Post-processing analysis of transient-evoked otoacoustic emissions to detect 4 kHz-notch hearing impairment – a pilot study

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
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Summary

Background: To identify a parameter to distinguish normal hearing from hearing impairment in the early stages. The parameter was obtained from transient-evoked otoacoustic emissions (TEOAEs), overcoming the limitations of the usually adopted waveform descriptive parameters which may fail in standard clinical screenings.

Material/Methods: Audiometric examinations and TEOAE analysis were conducted on 15 normal ears and on 14 hearing-impaired ears that exhibited an audiometric notch around 4 kHz. TEOAE signals were analyzed through a multivariate technique to filter out the individual variability and to highlight the dynamic structure of the signals. The new parameter (named radius 2-dimension – RAD2D) was defined and evaluated for simulated TEOAE signals modeling a different amount of hearing impairment.

Results: Audiometric examinations indicated 14 ears as impaired-hearing (IH), while the TEOAE ILO92 whole reproducibility parameter (WWR) indicated as IH 7 signals out of 14 (50%). The proposed new parameter indicated as IH 9 signals out of 14 (64%), reducing the number of false negative cases of WWR.

Conclusions: In this preliminary study there is evidence that the new parameter RAD2D defines the topology and the quantification of the damage in the inner ear. The proposed protocol can be useful in hearing screenings to identify hearing impairments much earlier than conventional pure tone audiometry and TEOAE pass/fail test.

key words: otoacoustic emissions • acoustic trauma • recurrences quantification analysis • inner ear • ear model

Abbreviations: **NIHL** – noise-induced hearing loss; **OAE** – otoacoustic emission; **TEOAE** – transiently evoked otoacoustic emission; **OHC** – outer hair cell; **HL** – hearing level; **IH** – impaired-hearing; **PCA** – principal component analysis; **PTT** – pure-tone threshold; **RAD2D** – 2-dimensional radius; **WWR** – whole waveform reproducibility; **RQA** – recurrences quantification analysis

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BACKGROUND

Environmental noise has become a serious socio-economic problem in many industrialized countries, and a large portion of the population is exposed to urban noise; noise-induced hearing loss (NIHL) is one of the most prominent occupational diseases in Europe [1,2]. The main significant event in NIHL regards the outer hair cells (OHC) within the Organ of Corti [3]. It is well known that, after noise exposure, OHCs death occurs, which in turn leads to a loss of cochlear amplification and thus to a permanent threshold shift, as reported in previous work by our group using a guinea pig model exposed to noise [4–6].

In humans, the diagnosis of hearing impairment is currently based on clinical and audiometric evaluation. The audiological characteristics of noise-induced hearing loss include hearing threshold shift at high frequencies, presence of recruitment, reduction in the level of evoked otoacoustic emission (OAEs), and impairment of speech intelligibility. Particular focus is devoted to the analysis of audiograms and OAE tests which, as single diagnostic tools or in combination, may fail to provide early diagnosis since scientific consensus is lacking regarding screening protocols and optimal audiological findings for the early detection of NIHL [7–9].

Specifically:
a. NIHL does not simultaneously affect all frequencies – pure tone audiometry usually shows a gradual progression and the first impairment begins around the frequency of 4 kHz, with a typical notch at 4 kHz and, at times, 6 kHz frequencies [10,11]. However, there are no accepted standards for describing or quantifying audiometric notches [12,13].
b. OAEs tests are non-invasive and do not require co-operation from the patient, as does behavioral audiometry; still, 30 years after their discovery, clinical applications of OAEs are largely limited to qualitative pass/fail testing [14]. OAEs are sounds generated in the inner ear by the activity of the cochlear amplifiers [15,16]; they can be recorded when the auditory periphery is solicited by an external acoustic stimuli, such as brief click (i.e., Transient evoked OAE or TEOAE) or 1 or 2 simultaneous pure tones (i.e., stimulus-frequency OAEs and distortion product OAEs), and even in the absence of stimulation (i.e., spontaneous OAEs). Protocols based on TEOAEs are a widely used method for identifying hearing losses [17–20] and, as DPOAEs, may provide an early indication of cochlear damage before evidence for NIHL appears in pure-tone audiometry [21–28]. Lucertini et al. [21] compared TEOAE parameters with pure tone audiograms to determine early indications of cochlear damage; results showed that TEOAE spectral parameters can discriminate between non-exposed normal subjects and subjects with unilateral noise-induced hearing loss. However, the validity of TEOAE measurements is hampered by their *subject-dependent* variations [14,21,29].

