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EchoScan: A new system to objectively assess peripheral hearing disorders

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Abstract

Pure-tone air-conduction audiometry (PTA) is the reference clinical test used in Europe and the United States to measure the extent of hearing loss. It is a subjective, behavioral test, which measures thresholds of hearing sensations and perceptions based on patient responses to frequency-specific pure-tone stimuli. PTA can detect hearing problems due to cochlear or retro-cochlear impairment, without identifying the source of the problem. In contrast, cubic distortion product otoacoustic emissions (DPOAEs) detect inner-ear dysfunctions, particularly those involving the outer hair cells sensitive to noise and ototoxicants. Recently, ototoxicants were shown to have an action on the central nuclei driving the middle-ear acoustic reflex. Therefore, a new device, called EchoScan, was conceived to collect and measure performance both in the middle- and inner-ear. Its originality: the use of a battery of DPOAE measurements associated with contra-lateral acoustic stimulation. Changes in DPOAE amplitude due to ageing and gender were incidentally detected and EchoScan was more sensitive than impedancemetry to detect the stapedial reflex. EchoScan can be used both in clinical investigations and in occupational medicine, especially for the auditory follow-up of people exposed to noise or ototoxic agents. EchoScan could be promising to assess early detection in programs to prevent hearing loss.

Keywords: DPOAE, hearing loss, noise, stapedial reflex

Introduction

Pure-tone air-conduction audiometry (PTA) is a subjective test relying on a patient's capacity to determine thresholds of hearing sensations to frequency-specific acoustic stimuli. Given the plasticity of the central auditory system, which can compensate slight inner-ear dysfunctions, threshold shifts measured by PTA may underestimate cochlear injuries.[1-4] As a result, PTA should be completed by supplementary prevention tools. Today, clinicians and occupational physicians can measure distortion-product otoacoustic emissions (DPOAEs) to detect inner-ear dysfunctions, while isolating possible central influences. When two-tone stimulations with frequencies f1 and f2, known as primaries, are presented simultaneously to the ear canal, several DPOAEs can be measured in only few seconds. The most

prominent DPOAE is the cubic-difference DPOAE at 2f1-f2. The amplitude is much larger than that of other distortion products, and its existence requires a frequency-selective compressive nonlinearity in basilar membrane mechanics in the region where the primaries overlap.[5,6] This nonlinearity is mainly due to the motility of outer hair cells.[7] These cells are sensitive to noise[8,9] and ototoxic agents.[10,11]

On the other hand, the number of outer hair cells decreases with age.[12] As a result, DPOAEs should be more suitable than PTA for detecting sub-clinical threshold alterations induced by a noise and ototoxic agents (solvents). Combined with contralateral acoustic stimulation, DPOAEs can be measured prior to, during and after triggering the stapedial reflex (middle-ear reflex: MER) providing useful information on the central nervous elements driving the middle-ear function.[13,14] In order to evaluate the middle-ear and the outer-hair cell functions, the authors have designed a new device, and a specific procedure that they named EchoScan to optimize the measurement of the DPOAEs prior to, and during a simultaneous contralateral stimulation.

One of the aims of this study, conducted in hospital (CPP 10.0702; Affsaps UEC/AnnR/DA/2010-212), was to test whether EchoScan was capable of detecting a gender effect[15]

and an age-related decline[16] by measuring either the DPOAE magnitudes or the MER thresholds. Of particular interest were the effects of certain chemicals on the stapedial reflex and as such the investigators focused on how effectively EchoScan elicited MER thresholds.[14,17]

Study participants

A population of fifty volunteers aged from 20 to 65 years old (24 women and 26 men) were included in this study [Table 1]. Hearing was tested by PTA (Interacoustics AC 40) for frequencies ranging from 500 to 8000 Hz. The subjects who suffered from 30 dB hearing loss at frequencies less than 4000 Hz were excluded from our population. Normal (type A) acoustic compliance was also checked by immittance (GSI Tympstar, 2000-97XX). Middle-ear immittance was performed in each ear using a 226 Hz probe tone with a static pressure change in the outer canal of 200 daPa/sec, varying from 200 to -200 daPa. Subjects had to have a stapedial reflex to be included in our population.

