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Severe obstructive sleep apnea is associated with cochlear function impairment

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Abstract
Purpose The purpose of this study is to investigate the association between obstructive sleep apnea (OSA) with middle ear acoustic transference and cochlear function.
Methods Male individuals with and without mild, moderate, and severe OSA according to standard criteria of full polysomnography and no co-morbidities were studied. Subjects with BMI ≥40 kg/m^2, present or past treatment for OSA, with heart failure, diabetes, hypertension, dyslipidemia, stroke, use of chronic medications, and previous history of risk for hearing loss were excluded. All subjects were submitted to full polysomnography, evaluation of wideband acoustic immittance by energy of absorbance (EA), and distortion product otoacoustic emissions (DPOAE).
Results We studied 38 subjects (age 35.8 ± 7.2 years, BMI 28.8 ± 3.8 kg/m^2) divided into no OSA (n = 10, age 33.6 ± 6.4 years, BMI 26.9 ± 4.1 kg/m^2), mild (n = 11, age 32.8 ± 2.9 years, BMI 28.5 ± 3.5 kg/m^2), moderate (n = 8, age 34.1 ± 6.8 years, BMI 29.6 ± 3.3 kg/m^2), and severe OSA (n = 9, age 41.2 ± 9.2 years, BMI 30.5 ± 3.8 kg/m^2). EA was similar between groups. In contrast, patients with severe OSA presented significantly lower DPOAE amplitudes when compared to the control, mild, and moderate OSA groups ($p \leq 0.03$, for all comparisons).
Conclusions Acoustic transference function of middle ear is similar in adults with and without OSA. Severe OSA is independently associated with cochlear function impairment in patients with no significant co-morbidities.

Keywords Obstructive sleep apnea · Hearing · Cochlea · Acoustic impedance · Middle ear

Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent partial or complete obstruction of the upper airway during sleep [1]. OSA is highly prevalent and has been linked to a wide range of cardiovascular, metabolic, and neurocognitive disorders and may lead to increased morbidity and mortality [2]. Episodes of OSA are characterized by imbalance of pressure in the upper airway during inspiration. Specifically, this imbalance occurs in the oropharynx and nasopharynx, where Eustachian tube is situated and acts communicating the nasopharynx to the middle ear [3]. The opening of Eustachian tube is induced by soft palate elevation and results in aeration and equalization of middle ear pressure with ambient pressure, in order to optimize the middle ear acoustic transference function up to the cochlea [4]. It has been demonstrated that an air pressure directed to the nasopharyngeal region affects the middle ear pressure [5, 6]. Therefore, OSA and its consequent change of pressure in the upper airways during sleep would result in installation of a negative pressure environment in the middle ear. This negative pressure environment created in the

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middle ear during sleep, acting chronically over time, could lead to an irreversible alteration in the middle ear function of acoustic transference. In addition, intermittent hypoxia another hallmark of OSA, triggers a cascade of intermediate mechanisms including activation of the sympathetic nervous system, increased blood pressure, increased heart rate and consequent stress of the myocardial wall, oxidative stress and systemic inflammation, activation of platelets, increased blood plasma viscosity, and decreased vascular endothelial function that may affect several organs [7]. It has been suggested that intermittent hypoxia can lead to cochlea hair cell loss (apoptosis or necrosis) due to deficiency of nourishment [8].

The main purpose of this study was to investigate the middle ear acoustic transference and cochlear function among subjects with a wide range of OSA severity. To this end, we carefully excluded the frequent co-morbidities frequently present among patients with OSA that may affect ear function.