Taken together, constraints to the early diagnosis are patient's co-operation in conventional audiometry and subject's variance in TEOAEs; both issues can be controlled and reduced by mathematical procedures.

In this preliminary report we propose a mathematical screening protocol able to detect and quantify the magnitude of hearing loss. A quantification parameter, called henceforth 2-Dimensional Radius (RAD2D), is extracted from the TEOAE waveform by means of a non-linear signal analysis process referred to as recurrence quantification analysis (RQA) [30] along with Principal Component Analysis (PCA) [31]. RQA is an efficient and relatively simple tool in the analysis of many physiological signals [32,33] and accounts for the deterministic structure of TEOAE signals; PCA is a multivariate statistical analysis successfully applied to TEOAEs signals since it minimizes redundant information [34,35]. The proposed RAD2D parameter is a global parameter (comparable to whole waveform reproducibility-WWR), but, as will be shown, the embedding procedure in RQA tools permits observation of the "fine structure" of the waveform. With respect to the typical frequency-specific bands analysis obtained by using the Fourier transform, this extracted parameter, RAD2D, is expressed by an easily comparable numeric value in the same way as the WWR parameter. Furthermore, this mathematical quantification of TEOAE's fine structure reduces the individual variability and can be easily applied to detect hearing impairments in the early pathologic stage.

In the present study, the mathematical procedure is applied to TEOAEs recorded in normal ears and in ears exhibiting a notch at 4 kHz greater than 30 dB HL (hearing level), and the obtained parameter is compared with the conventional analyses (audiometry and TEOAE whole waveform reproducibility). To optimize and validate the procedure, an electronic model of the ear, developed by Giguère and Woodland [36] and applied in a previous work [37], is used to simulate TEOAE signals both in normal ears and in ears with different amounts of cochlear damage.

Taken together, the aims of this paper are: 1) to compare the measured TEOAE among normal and IH ears; 2) to simulate normal and IH ears by using the electronic model of the ear with a selective damage corresponding to a 4 kHz notch; 3) to obtain simulated TEOAE and to compare them with the measured ones; 4) to estimate the RAD2D parameter in the electronic model and to compare the obtained RAD2D values with those evaluated in the normal and IH recorded TEOAE.

MATERIAL AND METHODS

Signal detection and clinical evaluation

The present study was carried out on 29 ears from 21 subjects (average age =38.7±8.12 years). Of these, 14 ears were from 11 impaired-hearing (IH) subjects, and the remaining 15 ears were from 10 subjects with normal hearing. IH subjects (average age =41.3±6.5 years) were included in this study if pure-tone audiometry revealed a 4 kHz notch >30 dB HL. These patients had a positive history for occupational or hobby-related noise exposure. The normal hearing subjects (Normal group, average age =36.3±9.0 years) had no significant noise exposure. None of the subjects had any background of hereditary hearing loss or ear infections, and were fully informed of the aim, design, and clinical applications of this study. The study was approved by the Ethics Committee of the Catholic University, Rome, Italy, and the investigations were performed in accordance with the principles of the Declaration of Helsinki. All subjects underwent

a baseline hearing evaluation: otoscopic examination and 226-Hz probe tone tympanometry were used to exclude middle ear pathologies. Conventional pure tone audiometric testing was carried out in a soundproof room and the pure-tone thresholds (PTT) of each ear were measured at 0.25, 0.50, 1, 2, 4, and 8 kHz with a clinical audiometer (AC-40, Interacoustics Co, Assens, Denmark). Classification of patients was obtained by using a PTT value at 4 kHz.

The Otodynamic Analyzer (ILO92, Otodynamics Ltd, Hatfield, U.K.) was used to record the TEOAE signals by inserting a SGS-type general purpose TEOAE probe into the external ear canal. The TEOAE recordings were carried out in a standard hospital room, corresponding to the usual clinical setting for these measurements. The automated differential non-linear test paradigm was used: the stimulus was characterized by a train of 4 clicks, 3 with the same amplitude and polarity, followed by a fourth with a 3-fold amplitude and opposite polarity with respect to the preceding ones. The 80 µs clicks presented at 50/s were 75–85 pe dB SPL. The responses were obtained, evaluating an average among 260 stimuli trains (1040 clicks) stored into 2 different buffers (A and B) for a total of 2080 clicks [38]. The value of the automatically computed correlation or reproducibility between the 2 obtained waveforms (A and B) of an OAE signal is termed Repro or whole waveform reproducibility (WWR) (Pearson correlation coefficient *100). According to the clinical settings, when the WWR value is >70% and the SNR is higher than 3 dB, the signal is considered as physiological (ILO92 Test is Pass), whereas a WWR value <70% indicates the presence of a possible hearing malfunction (ILO92 Test is Failed) [39]. In the measured data, the mean SNR given by the ILO92 was 13.04 dB for the normal ears and 3.96 dB for the IH ears.

