

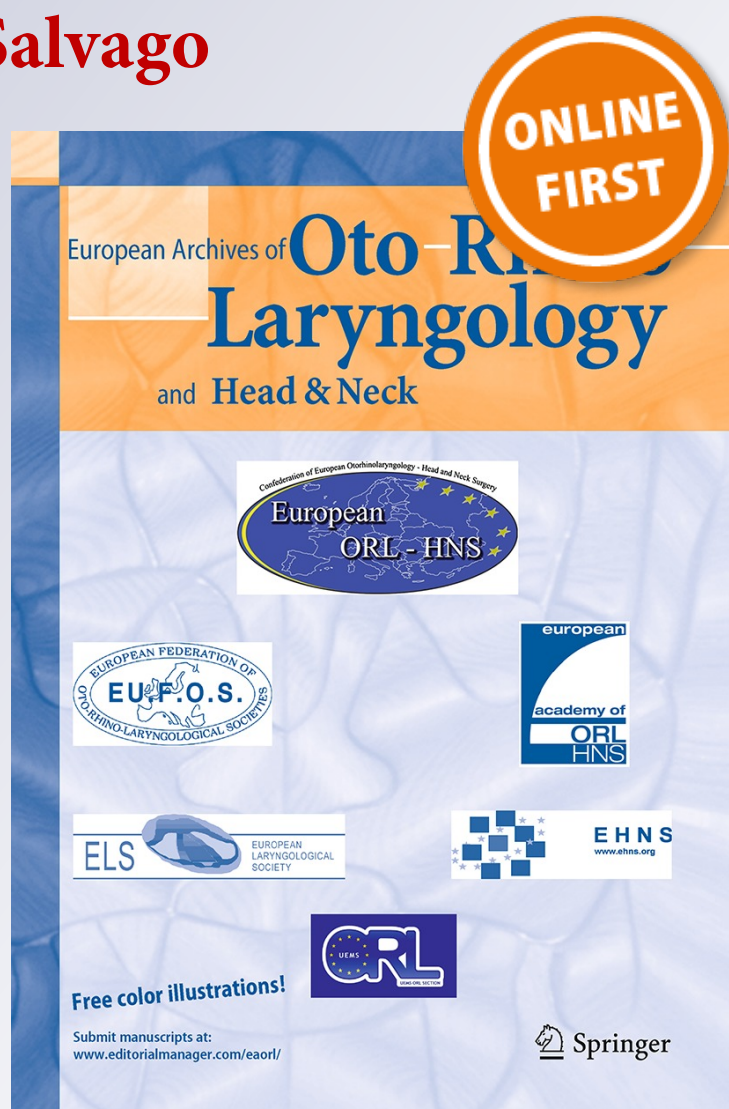
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Audiologic profile of OSAS and simple snoring patients: the effect of chronic nocturnal intermittent hypoxia on auditory function

Francesco Martines¹ · Antonella Ballacchino² · Federico Sireci¹ · Marianna Mucia^{1,2} · Eleonora La Mattina² · Serena Rizzo² · Pietro Salvago^{1,3}

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Abstract The objective of this work was to study the effect of nocturnal intermittent hypoxia on auditory function of simple snoring patients and subjects affected by OSAS; we compared the audiologic profile with the severity of OSAS to detect early signs of cochlear damage. One hundred-sixty patients underwent overnight polysomnography, micro-otoscopy, multi-frequency audiometry, acufenometry, TEOAE recording and d-ROMs test. All subjects were divided in four groups, based on presence/absence of AHI (simple snoring without OSAS, mild OSAS, moderate OSAS, severe OSAS). Sixty (37.5 %) patients were not affected by OSAS, 58 (36.25 %) presented a mild OSAS, 18 (11.25 %) a moderate OSAS and 24 (15 %) a severe OSAS; the 57.14 % of moderate to severe OSAS suffered from tinnitus with respect to the 31.03 % of mild OSAS ($P = 0.024$). A higher percentage (41.66 %) of hearing loss was found among individuals with moderate to severe degree of OSAS ($P < 0.0001$). All groups were characterized by a mean hearing threshold <25 dB HL for 0.25–3 kHz frequencies and a progressive decrease in hearing sensitivity, particularly for 6–16 kHz frequencies ($P < 0.05$). The analysis of otoacoustic emissions SNR mean values

evidenced a significant difference between simple snoring and severe OSAS individuals for 3 and 4 kHz frequencies ($P < 0.05$). d-ROM levels resulted higher in patients with severe OSAS with respect to simple snoring subjects ($P = 0.004$). Our data underline the key role of chronic nocturnal intermittent hypoxia in the development of an early cochlear damage and a more marked high-frequency hearing loss in case of severe OSAS ($P < 0.05$).

