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Research paper

Accuracy of velocity distortion product otoacoustic emissions for estimating mechanically based hearing loss

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ABSTRACT

Distortion product otoacoustic emissions (DPOAEs) measured as vibration of the human eardrum have been successfully used to estimate hearing threshold. The estimates have proved more accurate than similar methods using sound-pressure DPOAEs. Nevertheless, the estimation accuracy of the new technique might have been influenced by endogenous noise, such as heart beat, breathing and swallowing. Here, we investigate in an animal model to what extent the accuracy of the threshold estimation technique using velocity-DPOAEs might be improved by reducing noise sources.

Velocity-DPOAE I/O functions were measured in normal and hearing-impaired anaesthetized guinea pigs. Hearing loss was either conductive or induced by furosemide injection.

The estimated distortion product threshold (EDPT) obtained by extrapolation of the I/O function to the abscissa was found to linearly correlate with the compound action potential threshold at the f_2 frequency, provided that furosemide data were excluded. The standard deviation of the linear regression fit was 6 dB as opposed to 8 dB in humans, suggesting that this accuracy should be achievable in humans with appropriate improvement of signal-to-noise ratio. For the furosemide animals, the CAP threshold relative to the regression line provided an estimate of the functional loss of the inner hair cell system.

For mechanical losses in the middle ear and/or cochlear amplifier, DPOAEs measured as velocity of the umbo promise an accuracy of hearing threshold estimation comparable to classical audiometry.

1. Introduction

Distortion product otoacoustic emissions (DPOAE) are sound-pressure signals recorded in the ear canal, but generated in the cochlea when stimulating simultaneously with two continuous tones of frequencies f_1 and f_2 ($f_1 < f_2$). They result from nonlinear interaction of the two tones in the cochlea (Kemp, 1979), near the characteristic place of the f_2 frequency on the basilar membrane (Robles et al., 1991). In mammals, the strongest intermodulation distortion product occurs at the cubic difference frequency, $2f_1 - f_2$, and represents to date the most widely studied DPOAE (Lonsbury-Martin and Martin, 1990; Probst et al., 1991; Shera, 2004). Responsible for the generation of the DPOAE is mechanical nonlinearity in the cochlea (Kemp, 1978), specifically, in the mechanoelectrical transduction channels of the stereocilia of the outer hair cells (OHCs) (Frank and Kössl, 1996, 1997). Electromechanical force produced in response to the OHC receptor potential (Dallos, 1992), and perhaps also current (Martin and Hudspeth, 1999; Kennedy et al., 2006), appears to be the basis of cochlear amplification. Should the cochlear amplifier be damaged, for example by diseases, aging, ototoxic therapy or sound overexposure, the result is sensorineural hearing loss and the decrease or absence of the DPOAEs (Probst and Hauser, 1990; Gorga et al., 1993; Kummer et al., 1998; Kemp, 2002). Consequently, the importance of the DPOAE lies in diagnosing objectively and non-invasively the functional state of the cochlear amplifier. Nevertheless, the clinical application of the DPOAE is still limited to a dichotomous decision as to whether the cochlea is normal or impaired. Several studies have attempted to extend the application of DPOAE beyond this categorisation, especially in the direction of hearing threshold estimation. Some of these studies examined the correlation between DPOAE level or its signal-to-noise ratio (SNR) and hearing threshold in humans (Probst and Hauser, 1990; Lonsbury-Martin and Martin, 1990;

Abbreviations: ABR, auditory brainstem response; CAP, compound action potential; DPOAE, distortion product otoacoustic emission; EDPT, estimated distortion product threshold; EP, endocochlear potential; IHC, inner hair cell; I/O function, input/output function; LDV, laser Doppler vibrometer; ME, middle-ear effusion; OCF, ossicular chain fixation; OHC, outer hair cell; SD, standard deviation; SNR, signal-to-noise ratio; TM, tympanic membrane; V_{DP}, velocity of the vibration-DPOAE; V_2, velocity of the stimulus at the f_2 frequency; v-EDPT, estimated velocity distortion product threshold

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Martin et al., 1990; Kimberley et al., 1994; Gorga et al., 1993; Kummer et al., 1998; Janssen et al., 1998) and animals (Le Calvez et al., 1998). They provided scatter plots and/or the correlation coefficient between the two variables, but none quantified the accuracy of the hearing threshold estimate. Other studies investigated the relationship of DPOAE threshold to auditory threshold (Martin et al., 1990; Nelson and Kimberley, 1992; Kimberley and Nelson, 1989), but again did not quantify the accuracy of the threshold estimate.

Recently, Boege and Janssen (2002) proposed an elegant method to predict thresholds in humans based on individual DPOAE input–output (I/O) functions. In this approach, the I/O functions were measured using a primary-level separation chosen according to the scissor paradigm (Kummer et al., 1998, 2000): $L_1 = 0.4L_2 + 39$ dB SPL, with L_2 between 25 and 65 dB SPL. Such a primary-level setting generates approximately equal velocities for f_1 and f_2 on the basilar membrane near the characteristic place of f_2 and has the advantage of yielding higher DPOAE amplitudes at low and moderate stimulation levels compared with paradigms using a fixed level difference between the primaries. The I/O functions measured using this paradigm presented a linear dependency of the DPOAE sound pressure (in μPa) on the primary-level L_2 (in dB SPL). When the linear regression fit to the I/O function satisfied certain inclusion criteria (regarding the quality of the fit), extrapolation of the regression line to the L_2 axis delivered the so-called estimated distortion product threshold (EDPT). The EDPT represents the value of L_2 for which the sound pressure of the DPOAE is equal to zero, and was found to be well-correlated with the hearing threshold at f_2 (correlation coefficient = 0.65–0.83; Boege and Janssen, 2002; Gorga et al., 2003). Despite its success, the method did not allow estimation of the DPOAE threshold in about 30% of the I/O functions, simply because these I/O functions did not satisfy the inclusion criteria. Moreover, the standard deviation of the threshold estimate was as high as 10.9 dB. Such statistical uncertainty can lead to an individual error in the threshold estimate of up to 40 dB (Schmuziger et al., 2006). Partly responsible for the limited performance of the method might be calibration errors of the closed sound field and the so-called fine-structure of the DPOAE. Moreover, the accuracy will depend on the relative amounts of neural and mechanical damage (Kemp, 2002).