The examined ears were classified as normal hearing or IH ears according to their pure tone thresholds at 1, 2, 4 and 8 kHz. In particular, the subjects with a pure-tone threshold value greater than 30 dB HL at 4 kHz were assigned to the IH group even though their WWR value was high (WWR ≥70% and Pass at ILO92 test).

The ear model

To optimize and validate the procedure, TEOAE have been numerically simulated using an electronic model of the whole ear, originally introduced by Guiguère and Woodland [36,40] (1994) and used in other TEOAEs analysis [37,41] and other studies [42]. The electronic model was implemented into a standard electrical simulation tool (PSpice®) [43]. The electronic model is based on the electro-acoustic analogy, where the acoustic mass of cochlea fluids is represented by inductors; the acoustic resistance, mass and stiffness of the basilar membrane are represented by shunt resistors, inductors and capacitors, respectively; and the OHC active processes are represented by non-linear voltage sources (details of the circuit are in [37]). In the electronic model of the ear, the cochlea is divided into several sections (termed partitions) from the base to the apex. Sixty-four partitions are used to segment the cochlea, so that, being the whole uncoiled cochlea 3.5 cm long (comprising a total of about 12000 cells), each partition corresponds to a cochlear portion of 0.0547 cm and about 188 cells. In order to simulate the noise-induced OHC damage corresponding to the

experimental IH condition, the suppression of cochlear amplification is obtained by zeroing the gain of some of the generators within the cochlear partitions. In particular, to establish different damage levels, a localized suppression of an increasing number (ranged from n=2 to n=10) of adjacent cochlear amplifiers is applied close to the characteristic frequency (CF) of 4 kHz. To simulate TEOAE measurements, the input voltage was a rectangular pulse 80 µs in duration, with an amplitude corresponding to a stimulus level of 80 pe dB SPL. Finally, to eliminate the initial ringing, the first 2.8 ms of the simulated TEOAE signals were excluded from the successive analysis.

RQA-PCA of TEOAE signals

The WWR value of TEOAEs in IH subjects with a 4 kHz notch can be >70% as in normal hearing subjects. Consequently, the usual waveform descriptive parameters are of no assistance in detecting cochlear pathology. In the present study, TEOAE signals were analyzed by RQA and PCA techniques to reduce inter-subject variability and the dynamical structure of signals were investigated rather than signal-level differences. RQA introduces few parameters (named RQA descriptors) descriptive of the global complexity of a signal and computed from the so called "recurrence plot" [32-33].

To build the recurrence plot, the time behavior of the original signal was represented by a series of 512 points equally spaced in time (e.g., *{a1 a2 …. a 512} where ai represents the value of the signal corresponding to the i-th time position*). Then, the series was arranged in successive columns (the columns number is defined by the "embedding dimension" parameter N), each-one obtained by applying a delay in time (lag parameter) to the original sequence, thus creating an "embedding matrix", as in equation 1.

$$
\begin{bmatrix}
a_1 & a_3 & \dots \\
a_2 & a_4 & \dots \\
\dots & \dots & \dots \\
a_{512} & 0 & \dots
\end{bmatrix}
=
\begin{bmatrix}
e_{1,1} & e_{1,2} & \dots & e_{1,N} \\
e_{2,1} & e_{2,2} & \dots & e_{2,N} \\
\dots & \dots & \dots & \\
e_{512,1} & 0 & \dots & e_{512,N}
\end{bmatrix}
\tag{1}
$$

Finally, the recurrence plot was built, drawing a black dot (named recurrent point) in the represented space if the distance between the corresponding rows (the distance between the j-th and the (jth+1) row is $\sqrt{\sum_{i=1}^{512}(a_{j,i}-a_{j+1,i})^2}$) of the embedding matrix was lower than a fixed value (radius). In the obtained plot, the horizontal and vertical axes represented the relative position of the 512 points into the TEOAE waveform. RQA descriptors were then calculated on the basis of the number and the location of dots in the recurrence plot. In particular, percent of recurrence (Rec) is the percentage of recurrence points in a recurrent plot; percent of determinism (Det) is the percentage of recurrence points which form diagonal lines and it indicates the degree of deterministic structure of the signal; entropy (Ent) is the Shannon entropy of the probability distribution of the diagonal line lengths and is linked to the richness of deterministic structure. The presence of horizontal and vertical lines in the recurrence plot shows that part of the considered signal matches closely with a later sequence. Based on experience gained in previous research, the delay in the embedding

procedure (lag) was set to 1; the number of the embedding matrix columns (embedding dimension, N) was 10; and the cut-off distance (radius) was 15.