In summary, the selection of the subjects was essentially based on the PTA results, and the detection of the stapedial reflex at one or more frequencies by impedance audiometry. Anamnesis was also performed to exclude subjects who had suffered the influence of noise and ototoxic agents.

Methods

All measurements were performed in a sound-attenuated booth located in the Otolaryngology department (ENT) of University hospital Nancy, France. Three sets of measurements were taken on two consecutive days: D (1 set) and D+1 (two sets taken at a 1-hour interval). A possible effect of time of day on our results[18] was minimized by performing tests on days D and D+1 with identical schedules.

Input/Output DPOAE procedure

The DPOAE probe (Etymotic Reasearch ER10C) contained 2 transducers, with a bandwidth ranging from 200 Hz to 12 kHz at ± 10 dB. These generated f1 and f2, chosen to generate distortion-product otoacoustic emissions (DPOAEs) defined as 2f1-f2. The f2/f1 ratio was 1.2. The levels of the primaries were L2 = L1- 6 dB HL.[19-21] Two synthesizers (Pulse, B and K 3610) were connected to the probe to deliver f1 and f2 in the ipsilateral (left) ear; the highest intensity was limited

Table 1: Population distribution as a function of gender and age

Gender	Age range (years)					
	20-29	30-39	40-49	50-59	60+	Total
Female	7	6	2	8	1	24
	29.17%	25.00%	8.33%	33.33%	4.17%	100.00 %
Male	8	12	4	1	1	26
	30.77%	46.15%	15.38%	3.85%	3.85%	100.00 %
Total	15	18	6	9	2	50
	30%	36%	12%	18%	4%	100 %

to 70 dB HL so as not to activate the middle-ear acoustic reflex. Four couples of frequencies were tested in the current investigation: (1000/1200), (2000/2400), (3000/3600), (4000/4800) Hz.

DPOAEs were recorded with a microphone which was also placed in the probe. The three transducers were enclosed in the probe, whose tip was inserted into the subject's external ear canal. DPOAE amplitude was determined from a linear averaged (N = 4) spectrum of 250 ms with a frequency resolution of 8 Hz. For each frequency couple, DPOAE amplitudes were acquired as a function of primary intensities, which increased from 49 to 70 dB HL in 3 dB steps.

An Ear Simulator Type RA0045 GRAS (IEC 711) was used to perform a calibration procedure according to standards ISO 389-2 and IEC 60318-4. This ensured that f1 and f2 were always emitted at the target intensities. Notice that the intensities used to generate DPOAEs will be expressed in dB HL to be consistent with the usual convention. In contrast, the amplitude of the DPOAEs measured with EchoScan will be expressed in dB SPL.

The equivalence between the DPOAE stimuli from dB HL to dB SPL is illustrated by two examples. Using the ER10C probe driven by a 1 V sinus tone, the pressure level measured by the ear simulator type RA0045 GRAS (CEI 711 and CEI 60318-4:2010) was 67.5 dB SPL at 2 kHz and 81 dB SPL at 4 kHz. The equivalent hearing level value was 56.0 dB HL at 2 kHz and 66.0 dB HL at 4 kHz.

DPOAE pattern across frequency: DPgram

Participants were screened for DPOAEs across the f2 frequency ranging from 1008 to 8064 Hz, with a constant stimulation level: L1 = 62 dB HL and L2 = 56 dB HL. Notice that the measures of f1 and f2 were expressed in dB HL to make the comparison with PTA easier. In contrast, the DPOAE amplitude was measured in dB SPL, which is the usual convention. DPOAE pattern across frequency, or DPgrams were performed up to 8 kHz to make comparisons with PTA data possible.

