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Research paper

Study of auditory function in patients with chronic obstructive pulmonary diseases

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Abstract

This study was designed to measure auditory function in patients with chronic obstructive pulmonary diseases (COPDs) who generally suffer from chronic hypoxemia. Control and COPD subject groups received a battery of tests to assess overall hearing sensitivity and peripheral (end-organ and eighth-nerve) and brain-stem auditory function, as well as blood-gas analysis. Results showed a statistically significant difference for all audiological measures between the control group and a COPD subgroup – the presumptive hypoxic subjects (partial oxygen tensions, PO_2, <75 mm Hg). Correlation analyses of results from all subjects (regardless of PO_2) also revealed significant covariance with PO_2 for overall, RMS, amplitude of click-evoked otoacoustic emissions (RA), hearing threshold level, and auditory brain-stem response (ABR, I-V inter-peak latency). χ^2 or Fisher's exact tests were statistically significant for frequencies of cases classified according to a criterion PO_2 of 70 mm Hg (putative critical O_2 for completely normal auditory function) and either hearing thresholds falling below or RA values above 1.5 standard deviations of the control-group means, respectively. However, χ^2 was not significant for a comparable criterion of ABR I-V IPL. In general, clinically significant hearing loss was uncommon in COPD patients, and the observed effects represented relatively small changes in the auditory measures examined. Still, overall, changes were in the direction of poorer function, and these results suggest physiologically significant impact of chronic hypoxemia and the need for further study to evaluate thoroughly this medical condition as a potential risk factor for audio-vestibular dysfunction.

Keywords: Hypoxia; Hypoxemia; Chronic obstructive pulmonary disease; Electrocochleography; Auditory brain-stem response; Otoacoustic emissions; Audiometry

1. Introduction

Chronic obstructive pulmonary diseases (COPDs) are characterized functionally by a decrease in expiratory flow rates. In addition, patients with a COPD have uneven ventilation, which results in arterial hypoxemia and hypercapnia. These functional abnormalities can be detected and quantified by pulmonary function tests, as well as by measurement of arterial blood gases (Niewoehner and Sobonya, 1989). Hypoxemia, a reduction in

Abbreviations: ABR, auditory brain-stem response; AP, (whole-/eighth-nerve) action potential; CEOAE, click-evoked otoacoustic emission; COPD, chronic obstructive pulmonary disease; dB, decibel; DPOAE, distortion product otoacoustic emission; ECMO, extracorporeal membrane oxygenation; ECochG, electrocochleography; EP, endocochlear potential; HTL, hearing threshold level; Hz, hertz (cycles/second); IHC, inner hair cell; IPL, inter-peak latency; mm Hg, millimeters mercury; ms, millisecond; *N*, number; O_2, oxygen; OHC, outer hair cell; *p*, probability; PCO_2, partial carbon dioxide tension; PO_2, partial oxygen tension; RA – root-mean-square, (RMS) amplitude; SP, (cochlear) summating potential; SPL, sound pressure level

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partial oxygen tension (PO_2), can be observed in practically every known pulmonary disease entity. Consequently, hypoxemia is an indicator of abnormal pulmonary gas exchange, and the arterial PO_2 can also serve as a test of pulmonary function. Hypoxia, a decrease in tissue oxygen tension, is a consequence of hypoxemia (Klocke, 1989).

The transduction mechanism of the inner ear is highly dependent upon the cochlear oxygen supply, such that any large reduction in oxygen locally will be accompanied by a loss in sensitivity (Lawrence et al., 1975; Gafni and Sohmer, 1976; Sohmer et al., 1986). In addition, many studies have documented that the reduction of oxygen supply to the cochlea causes marked effects on the cochlear potentials (Perlman et al., 1951; Konishi et al., 1961; Lawrence et al., 1975; Dallos, 1973b; Prazma et al., 1978). Also, Rebillard and Lavigne-Rebillard (1992) and Rebillard et al. (1993) recorded a decrease in the magnitude of both distortion product otoacoustic emissions (DPOAEs) and the endocochlear potential (EP) under hypoxia.

Various reports have documented modifications of the auditory brainstem responses (ABR) and of cortical auditory evoked potentials upon exposing experimental animals to hypoxia. Such modifications were obtained at a very low level of the arterial PO_2 (Lucertini et al., 1993).

