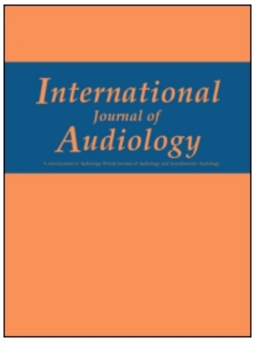

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The Role of Tuning Curve Variables and Threshold Measures in the Estimation of Sensory Cell Loss

Key Words
Tuning curve
Sensory cell loss
Threshold shift
Evoked potentials
Frequency selectivity

Abstract

Auditory-evoked potential tuning curves were collected at six frequencies before and 30 days after various noise exposures in 363 chinchillas using a simultaneous masking paradigm. Traditional bivariate and multiple linear regression/correlation analyses were performed in an effort to determine the extent to which sensory cell damage could be estimated from a knowledge of audiometric and tuning curve variables. The results showed strong correlations between percent outer hair cell (%OHC) loss and permanent threshold shift (PTS) and between %OHC loss and the tuning curve variables $Q_{10\ dB}$ and high- and low-frequency slopes (S_{HF}, S_{LF}). The correlations were strongest between PTS and %OHC loss. However, the proportion of variability (r^2) in %OHC loss attributable to variability in the predictor variable(s) (i.e., PTS) could be increased significantly by adding the $Q_{10\ dB}$ of the tuning curve whose probe frequency was centered in the octave band length of the cochlea corresponding to the frequency at which the PTS occurred. The r^2 values could be further increased by including audiometric and tuning curve variables from frequencies adjacent to the octave band being evaluated.

Introduction

Evidence from physiological and psychophysical experiments in human and animal models has shown that frequency selectivity is impaired in cochleas with various types of sensory cell pathologies [1–9]. On the basis of such studies, the tuning curve (TC) has been established as one measure of auditory function that reflects pathological changes in the cochlea.

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Several studies using VIIIth-nerve, single-unit recordings in the noise-damaged cochlea have shown either broadened, elevated or absent TC tips and hypersensitivity of the low-frequency portion of the TC [4, 7, 10–12]. Liberman and Dodds [7], for instance, showed a variety of changes in TCs following noise-induced sensory cell loss in the cat. Damage to the inner hair cells (IHCs) accompanied by damage to the first row of outer hair cells (OHCs) was associated with TC of normal shape, but of elevated threshold. Depending on the degree of OHC damage, the TC could lose the sharp tip, although with lesser amounts of damage small sharply tuned notches were seen on the high-frequency slope. Selective damage to the OHCs was associated with elevated tips and hypersensitivity of the low-frequency portion of the TC. Complete destruction of the OHCs in a region with normal-appearing IHCs was also associated with a bowl-shaped TC. Thus, TCs obtained from single units are unusually sensitive to sensory cell pathologies such as cilium defects or the row in which outer sensory cells are lost. In addition, shifts in the characteristic frequency of neurons from regions of OHC loss concomitant with threshold shifts of 40 dB or more have also been reported [11, 13].

The psychophysical TCs or the TCs obtained with gross electrophysiological measures (e.g., evoked potentials) show features in common with single unit TCs. However, these measures in both human and animal models, understandably, do not have the sensitivity to pathologies that the VIIIth-nerve single-unit TCs have. Nevertheless, TCs obtained using psychophysical and gross potential techniques do show some systematic changes in common with single-unit TCs in the pathological cochlea.

In sensorineural hearing-impaired listeners [14], for instance, the TC becomes less sharply tuned as absolute thresholds increase up to approximately 50 dB HL, above which very little frequency resolution remains. Similar results have also been reported in sensorineural hearing-impaired human subjects [2, 15] and in the chinchilla [9, 16]. In addition, spread of masking effects, with the most common pattern being a shallow low-frequency slope (S_{LF}) accompanied by a sharp high-frequency slope (S_{HF}), have often been reported in the physiological and psychophysical TC of the sensory-damaged cochlea [7, 10, 15–19]. In agreement with Khanna and Leonard [20] who reported that the mechanical properties of the OHCs affect tuning, our data from TCs collected using auditory-evoked potentials indicated that changes in tuning were also primarily related to the population of OHCs [9]. Physiological measures of tuning in animal models, which have to a large extent been substantiated by psychophysical and physiological data from humans with various cochlear pathologies, suggest that phenomenologically there are parallels between the behavior of the auditory system in different species. Thus, an analysis of the data from an animal model may illustrate the potential value or application of TC measures for diagnostic purposes in the clinical setting. This is especially true in those individuals reporting speech recognition difficulties despite normal pure-tone thresholds [21].

Over the past several years, we have had the opportunity to collect large numbers of TCs from chinchillas that have been exposed to a variety of noises. The TCs were obtained from a simultaneous masking paradigm using evoked potentials recorded from the inferior colliculus. The rational for collecting TCs on over 350 animals was that the TC, in combination with the audiogram, might prove to be more diagnostic of peripheral pathology than measures of pure-tone thresholds alone. We, therefore, examined the relative contribution of permanent threshold shift (PTS) and three

TC variables (i.e., $Q_{10\,dB}$, S_{LF} and S_{HF}) across the entire cochlea to the prediction of sensory cell loss within any specific octave band length of the cochlea using linear and multivariate statistical analyses.

Methods

Subjects

Three hundred and sixty-three chinchillas *(Chinchilla laniger)* were used. The animals, which varied in age from approximately 6 months to 2 years, were acquired from commercial breeders and were in good health throughout the period of study. A chronic bipolar, platinum EEG electrode with electrode lengths of 7.5 mm (probe) and 2.5 mm (ground) was implanted into the region of the inferior colliculus for single-ended recordings of the auditory evoked potential (AEP) [22, 23]. During the same surgical procedure, the left cochlea on each animal was destroyed. The animals were allowed to recover for at least 2 weeks before AEP testing began.

AEP Threshold Procedure

Hearing thresholds were estimated on each animal using the AEP. The animals were awake during testing and restrained in a yoke-like apparatus to maintain their heads in a constant position within the calibrated sound field. AEPs were collected to 20-ms tone bursts (5 ms rise/fall time) presented at a rate of 10 bursts per second. A general-purpose computer was used to acquire the evoked potential data and control the frequency, intensity and timing of the stimulus. Averaged AEPs were obtained from 250 presentations of the 20-ms signal. Each waveform was stored on disk for later analysis.