Input/Output middle-ear reflex procedure

The earphone used to trigger the stapedial reflex was an Etymotic Research ER4 B, with a bandwidth ranging from 20 Hz to 16 kHz at ± 4 dB. It was fitted into the contralateral (right) ear, whereas the DPOAE probe was placed in the ipsilateal (left) ear. The contralateral emitter was calibrated as described for the DPOAE probe emitters. The noise was an 800 Hz band noise centered on a frequency, varying from 500 to 4000 Hz. Each burst lasted up to 2 seconds. The contralateral noise was synthesized by a B and K Pulse 3610, and emitted at an intensity between 65 and 95 dB HL. The upper intensity limit was fixed at 95 dB HL to preserve participants' hearing. The procedure was performed to detect a decrease in DPOAE amplitude induced by activation of the stapedial reflex.

Data recording schedule

Table 2 describes the schedule of the investigations carried out in the study.

EchoScan

A patent application has been lodged for EchoScan Figure 1 and the process used to measure the trigger threshold of the MER as a function of frequencies chosen based on a previous DPOAE I/O analysis.

Table 2: Test schedule summarizing the main steps and hearing tests performed in this study

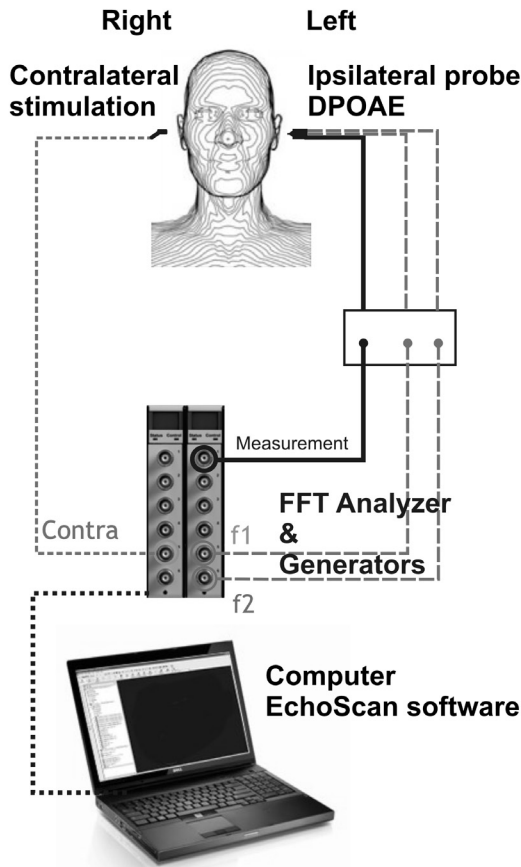| Hearing tests	Day D	Day D + 1 (2 sets of measurements)
	EchoScan	EchoScan
Pure-tone audiometry from 500 to 8000 Hz	I/O DPAOE f2: 1200, 2400, 3600, 4800	I/O DPAOE f2: 1200, 2400, 3600, 4800
	DPgram from f2: 1008 to 8064 Hz at 56 dB HL	DPgram from f2: 1008 to 8064 Hz at 56 dB HL
Acoustic compliance test	Trigger thresholds	Trigger thresholds
Impedancemetry to measure stapedial reflex from 500 to 4000 Hz	I/O MER from 500 to 4000 Hz	I/O MER from 500 to 4000 Hz

Statistical analysis

Statistical analyses were performed using mixed linear random effect models to evaluate the effects of age and gender. The significance of the MER threshold was determined by Student's *t-test*. Statistical significance was defined at an alpha level of 0.05 (significant at 95%). The linear association between the middle-ear reflex threshold elicited by both impedance audiometry and EchoScan was measured by calculating correlation (Pearson's product moment correlation coefficient). Generally, the level of significance is indicated in tables by: * at 5%, and *** at 1/1000. All analyses were designed and performed by PW statistical consulting www.pw-statistical-consulting.eu.

