applying a thin tube to the tip of the probe and determined that no artifacts were formed.

In our study, we inserted the cannula prepared from the feeding tube (No: 8) approximately 1 mm in diameter to the end of the new type E neonate probe to insert the probe into the outer ear canal. The effects of hypoxia on hearing after apnea attack with the animal model were evaluated with DPOAE in this study. Statistically significant differences were detected in the hypoxia group between 8003.9 Hz and 10078.1 Hz before and after tracheostomy ($p<0.05$). The data obtained in our study were parallel to the literature.

The effects of obstructive sleep apnea syndrome (OSAS) on hearing have been evaluated in many studies performed previously in patients with OSAS. It has been shown that hypoxemia, which is even short-term and mild in children with obstructive sleep apnea syndrome, has an effect on hearing levels and may affect cochlear function [7]. Our findings were parallel with the results obtained in this study. Studies on patients with OSAS with brain evoked response audiometry and ABR indicated that chronic hypoxic-hypercapnic status might have some effects on the cochlea and brain stem. These studies also support our findings [22, 23].

In another study, the prevalent and high-frequency threshold in the OSAS group of the same age was worse than the adult group [4].

Conclusion

In our study, there was a significant difference in the high frequency after hypoxia. There was no significant difference in low frequencies. We think that high-frequency loss was occurred during 10 seconds of hypoxia. After acute hypoxia becomes chronic, similar differences may occur in thesefrequencies. In conclusion, in our study, a statistically significant decrease was observed in 8003.9 Hz and 10078.1 Hz with hypoxia in rats. When the normoxic state is restored, measurements should be supported by further studies to determine whether this decrease is reversible or not.

Ethics Committee Approval: The Inonu University Faculty of Medicine Experimental Animal Researches Ethic Committee granted approval for this study (date: 27.12.2011, number: 2011/A-102).

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – MTC; Design – MA; Supervision – MA; Fundings – MTC; Materials – MTC, CFK; Data collection and/or processing – CFK; Analysis and/or interpretation – MTC, MA; Literature review – MTC, CFK; Writing – CFK, MTC; Critical review – CFK.

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