Thresholds were measured using an intensity series with 5-dB steps at octave intervals from 0.5 to 16 kHz and at the half-octave frequency of 11.2 kHz. Threshold was determined to be one half step size (2.5 dB) below the lowest intensity that showed a 'response' consistent with the responses seen at higher intensities (see Salvi et al. [24] for a discussion of objective and subjective, i.e., visual, threshold determinations). The average of at least three separate threshold determinations with standard deviations no greater than 5 dB at each frequency, obtained on different days, was used to define the preexposure audiogram. At least 30 days after the exposure ended, final audiograms were constructed using the average of three separate threshold determinations at each of the seven preexposure frequencies. Permanent threshold shift (PTS) was defined as the difference between the postexposure and preexposure thresholds at each individual test frequency.

AEP Tuning Curves

Preexposure and postexposure AEP tuning curves were collected on each chinchilla using a simultaneous masking paradigm [9, 23–25] at each octave frequency from 0.5 to 8.0 kHz and at 11.2 kHz. The probe duration was 20 ms and the intensity was set at 15 dB above the mean AEP threshold for that frequency. The continuous tone masker was increased from below the masked threshold over a 35-dB range in an intensity series similar to that used for threshold testing [i.e., at a low enough masker level a clear response was obtained; as masker intensity was increased the response either eventually disappeared (i.e., was effectively masked), or persisted until the output limitation of the instrumentation was reached (i.e., between 85–100 dB)]. Masked threshold was taken as the intensity midway between the lowest intensity where a response was present and the next highest intensity where it was absent. Table 1 presents the pure-tone masking frequencies used for each probe tone. The masker frequencies for each of the six probe tones were chosen to provide an estimate of the masking function for a broad frequency region around the probe. Masked thresholds at frequencies above and below the probe tone using AEP procedures produce an asymmetric 'V'-shaped tuning curve similar to psychophysical tuning curves [23].

Tuning Curve Analysis

Three parameters were computed for each individual tuning curve: the slopes of the tuning curve function (dB/octave) taken from the probe or characteristic frequency to the higher masking frequencies (S_{HF}) or to the lower masking frequencies (S_{LF}), and $Q_{10\,dB}$, defined as the characteristic frequency divided by the bandwidth of the tuning curve 10 dB higher than the threshold at that characteristic frequency, i.e.,

$$Q_{10\,dB} = \frac{CF}{f_2 - f_1} \qquad (1)$$

where CF is the characteristic frequency (considered to be the frequency in hertz of the lowest masked threshold on the tuning curve); f_2 and f_1 represent the frequencies at which the masking function crosses a line 10 dB higher than the threshold at CF (details of the computer-based rules for calculating slopes and Q values are described by Davis et al. [9]). Alternatively,

Table 1. Evoked-potential tuning curve probe and masker frequencies

Probe, kHz	Masker frequencies, kHz									
0.5	0.15	0.20	0.30	0.40	0.52[1]	0.60	0.65	0.75	1.30	2.20
1.0	0.15	0.20	0.40	0.55	0.80	1.05[1]	1.30	1.70	1.90	2.50
2.0	0.30	0.75	0.90	1.30	1.70	2.05[1]	2.20	3.00	3.50	4.00
4.0	0.45	1.30	2.20	3.00	3.50	4.10[1]	4.50	5.00	5.60	6.00
8.0	0.45	1.30	2.50	5.90	7.00	8.10[1]	9.30	11.00	12.70	14.00
11.2	1.00	4.00	7.00	9.00	11.00	11.50[1]	12.00	13.00	14.50	16.00

[1] Indicates the frequency used as CF for calculation of tuning curve statistics.

if the lines defined by S_{HF} and S_{LF} describe a triangle with the vertex at CF, $Q_{10\,dB}$ could be computed as:

$$Q_{10\,dB} = [2^{(10/S_{HF})} - 2^{(-10/S_{LF})}]^{-1} \qquad (2)$$

The formulae for calculating $Q_{10\,dB}$ using the definition (1) or by using the high- and low-frequency slopes (2) may yield slightly different values because of differences in the direction of error made by using regression lines with less than perfect correlations. That is, when using the definition for calculating $Q_{10\,dB}$, frequencies above and below the CF (i.e., f_1, f_2) are computed using two regression equations, and, therefore, errors of estimate will occur along the abscissa or frequency axis. Conversely, when using the high- and low-frequency slopes to compute $Q_{10\,dB}$, errors will occur along the ordinate or intensity axis. However, even though slightly different values are computed using the two different methods, the values are highly correlated and factors that affect one calculation (e.g., PTS or sensory cell loss) will be likely to affect the other. The second method for computing $Q_{10\,dB}$ will be used in the remainder of this report.

Noise Exposures

The noises to which the animals were exposed varied from very short duration, acute exposures at high intensities, to relatively long-term (5 day), low-level exposures. The noises were varied: impulse noise and impact noise comprised the majority of exposure conditions (≈ 75%), while the remainder were either continuous broad-band noise, octave band noise, or combinations of any of these classes of noise. The noise levels varied from relatively low levels of continuous noise (80 dB SPL) to very high peak intensities of impulse noise (165 dB), while the energy spectra of the noises in the majority of cases (> 95%) were confined to the 0.25- to 2.5-kHz region. The specific exposures are not detailed because, for this data analysis, noise was used simply as a vehicle for producing various patterns of cochlear damage and hearing deficits.

Histological Analysis

Following postexposure testing, each animal was anesthetized and then euthanized by decapitation and the right auditory bulla removed and opened widely (the left bulla was also removed to establish that the left cochlea was destroyed during the AEP electrode implant procedure). The cochleas were fixed with 2.5% glutaraldehyde in Veronal acetate buffer (final pH = 7.3, 605 mosm). After at least 12 h fixation, each cochlea was postfixed in 1% OsO_4 in Veronal acetate buffer, washed in buffer and dehydrated to 70% ETOH. The entire basilar membrane and stria vascularis were piecewise dissected free from their bony attachments and mounted in glycerin on glass slides for a surface preparation, light-microscopic assay of the sensory cell population [26]. Sensory cell counts which eventually yield cochleograms were performed at magnifications of ×500 using a Zeiss-Nomarski light microscope. A frequency-place map established by Eldredge et al. [27] was used to superimpose frequency coordinates on the length coordinate of the cochleogram so that audiometric data could be directly related to the sensory cell populations along the length of the cochlea. The total number and percentage of inner and outer sensory cells lost within octave band lengths of the cochlea centered at 0.125 kHz through 16 kHz in 8 octave steps were calculated.