Keywords OSAS · Hearing loss · Tinnitus · Multi-frequency audiometry · TEOAE

Introduction

Affecting ≥ 4 % of men and 2 % of women, obstructive sleep apnea syndrome (OSAS) is a condition characterized by intermittent obstruction of the upper airways with consequent repetitive episodes of apnea and/or hypopnea, desaturations and an altered sleep pattern. With respect to the general population, patients with OSAS often suffer from daytime sleepiness, morning headache, reduced memory and concentration capacity, endocrine and metabolic derangements; the presence of OSAS is considered an independent predictor for cardiovascular pathologies like hypertension, coronary artery disease and stroke [1–3].

The repeated episodes of hypoxia and normoxia are considered the main factors influencing the production of reactive oxygen species (ROS) and the promotion of oxidative stress, endothelial dysregulation, activation and propagation of inflammatory cascades with vascular dysfunction, reduced basal and functional capillarity rarefaction with an additional risk of impaired peripheral perfusion [4, 5].

Therefore, OSAS may lead to cerebral vascular insufficiency resulting in hypoxia, acute hemodynamic change,

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decreased cerebral blood flow during episodes of apnea and ischemic injury to the cochlea [6–10]. Both inner ear and acoustic nerve are highly dependent on the oxygen supply; specifically the cochlea is sensitive to circulatory alterations because of its single terminal artery supply and insufficient collateral circulation [11].

Several reports investigated the relation between sleep disorders and auditory dysfunction, recognizing in OSAS patients a higher risk of impairment of neuronal and vascular function of the auditory pathway. Specifically, Muchnik et al. studying the auditory brainstem responses (ABR) of 79 OSAS individuals, evidenced a prolonged transmission time between waves I and III and I and V in the moderate and severe OSAS subgroups with respect to healthy subjects [12]. Kotterba et al. analyzing data relative to 20 patients affected by severe OSAS, found prolongations of wave latency I ($P \leq 0.001$) and interpeak latency I–V ($P \leq 0.001$) in the 60 % of the total sample, with 9 (45 %) subjects characterized by pontomesencephal lesions [13]. The auditory pathway sensitiveness to reduced oxygen levels was also investigated by Atiş et al. who recorded the ABR of 21 patients with severe chronic obstructive pulmonary disease, with the 76.1 % of the sample showing ABR abnormalities like prolonged wave I peak latencies (42.8 %), wave V peak latencies (38.1 %) and III–V interpeak latencies (38.1 %) [14]. Recently Casale et al. comparing audiological data of 18 patients with severe OSAS and 21 simple snoring subjects, evidenced prolonged mean latencies of waves I, III, V ($P < 0.05$) and a significantly ($P < 0.01$) higher pure-tone audiometry (PTA) in OSAS group with respect to healthy people [15].

Basing on these instrumental evidences, purpose of our work was to study the effect of chronic nocturnal intermittent hypoxia on auditory function of simple snoring patients and subjects with various degrees of OSAS; we compared also their audiologic profile with the severity of OSAS to detect early signs of cochlear damage.

Materials and methods

One hundred and seventy-two snoring patients (107 males and 65 females), ranging 38–55 years of age, were examined from January 2012 to June 2014 at the Hearing Section of the Department of Bio-technology of Palermo University. Individuals with any middle or inner ear pathology (e.g., cranio-facial abnormality, syndromes associated to hearing loss, otosclerosis, acoustic neuroma, chronic otitis, previous myringotomy, VT insertion or tympanoplasty) or medical diseases which affect or are suspected to affect hearing (e.g., diabetes mellitus, untreated hypertension, noise exposure, hypercholesterolemia, history of ototoxic drugs administration) or

coexisting psychiatric disorders were excluded from this study.

Each patient enrolled in our study underwent an overnight polysomnography (PSG) for suspected OSAS, a physical examination of the ears through micro-otoscopy, a complete audiologic evaluation and d-ROMs test.

The study protocol was completely explained to patients and written informed consent was obtained from each subject. The study design was approved by the Palermo University Human Research Ethics Committee.