Results

DPOAE input/output function

The DPOAE growth curves presented in Figure 2 are based on data obtained with subject # 7. They are representative of the majority of results. As illustrated in Figure 2a, the

Figure 1: Details of the EchoScan. f1 and f2: primary frequencies. f2/f1 = 1.2. FFT: Fast Fourier Transform
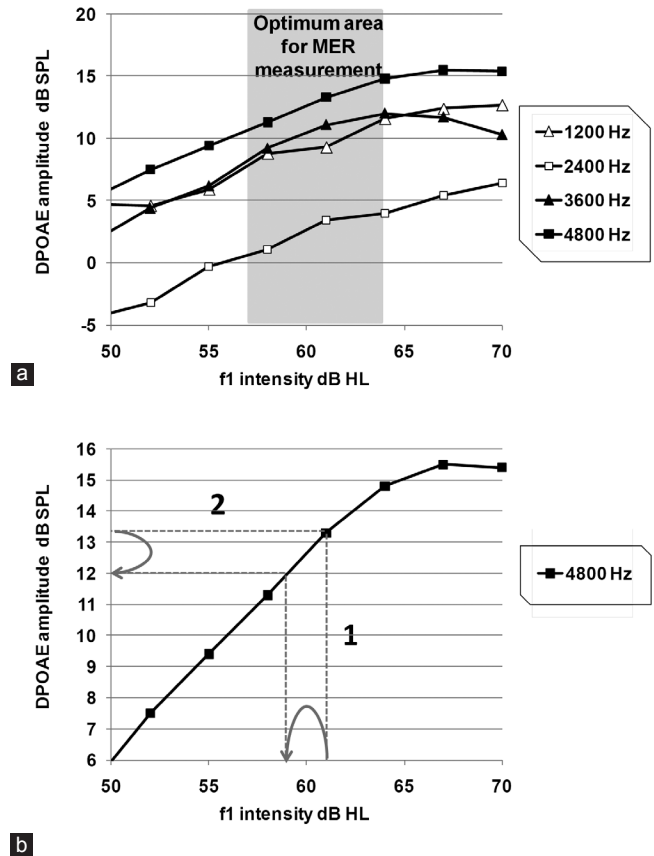

Figure 2: DPOAE amplitude *vs.* f1 intensity. Data for subject #7 are reported. (a) The grey area corresponds to the linear portion of the DPOAE growth curve, which was subsequently used to evaluate the trigger threshold of the middleear reflex. (b) (1) A reduction in f1 intensity leads to a reduction in DPOAE amplitude (2) The frequency panels in (a,b) correspond to F2

intensity-magnitude DPOAE relationship was linear up to 65 dB HL at 3600 Hz and 4800 Hz. Above 65 dB HL the DPOAE amplitude saturated. It is important to determine the level of saturation so as not to underestimate the middle-ear reflex threshold. Indeed, when DPOAE amplitudes are saturated (e.g. over 65 dB HL at 4800 Hz) the MER trigger could have no effect on the DPOAE amplitude, and therefore remain undetectable. As a result, the choice of the primary intensities was determinant at this point in the experiment so as to avoid saturation of the growth curves Figure 2b.

DPOAE input/output *vs.* age and gender

Ageing and gender effects were observed at 4800 Hz [Table 3]. The decrease in amplitude, 0.14 dB per year noted at 4800 Hz was determined to be significant by the mixed random effects model. On the other hand, differences between men and women were only observed at the highest frequencies: A 1.8-dB difference was noted at 3600 Hz, and a significant 3.7 dB difference at 4800 Hz. Moreover, our findings showed that DPOAEs were present and repeatable for each volunteer across the time-period studied (Days D and D+1), for all the frequencies considered. The between-subjects variations were less than 5 dB, which is comparable to the variability generally reported with PTA. The "Intercept" term listed in Table 3 corresponds to the mean value predicted by the mixed random effects model for a 20 year-old man.