Relatively few studies, nevertheless, have been dedicated to the effects of hypoxia on the human auditory system and only rarely have significant changes been reported. Hendricks-Munoz and Walton (1988) documented increased risk for hearing loss in infants with persistent pulmonary hypertension, and they reported an increased risk for progressive loss in these babies. In adults, Hansen (1988) suggested that daily exposure to hypoxia gradually reduces cochlear function. Mills and Ryals (1985) also reported a prolongation of brainstem transmission time resulting from carotid artery disorder in adults. However, Sohmer et al. (1982) concluded that hypoxic and hypercapnic conditions do not have a depressant effect on the ABR. Moski et al. (1981) also reported normal ABRs in patients with obstructive sleep apnea. In 1993, Lucertini et al. reported an absence of statistically significant changes of middle latency responses due to hypoxia. On the other hand, they noticed a significant latency increase in steady state responses during hypoxia with immediate recovery upon return to pretest normoxic levels. They attributed the absence of significant modifications of ABRs during such experiments to the functional and metabolic characteristic of the brainstem auditory pathways or the insufficient level of hypoxia that can be reached safely in experiments on humans.

It thus is conceivable that the recurrent/chronic hypoxia potentially caused by COPD may stress the auditory system in ways heretofore unappreciated via results of acute animal or human research. To further assess the possible effects of oxygen deprivation on the auditory system, the following research questions were addressed:

- Does hypoxia in COPD affect human auditory function at some level, particularly of the lower auditory pathway (i.e. the function of outer hair cells, inner hair cells, cochlear nerve and/or the auditory brainstem)?
- Are some clinical tests more sensitive to changes in auditory function in patients with COPD than others?
- Is there a critical level of PO_2 that can produce significant change in a given audiological measure?

2. Materials and methods

2.1. Subjects

This study was carried out in the Sohag University Hospital, Egypt.

Two groups of subjects were examined in this study. The patient group comprised 60 subjects (38 females, 22 males) with COPD who were recruited from the Department of Chest Diseases. The control group had no history of COPD and included 18 females and 12 males. The subjects of both groups had no history of hearing loss or any ear pathology, other medical diseases that affect or are suspected to affect hearing (e.g. diabetes mellitus and hypertension, noise exposure, or ototoxic drug therapy). They ranged in age between 20 and 50 years.

2.2. Procedures

All subjects received an otoscopic examination, a routine audiometric evaluation and acoustic immittance testing. Cases found to have middle ear problems were excluded as these problems are not expected, a priori, to be related to pathology under study (according to the literature), yet they can adversely effect results of the evoked response tests of interest. The following procedures were performed on all subjects of the study.

2.2.1. Click-evoked otoacoustic emission (CEOAE)

Testing of CEOAEs was accomplished using the Otodynamic ILO88 system (Kemp et al., 1990). The stimulus was an acoustic click of brief duration (created by a 80 μs pulse) and an intensity level of 83 dB peak-equivalent sound pressure level (SPL). The recorded otoacoustic responses were averaged over 260 stimulus repetitions with an analysis window of 20 ms. The so-called "nonlinear click" (paradigm) was used wherein every fourth pulse driving the transducer is three times larger and of opposite polarity than the preceding three. Consequently, OAE energy deriving from non-linear growth of the recorded response is emphasized (i.e. averaging responses over stimulus repetitions). Linear growth components, most notably the incident/stimulus sound energy and its echoes in the ear canal, tend to be cancelled. The response analysis included the parameters of wave reproducibility (expressed as the correlation between two waveforms, namely for responses stored in buffers A and B, acquired alternately) and the signal-to-noise ratio (computed from the sum and differences of the A and B records). Three or more responses were recorded in each subject to assure, if present, the best reproducibility and minimum signal-to-noise ratio for each subject. The response amplitude (RA = overall root-mean-square value of the OAE signal) was used for purposes of statistical analyses (see below).

2.2.2. Electrocochleography (ECochG) and ABR testing

Combined auditory evoked potentials and electrocochleography was accomplished using a dual-channel system (one channel for each ear), the Nicolet Spirit, version 1.5. An extratympanic electrode – the TIPtrode – was used as an ear canal electrode (Ferraro et al., 1986; Ruth et al., 1988a,b). This electrode is known to provide reliable recordings, and it has the advantage of being non-invasive and well tolerated (Ruth, 1990). The design of the TIPtrode allowed the delivery of the stimulus

from a tubal insert earphone, namely through the electrode itself. The other electrodes in the montage were the conventional disk type. One was affixed on the scalp at the middle of the forehead at hairline and served as the active for purposes of recording the brainstem potentials in a combined ECochG-ABR recording (Durrant, 1986, 1988). The other one was affixed at nasion and served as ground. The electrode impedance for the ear canal electrode, as well as the surface electrodes, was typically less than 5 kΩ. The negative peak of the AP, produced an upward deflection as the ear canal lead was routed to the inverting (−) input of the pre-amplifier, and the forehead lead was connected to the non-inverting input, apropos the convention of representing peaks of brainstem components as positive deflections. The time window was 10ms, and the filter band pass was set from 30 to 3000 Hz.