Twelve patients were excluded from the study because of cranio-facial abnormality (1 case), history of ototoxic drugs administration (5 cases), otosclerosis (2 cases), chronic otitis (3 cases) and previous tympanoplasty (1 case); 160 subjects were enrolled and divided in four groups, based on presence/absence of AHI (apnea + hypopnea per hour of sleep) and according to international guidelines [16]: (1) simple snoring without OSAS; (2) mild OSAS; (3) moderate OSAS; (4) severe OSAS.

Diagnosis of OSAS was made through modified portable sleep apnea monitoring through a polygraphy Mesam-8 Polymesam, with recording of abdominal and chest movements, body position, snoring, oxygen blood saturation, pulse rate, oro-nasal airflow (nasal air pressure). According to international guidelines, an AHI < 5 was considered suggestive of simple snoring without OSAS; OSAS was classified in “mild” ($5 < \text{AHI} < 15$), “moderate” ($15 < \text{AHI} < 30$) and “severe” ($\text{AHI} > 30$) [16].

Audiological assessment was performed by multi-frequency audiometry (considering the frequencies 0.25–0.5–1–2–3–4–6–8–9–10–11.2–12.5–14–16 kHz), tympanometry with stapedius reflex and Transient-evoked otoacoustic emissions (TEOAE diagnostic) for each ear.

Audiometric threshold was considered as the pure tone average (PTA) for the frequencies 0.5–1–2–4 kHz and divided in: normal hearing (< 20 dB); mild hearing loss (21–40 dB); moderate hearing loss (41–70 dB); severe hearing loss (71–90 dB); profound hearing loss (> 90 dB).

Acufenometry included pitch masking (matching the frequency of the tinnitus with a variety of stimuli) and loudness matching (estimating the loudness of tinnitus with a pure tone or noise); the difference between the hearing threshold and the sensation level was considered tinnitus loudness (0–5 dB, 5, 10, 15, > 15 dB above the hearing threshold) [17–20].

TEOAE measurements were evaluated in reproducibility (expressed as the correlation between two waveforms, namely for responses stored in buffers A and B, acquired alternately) and were recorded by using as “PASS” criteria a signal-to-noise ratio (SNR) ≥ 6 dB in four of five 1/2 octave frequency bands at 1, 1.5, 2, 3, and 4 kHz. The tool used was the ‘SENTIERO by Path Medical GmbH’, that is based on the nonlinear cross-correlation method (ILO88) of

TEOAE recording. The TEOAE diagnostic was conducted by placing a small probe tip from the 'Path Medical' (3.9 mm diameter × 11.7 mm) inside the patient's ear canal; when powered on, the instrument initiated a routine self-calibration before recordings were made. The click rate was approximately 97 per second and each stimulus (at the probe loudspeaker output) consisted of a single 80 µs square pulse. To eliminate passive mechanical artifacts from the recorded waveform, stimuli were presented in blocks of four stimuli: three small positive polarity stimuli followed by one big negative polarity stimulus three times as large. Click peak stimulus level was 80 dB SPL. Emissions elicited from the outer hair cells in response to the clicks were picked up by the internal microphone of the equipment and were windowed and filtered to remove unwanted signals; all response data outside a window from 5 to 13 mS, after the stimulus, were removed to eliminate the stimulus signal.

Reactive oxygen metabolites (ROMs) levels were measured in serum samples by the Diacron reactive oxygen metabolites (d-ROM) test. It is based on the reaction of hydroperoxides of a biological sample with transition metals (iron) that catalyze the formation of free radicals which then oxidize an alchilamine forming a colored radical detected by photometry at 505 nm.

Ten mL of blood is mixed with 1 ml of an acidic (PH 4.8) buffer reagent (R2) in order to release iron from plasma proteins that will react with peroxides of the blood to form free radicals, and then 10 mL of a chromogen reagent (R1 reagent, alchilamine) are added forming a pink-colored derivative. This colored derivative is photometrically quantified and the optical density is directly proportional to the concentration of ROMs [21]. Reference values of d-ROMs test are between 250 and 300 Carratelli Units (CARR U), independently of gender and age; values higher than 300 CARR U indicate, after a border-line bracket (301–320 CARR U), progressively increasing levels of oxidative stress: 321–340 CARR U—low level oxidative stress; 341–400 CARR U—middle level of oxidative stress;

401–500 CARR U High level of oxidative stress; >500 CARR U Very high level of oxidative stress [22].