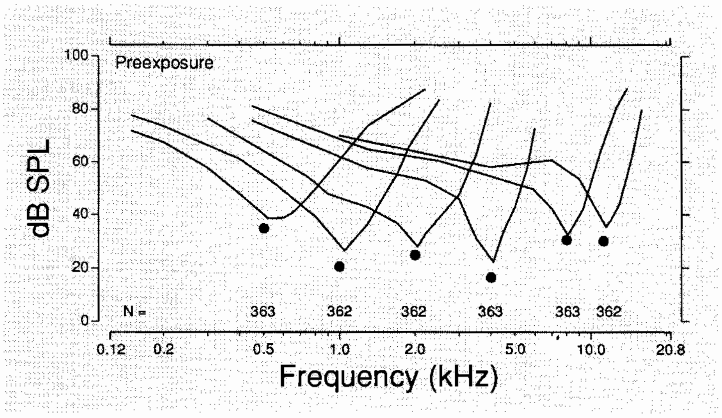

Fig. 1. Mean preexposure tuning curves for the entire experimental population at each probe frequency. N = Sample size; ● = probe tone.

Table 2. The preexposure thresholds for 363 subjects and preexposure tuning curve statistics, $Q_{10\,dB}$, computed using equations (1) and (2), high-frequency slope (S_{HF}) (dB/octave) and low-frequency slope (S_{LF}) (dB/octave)

Probe kHz	Threshold dB SPL		$Q_{10\,dB}$ (1)			$Q_{10\,dB}$ (2)			S_{HF}			S_{LF}		
	mean	s	mean	s	N	mean	s	N	mean	s	N	mean	s	N
0.5	19.8	6.0	1.561	0.701	334	1.746	0.520	347	25.9	9.4	358	24.2	7.8	362
1.0	5.5	6.5	2.458	0.941	357	2.526	0.579	360	46.7	11.9	360	27.1	8.4	362
2.0	9.8	6.7	2.828	1.668	357	2.211	0.734	349	46.4	19.2	360	22.3	12.1	361
4.0	1.3	7.6	4.315	1.725	362	4.613	1.272	361	84.3	25.2	363	52.6	19.6	363
8.0	15.6	7.2	3.836	2.000	348	3.786	1.429	336	75.4	25.0	360	38.4	22.6	361
11.2	15.1	8.5	5.306	3.778	350	4.580	1.832	348	84.6	28.9	362	52.2	30.0	361

N = Sample size; s = standard deviation.

Results

Table 2 presents the preexposure thresholds for the entire sample of 363 chinchillas. These thresholds are consistent with Miller's [28] behavioral threshold data for the chinchilla when the effects of temporal integration [29] are considered. Figure 1 illustrates the mean preexposure AEP TCs obtained on the total sample of 363 chinchillas. The ordinate and abscissa represent the intensity and frequency, respectively, of a continuous tone that just masks the probe tone which is indicated with a solid symbol. These mean TCs are similar to those reported for a subset (n = 154) of the present sample by Davis et al. [9] and the behavioral data reported by Salvi et al. [23]. Also presented in table 2 are the average values of $Q_{10\,dB}$ (computed using both formulae), S_{LF}, and S_{HF}, for the entire population of preexposure tuning curves. The values of $Q_{10\,dB}$ increase with increasing frequency, ranging from 1.56 at the 0.5 kHz probe frequency to 5.31 at 11.2 kHz. The low- and high-frequency slopes also increased as the probe signal frequency increased. The S_{LF} ranged

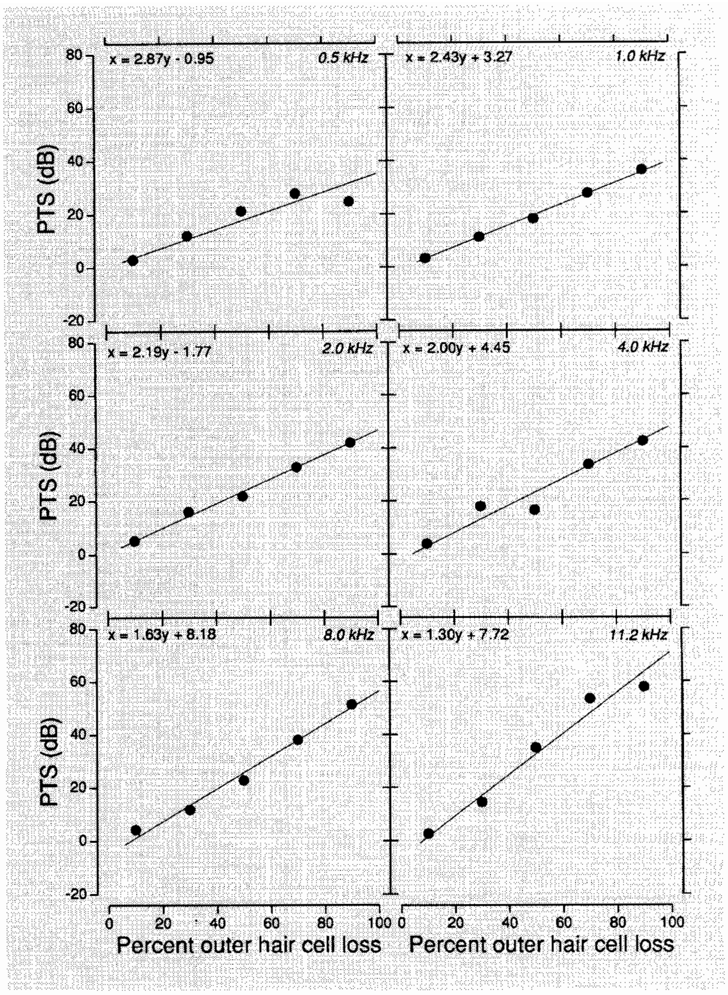

Fig. 2. Relation between PTS and %OHC loss at each probe frequency. The formula in the upper left corner of each panel is the linear regression predicting %OHC loss.

from approximately 22 to 53 dB/octave and the S_{HF} ranged from approximately 25 to 84 dB/octave.

When the PTS, cell loss and TC statistics are analyzed in the manner presented in Davis et al. [9], essentially identical results are obtained. Thus, the graphical presentation illustrating the systematic relations among PTS, cell loss and TC statistics will not be presented again in this paper. Instead, the analysis of these data focuses on the question to what extent can audiometric variables such as PTS and tuning curve statistics be used in the prediction of the status of the sensory cell population. Such an analysis may provide additional insights that are of use in the clinical setting.