The stimulus was an acoustic click created by a pulse of 0.1 ms duration with alternating polarity to cancel cochlear microphonic and stimulus artifact in the recording. The stimulus rate was 22.1 clicks/s, providing efficient data acquisition with little response decrement and good cancellation of line-frequency noise. The intensity level of the stimulus was relatively high (80 dB nHL) to allow for clear definition of the SP, which is generally difficult to see below 70 dB nHL with non-invasive recording techniques, (Ruth, 1990). The stimulus was presented 2000 times for each recording trial, and at least three trials/replications (see below) were made to permit confident identification of the response. When more than three replications were made, the three most robust and most well overlapping responses were used for purposes of analysis. This requirement was imposed in order to minimize stimulus artifact and enhance the signal-to-noise ratio (i.e. by combining repeated responses). There were 51 out of the total 60 patients and 30 control subjects meeting the criterion of a minimum of three replications.

2.2.3. Blood gas analysis

Blood-gas analysis was performed on both normal and clinical subjects in the Chest Department using conventional clinical methods. The blood sample was taken either from the radial artery, the brachial artery, or, in very rare cases, the femoral artery. The arterial puncture is considered to be painful and many examiners use a local anesthesia. The sample was taken with a heparinized syringe to avoid blood coagulation and subsequent destruction of red blood cells and bias of the oxygen sample. Once the sample was obtained, it was submitted immediately to the blood gas analyzer to avoid alteration in blood gas content (Klocke, 1989).

2.3. Data analysis

2.3.1. Hearing threshold level (HTL)

It was assumed that any effect of hypoxemia on auditory function would be systemic and, thus, most likely similar for both ears. Therefore, the average threshold across the tested frequencies (250–8000 Hz) for each ear was calculated and, in turn, averaged across ears to yield a single (mean) hearing-threshold-level (HTL) value for each subject.

2.3.2. Otoacoustic emission data (OAEs)

The response amplitude (RA) of the CEOAE was analyzed and compared between groups. As above and because of the similarity of the responses in the two ears (by visual inspection), the averaged amplitude was calculated across ears for each subject.

2.3.3. ECochG data

Both SP and AP-peak magnitudes were measured, as well as AP latency (see below). The SP magnitude was measured from the baseline to the shoulder preceding the onset of the AP. The AP amplitude was measured from the pre-stimulus baseline to the peak of the response. The magnitudes of SP and AP were calculated across ears for each subject yielding a single measure of SP and AP for each subject.

2.3.4. ABR data

The ABR records were measured for absolute latencies of the waves I (AP peak) and V and averaged across trials and ears. Specifically, the IPL I-V was calculated.

2.3.5. Blood gas data

The PO_2 level was determined for each subject and used as an indicator for the occurrence of hypoxemia. Normal level of PO_2 ranges from 75 to 115 mm Hg, (Mellemgaard, 1966).

2.4. Statistical considerations and analysis

The observed PO_2 was considered to be the independent variable, and all the audiological measures were considered as dependent variables. To validate the collapsing of data across ears, the data were analyzed by ear and found to show no statistically significant differences between ears for any of the test parameters, namely via two-sample t-test applied to the measures of HTL, RA of OAEs, AP and SP amplitudes of ECochG, and ABR I-V inter-peak latency. For the primary interests of the study, three "levels" of analysis were applied in sequence, a statistical design developed with the assistance of a statistical consultant and summarized as follows:

2.4.1. The first level of analysis

The most basic issue tested was whether auditory measures in the experimental group differ statistically from those of the control group, as in effect hypothesized. For this purpose, t-tests were performed for each measure to compare results of patients with low PO_2; the total number of hypoxic patients who had PO_2 below 75 mm Hg was 36 (compared to a control group of 30 subjects). The restriction of the clinical subjects included in this analysis was in deference to the simple fact that COPD subjects fluctuate in their PO_2; some subjects at date of examination thus had PO_2's that were normal. The latter subjects' data thus were excluded from this analysis but were included in the more global test of covariance of auditory measures with PO_2 and other tests described below. The t-test was used considering that the comparisons of specific interest could be specified/planned at the start of the investigation (auditory measure across groups); possible interactions across tests were of no conceivable interest or value. The statistical level of significance was considered to be $p \leqslant 0.05$, but, in deference to the repeated auditory measures, a Bonferroni correction was applied.