Methods

Participants

Male patients aged 20 to 55 years who had a full standard overnight polysomnography at our University Sleep Laboratory at the Heart Institute [9] were considered for participation. Patients with body mass index (BMI) ≥40 kg/m^2, treatment for OSA with continuous positive airway pressure (CPAP) or intraoral appliances, heart failure, diabetes, hypertension, dyslipidemia, stroke, and previous history of risk for hearing loss, including exposure to occupational noise, were excluded. The subjects were classified as not presenting OSA, presenting mild, moderate, or severe OSA, according to the standard index of apnea-hypopnea, being <5, ≥5 and <15, ≥15 and <30, and ≥30 events per hour of sleep, respectively [10]. Subjects with low risk of OSA were also invited to perform full polysomnography in order to increase the sample of subjects with no or mild OSA. This study was approved by the local ethics committee and all subjects provided written consent. All participants were assessed by air-conduction audiometry at octaves between 0.25 and 8 kHz, bone-conduction audiometry between 0.5 and 4 kHz (GSI 61, Grason Stadler, EUA) and brainstem auditory evoked response as previously reported [11].

Energy of absorbance

Acoustic immittance is a form of evaluation of middle ear function and generally refers to transfer of acoustic energy describing the ease (admittance—Y) or the opposition (impedance—Z) to the sound energy flow offered by system, being these two measures reciprocal (Y = 1/Z). The acoustic impedance observed in sound transmission of external auditory canal to the cochlea is determined by (a) mass, stiffness, and friction interaction, which are auditory system physical characteristics in the middle ear and (b) impedance of inner ear fluids. The stiffness effect of the system controls low frequency transmission, while the mass effect in the system governs the transmission of high frequencies [12].

Within the acoustic immittance, the energy of absorbance (EA) evaluates the middle ear acoustic transference function in a wide frequency range, quantifying a sound energy absorbed and reflected in the external acoustic meatus [13]. In this study, the EA was performed with Titan IMP440 (Interacoustics, Denmark) about 2 s after positioning of the olive in the ear canal. The acoustic stimulus used was click type with range frequency 226–8000 Hz on the 65 dB HL level. The responses were disposed for each 16 acoustic frequency bands: 250, 315, 400, 500, 630, 800, 1000, 1250, 1600, 2000, 2500, 3150, 4000, 5000, 6300, and 8000 Hz.

Distortion product otoacoustic emissions

Distortion product otoacoustic emissions (DPOAE) was performed using ILO2 92 DP Echoport V.6 (Otodynamics, London). Two frequencies (f1 and f2—pure tones) were presented simultaneously in a ratio f2/f1 = 1.22. The f1 and f2 level was 65 dB SPL and 55 dB SPL, respectively. Responses of f2 in frequencies 1001, 2002, 2832, 4004, 4761, and 5652 Hz were considered. The noise-floor level near or below 5 dB SPL was determined as a rule for stopping the stimulus sweeps, at all frequencies tested.

Statistical analysis

Statistical analysis were performed using R software version 3.2.2 (R Foundation, USA) and Minitab 17 (Minitab Inc., USA). The significance level for all tests was 5% ($\alpha = 0.05$). The nonparametric Kruskal-Wallis test was used to evaluate the homogeneity between groups of baseline age, body mass index (BMI), apnea and hypopnea index (AHI), and lowest oxygen saturation (SpO_2 min). Correlation analysis using Spearman's method was carried out among the amplitudes of DPOAE (on different frequencies) and minimum SpO_2 according to experimental groups. To evaluate the influence of OSA in EA and EOAPD, a three-way analysis of variance (ANOVA) with repeated measures on two factors was used. The Greenhouse-Geisser (1959) adjustment [14] was applied for the descriptive level associated with the Frequency factor. The method proposed by Holm was used for multiple comparisons (1979) [15].

