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Complex level alterations of the $2f_1–f_2$ distortion product due to hypoxia

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ABSTRACT

Objective: For diagnostic purposes and a better understanding of the pathophysiology of inner ear hearing disorders it would be of great interest to have parameters available that indicate inner ear hypoxia. In animal studies typical hypoxia-related alterations of the $2f_1–f_2$ distortion product otoacoustic emissions (DPOAE) such as a reversible level decrease and destabilization could be demonstrated. The goal of this study was to investigate whether these hypoxia-associated alterations can also be observed in humans because this might help develop a new diagnostic tool for patients with inner ear disorders.

Methods: In 16 volunteers DPOAE levels were continuously measured at first under normal room air conditions, during and after 8.5 h of oxygen deprivation (13% O_2) and during re-oxygenation. Saturation of oxygen of arterial blood (SaO_2) was monitored.

Results: The mean SaO_2 during the hypoxic interval was 78%. A significant decrease in DPOAE level under hypoxia occurred in five different test persons at one or more frequencies (f_2 = 1, 1.5, 2, 3, and 4 kHz). A destabilization of the DPOAE level with considerable fluctuations during hypoxia was observed in nine subjects at one or more frequencies. Furthermore, the so called 'post hypoxia effect' could be observed in five participants.

Conclusion: The observations made here have been described similarly in animal studies and seem to be characteristic of metabolic disorders of the cochlea caused by hypoxia. To our knowledge, this is the first study to examine DPOAE level alterations over time in humans under conditions of normobaric hypoxia. If DPOAE destabilization is observed in a clinical setting in patients with certain inner ear hearing disorders hypoxia can be suspected as one underlying pathophysiological cause which might influence treatment decisions.

1. Background

Reduced cochlear circulation leading to hypoxia is considered as one possible cause of hearing disorders like sudden sensorineural hearing loss or tinnitus. For diagnostic purposes and a better understanding of the pathophysiology of inner ear hearing disorders it would be of great interest to have parameters available that indicate inner ear hypoxia as specifically as possible.

Otoacoustic emissions reflect the functional status of the outer hair cells [1,2] which are usually damaged in sensorineural hearing loss [3]. In animal studies typical hypoxia-related alterations of the $2f_1–f_2$ distortion product otoacoustic emissions (DPOAE) could be demonstrated. Rebillard and Lavigne-Rebillard observed a reversible level decrease in DPOAEs during hypoxia and complex level alterations after re-oxygenation in guinea pigs [4]. Olzowy et al. found a reduction of DPOAE levels with an increased standard deviation (DPOAE destabilization) under hypoxia (SaO_2: 57–70%) in guinea pigs. After re-oxygenation DPOAE levels showed a short pronounced decrease (after SaO_2 levels had already recovered) before they recovered to pre-hypoxic values – an observation termed 'post hypoxia effect' [4,5].

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Very few data exist about DPOAE level alterations under hypoxia in human beings. Measurements of DPOAE levels in mountain climbers at extreme altitude, however, have suggested that hypoxia might also cause typical level alterations of DPOAEs in human beings [6,7]. In this study we investigated whether the characteristic DPOAE alterations observed in animals under hypoxia also occur in humans.

2. Subjects, materials and methods

16 (experimental group) plus eight (control group) healthy male volunteers (medical students) with no history of ear disease were enrolled in this study after their written informed consent was obtained. The median age was 23 years (range: 20–28) in the experimental group and 24 years (range 21–27) in the control group. Otoscopic examination and Valsalva maneuver revealed normal tympanic membranes. All participants had normal tympanograms (type A).

In the experimental group $2f_1–f_2$ DPOAEs were measured at f_2 = 1, 1.5, 2, 3, and 4 kHz (2 s per frequency, each frequency being measured every 10 s) first under normal room air conditions (21% oxygen), then immediately after the onset of oxygen deprivation, then after a mean of 8.5 h of oxygen deprivation (13% O_2) in the hypoxia chamber and finally after re-oxygenation (21% O_2). Each measurement cycle lasted 12 min. Hemoglobin oxygenation (SaO_2) was monitored and documented every 10 s using pulse oxymetry during the DPOAE measurements. Primary tone levels were set to 63 dB SPL (L_1) and 60 dB SPL (L_2). Frequency ratio was set to f_2/f_1 = 1.2.

DPOAEs were measured using an ER-10 probe (Etymotic Research), DP2000 software (Mimosa Acoustics) and a standard laptop. The arithmetic mean and standard deviation (SD) of DPOAE levels before, during and after hypoxia were calculated for every subject. Data from an hypoxic interval were only used for further analysis if the arithmetic mean of the DPOAE level after hypoxia stabilized in the range of ±1 dB of its pre-hypoxic level. Alterations of the mean DPOAE level were considered significant if they exceeded SD of three of the pre-hypoxic level. Statistical significance of mean DPOAE level differences was confirmed by Welch's *t*-test. In order to demonstrate DPOAE destabilization due to hypoxia variances of pre-hypoxic DPOAE levels were compared to variances of DPOAE levels under hypoxia using the *F*-test of equality/homogeneity of variances. Destabilization was assumed if variances were not homogenous according to the *F*-test. DPOAE levels were plotted versus time.