2.4.2. The second level of analysis

The second level of analysis, contingent upon significant findings at the first level, was directed at testing specifically the link of any differences observed to PO_2, per se. Data were collapsed across subject groups (patient and control groups, with a total of 81 subjects), and Pearson's product-moment coefficients were calculated between PO_2 and each auditory measure. Considering again the multiple measures in the same subjects, a conservative probability level was taken as indicative of a statistically significant correlation, i.e. $p \leqslant 0.01$.

2.4.3. The third level of analysis

The last level of analysis was directed toward testing a critical level of PO_2, namely 70 mm Hg, with PO_2's at or below this level being taken as abnormal for purposes of sustaining entirely normal auditory function. This analysis was applied uniquely to auditory measures wherein a significant correlation with PO_2 was observed in the second-level analysis. It thus was assumed likely that a critical level of PO_2 could be identified below which significantly frequent occurrences of decreased auditory measures would be observed. Consequently, contingency Tables were constructed and analyzed using the χ^2 test (or Fisher's exact test when cell counts fell below $N = 5$). For each audiological test, upon inspection of the data, a criterion for decreased response was taken as a value 1.5 standard deviation from the mean value observed in the control group. This is admittedly a very liberal criterion for "abnormal". However, the focus here was not the development of

diagnostic criteria per se. Indeed, as discussed below, high incidences of clinically significant abnormalities were not observed, but this does not preclude the importance of hypoxemia as a significant risk factor for auditory dysfunction, especially in long-standing disease. Rather, the purpose simply was to explore whether or not any value of the response, in the direction of abnormal, could be found in more subjects than not presenting PO_2's below the lower limit of the normal range, namely with an acceptable level of statistical significance.

3. Results

3.1. Hypoxic COPD patients versus controls

Tables 1 and 2 provide summaries of the descriptive statistics for control and patient groups individually. Two-sample *t*-tests (Table 3) revealed significant differences between the control group (30 subjects) and the hypoxic group (36 patients), namely for HTL, RA of CEOAEs, SP and AP of ECochG, and I-V IPL of the ABR.

3.2. Correlation between auditory measures and PO_2

Scatter plots of the auditory measures as a function of PO_2 are shown in Fig. 1, along with Pearson product-moment correlation coefficients ($N = 81$). Significant coefficients were observed for the following measures: HTL, RA of CEOAEs, and I-V IPL of the ABR, whereas no significant correlation was observed between PO_2 and either SP or AP of ECochG. However, it is not clear that the inherent limitations of non-invasive ECochG (e.g. distance from generators and high electrode impedance) permits adequate precision or reliability of measurement of SP and AP to demonstrate significant covariance of measures.

Table 1
Means, standard deviations, and ranges of auditory measures for the control group ($N = 30$)

Measure	Mean	SD	Minimum	Maximum
HTL (dB)	12.83	2.28	8.75	20.00
RA (dB SPL)	10.43	2.39	6.90	15.65
SP (μv)	0.16	0.09	0.04	0.47
AP (μv)	0.56	0.27	0.19	1.19
I-V IPL (ms)	3.89	0.19	3.56	4.24
PO_2 (mm Hg)	100.4	8.6	89.3	119.0

Table 2
Means, standard deviations, and ranges of auditory measures for the hypoxic subgroup ($N = 36$)

Measure	Mean	SD	Minimum	Maximum
HTL (dB)	19.25	6.43	8.75	37.5
RA (dB SPL)	5.99	3.70	−0.05	11.45
SP (μv)	0.11	0.06	0.03	0.34
AP (μv)	0.41	0.15	0.19	0.73
I-V IPL (ms)	4.05	0.24	3.44	4.55
PO_2 (mm Hg)	65.1	13.0	32.9	73.9

Table 3
Two-sample *t*-test for PO_2, hypoxic subgroup versus normal group (degrees of freedom [df] = 64)

Measure	Mean difference	*t*-Value	Probability (*p*)
HTL (dB)	6.42	5.20	0.000
RA (dB SPL)	−4.40	−5.66	0.000
SP (μv)	−0.05	−2.49	0.008
AP (μv)	−0.15	−2.89	0.005
I-V IPL (ms)	0.15	2.78	0.004
PO_2 level (mm Hg)	35.9	13.1	0.000