The PCA technique was applied on the obtained RQA descriptors. PCA is a common statistical technique [31,33] which, exploiting the presence of correlations among the original variables, provides the possibility to reduce the starting data set dimension without consistent loss of information and with a separation of the different and independent features characterizing the data set. As a consequence, PCA describes the original data set with a lower number of new parameters, termed main components. As shown in a previous study [29], if a set of at least 70 representative TEOAE signals is chosen as input to the RQA-PCA analysis, the first 2 main components (PC1, PC2) explain more than 90% of the total variability in the data set. Moreover, having PC1 and PC2, by construction, zero mean and standard deviation equal to 1, if a set of TEOAE signals from normal ears are studied, 96% of them will fall within a circle centered in the origin of the PC1/PC2 plane, and with a radius equal to 2 (reference circle). In the present study, the PC1/PC2 plane was defined starting from a representative data set made by 118 signals measured from normal hearing subjects, in agreement with results of a previous study [37]. The explained variability of the representative data set used was 90.02%, 6.29%, and 3.68% for PC1, PC2, and PC3, respectively. The correlation between RQA parameters and PCs is described by the "factor score coefficients" (data not shown). The representative data set was used to define the circle in the PC1/PC2 plane in which the majority of TEOAE signals recorded in normal hearing subjects will fall. In this study, simulated signals, as well as the measured ones, were projected and analyzed into the reference circle of the PC1/PC2 plane defined by the 118 signals. Then, a reference parameter, termed the 2-Dimensional RADius (RAD2D) was introduced. RAD2D is defined in the PC1/PC2 plane as the Euclidean distance of 1 point representing a TEOAE signal from the plane origin:

$$RAD2D = \sqrt{PC1^2 + PC2^2} \qquad (2)$$

To determine the amount of damage, the ear model was used to simulate different levels of cochlear damage by zeroing a growing number of cochlear partitions, and the relation between the RAD2D value and the number of silenced partitions was evaluated. The obtained relation allowed correlating the RAD2D value obtained for all the measured signals with the entity of cochlear damage.

Statistical analysis of TEOAE waveform parameters

A statistical analysis was performed on 15 parameters: a) the age of the participants, b) the whole waveform reproducibility, c) 6 audiometric levels (at 250 Hz, 500 Hz, 1 kHz, 2 kHz, 4 kHz and 8 kHz), d) 3 RQA parameters (Rec, Det, Ent), e) 3 PCA coordinates (PC1, PC2 and PC3), and f) the RAD2D parameter calculated from the first 2 principal components PC1 and PC2 (see eq. (2)). RQA, PCA and RAD2D values were analyzed both in measured and simulated TEOAEs. All possible Pearson's correlations between these 15 parameters were evaluated. A 2-sample t-test comparison was made between normal and IH ears for each
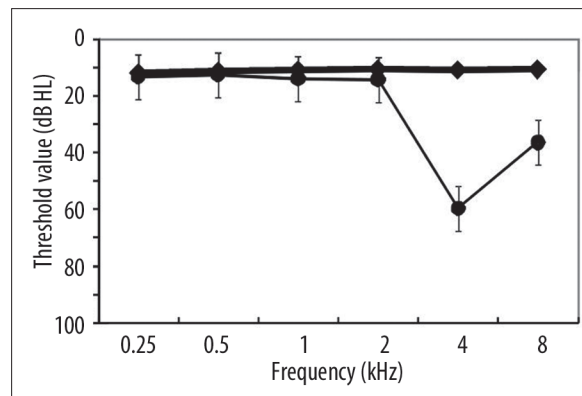

Figure 1. Mean pure-tone hearing thresholds (PTT) averaged across ears of the Normal (bold line) and IH (thin line) groups. Bars represent the standard deviation from the mean. IH ears included in this study showed a 4 kHz notch greater than 30 dB HL using pure-tone audiometry; at this frequency the mean threshold level was 59.6±17.4 dB HL.

variable separately; moreover, a multi-variable ANOVA test was also conducted, comprising both WWR and the RQA parameters. All the statistical data were calculated using a commercial statistical package (Systat, v.10.2, Chicago, IL).