Statistical analysis was conducted with Matlab® computer programme; χ^2 test, odds ratio (OR) and/or exact test of Fisher test were used, following usual conditions of application. Significance was set at 0.05.

Result

A total of 160 subjects were analysed; 103 (64.37 %) were males and 57 (35.63 %) were females with a male/female ratio of 1.8. The age of patients ranged from 38 to 55 years, with a mean age of 46.19 ± 7.01 years.

Table 1 shows the presence/absence and degree of OSAS among the subjects included in the study: 60 (37.5 %) patients were not affected by OSAS, 58 (36.25 %) presented a mild OSAS, 18 (11.25 %) a moderate OSAS and 24 (15 %) a severe OSAS. A statistical significant difference in the severity of OSAS was evidenced among the sex, with a higher percentage of males suffering from severe OSAS ($P = 0.01$). In fact the 20.38 % (21/103) of males had a AHI value >30 with respect to the 5.26 % (3/57) of females.

The 33.75 % (54/160) of patients were affected by tinnitus, without significant difference among the sex; 42 subjects (42 %) with and 12 (20 %) without OSAS reported tinnitus ($P = 0.004$); an association between degree of OSAS and tinnitus prevalence was evidenced, with the 57.14 % of cases of moderate to severe OSAS suffering from tinnitus with respect to the 31.03 % of mild OSAS ($P = 0.024$). In the majority of cases tinnitus pitch was matched to tones in the 4000–8000 Hz range (64.81 %), but no significant difference between subjects with various degree of OSAS was found.

Audiological assessment of the total cohort revealed a normal hearing, a mild and a moderate hearing loss in the 70.94 % (227/320 ears), the 25.93 % (83/320 ears) and the 3.12 % (10/320 ears) of cases respectively; a slight

Table 1 Audiologic characteristics, mean PTA and d-ROM test of the cohort

GROUP	Patients N (%)	Tinnitus N (%)	Normal hearing N (%)*	Hearing loss N (%)*	PTA _{0.25–8} kHz (dB HL)	PTA _{9–16} kHz (dB HL)	d-ROM test (CARR U)
No OSAS	60 (37.5)	12 (20)	87/120 (72.5)	33/120 (27.5)	21.42	36.6	309.45 ± 43.11
Mild OSAS	58 (36.25)	18 (31.03)	91/116 (78.45)	25/116 (21.55)	23.25	46.38	314.36 ± 53.05
Moderate OSAS	18 (11.25)	9 (50)	20/36 (55.56)	16/36 (44.44)	27.05	64.97	314.05 ± 39.2
Severe OSAS	24 (15)	15 (62.5)	29/48 (60.42)	19/48 (39.58)	26.83	67.43	363.33 ± 70.58
Total	160 (100)	54 (33.75)	227/320 (70.94)	93/320 (29.06)	23.52	47.77	323.29 ± 56.87

* Calculated on the total ears

difference in the prevalence of hearing loss was evidenced between patients with (30 %) and without (27.5 %) OSAS ($P = 0.23$). Specifically a higher percentage (41.66 %) of hearing loss was found among individual with a moderate to severe degree of OSAS ($P < 0.0001$). All subjects affected by moderate sensorineural hearing loss referred subjective tinnitus ($P < 0.001$).

Figure 1 depicts the average multi-frequency audiometry thresholds levels according to the presence/absence and degree of OSAS. It is well shown that all groups were characterized by a mean hearing threshold <25 dB HL for 0.25–0.5–1–2–3 kHz frequencies and a progressive decrease in hearing sensitivity, with a peak >60 dB HL for 11.2–12.5–14–16 kHz frequencies in case of moderate to severe OSAS. In fact, the audiograms relative to subjects with AHI >15 were represented by “sky-fall” curves, differently from mild OSAS group, characterized by a high-frequency “gently sloping” audiogram. From the comparison of the mean hearing thresholds, a statistical significant difference was evidenced between severe and mild OSAS groups for 6–8–9–10–11.2–12.5–14–16 kHz frequencies ($P < 0.05$).