To evaluate the effects of PTS on OHC losses, the %OHC losses in each octave band length of each cochlea were divided into discrete percentage bins as follows: %OHC $<20\%$; $20\% \leq$ %OHC $<40\%$; $40\% \leq$ %OHC $<60\%$; $60\% \leq$ %OHC $<80\%$; and %OHC $\geq 80\%$. The mean value of PTS corresponding

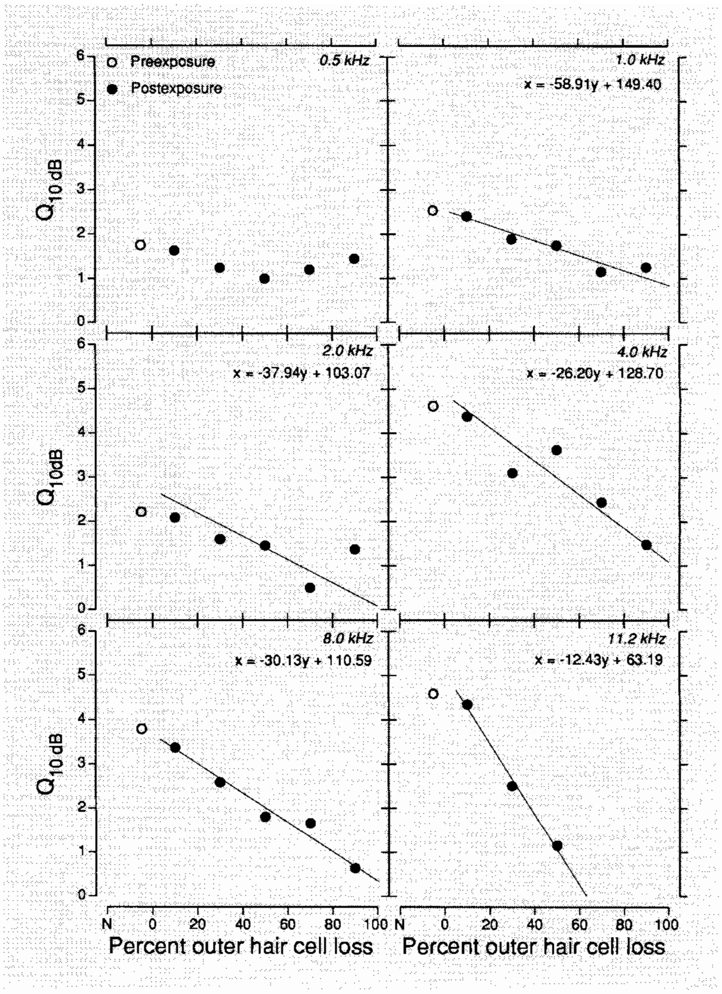

Fig. 3. Relation between $Q_{10\,dB}$ and %OHC loss at each probe frequency. The formula in the upper right corner of each panel is the linear regression predicting %OHC loss.

to the data in each of these bins was then computed. This analysis focuses upon prediction of OHC losses only and does not include predictions of IHC losses. The IHC data were omitted because the amount of IHC loss is relatively small when threshold shifts are less than about 40 dB which was the case with most of our experimental sample and can be estimated from knowledge of the OHC losses [30]. Figure 2 illustrates the results of such a categorization of the PTS and OHC data. The formulae displayed in the upper left corner of each panel describe the linear regression predicting %OHC loss from PTS for each probe frequency. These data which show a strong positive correlation at each test frequency agree with the results reported by Hamernik et al. [30] (the partitioning of the data into five bins represents a coarser analysis than that performed by Hamernik et al. [30]). In their analysis, bins representing 10 dB of PTS were formed and related to %OHC loss by an exponential function. In the present analysis, the coarser partitioning of the data results in func-

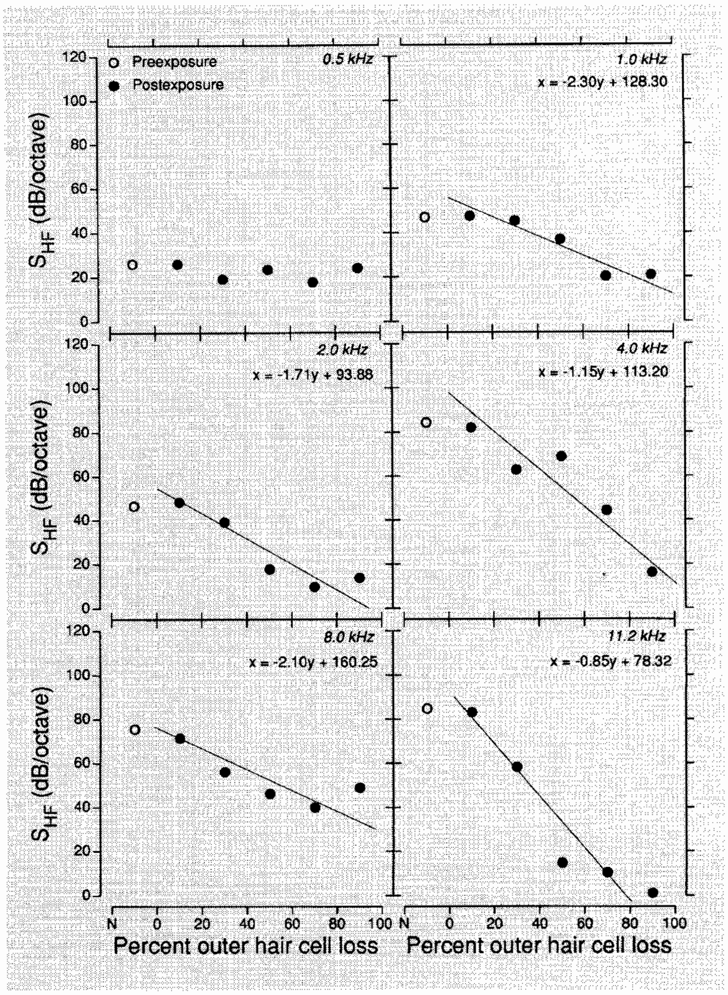

Fig. 4. Relation between S_{HF} and %OHC loss at each probe frequency. The formula in the upper right corner of each panel is the linear regression predicting %OHC loss.

tions that are adequately described by a simple linear function. It is interesting to note that the slope of the relationship between PTS and %OHC changes systematically from low to high frequencies. This observation is consistent with the results obtained by Prosen et al. [31] and Altschuler et al. [32] who suggest that low-frequency information can be processed in basal as well as apical portions of the mammalian cochlea. Thus, low-frequency thresholds which are better than expected based upon the OHC population in apically damaged cochleas may be the result of the transduction of low-frequency information in more normal basal regions of the cochlea.