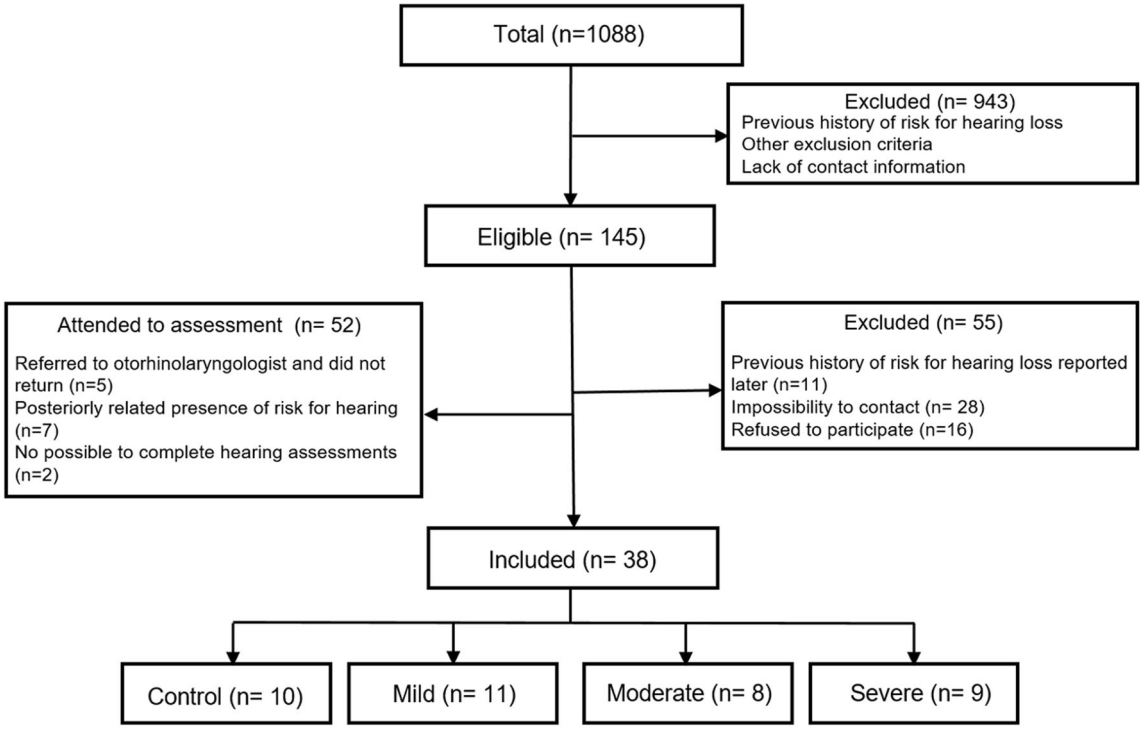

Fig. 1 Flowchart of eligible participants, excluded and distribution of the sample for the study groups

Results

Medical charts of 1088 subjects who had underwent polysomnography at the Sleep Laboratory, Heart Institute were reviewed but the majority were excluded because of the presence of co-morbidities (Fig. 1). The time lag between the PSG and the hearing assessment was 22.4 ± 14.9 weeks. The final sample consisted of 38 subjects. Table 1 presents the descriptive measures of the control variables for the study. The results of air-conduction audiometry at octaves between 0.25 and 8 kHz, bone-conduction audiometry between 0.5 and 4 kHz, and brainstem auditory evoked response were previously reported [11]. The groups did not differ in auditory thresholds in pure tone audiometry. Only a single patient of severe OSA group presented average thresholds >25 dB HL for frequencies of 250, 500, and 1000 Hz, exceeding 1 dB over normality thresholds. All groups presented normal tympanometric values.

Energy of absorbance

In general, it was verified that the EA between 226 and 8000 Hz of all groups were similar. Figure 2 represents the EA average profiles at 16 frequencies in both ears according to the groups.

There was a significant interaction between the Group and Frequency factors ($p < 0.02$). For the multiple comparisons, the moderate OSA-group presented a higher average than mild OSA-group at 8000 Hz frequency ($p = 0.003$).

Distortion product otoacoustic emissions

Subjects with severe OSA showed lower DPOAE amplitude values in all frequencies and in both ears (Fig. 3). Analyzing the effects of Group, Ear, and Frequency, only the Ear factor did not show significant difference ($p = 0.99$). DPOAE amplitudes values were different between groups ($p = 0.007$).