RESULTS

Comparison between TEOAEs recorded in normal and IH ears

The subjects' age distributions of the 2 groups was not statistically different (t-test p=0.095). The recorded TEOAEs in all ears of the Normal group and in 50% ears (7/14) of the IH group had the WWR ≥70%. In Figure 1, the audiogram levels (mean values and standard deviations) are shown for the normal hearing ears (bold line) and for the IH ears (thin line). At 0.5, 1, 2 kHz no differences were found – on the contrary, the audiometric thresholds belonging to IH ears were characterized by a deep and narrow notch close to 4 kHz, that in all patients was higher than 30 dB HL with a mean value of 59.6±17.4 dB HL, as compared to the flat shape of the normal hearing audiograms. The standard deviations demonstrated a large variability in IH subjects at 4 kHz and 8 kHz.

Figure 2 shows the recurrence plots (Figure 2A, B) of measured TEOAE signals (Figure 2C, D) from a normal hearing subject (left side of Figure 2) and from an IH subject (right side of Figure 2). Comparing Figure 2A and B, it is clear that recurrence plots distinguish between normal hearing and IH TEOAEs, especially in terms of a reduction in the deterministic structure.

TEOAE simulation in the electronic model and comparison with measured TEOAEs

The profile of the traveling wave along the basilar membrane (BM volume velocity) simulated by the electronic model of the ear is shown in Figure 3 for normal hearing (bold line) and IH (shaded grey line) ear. In this case, IH was simulated by zeroing the generators gain in 2 consecutive cochlear partitions working close to 4 kHz. BM volume velocity was obtained by using a pure tone stimulus at 4 kHz and by
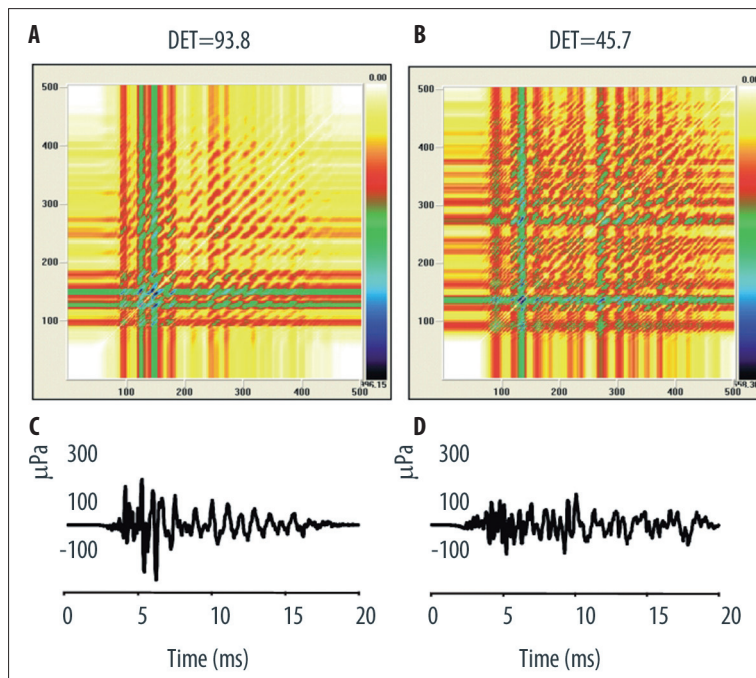
Figure 2. Recurrence plots[*] (**A, B**) obtained from the RQA analysis of the TEOAE waveforms depicted in the bottom panels (**C, D**). Panels **A and C** refer to a normal ear, while panels **B and D** refer to an IH ear. A decreasing determinism in the IH TEOAE waveform can be observed. (*) Visual Recurrence Analysis, version 4.9. Copyright© 1996–2006 Eugene Kononov.

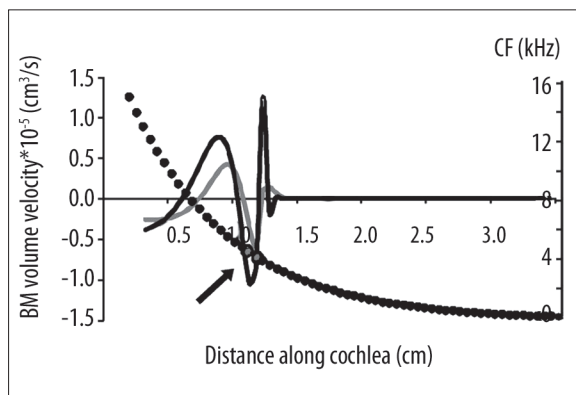**Figure 3.** The profile of the traveling wave in the basilar membrane (BM volume velocity) simulated by the electronic model of the ear. The lines show the volume velocity at a fixed instant (8.9 ms) after the onset of the stimulus. The bold line corresponds to the simulation of the normal hearing ear whereas the shaded grey line to the simulation of noise damage. The full circles represent the characteristic frequencies (CF) along the cochlea (axis on the right, kHz), the open circles (see arrow) are relative to the two partitions where the generators gain have been switched off (3854 Hz and 4145 Hz) in the simulated IH signal.