DPOAE patterns across frequencies: DPgram

As shown in Table 3, significant ageing and gender effects were observed at 4800 Hz, but higher frequencies, namely 6528 and 8064 Hz also showed these effects [Table 4]. DPgram gave clearer ageing effects than DPOAE I/O measurements, because it screened frequencies up to 8 kHz. A significant decrease in amplitude, of approximately 0.19 dB per year, was observed from 4800 Hz to 8064 Hz. Similarly, the differences between men and women were mainly observable at the highest frequencies. In general, the gender effect accounted for a 4 dB difference. Once again, our findings showed that DPOAEs were present, and reproducible in all volunteers for the time-period studied (Days D and D+1), for all frequencies tested. The

intercept listed in Table 4 corresponds to values predicted by the mixed random effects model for a 20 year-old man.

Comparing DPgram with subjective thresholds across frequencies

Subjective auditory thresholds were obtained using a typical PTA approach, whereas EchoScan was used to perform objective auditory measurements. The variations in DPgram amplitudes were quite similar [4-5 dB] to those measured with PTA [Table 5]. The different patterns observed for PTA and DPgram may be due to calibration differences. Two different standards were used for calibrate our equipments: standard ISO 389-2 and IEC 60318-4 for the EchoScan probe, and standard IEC 60645 for the audiometer.

In addition, we used dB HL to express PTA results, according to the consensus, whereas DPgram results were expressed in dB SPL. Note that the PTA measures were collected at the thresholds, whereas the DPgram was obtained with L1 = 62 dB HL (§3.1). These two measurements are not obtained in the same range of intensities. Moreover, PTA is a auditory sensory threshold, which is the result of the entire auditory system, from the auditory receptor to the cortical area. In contrast, DP gram mainly reflects the outer hair cell function. All these reasons can explain the difference of pattern observed between the PTA and DPgram curves. Nevertheless, line 2000 Hz and column 8064 Hz in Table 6 show relevant correlations (R>0.15) between the DPgram and PTA values.

MER thresholds elicited with echoscan, as a function of age

Although we did not find any gender difference for MER thresholds, an ageing effect at 4000 Hz was detected. The values obtained with a random-intercept proportional odds model are reported in Table 7. In spite of between-subject variations, the age effect was significant at the highest frequency tested.

Table 3: Statistical analysis of DPOAE amplitudes as a function of age and gender

DPOAE max dB SPL	f2=1200 Hz	f2=2400 Hz	f2=3600 Hz	f2=4800 Hz
Ageing effect (dB/year)	-0.08	-0.05	-0.07	-0.14*
SE	0.06	0.05	0.06	0.06
Gender effect (dB)	0.52	0.25	1.83	3.73*
SE	1.33	1.25	1.29	1.46
Intercept	13.90 ***	8.791 ***	9.073 ***	14.07 ***
SE	2.15	1.98	2.13	2.36
between-subject SD	4.19	3.99	4.36	4.96
same-subject SD	0.91	1.03	0.71	0.77
n measurements	112	121	137	143

* and *** correspond to respectively 5% and 0.1% level of significance, SE: Standard error; SD: Standard deviation; Intercept: mean value predicted by the mixed random effects model for a 20 year-old man

Table 4: Statistical analysis of DPgram amplitudes as a function of age and gender

DPgram L1= 62 dB HL	f2 Frequency (Hz)								
	1008	1200	2016	2400	3264	4032	4800	6528	8064
Ageing effect (dB/year)	-0.06	-0.02	-0.03	-0.02	-0.10	-0.10	-0.18*	-0.20*	-0.19*
SE	0.05	0.07	0.06	0.06	0.06	0.07	0.07	0.07	0.07
Gender effect dB	-0.92	-1.47	-1.64	-1.85	2.04	3.89	4.34*	3.66*	1.98
SE	1.16	1.56	1.45	1.37	1.38	1.78	1.76	1.65	1.55
Intercept	10.945 ***	10.81 ***	6.819 ***	5.37 ***	3.67 ***	5.33 ***	9.24 ***	10.30 ***	7.87 ***
SE	0.99	1.42	1.32	1.30	1.26	1.60	1.61	1.54	1.43
btw subject SD	3.24	4.73	4.82	4.48	4.67	5.93	5.98	5.48	4.94
same-subject SD	1.28	1.12	1.04	0.99	0.10	0.92	0.74	1.63	2.90
n measures	96	110	123	128	140	138	142	137	128