3.3. Critical level of PO_2

Contingency tables employed to carry out χ^2 (or Fisher's exact) tests are presented as Tables 4–6. Table 4 summarizes the frequencies of COPD subjects with PO_2 above versus below 70 mm Hg who demonstrated reduced values of RA of CEOAEs. In patients with low PO_2 (i.e. below 70 mm Hg) only about 28% had RAs above 6.84 dB, whereas 72% had lower RAs. The observed χ^2 was statistically significant. Likewise, for HTL (Table 5), the Fisher's exact test revealed statistically increased frequencies of subjects with thresholds elevated in reference to the criterion of 16.24 dB HL. In the case of ABR I-V interval (Table 6), the χ^2 test failed to reveal a significant difference in proportions among cells according to a criterion of 4.18 ms.

4. Discussion

4.1. Hearing threshold level of pure tone audiometry (HTL)

The results of the present study demonstrated a significant difference in HTL between the control group and the patient group (Table 3) and a significant correlation between the level of PO_2 and HTL of pure tone audiometry (Fig. 1). These results are in a good agreement with those of Hansen (1988) who found poorer hearing at 500 and 1000 Hz in patients with postural hypotension. He attributed this hearing loss to cochlear hypoxia resulting from decreased cochlear blood supply. Results of the present study are also in agreement with those of McFarland (1937), cited in Burkett and Perrin (1976). He found threshold shifts at eight pure tone frequencies for 10 subjects during an expedition at high altitudes. The threshold shift varied from a mean of 1.5–6.5 dB when the altitude changed from sea level to 5300 m. He also noticed that adaptation minimized the altitude effects because of adaptive changes to compensate for hypoxia. The presently reported results did not permit evaluation of hearing thresholds of patients before they developed hypoxia; nevertheless, the significant correlation of HTL with PO_2 and other considerations (below) argue for an effect of PO_2, per se.

Reduction in auditory sensitivity under acute hypoxia has been attributed to a metabolic sensitivity of various electrochemical potentials in the inner ear, (Sohmer et al., 1989; Carlile and Paterson, 1992). These potentials result from the active transport of Na/K ions by metabolically active pumps, and it has been suggested that a