More recently, it has been demonstrated in humans (Dalhoff et al., 2007; Turcanu et al., 2007) that, when DPOAEs are measured as vibrations of the umbo, the accuracy of the threshold estimation method proposed by Boege and Janssen (2002) is increased. The vibration DPOAEs, called velocity-DPOAEs (V_{DP}), presented I/O functions demonstrating the same behaviour as the acoustically measured functions, i.e. V_{DP} was directly proportional to the logarithm of the velocity of the second primary (Dalhoff et al., 2007). Similarly, extrapolation of the regression line fitted to the I/O function yielded the EDPT, which provided an estimate of the hearing threshold with a standard deviation of 8.6 dB. Nevertheless, vibration measurements of the DPOAE on the human eardrum (found to be in the range of some picometers) might have been influenced by extraneous noise such as heart beat, breathing and swallowing (in the range of micrometers) and needed longer averaging times than the acoustic measurements.

In order to investigate to what extent the accuracy of the DPOAE threshold estimation technique might be improved by reducing extraneous noise, an animal model was investigated in the present study. The main advantage of the animal model resides in the possibility of reducing extraneous noise by fixing the head of the animal. An additional advantage is that the reference threshold can be more accurately determined and also readily manipulated. Guinea pig was chosen as the experimental model because a scissor paradigm has already been developed for this animal (Michaelis et al., 2004) and because of extensive evidence that their DPOAE generation mechanism is similar to that of humans (Withnell et al., 2003). Both normal-hearing and hearing-impaired animals were included, without attempting to build groups of pathologies, but rather to incorporate hearing losses of different degrees.

2. Material and methods

2.1. Animals

The study included 19 guinea pigs from our breeding house. Because of our interest in testing the accuracy of the threshold estimation method, in addition to young normal-hearing animals, we included animals presenting hearing impairment of various aetiologies and severities. The hearing-impaired animals derived either from acute experiments with normal-hearing animals or were selected from aged breeding pairs. Efforts were made to obtain animals with thresholds spanning a relatively wide region of 0–50 dB SPL, rather than just well-defined groups of impairments.

Ten animals (350–650 g) were normal-hearing, as indicated by the presence of Preyer's reflex and normal thresholds of the compound action potential (CAP). After completing the umbo vibration measurements, 8 of these animals were hearing-impaired using furosemide and the vibration responses re-measured. Furosemide was injected intraperitoneally (ip.) in 6 animals (90–140 mg/kg) and intravenously (iv.) in 2 animals (80 mg/kg).

In 4 animals (300–650 g) with a Preyer's reflex, a middle-ear effusion (ME) was simulated by allowing condensate formed on the CAP electrode, due to the closed-bulla humidity, to flow onto the posterior quadrants of the eardrum. Condensation was induced by not warming the CAP electrode before its positioning on the round-window membrane (see Section 2.2). Approximately 40–70% of the medial surface of the eardrum was covered by the fluid.

Five animals (880–1170 g) without a Preyer's reflex were selected from our aged breeding pairs (age = 1–3 years). Elevated CAP thresholds and reduced mobility of the ossicular chain, ascertained by *post-mortem* instrumental palpation, suggested that these animals suffered conductive hearing loss due to ossicular chain fixation (OCF).

2.2. Surgical preparation

Animals were premedicated with atropine-sulphate (0.25 mg/kg) and anaesthetised with a mixture of ketamine hydrochloride (Ketavet; 50 mg/kg) and xylazine (Rompun; 8 mg/kg). Anaesthesia was maintained by intraperitoneal administration of full doses every hour or when indicated by the presence of the paw withdrawal reflex. Rectal temperature was maintained at 38.5 ± 0.5 °C using a thermostatically controlled heating blanket.

Animals were placed in a prone position. The bone on the vertex was exposed and a head-holder was glued to the skull with dental cement to reduce extraneous movement of the head due to heart beating and breathing. The left pinna and outer portion of the external ear canal were removed up to the level of the bony part of the external ear canal. Using an ENT-operational microscope (OPMI ORL, Carl Zeiss AG, Oberkochen, Germany), the remnant external ear canal was cleaned and the eardrum was examined to ensure its normality. The bulla was opened by a retroauricular approach. The small opening (1–2 mm) served for placing the CAP electrode on the round window and for placing a ventilation tube (0.5 mm ID × 70 mm long) in the bulla to ensure pressure equalization between the middle ear and the environment. The remnant bulla opening was sealed with dental cement. The CAP electrode was warmed to body temperature prior to positioning on the round-window membrane (except in ME animals; see Section 2.1). The tip of an ER-7C probe-microphone tube (Etymotic