* and *** correspond to respectively 5% and 0.1% level of significance, SE: Standard error; SD: Standard deviation; Intercept: mean value predicted by the mixed random effects model for a 20 year-old man

MER thresholds: EchoScan *vs.* impedance audiometry

MER thresholds at less than or equal to 95 dB HL were much better measured by EchoScan than by impedance audiometry. For instance, with impedance audiometry, 25% of MER thresholds could not be measured, whereas EchoScan only failed to find a threshold for 8% of measurements, regardless of frequency.

The comparison of threshold values measured with EchoScan and by impedance audiometry is illustrated in [Figure 3]. The

X-axis represents the MER thresholds obtained by impedance audiometry, whereas the Y-axis corresponds to the MER thresholds obtained with the EchoScan. Equal sensitivity between the two tests would have resulted in values clustered along the diagonal red line. Obviously, EchoScan measures the stapedial reflex more sensitively.

Discussion

The findings reported in this study show a frequency-by-frequency correspondence between human DPOAES and PTA [Table 6]. However, the advantage of DPOAEs is that they provide an objective measurement to evaluate biomechanical aspects of acoustic information processing

Table 5: Pure-tone audiometry (PTA) and DPOAE levels across frequency (DPgram)

DPgram Hz		1008	1200	2016	2400	3264	4032	8064
Mean dB SPL		9.34	10.13	5.83	4.29	3.15	5.56	5.95
SD			3.2	4.53	4.72	4.35	4.63	5.96	5.68
PTA Hz	500	1000		2000		3000	4000	8000
Mean dB HL	11.78	11.98		10.72		9.26	10.19	11.2
SD	3.80	4.82		4.52		5.57	5.36	7.89

SD: Standard deviation. f1 & f2 generation were expressed in dB HL, whereas 2 f1-f2 amplitude was expressed in dB SPL. L1(f1)=62 dB HL and L2(f2)= 56 dB HL