The 45 % (27/60) of simple snoring and the 24 % (24/100) of OSAS patients passed the TEOAEs recording ($P < 0.05$). Specifically SNR mean values (Fig. 2), calculated for each ear, were respectively of 8.28 ± 4.56 (1 kHz), 12.60 ± 5.66 (1.5 kHz), 10.12 ± 6.38 (2 kHz), 3.85 ± 3.76 (3 kHz) and 2.39 ± 2.78 (4 kHz) in patients with OSAS and of 7.46 ± 5.19 (1 kHz), 12.16 ± 6.90 (1.5 kHz), 9.58 ± 6.40 (2 kHz), 5.00 ± 4.93 (3 kHz) and 3.76 ± 4.37 (4 kHz) in no OSAS subjects; a significant difference was found only between simple snoring and severe OSAS individuals for 3 and 4 kHz frequencies ($P < 0.05$).

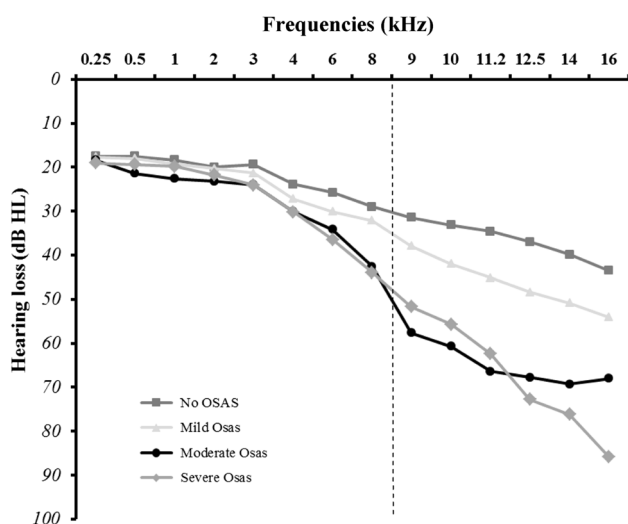


Fig. 1 Average multi-frequency audiometry thresholds levels in patients with and without OSAS

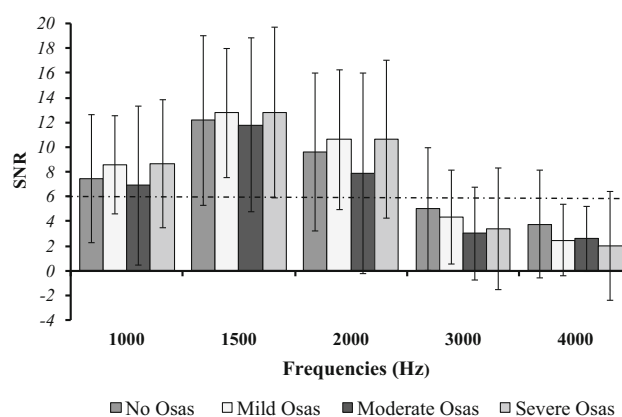


Fig. 2 TEOAEs in patients with and without OSAS: analysis of SNR data

The analysis of ROM levels (Table 1), measured using the d-ROM test, showed a mean value of 323.29 ± 56.87 CARR U for the total cohort with a significant difference ($P = 0.004$) between patients with severe OSAS (363.33 ± 70.58 CARR U) and simple snoring subjects (309.45 ± 43.11 CARR U); additionally a higher mean ROM level (341.11 ± 59.53 CARR U) was observed in individuals suffering from tinnitus ($P = 0.035$).

Discussion

The adverse consequences of decreased cerebral blood flow during episodes of apnea were previously studied; the inner ear represents an anatomical location extremely susceptible to hypoxic/anoxic injury due to the formation of ROS and increased oxidative stress, which in turn activate inflammatory and immune responses leading to vascular and metabolic complications [23–25]. Particularly the cochlear outer hair cells of the basal turn suffer from the free-radical damage, probably because of their significant lower activity of glutathione-related antioxidant enzymes [26].

Different authors in the past examined the effects of sleep apnea episodes on auditory sensitivity and the possible association between OSAS and hearing disorders [27, 28], analyzing mainly the auditory brainstem function through ABR recording. However, to our knowledge, few of them focused on the inner ear dysfunction and data about TEOAEs and high frequencies (9–16 kHz) audiometry are scarce.