Figures 3–5 illustrate the results of categorizing the $Q_{10\ dB}$, TC slope data and OHC losses similar to that performed for the OHC and PTS data. With the exception of the 0.5-kHz probe tone, each TC statistic shows a strong linear relation to %OHC loss (the $Q_{10\,dB}$ and S_{HF} data at 0.5 kHz showed little variability in the independent variable and therefore the regression line is not valid and

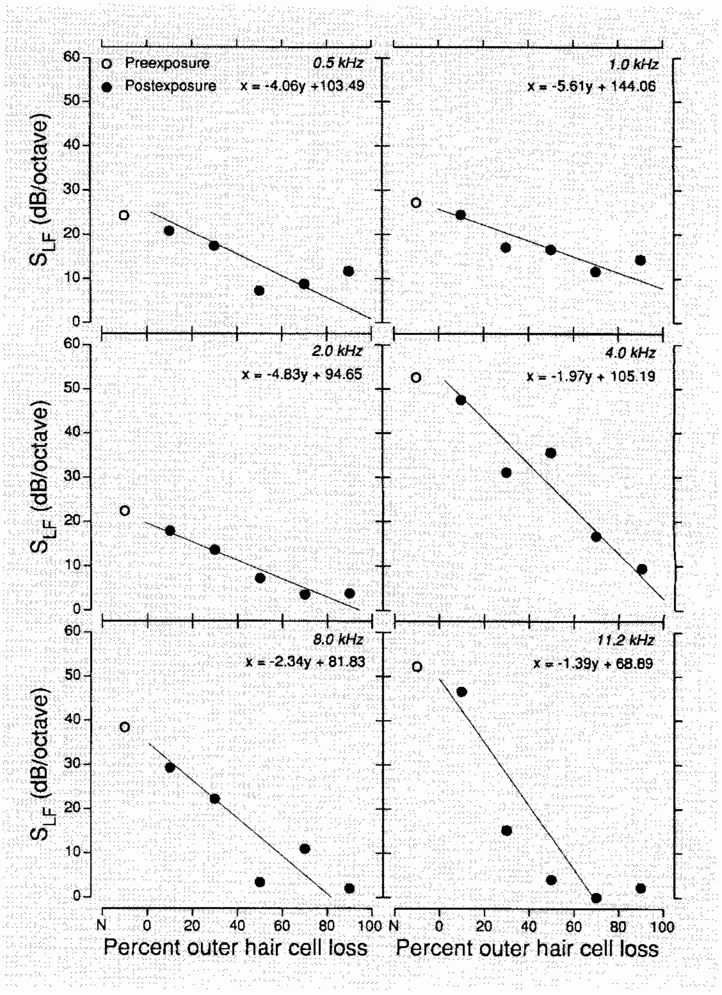

Fig. 5. Relation between S_{LF} and %OHC loss at each probe frequency. The formula in the upper right corner of each panel is the linear regression predicting %OHC loss.

thus not displayed). In general, the slopes of the regression lines predicting %OHC loss systematically increased (became less negative) with increasing probe tone frequency except at 8.0 kHz.

The traditional bivariate linear regression analyses describe the relationship between a single independent (predictor) variable and a single dependent (predicted) variable. Multiple linear regression and correlation analyses allow one to describe the relationship between a number of predictor variables and the single predicted variable. Given our multiple audiometric measures, a series of multiple regressions and correlations were performed using PTS and each of the TC metrics (e.g., $Q_{10\ dB}$, S_{HF} and S_{LF}) as predictor variables and %OHC loss as the predicted variable. Since sensory cell losses in a specific region of the basilar membrane are expected to primarily affect measures of auditory function that are determined within or very near to the damaged region, the first multiple correlations were performed using audiometric variables only at the probe tone frequency. Thus, %OHC loss in an octave band length of the cochlea was related to the PTS at that frequency alone and in combination with $Q_{10\,dB}$, or with S_{HF} and S_{LF} for the TC whose probe was at that frequency. The analyses produced measures of correlation (r) and determinance (r^2) and formulae relating the %OHC loss to the predictor variables.

Three sets of multiple regressions and correlations were performed for each probe frequency: PTS only; PTS and $Q_{10\,dB}$; and PTS, S_{HF} and S_{LF}. The regression equations predicting the %OHC loss in the octave band length of the cochlea centered at frequency f, from these three analyses are of the form:

$$\%OHC_f = b\ (PTS)_f + a \quad (3)$$
$$\%OHC_f = b_1\,(PTS)_f + b_2\,(Q_{10\,dB})_f + a_1 \quad (4)$$
$$\%OHC_f = b_3\,(PTS)_f + b_4\,(S_{HF})_f + b_5\,(S_{LF})_f + a_2 \quad (5)$$

where the b's and a's represent the regression coefficients.

While we might expect that the greatest effect on %OHC loss at a given region of the basilar membrane would be related to the PTS at the frequency transduced by that region, the amount of PTS in regions immediately adjacent to the probe frequency may also add to the predictive value provided by the PTS at the probe frequency. Therefore, a second series of three multiple correlations were performed predicting %OHC loss in a given octave band length of the cochlea from the audiometric variables at the probe and the two adjacent frequencies (i.e., an octave on either side of the probe). Thus, at the 1.0 kHz probe frequency, equation (3) would become:

$$\%OHC_{1.0} = b_6\,(PTS_{0.5}) + b_7\,(PTS_{1.0}) + b_8\,(PTS_{2.0}) + a_3 \quad (6)$$

where the b's and a_3 are the regression coefficients. Equations (4) and (5) would be similarly expanded with six and nine coefficients, respectively, and each with a constant (a_x).