Table 6: Coefficient of correlation (R value) between PTA and DPgram values

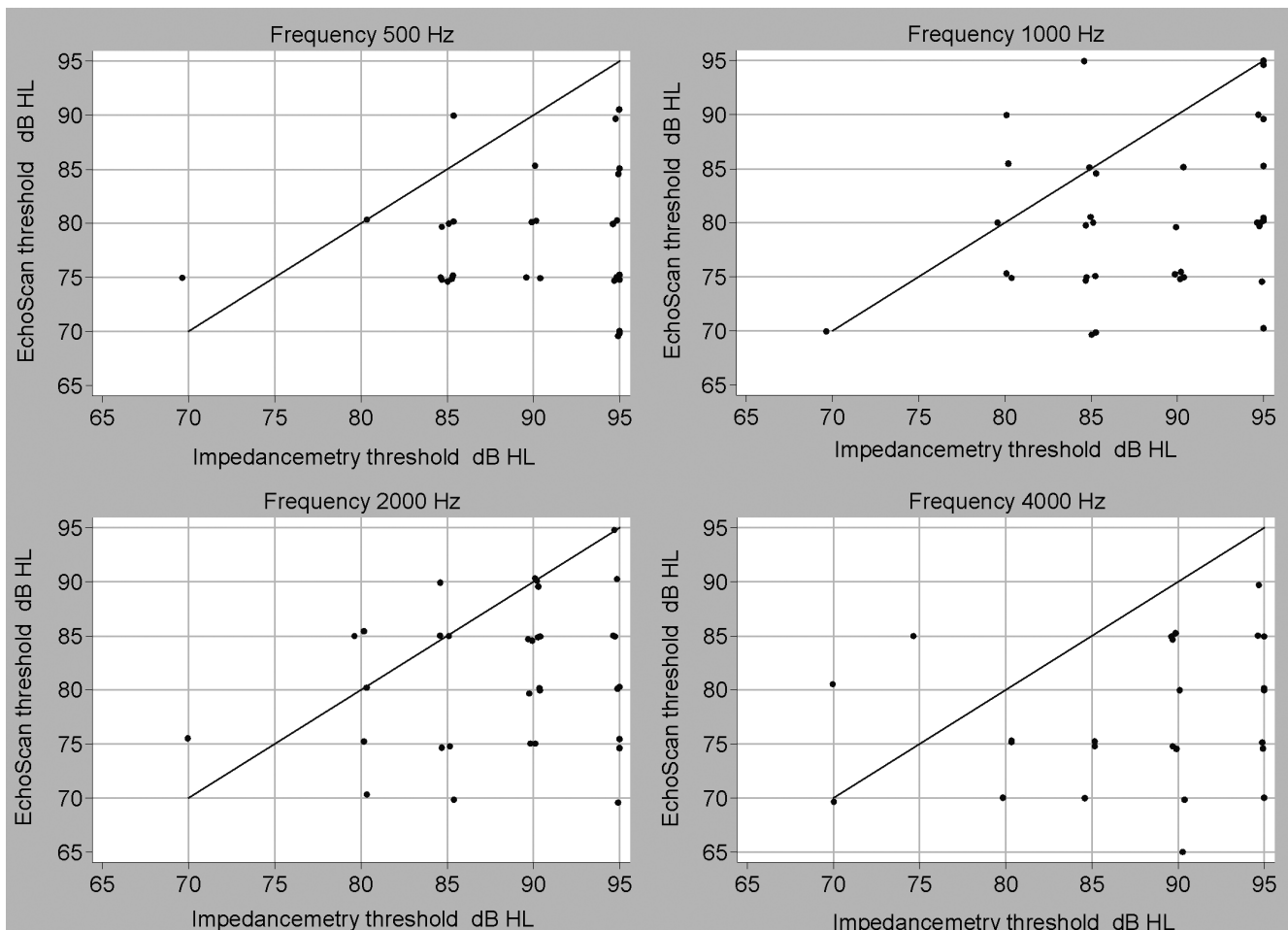| DPgram / PTA	2016 Hz	2400 Hz	3264 Hz	4032 Hz	4800 Hz	8064 Hz
2000 Hz	0.32	0.41	0.49	0.37	0.38	0.42
3000 Hz	0.08	-0.07	0.18	0.07	0.14	0.37
4000 Hz	0.01	-0.11	0.20	0.15	0.27	0.27
8000 Hz	-0.04	0.06	0.22	0.23	0.27	0.38

Figure 3: Comparison between stapedial reflex thresholds measured by impedance audiometry and with EchoScan; X axis: Impedance audiometry threshold in dB HL. Y axis: EchoScan threshold in dB HL

Table 7: Thresholds of middle-ear reflex elicited with DPOAE measurements as a function of age

Frequency Hz	Age classes years	Measurements n	Mean dB HL	SD
500	20	13	77.1	7.1
	30	16	77.0	4.9
	>40	17	79.4	4.9
1000	20	13	81.7	7.5
	30	16	78.9	4.9
	>40	16	80.3	7.2
2000	20	13	79.8	5.4
	30	16	80. 8	4.9
	40	15	82.0	5.9
4000*	20	13	76.9	7.2
	30	16	79.5	5.6
	>40	16	82.5	6.8

*corresponds to a 5% level of significance

within the cochlea.[22,23] Two separate portions of the input-output DPOAE growth curve were found with EchoScan for subjects with normal hearing: a linear and a saturated portion above 65 dB. DPOAE levels across frequency (DPgrams) are repeatable for the same subject Table 3, and although a between-subjects variation was measured, the degree of variation is very close to that obtained with PTA measurements [Table 5]. As a result, DPOAEs allow objective screening of cochlear performance over a wide frequency bandwidth. This is why DPOAEs were developed as an audiometric tool to detect cochlear hearing loss in newborns and infants.[24] Surprisingly, DPOAEs are not used to perform clinical investigations in routine, and the technique is even ignored in occupational medicine.