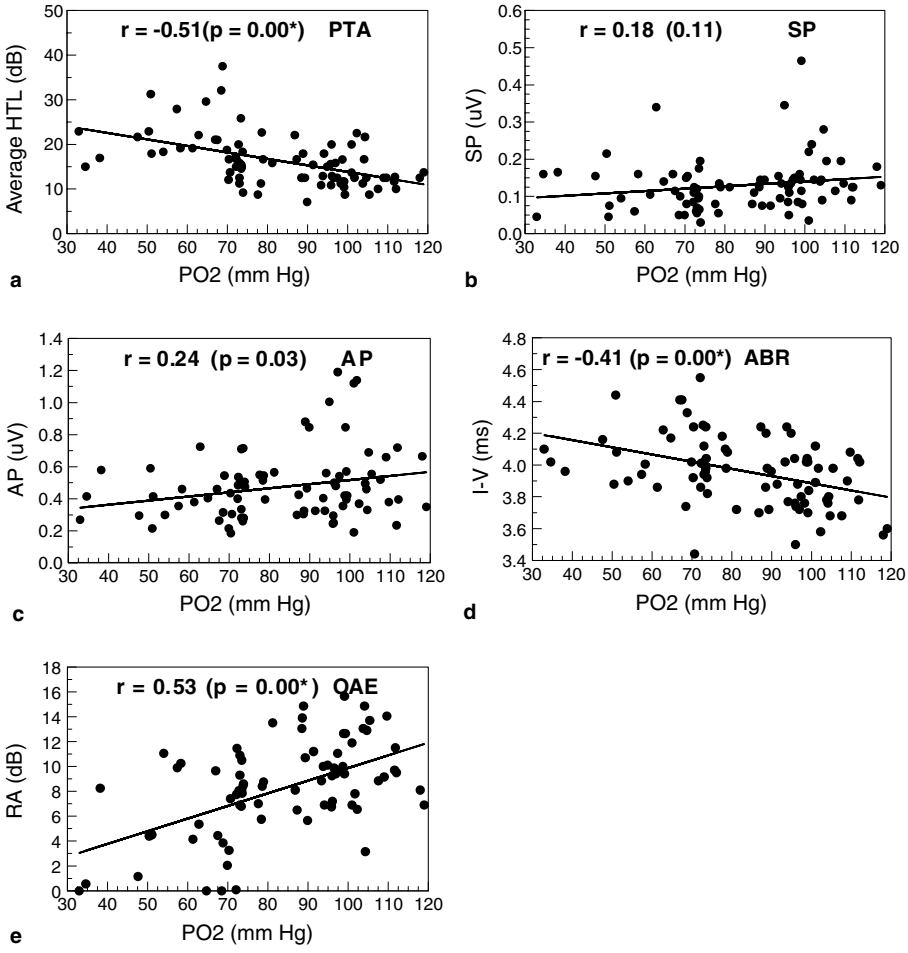

Fig. 1. Scatter plots of auditory measures employed in this investigation as a function of PO_2 (partial oxygen tension) at the time of study: (a) HTL, PTA – hearing threshold level from pure tone audiometry; (b) SP – summating potential; (c) AP – whole-nerve action potential; (d) I-V, ABR – inter-peak latency of the auditory brainstem response; (e) RA, OAE – root-mean-square amplitude of otoacoustic emission. Indicated in each panel is the product-moment correlation coefficient (r) and its probability level (p), with an asterisk highlighting those p-values less-than-or-equal to the adopted criterion of the 0.01 level of statistical significance ($N = 81$).

Table 4
Frequencies and percentages according to criterion PO_2 and RA of CEOAE; $\chi^2 = 14.25$, $p = 0.000$, $N = 51$

PO_2 level	RA $\geqslant$ 6.84 dB	RA $<$ 6.84
Above 70 mm Hg	23 69.7%	10 30.3%
Below 70 mm Hg	5 27.8%	13 72.2%

Table 6
Frequencies and percentages according to criterion PO_2 and I-V inter-peak latency of ABR; $\chi^2 = 19.59$, $p = 0.000$, $N = 51$

PO_2 level	I-V $\leqslant$ 4.18	I-V $>$ 4.18
Above 70 mm Hg	28 84.8%	5 15.2%
Below 70 mm Hg	13 72.2%	5 27.8%

reduction in the availability of O_2 would compromise the process (Gafni and Sohmer, 1976). If this is also the case in chronic hypoxia, it is possible that auditory compensation could be related to an up-regulation of the number of the ion pumps in response to reduced O_2. Additionally, Johnstone and Sellick (1972) explained the reduction in auditory sensitivity via a decrease of EP; this potential contributes to the extraordinary high sensitivity of the mammalian cochlea.

Table 5
Frequencies and percentages according to criterion PO_2 and average HTL of pure tone audiometry, Fisher's exact test, $p \leqslant 0.05$

PO_2 level	HTL $\leqslant$ 16.24 dB	HTL $>$ 16.24 dB
Above 70 mm Hg	17 51.5%	16 48.5%
Below 70 mm Hg	1 5.6%	17 94.4%

In addition, it was demonstrated that subjects with PO_2 levels below 70 mm Hg were significantly more likely to have HTLs somewhat elevated, namely to 16.24 dB and above. While this is not considered to be clinically abnormal hearing, these results suggest this PO_2 level to be "critical" for the most normal HTLs, and that subjects with PO_2 below

70 mm Hg are at greater risk for clinically significant hearing loss than otherwise. Therefore, these results are in general agreement with Gafni and Sohmer, 1976) who found that the depression of the EP took place only at PO_2 values within the 20–30 mm Hg range.

4.2. Click-evoked OAE

The results revealed a significant difference between the control and hypoxic groups in the RA of CEOAEs (Table 3). By virtue of the design of the study (i.e. limiting confounding variables) and results of the correlation analysis (Fig. 1), this difference appears to be attributable directly to the difference in PO_2 between the two groups.

These findings are consistent with those of Telischi et al. (1995). Their study of acoustic neuroma patients demonstrated significant difference in the amplitude of both CEOAEs and DPOAEs between the tumor group and the non-tumor group. They attributed this difference to cochlear hypoxia that is expected to result from compression of the cochlear vasculature by the tumor. They also found that the reduction or the absence of transient evoked OAEs for the affected ears was consistent with the average amount of hearing loss indicated by behavioral audiometric evaluation. The reduction of CEOAEs by acoustic neuromas was observed also by others, such as Bonfils and Uziel (1988).