Table 3. Coefficients of determinance (r^2) of % OHC loss with PTS and selected tuning curve variables

Probe kHz	f(PTS)	f(PTS $Q_{10\,dB}$)	f(PTS S_{HF}, S_{LF})
Probe tone frequency only			
0.5	(A_1) 0.43	(B_1) 0.43*	(C_1) 0.43*
1.0	0.65	0.65	0.66*
2.0	0.66	0.69*	0.68*
4.0	0.61	0.61	0.65*
8.0	0.70	0.74*	0.70
11.2	0.71	0.75*	0.72*
Probe tone and adjacent frequencies			
0.5	(A_2) 0.47	(B_2) 0.50*	(C_2) 0.48*
1.0	0.66	0.66*	0.68*
2.0	0.71	0.76*	0.73*
4.0	0.70	0.70*	0.72*
8.0	0.75	0.78*	0.76*
11.2	0.74	0.78*	0.75*
All frequencies			
0.5	(A_3) 0.49	(B_3) 0.55*	(C_3) 0.51*
1.0	0.66	0.67*	0.69*
2.0	0.72	0.79*	0.74*
4.0	0.70	0.75*	0.73*
8.0	0.75	0.81*	0.78*
11.2	0.74	0.82*	0.76*

* Significantly greater than r^2 for f(PTS).

A final series of three multiple regressions and correlations were computed predicting %OHC in a single region of the cochlea from audiometric variables at all six probe frequencies.

Table 3 presents the coefficients of determinance (r^2) for the nine analyses performed. Inspection of the table reveals that variability in PTS predicts over 60% of the variability in %OHC losses for frequencies of 1.0 kHz and above, even if only the PTS at the frequency corresponding to the octave band length at which the OHC losses occur is used (column

Table 4. Regression equations for %OHC loss with audiometric and tuning curve variables at the probe and adjacent frequencies

$\%OHC = f(PTS)$				
$\%OHC_{0.5}$ =		0.58 $PTS_{0.5}$	+ 0.54 $PTS_{1.0}$	+ 4.38
$\%OHC_{1.0}$ =	0.00 $PTS_{0.5}$	+ 1.46 $PTS_{1.0}$	+ 0.29 $PTS_{2.0}$	+ 4.57
$\%OHC_{2.0}$ =	1.01 $PTS_{1.0}$	+ 0.88 $PTS_{2.0}$	+ 0.00 $PTS_{4.0}$	+ 1.70
$\%OHC_{4.0}$ =	0.86 $PTS_{2.0}$	+ 0.63 $PTS_{4.0}$	+ 0.19 $PTS_{8.0}$	+ 0.34
$\%OHC_{8.0}$ =	0.42 $PTS_{4.0}$	+ 0.63 $PTS_{8.0}$	+ 0.47 $PTS_{11.2}$	+ 0.05
$\%OHC_{11.2}$ =	0.48 $PTS_{8.0}$	+ 0.74 $PTS_{11.2}$		+ 0.39
$\%OHC = f(PTS, Q_{10\ dB})$				
$\%OHC_{0.5}$ =	0.59 $PTS_{0.5}$	+ 0.40 $PTS_{1.0}$	+	
	–0.42 $Q_{0.5}$	+ 0.26 $Q_{0.5}$		+ 5.05
$\%OHC_{1.0}$ =	0.00 $PTS_{0.5}$	+ 1.47 $PTS_{1.0}$	+ 0.30 $PTS_{2.0}$	+
	0.00 $Q_{0.5}$	+–0.32 $Q_{1.0}$	+ 0.00 $Q_{2.0}$	+ 5.17
$\%OHC_{2.0}$ =	1.07 $PTS_{1.0}$	+ 0.42 $PTS_{2.0}$	+ 0.00 $PTS_{4.0}$	+
	–0.59 $Q_{1.0}$	+ 0.77 $Q_{2.0}$	+–0.18 $Q_{4.0}$	+ 4.80
$\%OHC_{4.0}$ =	0.68 $PTS_{2.0}$	+ 0.70 $PTS_{4.0}$	+ 0.00 $PTS_{8.0}$	+
	0.25 $Q_{2.0}$	+ 0.00 $Q_{4.0}$	+ 0.00 $Q_{8.0}$	+ 1.41
$\%OHC_{8.0}$ =	0.43 $PTS_{4.0}$	+ 0.46 $PTS_{8.0}$	+ 0.33 $PTS_{11.2}$	+
	–0.29 $Q_{4.0}$	+ 0.48 $Q_{8.0}$	+ 0.00 $Q_{11.2}$	+ 0.23
$\%OHC_{11.2}$ =	0.42 $PTS_{8.0}$	+ 0.49 $PTS_{11.2}$	+	
	0.18 $Q_{8.0}$	+ 0.25 $Q_{11.2}$		+–1.02

A_1). Adding the information from adjacent frequencies increases this percentage by one to nine percent (column A_1 vs. A_2), while adding the rest of the audiometric frequencies results in no or very low increases in predictability over the probe and adjacent frequency analyses (column A_2 vs. A_3).

When %OHC loss is predicted as a function of PTS and $Q_{10\ dB}$ or PTS and TC slopes, r^2 is significantly increased relative to PTS alone for many of the analyses. In general, the %OHC loss predicted by PTS and $Q_{10\ dB}$ (columns A_2, B_2, C_2) is greater than that predicted by either PTS alone or PTS and the slopes. The regression coefficients in the form of equation (6) for each probe frequency for the analyses using the PTS and $Q_{10\ dB}$ measures at the probe and adjacent frequencies are presented in table 4. These regression coefficients were obtained from a stepwise multiple regression (SPSS release 4) of %OHC loss as a function of PTS and $Q_{10\ dB}$. The probability of putting a factor into the regression was set at 0.15 and the probability for removing a factor was set at 0.20 [33]. The increase in r^2 which results from including either additional variables (i.e., tuning curve statistics) or additional frequencies, suggests that the multiple correlations using PTS and $Q_{10\ dB}$ at the probe and adjacent frequencies should be the analysis of choice. This conclusion is based on the fact that (1) the PTS and $Q_{10\ dB}$ analysis r^2 values are usually higher than either the PTS alone or PTS and slope values; and (2) the change in r^2 from adding the adjacent variables is almost always greater than the additional change obtained by including the rest of the audiometric frequencies.