By triggering the MER with a contralateral noise prior to, during and after DPOAE measurements, EchoScan allows study of both the inner-and middle-ear physiologies, provided that primary intensities are chosen within the linear portion of the DPOAE growth curve.[25] By taking these precautions, this equipment could be used as a valuable system to screen for early signs of cochlear and middle-ear impairments. As far as the stapedial acoustic reflex is concerned, Venet *et al*, showed the importance of eliciting the MER threshold in a hearing-loss prevention program. These authors showed that, in rats, the MER amplitude is sensitive to ototoxic agents, such as aromatic solvents.[17] Thus, where multiple exposures are a problem, both inner-ear and middle-ear physiologies should be measured to appreciate the risk run by people exposed to both noise and ototoxic agents.

Before studying hearing loss, it is essential to keep in mind the decline in auditory performance with advancing age.[12] Because the kinetics of presbycusis has become better known due to the increasing number of older people in our society, many studies documenting age-related hearing loss using either PTA or DPOAEs have been published.[16,26-29] Based on findings reported in the present study, EchoScan can be used to detect age-related hearing loss. Indeed, a significant decrease in DPOAE amplitude was found in high-frequencies as a function of age [Table 2: -0.134 dB per year, and Table 4]. Based on data reported in [Tables 3, 4, and 7], we can state that EchoScan is suitable to detect and monitor the kinetics of presbycusis. In line with the findings of Lonsbury-Martin *et al*., this study also shows a gender-by-frequency interaction whereby female volunteers had larger DPOAEs amplitude than males [Table 2: 3.7 dB] at f2 = 4800 Hz. Therefore, as for the ageing effect, the sensitivity of DPOAE measurements with EchoScan is sufficient to detect DPOAE changes due to gender differences, as recently reported by McFadden.[30]

The major finding of this study concerns the detection of MER. Due to the sensitivity of the MER to certain ototoxicants, EchoScan was designed to allow easy measurement of the MER by clinicians and occupational physicians. In addition, EchoScan is the first equipment allowing evaluation of both inner-ear and middle-ear functions with a single set of hearing tests. The expected ageing effect on the MER at 4000 Hz was observed. This is likely due to age-related hearing loss in some subjects, which alone can explain a significant increase in MER thresholds.

In conclusion, the major aim of the current work was to test the efficiency of EchoScan and to offer it as alternative to subjective PTA for the detection of early-stage hearing impairments. It will be interesting to see it applied in occupational medicine. The clinical tests performed showed that EchoScan can provide innocuous, sensitive, objective, and reliable measurements of both inner- and middle-ear performances in subjects with normal hearing, taking both the age and gender of subjects into account. DPOAEs were present and reproducible over a contiguous 24-hour period (days D and D+1), for f2 frequencies ranging from 1200 to 4800 Hz, and for primary levels varying between 55 and 75 dB SPL. The results obtained with EchoScan have shown: (1) a clear influence of presbycusis, and (2) an unexpected extensive influence of gender on DPOAE magnitudes. These influences were quite obvious in the high frequencies. The findings in this study demonstrate that EchoScan detects stapedial reflex thresholds more sensitively than impedance audiometry. Consequently, EchoScan is directly relevant to clinical settings allowing the incorporation of high-frequency DPOAEs into clinical protocols. In addition, EchoScan could be still more convincing in occupational medicine, where it could be used to follow up workers' hearing. It should be a promising tool to evaluate the early stages of presbycusis, the impact of ototraumatic and ototoxic agents on the cochlea, and the impact of occupational chemicals on the middle-ear reflex. It is very suitable for early detection in a hearing conservation program.

Perspectives

The EchoScan is currently being used in the workplace to test a cohort of noise-exposed workers. The aim of this first investigation is to test (1) the efficacy of the device in occupational environments (2) and the sensitivity of DPOAEs associated with a contralateral stimulus after a single working day in a moderate-intensity noise. This first on site investigation will be followed by other tests with workers exposed either to solvent or to noise and solvent.

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