The present findings are also in agreement with those of the study of Rebillard and Lavigne-Rebillard (1992) and Rebillard et al. (1993); they found a reduction in the output level of the DPOAEs in guinea pigs artificially ventilated with a gas mixture containing different percentages of O_2, namely when the percentage of O_2 in the respired gas mixture was below 10%. It is widely accepted that the stimulus-evoked otoacoustic emissions are the direct reflection of the motion of the basilar membrane, amplified by cochlear active mechanisms (e.g. see Rebillard and Lavigne-Rebillard, 1992). This active process is commonly attributed to the OHCs (e.g. see Brownell et al., 1985). Therefore, the reduction in the RA of CEOAEs observed in some hypoxic patients in this study can be attributed reasonably to the vulnerability of the OHCs to a PO_2 level reduction.

However, the present results are not in agreement with findings of Sawada et al. (1999). They did not find significant change in CEOAEs or DPOAEs in chinchillas during hypoxia, but they observed a significant increase in wave-V ABR threshold. They concluded that IHC function is more sensitive to O_2 deprivation than that of OHCs during prolonged mild cochlear hypoxia. They drew this conclusion on the basis of results in one animal showing significant change in both TEOAE and DPOAE after ABR threshold elevation. Conceivably, differences in results of our two studies somehow reflect differences in degree of hypoxia involved in each, although OHCs are expected to be the more vulnerable to hypoxia. Indeed, results of the χ^2 test (Table 5) in the present study suggest importance of PO_2 level (i.e. 70 mm Hg or above) for entirely normal OAE output, and thus normal cochlear amplifier function. Still, the correlation between RA and PO_2 was far less than perfect; the unexplained portion of variance may be attributed to other factors. These could include a compensation effect (Carlile et al., 1992), or variability thereof, and the great variability in the duration of exposure to hypoxemia likely among the clinical subjects studied (perhaps as much as a 30-year range). Nevertheless, these findings suggest the CEOAE to be a sensitive test for detecting small changes in hearing function in patients suffering COPD with hypoxemia.

4.3. Summating potential (SP)

This study also demonstrated a significant difference between the control and patient groups with respect to SP magnitude. This finding is in accord with the reduction of cochlear potentials due to hypoxia in the studies of Konishi et al. (1961), Dallos (1973a), and Brown et al. (1983). Konishi (1979) attributed the rapid decline of the EP during anoxia to the sum of a rapid inactivation of the oxygen-sensitive electrogenic positive potassium pump in the stria vascularis and the negative potassium diffusion potential across the cochlear partition. Therefore, lowering O_2 content in the arterial blood is accompanied by depression of EP (Gafni and Sohmer, 1976). The decline of EP is well documented by various other investigators (Dallos, 1973b; Prazma et al., 1978; Rebillard and Lavigne-Rebillard, 1992). Therefore, the change in SP with hypoxemia could be attributed to the vulnerability of EP to O_2 deprivation. Davis' (1957) classical model of hair cell transduction, upheld in general terms by decades of research findings, suggest hair-cell receptor potentials to be substantially dependent upon the EP, namely as a driving electromotive force, together with the cell's membrane resting potential, across its hair-bearing surface.

Durrant et al. (1998) attributed the SP recorded from the round window (the likely source of SP recorded via extratympanic methods) to both OHCs and IHCs. Because the the SP was elicited at high intensities in the present study (the stimulus was a click of 80 dB nHL), it likely derived predominantly from IHCs. Susceptibility of IHCs, as well as OHCs, to PO_2 decrement is reasonably expected; therefore, it was assumed to account for the findings of Sawada et al. (1999), as well. Sensitivity of both HCs certainly would add to the overall vulnerability of the cochlea.

The effect of acute O_2 deprivation on the cochlear potentials (including SP), on the other hand, tends to be reversible (Konishi et al., 1961; Dallos et al., 1972; Prazma et al., 1978; Rebillard and Lavigne-Rebillard, 1992). This reversibility is perhaps consistent with the poor correlation between SP and PO_2 level found in the present study. A poor correlation also was reported by Rebillard et al. (1993), wherein they noticed that the SP was only mildly affected by hypoxia.

4.4. Compound action potential of the auditory nerve (AP)

The results suggested a significant difference in AP amplitude between the control group and the patient group. This finding is in agreement with results of the study of Dallos (1973b) who observed that the AP was dramatically affected by O_2 deprivation within seconds of the anoxic period. Under extreme deprivation, the AP disappeared completely, yet, when the cochlea's O_2 supply was restored, the AP returned nearly to its normal value. Rebillard et al. (1993) also found a reversible reduction of AP by hypoxia. The profound influence of O_2 availability on the AP is most likely a manifestation of the sensitivity of the spike initiation process to O_2 deprivation. However, poor correlation between PO_2 and AP (Fig. 1) was found in the present study. On the other hand, such extreme forms of hypoxia are unlikely to be reached in human experiments or under clinical conditions, as studied here. Indeed, the lowest level of PO_2 observed was 32.9 mm Hg, and only 10 patients had severe hypoxia, i.e. below 60 mm Hg.