Discussion

Unlike most of the currently available studies which have involved relatively few experimental animals, we expected that if a large sample of TCs from normal and damaged ears could be assembled, this data base would provide a means of predicting the status of the sensory elements of the cochlea (e.g., OHC loss) from measures of auditory threshold and tuning. The results presented in this paper show a systematic relation between the amount of OHC loss, PTS and the variables which define tuning. Detectable changes in the status of the OHC population corresponding to a given probe frequency can best be predicted by using the PTS and $Q_{10\,dB}$ determined at the probe frequency and at probe frequencies immediately above and below the given frequency. Information provided by the slopes of the TC do not strengthen the prediction provided by PTS and $Q_{10\,dB}$, and are not as good a predictor in conjunction with PTS. However, measures of PTS alone can provide a reasonably good indication of the amount of OHC loss at the probe frequency corresponding to the octave band region of the cochlea that manifests the damage, and adding PTS predictors for frequencies adjacent to the probe frequency significantly improves the predictions (table 3).

Using the regression factors calculated from the various multiple regression analyses, one may obtain several estimates of the OHC population on the basis of the audiogram alone. However, the statistical approach used to estimate OHC losses should provide estimates of pathology that are consistent with current knowledge of noise-induced hearing loss and the effects of cochlear pathologies in general. For example, if a single frequency, f_1, exhibits an elevated threshold and the remaining frequencies are normal, the OHC losses will most likely be less in the affected octave band length of the cochlea than when the same elevated threshold at f_1 is combined with severely elevated thresholds at adjacent frequencies or throughout the cochlea. Similarly, the 'edges' of a lesion can affect adjacent normal regions of the cochlea and these effects can be different depending upon whether the normal region is apical or basalward of the loss. The following two hypothetical cases provide simple examples illustrating the differences in the estimates of OHC loss when the assumption of octave band independence is used in the statistical analysis and when independence is not assumed. These examples also highlight the basic conclusions resulting from the statistical analysis.

The insert in the top panel of figure 6 illustrates a hypothetical audiogram with a 25-dB hearing loss at 4 kHz and essentially normal hearing (5 dB HL) at all other test frequencies. The %OHC losses for this hypothetical subject shown in figure 6 were calculated using the regression equations shown in tables 4 and 5. The upper panel displays the predicted %OHC loss using PTS measures alone while the bottom panel illustrates the predictions based on using PTS and $Q_{10\,dB}$ measures. Within each panel, predictions of %OHC loss were made using the audiometric measures and the appropriate regression equations at the probe frequency only (solid bars; regression equations in table 5), at the probe and adjacent frequencies (open bars; regression equations in table 4) or at all audiometric frequencies (shaded bars). As previously noted, the estimates of %OHC loss using the probe and adjacent frequency measures as predictors accounted for up to 78% of the variability in %OHC loss and that including all audiometric frequencies added little to the predictions (table 3). An inspection of figure 6 reveals that there are, in fact, only slight differences between the predictions based on audiometric data from the probe and adjacent

Table 5. Regression equations for %OHC loss with audiometric and tuning curve variables at the probe frequency only

$\%OHC = f(PTS)$

$\%OHC_{0.5} = 1.22\ PTS_{0.5} + 5.79$
$\%OHC_{1.0} = 1.75\ PTS_{1.0} + 5.44$
$\%OHC_{2.0} = 1.64\ PTS_{2.0} + 1.92$
$\%OHC_{4.0} = 1.48\ PTS_{4.0} + 4.19$
$\%OHC_{8.0} = 1.42\ PTS_{8.0} + 0.62$
$\%OHC_{11.2} = 1.14\ PTS_{11.2} + 1.94$

$\%OHC = f(PTS, Q_{10\ dB})$

$\%OHC_{0.5} = 1.23\ PTS_{0.5} + -0.20\ Q_{0.5} + 6.15$
$\%OHC_{1.0} = 1.75\ PTS_{1.0} + 0.00\ Q_{1.0} + 5.44$
$\%OHC_{2.0} = 1.26\ PTS_{2.0} + 0.39\ Q_{2.0} + 3.29$
$\%OHC_{4.0} = 1.48\ PTS_{4.0} + 0.00\ Q_{4.0} + 4.19$
$\%OHC_{8.0} = 1.05\ PTS_{8.0} + 0.44\ Q_{8.0} + 0.19$
$\%OHC_{11.2} = 0.91\ PTS_{11.2} + 0.35\ Q_{11.2} + 0.46$

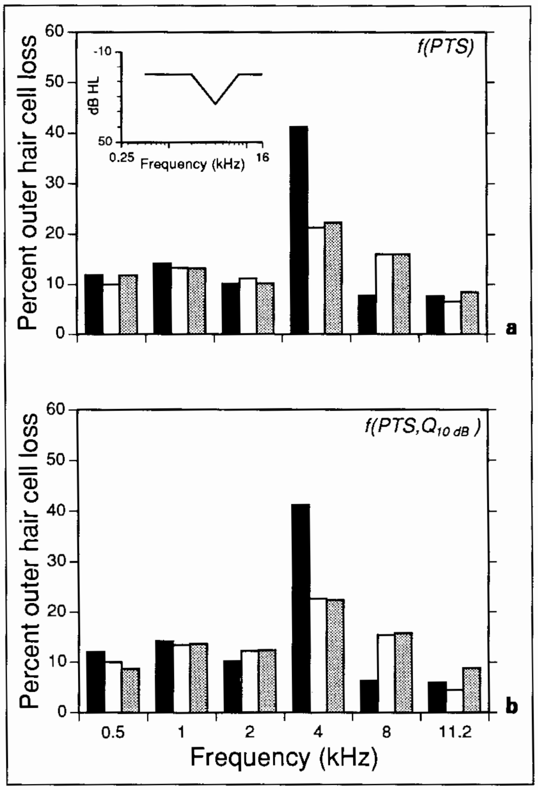

Fig. 6. Predicted %OHC loss for a hypothetical hearing loss (**a**) based on the regression coefficients for probe frequency only (solid bars), probe and adjacent frequencies (open bars) and all frequencies (shaded bars). **a** Predictions based on PTS. **b** Predictions based on PTS and $Q_{10\ dB}$.

frequencies and those based on data from all of the audiometric frequencies (open versus shaded bars). Therefore, the regression equations obtained from the multiple linear regression using all audiometric frequencies are not presented. Also evident in this example is that the use of the $Q_{10\ dB}$ metric did not appreciably alter estimates of the pathology (upper versus lower panels).