Table 1 Descriptive measures and comparison of variables: age, BMI, AHI, and minimum SpO2 among groups

	Control ($n = 10$)	Mild ($n = 11$)	Moderate ($n = 8$)	Severe ($n = 9$)	p value*
Age (years)	33.6 ± 6.4	32.8 ± 2.9	34.1 ± 6.8	41.2 ± 9.2	0.08
BMI (kg/m^2)	26.9 ± 4.1	28.5 ± 3.5	29.6 ± 3.3	30.5 ± 3.8	0.15
AHI	2.8 ± 1.6	11.1 ± 2.5	21.3 ± 3.7	56.1 ± 15.9	*0.000000147*
Minimum SpO_2 (%)	90.5 ± 2.2	84.6 ± 3.4	84.4 ± 3.2	69.8 ± 9.9	*0.0000347*

Data expressed as mean ± standard deviation

*Kruskal-Wallis test ($\alpha = 0.05$)

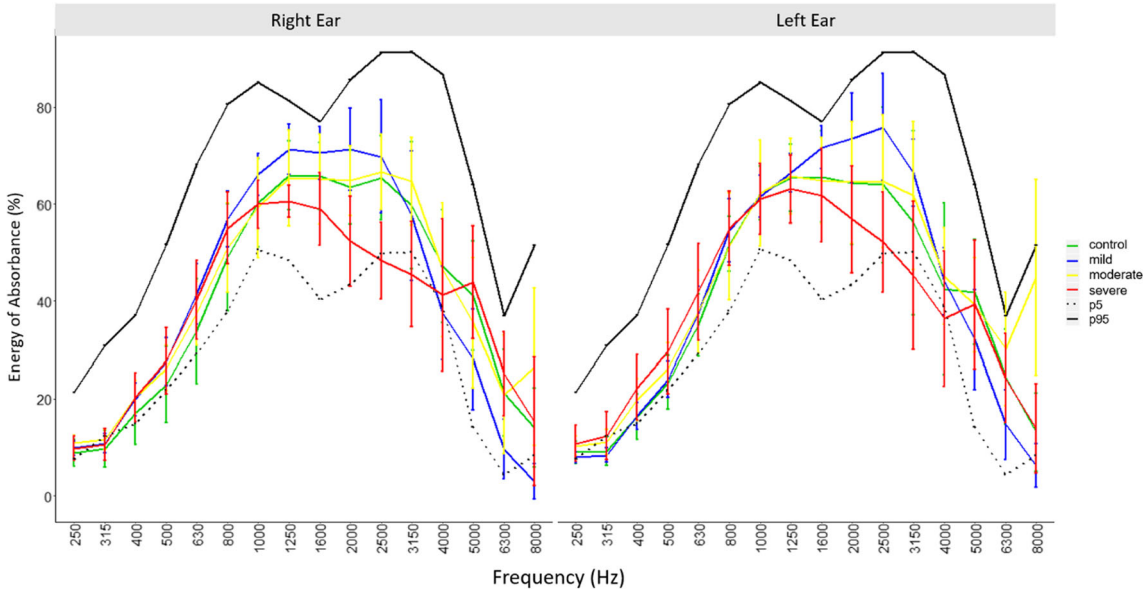

Fig. 2 Representation of average profiles with respective intervals with confidence of 95% of EA to 16 frequencies according to Group and Ear Side; *p5* 5% percentile of normative data provided by Titan; *p95* 95% percentile of the normative data provided by Titan

The control-group, mild- and moderate-OSA-groups had higher DPOAE amplitude values when compared to severe OSA group ($p = 0.02$, $p = 0.03$, and $p = 0.01$, respectively). DPOAE amplitudes showed differences between frequencies ($p < 0.001$). The low frequencies presented highest DPOAE amplitude average when compared to high frequencies. We found no correlation between DPOAE and SpO2 min (Table 2; $p > 0.05$; Fig. 4).

Discussion

There is mounting evidence that OSA may be associated with alterations in the auditory system [16–20]. Our study contributes to the field by showing novel findings. To the best of our knowledge, this was the first study to investigate the middle ear wideband acoustic transference function by EA in adults with OSA. EA is a more sensitive method that is able to detect the presence of some pathological conditions of the middle ear when compared to the clinical conventional tympanometry method [21–23]. Overall, measures of EA of all groups of this study were within the normal range [13], suggesting therefore that OSA does not affect primarily middle ear acoustic transference function. In addition, we have shown that patients with severe OSA presented worse DPOAE responses than patients with no OSA or mild to moderate OSA suggesting impairment of cochlear hair cells.