From the analysis of our data it is well shown that OSAS patients suffer of hearing impairment, particularly when we compare those with moderate to severe OSAS with simple snoring subjects ($P < 0.0001$). In addition, a higher percentage (42 %) of tinnitus was found among individuals with OSAS with respect to patients without OSAS (20 %) with a peak (62.5 %) in case of severe OSAS ($P = 0.024$).

and a tinnitus pitch recognized mainly in the frequency range of 4–8 kHz (64.81 %). The study of audiometric thresholds of the whole sample (Fig. 1), conducted with the multi-frequency audiometry, evidenced superimposable audiometric curves in patients with and without OSAS when considering the frequency range from 0.25 to 3 kHz. From the comparison of 4–16 kHz frequencies audiometric values instead it was possible to evidence a progressive lowering in hearing threshold, with a statistical significant difference between severe and simple snoring patients for 3–16 kHz frequencies ($P < 0.01$). This is in line with Casale et al. data, who observed a significant difference ($P < 0.01$) in the 4 kHz auditory thresholds between individuals with AHI >30 and subjects without OSAS [15]. Our findings are supported also by Kilic et al. who, studying the high frequencies audiograms of 42 subjects with chronic asthma, found lower PTA_{10–20 kHz} values in hypoxic and non-hypoxic asthma patients with respect to healthy controls ($P < 0.05$) [29].

The recording of TEOAEs revealed a low SNR for 3 and 4 kHz frequencies, with more than 50 % of patients with values <6 (Fig. 2). Particularly, as confirmed by Casale et al., a statistical significant difference was found between simple snoring and severe OSAS subjects for 3 and 4 kHz frequencies ($P < 0.05$) [15]. She et al. assessing 28 patients with OSAS before uvulopalatopharyngoplasty, observed a low prevalence of TEOAE (64.3 %) and a reduced 0.5–8 kHz amplitude of DPOAE, with an improvement of all variables studied after surgery [30]. Similar findings were reported by Xu et al. in children affected by OSAS, with a significant difference of DPOAE amplitude at 6–8 kHz between moderate to severe OSAS patients and control group [31]. These data may reflect the particular susceptibility of cochlear outer hair cells to insufficient blood flow and the early involvement of the basal turn of the cochlea [26].

Because of OSAS is a condition associated with an enhanced oxidative stress status [32, 33], the mean ROS levels of our cohort were evaluated with d-ROM test which represents an overall estimation of oxidative stress throughout the body. A significant difference between mean ROS levels of patients with severe OSAS and simple snoring subjects was evidenced ($P = 0.004$). On the contrary, other authors did not found an increased oxidative stress with respect to controls [34, 35].

For example, Simiakakis et al. studying 42 patients with AHI >15 and 24 controls (AHI <5) evidenced lower ROS levels (404.3 ± 98.3 CARR U, $P = 0.005$) but also a decreased antioxidant capacity (2057.2 ± 561.7 mmol/L, $P = 0.005$) in patients with OSAS. However, they concluded that factors like obesity or smoking can play a confounding role in enhancing d-ROM levels and in reducing antioxidant activity; additionally, hypoxia in

OSAS may act in inducing reduction of antioxidant capacity through the dysregulation of genes involved in the modulation of ROS or enzymes engaged in the production of the antioxidant barriers [21].

An imbalanced oxidative stress can lead to microcirculatory dysfunction, as demonstrated by Patt et al. who examined the endothelial function in OSAS patients free of cardiovascular diseases. They evidenced increased peroxynitrite production in the microvascular walls of patients with OSAS, indicating overproduction of NO and superoxide in the endothelial environment. The uptake of NO by superoxide explains the decreased NO availability and the consequent microcirculatory changes which resulted independent of age, weight, or sex and reversible with treatment [36]. Similar mechanisms could be responsible of a progressive impairment of inner ear where the NO production by cochlear vascular cells causes smooth muscle and pericyte relaxation by the inhibition of voltage-gated calcium channels and the activation of ATP-sensitive K⁺ channels in endothelial and smooth muscle cells of the spiral modiolar artery [37]. Thus the cochlear impairment and the associated hearing loss could represent an early marker of microcirculatory dysfunction in individuals with OSAS.

The present study, examining the inner ear function of patients with and without OSAS, underlines the key role of chronic nocturnal intermittent hypoxia in the development of auditory dysfunction and demonstrates a more marked high-frequency hearing loss in case of severe OSAS ($P < 0.05$). We suggest that TEOAEs recording and multi-frequency audiometry could represent helpful tools in recognizing the early cochlear damage that characterizes OSAS patients.

Compliance with the ethical standards

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

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