Subjects in this study were limited to a small closed room for a relatively long time which can cause physical and emotional stress. In order to make sure that observed DPOAE level alterations can be attributed to hypoxia and are not affected by these inconveniences eight subjects (control group) went through the same experimental steps as the experimental group continuously being exposed to normal room air conditions (21% oxygen).

The experimental protocol was approved by the Ethical Committee of the University of Munich (project number 087-10).

3. Results

In the experimental group the mean SaO_2 during the hypoxic interval was 78%. In two subjects DPOAE levels did not fulfill the stability criterion for any of the five frequencies (f_2 = 1, 1.5, 2, 3, and 4 kHz). The other 14 test persons showed stable DPOAE levels before and after hypoxia for at least one frequency. Altogether, out of 80 measurements that were made (16 subjects, each being tested at 5 different frequencies (f_2 = 1, 1.5, 2, 3, and 4 kHz) 38 fulfilled the stability criterion.

A significant decrease in DPOAE levels below pre-and post-hypoxic values after introduction of hypoxia occurred in five test persons at one or more frequencies and in twelve of 38 stable measurements (32%). The phenomenon occurred at all frequencies except 1500 Hz. An example is shown in Fig. 1.

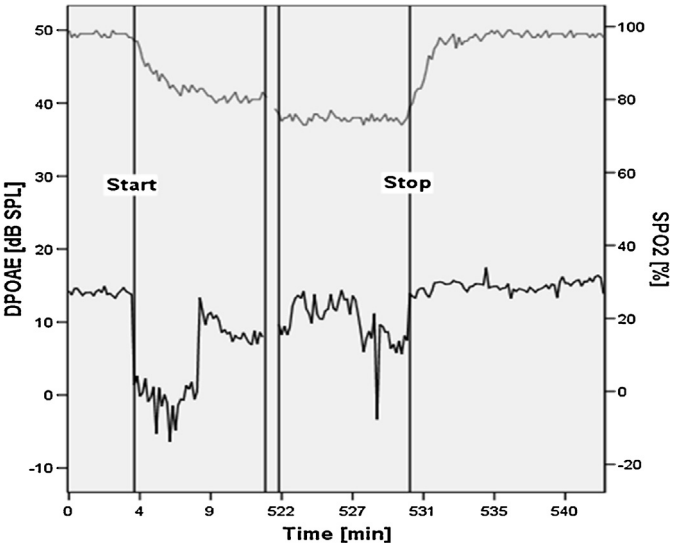

Fig. 1. DPOAE level (left vertical axis) and SaO_2 (right vertical axis) plotted versus time. Start and stop of the hypoxic interval are indicated. DPOAE levels decrease below pre- and post-hypoxic values after introduction of hypoxia.

A destabilization of the DPOAE level with considerable fluctuations during hypoxia was observed in nine subjects at one or more frequencies and in 13 of 38 stable measurements (34%). Again, the phenomenon occurred at all frequencies except 1500 Hz. DPOAE fluctuation occurred after stabilization of SaO_2 at their lowest levels and could be observed even toward the end of the hypoxic period more than eight hours after introduction of hypoxia. An example is shown in Fig. 2.

After re-oxygenation, SaO_2 picked up quickly. While SaO_2 recovered, in five test persons and in 18% of all stable measurements DPOAE levels decreased steeply before recovering to pre-hypoxic values ('post hypoxia effect', Fig. 3).

Fig. 4 provides an overview of the results.

In the control group the mean SaO_2 remained at 99% over the entire experimental phase. None of the subjects showed significant changes in DPOAE levels at any time.

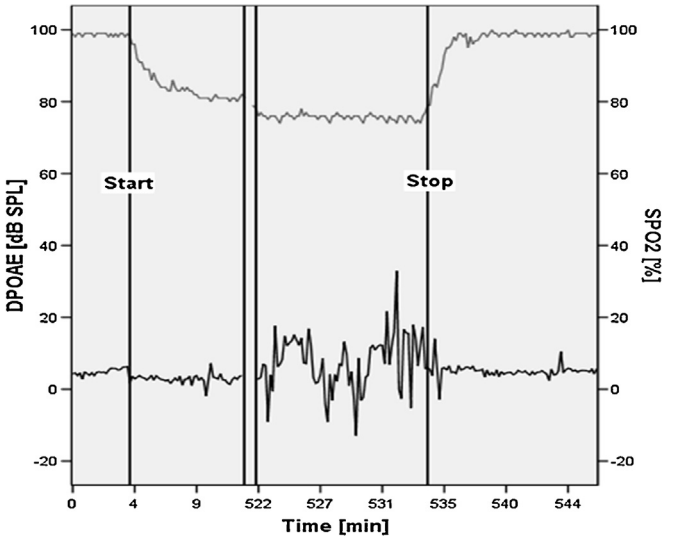

Fig. 2. DPOAE destabilize under hypoxia and re-stabilize quickly after reoxygenation.