plotting the current values evaluated in each cochlear section at a fixed instant of time (8.9 ms in Figure 3). The behavior evaluated for the normal hearing ear (bold line in Figure 3) is the typical BM volume velocity reported by several authors [36,41]. The black circle symbols placed upon the plot represent the value of the characteristic frequencies (CF) corresponding to the different positions along the cochlea. Comparing the BM volume velocity obtained in normal and IH ears, it is possible to observe that the largest difference is around the frequency of 4 kHz, as expected (see arrow and grey circles).

Table 1 reports the mean and standard deviation of the most significant parameters of TEOAE signals and RQA/PCA analysis. In particular, the first 4 rows of Table 1 refer to measured TEOAE from normal (row 1) and IH ears (row 2), showing the values of the considered parameters and the results of the statistical analyses between normal and IH data. Moreover, the last 2 rows show the corresponding data referring to simulated TEOAEs. In this case, the IH simulated signal (last row) was obtained by zeroing the generation gain of 6 partitions around the 4 kHz frequency. From Table 1 it can be seen that, on average, the percent of determinism (Det), entropy (Ent), and WWR significantly distinguished Normal from IH measured signals (see p of t-test, Table 1). Moreover, comparing rows 1 and 5 (normal) and rows 2 and 6 (IH), it is clear that the RQA parameters of the simulated signals were close to the mean values calculated for real ears, validating the use of the ear model to study TEOAE characteristics both in normal and in IH ears. RQA parameters were calculated both for measured and simulated signals, whereas WWR and PTT values were available only for measured signals.

RAD2D parameter evaluated in simulated and measured TEOAEs

RAD2D was evaluated by combining RQA and PCA techniques for simulated and measured TEOAEs. Figure 4 shows the RAD2D values calculated for simulated signals with an increasing number of silenced partitions (crosses). The dashed line in Figure 4 corresponds to the value of RAD2D (0.21) obtained by considering the mean values of the RQA parameters obtained from the 15 normal hearing ears, whereas the black bold line corresponds to the value of RAD2D (1.78) obtained from the mean values of the RQA parameters of the 14 IH ears.

Figure 4 shows that RAD2D grew approximately linearly with the number of zeroed partitions (amount of damage), so

Table 1. Mean (SD) value of most significant parameters.

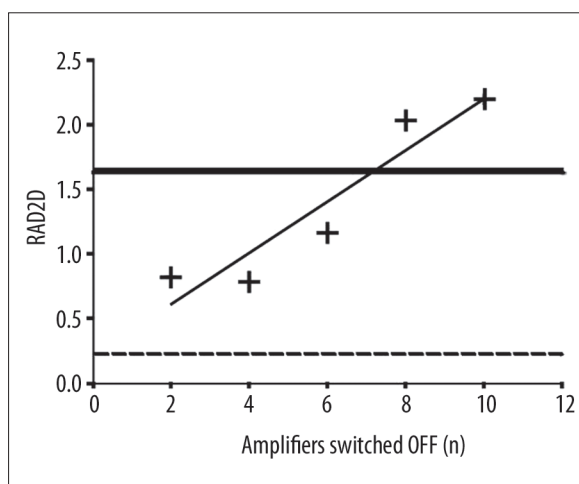| Group	N	RQA parameter			Reproducibility parameter	PTT
		Rec (%)	Det (%)	Ent (%)	WWR (%)	4 kHz (dB)
IH	14	16.66 (9.73)	68.30 (15.95)	4.37 (0.60)	65.10 (21.6)	59.64 (17.37)
Normal	15	20.79 (10.81)	79.95 (6.55)	4.78 (0.40)	93.40 (3.96)	11.00 (4.71)
p (t-test*)		0.365	**0.008**	**<0.001**	**<0.001**	**<0.001**
MANOVA		**p <0.001**				
Simul_IH		13.84	69.73	4.44		
Simul_Normal		20.87	81.93	5.19		

* Pooled variance.

Figure 4. The reference parameter RAD2D (crosses) as a function of the number of amplifiers switched off in the simulated signals. The linear fitting is plotted (thin line, slope 0.199, intercept at 0.204). The dashed line corresponds to the value of RAD2D (0.21) reckoned from mean RQA parameters of TEOAE from the 15 normal ears; the black bold line corresponds to the value of RAD2D (1.78) reckoned from mean RQA parameters of TEOAE from the 14 IH ears (see text for details).

that it is possible to represent the scaling of RAD2D with the number of silenced partitions with a line having a slope of 0.199 and intercept at 0.204 ($r^2= 0.883$) (thin line).