4.5. Inter-peak latencies (IPL) of ABR

Significant differences in ABR I-V IPL existed between the control group and the hypoxic group, and these differences were associated with differences in the level of PO_2 (Table 3), namely with a moderate negative correlation. These results are consistent with the finding of Carlile et al. (1992) who observed a shift in auditory sensitivity, as indicated by the latency of wave V, of 3–13.8 dB (mean 9.1 ± 1.6 dB) during rapid ascent to moderately high altitude, in six subjects out of nine. The remaining three subjects did not show any shift in auditory sensitivity because their PO_2 levels were still within the normal range. The investigators attributed this finding to the ability of the auditory system to compensate for reduced blood O_2. They also explained the failure of a second ascent in altitude to reduce the auditory sensitivity (although the level of O_2 saturation was the same as in the first ascent) by its ability to compensate for chronic mild hypoxia. They also suggested that the process of compensation was relatively slow (around 48 h).

The present findings are also in good agreement with results of some animal studies. Attias et al. (1990) found a prolongation in I-V IPL latency in rats exposed to hypoxemia accompanied by increase in latency of wave I. They suggested that the I-V prolongation observed could be taken as a sign of a central effect of hypoxia because this finding occurred only in the group exposed to hypoxia only or hypoxia and noise, but not in the group exposed to noise only, assuming that noise causes uniquely peripheral hearing loss.

A high incidence of prolonged I-V IPL has been found in infants undergoing extracorporeal membrane oxygenation (ECMO); such infants suffer respiratory failure (Schumacher et al., 1990). However, the cause of such prolongation was not due to respiratory failure, but rather to right-sided carotid artery ligation or right-sided jugular vein ligation, which are essential procedures in ECMO. The ligation of the right carotid artery will lead to relative ischemia of the auditory nuclei. In adults, Mills and Ryals (1985) also reported prolongation of brainstem transmission time (I-V IPL) to be associated with decreased carotid artery blood flow with subsequent hypoxia of the brain tissue. Thus, hypoxemia can be expected to have a depressant effect on brainstem transmission time, although not necessarily clinically significant at the levels of PO_2 observed in this study. However, findings of the present study are not in agreement with those of Moski et al. (1981) who failed to find prolongation of I-V inter-wave latency during sleep in patients with obstructive apnea. However, they may have simply failed to detect effects under the even more limited hypoxia potentially involved in such cases, due to the relatively short duration of oxygen-tension reduction and/or by virtue of the limited sample of subjects ($N = 6$) studied.

Results of this study also are at odds with those of Sohmer et al. (1989) wherein they described a significant depression in the amplitude of ABR and cortical auditory evoked potentials in cats at PO_2 values between 20 and 30 mm Hg. However, they found little or no change in the wave latencies. With levels of O_2 below 20 mm Hg, which are lethal to the animal, latency prolongations had been detected together with amplitude depression. On the one hand, it is tempting to suggest that the chronic nature of the cause of hypoxia in this study may have led to the finding of significant difference between the hypoxic and control groups. Yet, the O_2 levels observed here were far from extreme; indeed, 70 mm Hg was not found to be a critical level for I-V IPL (Table 6).

5. Conclusions

- Chronic hypoxemia can affect human auditory function, namely at the levels of the outer hair cells, inner hair cells, cochlear nerve, and the auditory brainstem.
- The outer hair cells appeared to be the most vulnerable to moderate chronic hypoxemia.
- The evoked otoacoustic emissions thus can be considered the most sensitive test to measure the auditory function in patients with chronic obstructive pulmonary diseases.
- 70 mm Hg can be considered a critical level of partial oxygen tension at which a change in some audiological measures, namely, the response amplitude of otoacoustic emission and the hearing threshold level of pure tone audiometry, can be expected to take place; a PO_2 above this criterion appears essential to completely normal auditory function.

In summary, it seems worthwhile to assess recurrent hypoxia thoroughly as a risk factor for audio-vestibular dysfunction, whether near- or long-term (life-span), namely to examine further the dynamics of the effects of

chronic hypoxemia via evaluation of the whole inner ear (i.e. by including balance testing) and scrutiny of possible interactions with other factors for hearing and/or vestibular loss.

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