The predictions based on the probe frequency alone (solid bars) assume that all of the octave bands along the cochlea are independent and, therefore, any damage or lesion in an octave-band region has no effect on, nor is affected by, the function of adjacent locations. Based on our knowledge of cochlear mechanics, it is clear that this assumption is not valid. Rather, it is more likely that sensory cell predictions for one region of the cochlea will be influenced by the status of adjacent regions. The subject depicted in figure 6 has an appreciable hearing loss at a single test frequency (4 kHz) with 'normal' hearing at all other frequencies. The assumption of independence among octave band lengths of the cochlea leads to a prediction of approximately 41% OHC loss. However, a restricted single-frequency hearing loss of this type might lead one to suspect a relatively localized and low-level sensory cell loss. The effect of including measures from the adjacent audiometric frequencies is to reduce the estimate of OHC loss from 41 to 21%.

The region of loss may also extend into adjacent octave band regions which are associ-

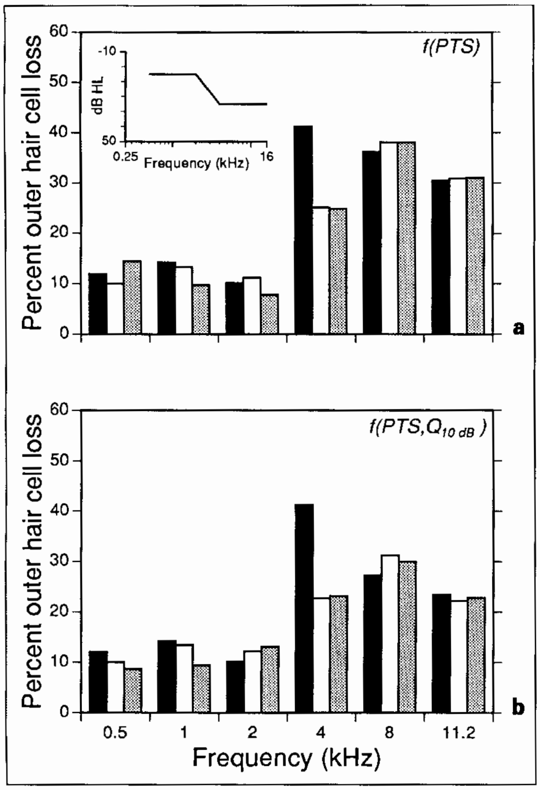

Fig. 7. Predicted %OHC loss for a hypothetical hearing loss (**a**) based on the regression coefficients for probe frequency only (solid bars), probe and adjacent frequencies (open bars) and all frequencies (shaded bars). **a** Predictions based on PTS. **b** Predictions based on PTS and $Q_{10\,dB}$.

ated with normal hearing. If the loss is sufficiently small, thresholds may not be shifted as in this chosen example. The predictions illustrated in figure 6 using the adjacent bands show an increased estimate of OHC loss in the octave band basalward (8 kHz) of the hearing loss from less than 8% to approximately 16%. An increase in predicted OHC loss did not occur in the octave band length apical to the lesion, a result that might be anticipated based upon our knowledge of the envelope of the traveling wave. Thus, relative to the location of the focal lesion, basal as opposed to apical sensory cells, should be either more adversely affected or the mechanical input to these cells altered. Thus, the assumption of independence among octave band lengths of the cochlea may result in two errors: (1) overestimating the OHC loss in a region showing impaired hearing but which is adjacent to normal hearing regions, or (2) underestimating the loss in a normal-hearing region when that region is adjacent to regions with appreciable threshold shifts.

Figure 7 depicts an audiogram showing 25-dB hearing losses in the high-frequency (4.0–11.2 kHz) range with 'normal' thresholds (5 dB PTS) at the lower frequencies along with the estimated OHC losses associated with such a high-frequency hearing loss estimated using the same approach as in the previous example. When adjacent frequencies are added to the analysis, estimates of OHC loss in the octave band length at the low frequency edge of the hearing loss (4 kHz) are reduced from approximately 41 to 25%. Adding adjacent frequencies to the analysis of the octave band region immediately apical to the hearing loss (2 kHz) had no appreciable effect on OHC loss predictions. While in the 8-kHz octave band, the presence of hearing threshold shifts on either side result in OHC loss estimates that are similar regardless which statistical approach is used. However, unlike the previous example including $Q_{10\,dB}$ in the analysis leads to predictions of loss that are 8–10% less within the region affected by the threshold shifts.

In conclusion, the results of this population study suggest that the information derived from the TC contributes relatively little to the prediction of OHC loss resulting from noise exposure. The relatively small increases in r^2 provided by TC variables (approximately 1–9%), suggests that PTS alone can serve as a reasonably reliable indicator of cochlear damage (OHC loss) provided that the effects of thresholds at adjacent frequencies are also considered. However, despite the above conclusion, there are situations in which subjects with relatively little or no hearing loss show distinct changes in TC metrics that provide audiometric evidence for noise-induced sensory cell loss [17].

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Animal Use

In conducting the research described in this manuscript, the investigators adhered to the *Guide for the Care and Use of Laboratory Animals* prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council [DHHS Publication No. (NIH) 86-23, revised 1985].

Intérêt de la mesure des seuils audiométriques et des courbes d'accord pour évaluer la destruction des cellules sensorielles

Chez 363 chinchillas, des courbes d'accord dérivées de la mesure des potentiels évoqués auditifs au moyen d'une technique de masquage simultané ont été établies à six fréquences avant et 30 jours après différentes expositions sonores. Des analyses statistiques classiques – régression et corrélation entre deux ou plusieurs variables – ont été conduites afin de déterminer jusqu'à quel point les lésions des cellules sensorielles pouvaient être évaluées à partir de la mesure des seuils audiométriques et de certains paramètres des courbes d'accord. Les résultats font apparaître de fortes corrélations d'une part entre le pourcentage des cellules ciliées externes détruites (%OHC) et les pertes auditives et, d'autre part, entre ce même pourcentage et les modifications du facteur de qualité ($Q_{10\,dB}$) ainsi que des valeurs des pentes aux hautes et basses fréquences des courbes d'accord (S_{HF}, S_{LF}). Les corrélations les plus élevées s'établissent entre les pertes auditives et la destruction cellulaire (%OHC). Cependant, la valeur du coefficient de corrélation (r^2) entre la destruction cellulaire et les variables prédictives (pertes auditives par exemple) pourrait être améliorée significativement en prenant en compte le facteur de qualité ($Q_{10\,dB}$) de la courbe d'accord dont la fréquence test est centrée dans la bande d'octave de la cochlée correspondant à la fréquence à laquelle surviennent les pertes auditives. La valeur de ce coefficient (r^2) pourrait encore être augmentée en considérant certains paramètres des seuils audiométriques et des courbes d'accord à des fréquences adjacentes à la bande d'octave étudiée.

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