Previous studies have evaluated different portions of the auditory system in patients with OSA. The interpretation of

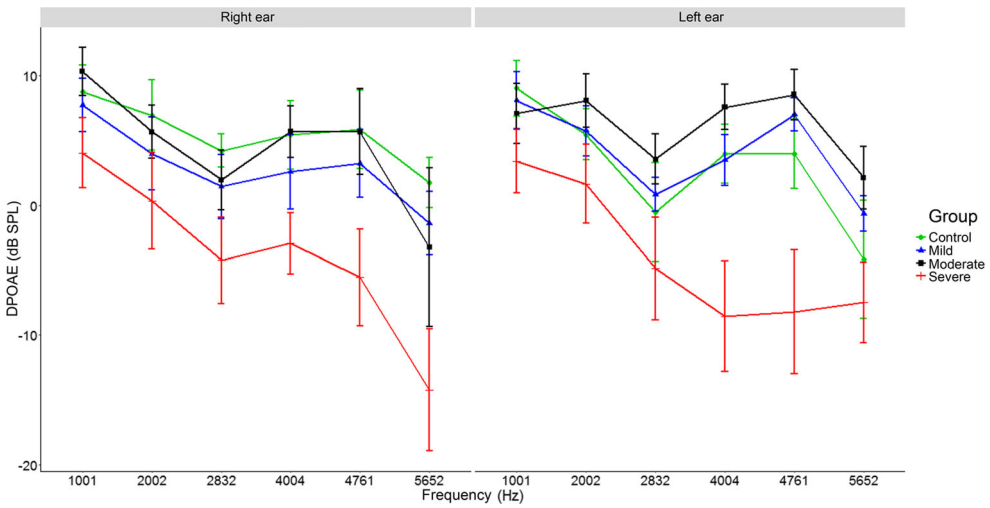

Fig. 3 Graphic with average profiles and their respective intervals with 95% confidence for amplitudes of distortion product otoacoustic emissions among groups in each ear

Table 2 Spearman correlation between DPOAE amplitudes and minimum SpO_2 to average of two ears per group and each frequency

	Control		Mild		Moderate		Severe	
Frequency	*R*	*p* value	*R*	*p* value	*R*	*p* value	*R*	*p* value
1001	0.51	0.1293	−0.09	0.7993	0.20	0.6287	0.03	0.9489
2002	0.29	0.4246	−0.02	0.9468	−0.12	0.7776	0.33	0.3914
2832	0.22	0.5501	−0.02	0.9574	−0.26	0.5284	0.08	0.8305
4004	−0.60	0.0656	−0.09	0.7993	0.07	0.8657	−0.12	0.7640
4761	−0.51	0.1293	−0.01	0.9787	0.23	0.5878	−0.47	0.2032
5652	−0.61	0.0587	−0.17	0.6091	0.23	0.5878	−0.01	0.9830

R correlation value

alterations in middle ear acoustic transference function depends on several factors, such as previous and or current history of recurrent middle ear infections and other evaluations such as air-conduction and bone-conduction audiometry. There is a wide variability in the normative values for EA measurement that may limit the capacity of the method to detect mild alterations [24]. In our study, we observed lower EA values around the frequency of 3150 Hz among patients with severe OSA when compared with the remaining groups (Figs. 2 and 3). This characteristic has also been observed in adults with alterations in middle ear due to otitis media with effusion [25]. However, this trend did not reach statistical difference among groups. In addition, we showed a lower EA in the frequency 8000 Hz among patients with mild and moderate OSA. However, the interpretation of this data is difficult because such alteration was not observed among patients with severe OSA. Moreover, as previously discussed, all EA values felt in the normal range in our study. Therefore, our study strongly suggest that OSA is not associated with major EA alterations.