It is important to note that the intercept value (0.20) was very close to the RAD2D value (0.21) evaluated from the mean values of the RQA parameters calculated on TEOAEs of normal ears. From the linear behavior extrapolated by the RAD2D simulated data it is possible to calculate the amount of damage corresponding to each measured signal, as the number of "hypothetical silenced partitions". In this way, since each partition corresponds to a specific portion of the uncoiled cochlea and to a specific number of OHC cells, a descriptor of OHC integrity (RAD2D value) is obtained.

In Table 2 the PTT at 4 kHz, WWR, and the newly proposed RAD2D parameter are reported for all the measured signals.

The RAD2D calculated for each signal of the 2 groups (Normal and IH) was statistically different (t-test p=0.004, the statistical power is 89.1% for α=5% and β=50%, and the minimum difference between means that can be observed with these samples is 0.35). Table 2 demonstrates that 9 IH signals (64%) had a RAD2D value >1.78, which was the mean value of the IH group. By defining an ear as normal if it scored a RAD2D <1.78, only 1 ear resulted in a false positive. From a clinical point of view, it is important to note that 2 ears (T2 and T3) were considered as normal from the standard ILO92 analysis because they had a WWR value >70% (false negative), whereas they had a RAD2D value >1.78, which corresponded to a damaged ear according to the newly proposed parameter.

From Pearson's correlation values obtained within the IH group, it is shown that: a) subjects' age did not correlate with either the audiometric levels or with RQA parameters (ie, the results were not biased by an aging effect); b) audiometric parameters did not correlate with RQA values (i.e., audiometric and RQA parameters carry independent information); and c) the new parameter RAD2D correlated negatively with WWR (r=–0.698), confirming that at large distances from the origin of the reference plane PC1/PC2, the auditory functionality was poorer.

DISCUSSION

Screening protocols are fundamental for the early diagnosis of hearing impairment, and neither audiogram tests nor the different TEOAE analyses provide sufficiently reliable diagnostic tools. The primary aim of this preliminary study was to propose an additional global parameter, RAD2D, useful in clinical applications to improve the early detection of cochlear damage in IH subjects with notches by way of a RQA/PCA procedure. Specifically, our results can be summarized as follows: a) the combined use of the RQA and PCA methods discriminated IH TEOAE from normal ones; b) the RAD2D was validated by adopting an ear model where the cochlea was assumed to be an active electronic circuit that includes OHC active processes; and c) the new parameter, RAD2D, by correlating the waveform dynamic structure of TEOAEs with the amount of damage, defined the topology and quantified the hearing impairment.

Table 2. Comparison of new reference parameter RAD2D in all measured TEOAE signals.

n. file	RAD2D	PTT(4kHz)	WWR
T9	**4.58**	80	**29**
T13	**4.31**	45	**62**
T5	**3.40**	90	**50**
T12	**3.14**	30	**59**
T14	**2.73**	60	**49**
T2 *	**2.55**	60	74
T10	**2.46**	70	**34**
T3 *	**1.95**	55	89
T11	**1.79**	40	**49**
T6	1.40	45	85
T8	1.16	80	90
T4	1.13	65	94
T1	0.56	70	82
T7	0.43	45	77
N6	**2.83**	10	95
N7	1.65	20	98
N4	1.57	20	98
N8	1.31	5	96
N14	1.28	10	88
N2	1.16	10	94
N10	1.15	10	88
N1	1.12	15	97
N12	1.07	10	97
N13	0.90	10	92
N5	0.86	15	92
N11	0.78	10	92
N3	0.54	5	85
N15	0.32	10	93
N9	0.05	5	96
IH FAIL	**9.00**	**14**	**7**

In bold: RAD2D >1.78; WWR values <70; * false negative.