Several previous cross-sectional studies have evaluated the cochlear function among patients with OSA using different methods. In general, all studies have shown that OSA is associated with cochlear hair cells impairment [16, 18, 20]. The mechanisms by which OSA may affect cochlear function are multiple and include blood hyperviscosity [26] and intermittent hypoxia [27]. In the current study, patients with severe OSA exhibited lower DPOAE amplitude values in all frequencies analyzed. Similar results were observed in studies that found worse DPOAE amplitudes in adults with severe OSA [16]. Additionally, our study revealed that DPOAE amplitudes differed among frequencies, which lower frequencies showed higher DPOAE mean values than in high frequencies. The outer hair cells located on cochlea basal region performs the mechanoreceptors function of high sound frequencies; these cells seem to be more susceptible to hypoxia condition [27].

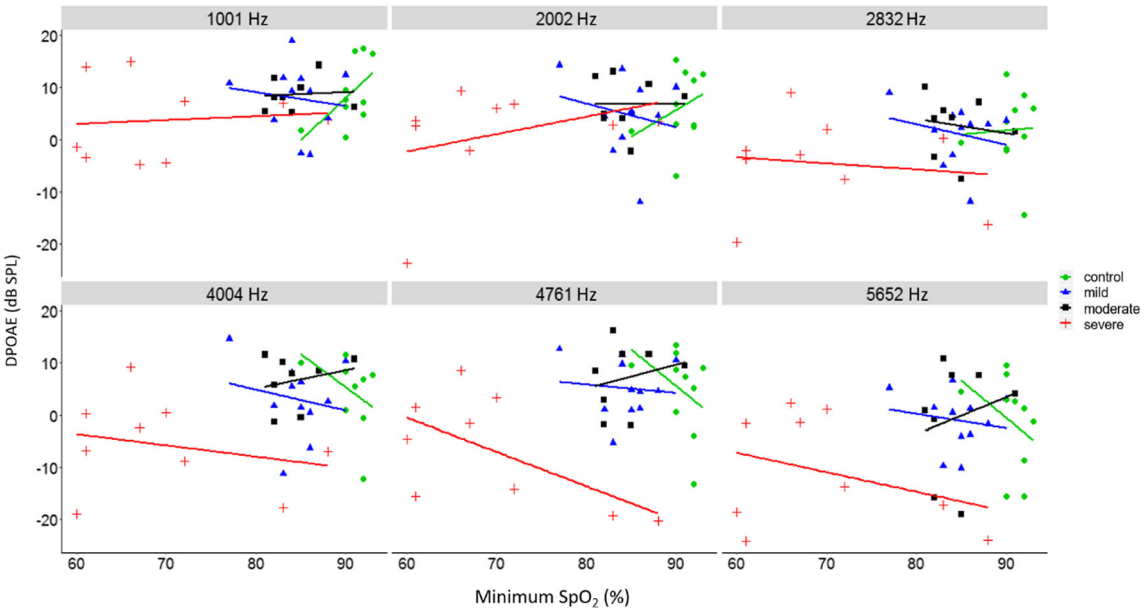

Fig. 4 Graphic of DPOAE amplitude values and minimum SpO_2 with average of ears according to group and frequency

One major limitation of the previous studies is the lack of complete control of co-morbid conditions that are frequently associated with OSA that are risk factors for auditory dysfunction [28, 29]. In contrast to the previous studies [16, 18, 19], we had very stringent entry criteria in order to avoid the inclusion of patients with co-morbid conditions and using any medication. One second factor is the method of OSA diagnosis. Casale et al. [16] and Martines et al. [20] used polygraphy, and other study used questionnaires [18]. In contrast, we used full polysomnography.

Our study has several limitations. We have only included males, and therefore our results cannot be extrapolated to the female sex. The final sample size was relatively small due to the stringent entry criteria. Patients with severe OSA had a nonsignificant trend to be older and more obese than the remaining group. On the other hand, this study design was able to exclude major confounding variable very common in the OSA field. The novel EA findings are difficult to interpret due to a lack of normative values as previously discussed. Finally, all cross-sectional studies are able to show associations, but cannot make definitive conclusions about a cause and effect.

In conclusion, our study showed that the middle ear acoustic transference function is similar between adults with and without OSA. In contrast, severe OSA impair cochlear function.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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