In this study RQA was applied without any previous mathematical assumptions and data manipulation (as in Fourier Transform) to both the simulated and recorded TEOAE. RQA method is particularly suited for signals which exhibit clear frequency dispersion over time, as well as signals characterized by high sensitivity and low specificity such as TEOAEs [10,44]. RQA parameters obtained from simulated signals were close to the mean values calculated for real ears, validating the use of the ear model to study TEOAE characteristics both in normal and in IH ears. In particular,

the specific selection of IH ears with a notch at 4 kHz larger than 30 dB HL, evidenced a decrease of determinism in the considered signals (i.e., Det and Ent values obtained for the IH signals were lower than those obtained for Normal signals). This loss of determinism can be considered a loss of deterministic structure, because the number of recurrence points was invariant (see statistic tests in Table 1). In this context, it is important to observe that the loss of structure of the signals depends on the number of active resonators which have lost their normal function, and that the same loss occurs both in simulated IH and measured IH signals. In fact, the amount of damage assessment is necessarily based on surviving signal frequency components rather than on missing ones. The PCA technique was then applied on the obtained RQA descriptors. On the basis of the above considerations, the combination of the RQA/PCA techniques, focusing on the dynamic regime of TEOAE, reduced individual variability which, masking the relevant features of the signals, is the most relevant problem occurring in standard TEOAE technique, thus confirming previous results [29,35,37,45]. The embedding procedure allowed expansion of the monodimensional signal into multidimensional space and produced few global parameters directly deriving from signal fine structure. The possibility to realize the RQA analysis on time windowing will in the future allow direct comparison with the results of time-frequency analysis [18,44,46].

The proposed parameter, RAD2D, may have a remarkable clinical interest – in fact, RAD2D not only discriminated between normal and IH TEOAEs, but it scaled on the basis of the integrity of cochlear amplification in IH ears. This result is of importance because IH ears are often characterized by a limited loss at a specific frequency (e.g., a deep notch at 4 kHz) and IH TEOAEs, often exhibiting high WWR, can be confused with ones from normal ears, as was the case in some of the patients examined in the present study (e.g., T2, T3 in Table 2). A first validation of the proposed parameter was obtained by studying simulated signals. The evidence that RAD2D value grew approximately linearly with the number of silenced amplifiers in the ear model confirmed that RAD2D quantitatively described the level of damage of IH. A second validation was obtained by comparing measured and simulated signals. By taking the RAD2D value of 1.78 as a threshold value (the intercept of the bold horizontal line of Figure 4) the RAD2D was able to identify 2 more cases with respect to WWR data of IH subjects; the mean normal RAD2D value (the intercept of the dashed horizontal line of Figure 4) was very close to the value predicted by the model simulating a normal ear.

In this study we used as WWR threshold value 70%, which is usually indicated in the clinical practice and is recommended in the manual setting of ILO92 [39]. Some researchers used a different threshold value (i.e. WWR 80%) when performing TEOAE measurements in an unavoidable low frequency noisy environment (nursery environment) [47]. If such a value was used to evaluate the IH ears of the present study, 9 ears out of 14 would have been recognized as IH ears by the WWR value. However, the RAD2D procedure would still be able to identify 2 more IH ears, thus confirming that the use of the 2 global parameters, WWR and RAD2D, can improve the early detection of hearing impairments through TEOAE analysis. With reference to

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the value chosen as threshold for the new RAD2D parameter, the 1.78 value was obtained as the mean value from the TEOAE recorded in the IH ears. This is a preliminary study, and further research with a higher number of IH ears should be conducted.

Other investigators studied hearing loss and compared TEOAE with DPOAE [28], finding a greater sensibility of TEOAEs with respect to DPOAEs, especially using frequency-specific bands parameters [47,48]. In general, however, a detailed assessment on the acoustic deficit cannot be achieved by a single approach. Thus, the use of the parameter obtained in the present research in conjunction with the TEOAE standard procedure can improve the percentage of successfully detected early stages hearing impairments that is fundamental for preventive measures to be applied [9,18]. Further implications concern the possibility of using TEOAE techniques reliably to monitor hearing function in noise-exposed and elderly populations. These implications are fundamental for prevention (e.g., early use of antioxidant agents [5,6]), for design of new hearing protector devices, and hearing-aid fitting strategies [42,49].

CONCLUSIONS

Although preliminary, the findings of this study illustrate a global parameter to be used for the clinical screening of hearing impairments. Being a global parameter, the RAD2D value could be easily used in conjunction with the reproducibility parameter, an improvement over using the many other parameters such as TEOAE reproducibility in frequency bands. The analysis of the TEOAEs of 4 kHz notch subjects, as chosen in this study, establishes the validity of the RAD2D parameter, as evidenced by: a) combining WWR value with RAD2D unrevealed 2 hearing impaired cases; b) the ear model, used to simulate the 4 kHz damage and to reproduce the corresponding TEOAEs, has validated the measured human signals; and c) the entity and location of the damage has been obtained. Finally, the benefit of this additional parameter could consist in the introduction into the clinical practice of a numeric value similar to a pass and fail criterion to assess cochlear function in different ear pathologies such as NIHL, ototoxicity, age-related hearing loss and other sensorineural hearing deficits.

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