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Acute endolymphatic hydrops

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Chapter 4

Effects of acute inner ear pressure changes on low-level distortion product otoacoustic emissions in the guinea pig

Valk WL, Wit HP, Albers FWJ.
Effects of acute inner ear pressure changes
on low-level distortion product otoacoustic emissions in the guinea pig.
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Introduction

As inner ear pressure and volume regulation are requisites for normal inner ear function, inner ear pressure changes are believed to be a primary factor contributing to cochleovestibular disturbances. For example, a decrease in perilymphatic pressure might be responsible for the often acute reversible sensorineural hearing loss in perilymphatic fistulas. Opposite, an endolymphatic hydrops, accompanied by an increased inner ear pressure, is generally believed to be the histopathological substrate in Menière's disease (Hallpike and Cairns, 1938). Further, increased intracranial pressures are associated with increased perilymphatic pressures since the perilymphatic space is linked to the subarachnoid space via the cochlear aqueduct. This structure is the main route for inner ear pressure equalisation (Carlborg et al., 1992). When inner ear fluid pressure is suddenly changed, pressure equalisation takes place within seconds (Wit et al., 1999). During activities like coughing, sneezing or changing posture perilymphatic pressure may undergo substantial fluctuations up to 10 mm Hg.

In the guinea pig, when pressure variation is in the normal physiological range, this does not influence cochlear function measured by compound action potentials (Böhmer, 1993). However, when pressure is changed pathologically, this might cause changes in cochlear function measured by low-level distortion product otoacoustic emissions (DPOAE). DPOAEs are measured in the external ear canal and describe responses that the cochlea generates in the form of acoustic energy (Kemp, 1978). Nowadays, these otoacoustic emissions are widely accepted to reflect the integrity of cochlear mechanical processes in general, and outer hair cell (OHC) function in particular (Kim, 1986). Through their association with OHCs and their sensitivity to environmental factors, DPOAEs are now frequently used to monitor cochlear function in experimental models of hearing loss. The $2f_1$-f_2 -product is the most prominent DPOAE which is decreased in outer hair cell pathology, induced by for example ototoxic drugs (Shi and Martin, 1997) or acoustic overstimulation (Emmerich et al., 2000). In addition, human otoacoustic emissions are proved to be very sensitive to modifications of intracranial pressure (de Kleine et al., 2000).

In a previous study an acute endolymphatic hydrops was created by injection of artificial endolymph into scala media in the guinea pig. When an acute endolymphatic hydrops was created, the inner ear pressure level increased by 22 Pa and resulted in a reversible drop in $2f_1$-f_2 -DPOAE of 2.6 dB (Valk et al., 2004). The precise mechanism of cochlear function change in these experiments prompted further investigation. In this study, by rapidly changing perilymph volume in scala tympani, inner ear pressure is changed without disturbing endolymph (Salt and DeMott, 1998). In this way, a relation between acute inner ear pressure changes and cochlear function measured by low-level $2f_1$-f_2 -DPOAEs might be found. This could gain insight into pathophysiological mechanisms in pathological pressure changes, as seen in Menière's disease and perilymphatic fistulas.

Materials and methods

Experiments were performed in 8 female albino guinea pigs (Harlan, The Netherlands; body weight 350-450g) with a positive Preyer reflex and a $2f_1$-f_2 -DPOAE of at least 10 dB above noise floor. Sequential artificial perilymph injections and perilymph aspirations were performed solely or alternately in one or both ears. Animal care and use were in accordance with the principles of the declaration of Helsinki and approved by the Groningen animal experiment committee (protocol number 2964).

General anesthesia was induced by intramuscular administration of ketamine/xylazine (60/3.5 mg/kg). Maintenance doses of the anesthetic were administered every hour. Muscle relaxation was obtained with succinylcholine (2.5 mg/kg). The animals were artificially ventilated through a tracheostoma (Columbus Instruments, model 7950) and body temperature was maintained at 38 _C with a heating blanket. The heart rate was monitored with a pair of skin electrodes placed on both sides of the thorax. The animal's head was kept in a stationary position by means of a steel bolt fixed to the skull with dental cement. Following a retroauriculair incision, the bulla and external auditory canal were exposed. Subsequently, the bulla was opened, equalizing middle ear pressure to normal air pressure (Zhang and Abbas, 1997) and exposing the round window. During the experiment the distortion product otoacoustic emissions were continuously measured using an Etymotic ER-10C DPOAE probe system. The ER-10C probe, consisting of two sound delivery tubes and a microphone port, was directly connected and fixated to a custom made conical connecting tube which was placed air-tight into the external auditory canal of the guinea pig. The two primary frequencies (f_1,f_2), evoking the $2f_1$-f_2 -distortion product, were generated by two separate oscillators (HP 4204A). After attenuation, the signals were delivered to the Etymotic ER-10C DPOAE probe system. The two primary frequencies were set at 6 kHz (f_1) and 7.5 kHz (f_2), f_2/f_1 -ratio = 1.25, with intensities set at respectively 65 dB SPL (L_1) and 55 dB SPL (L_2). The sound system was calibrated for the primary frequencies with a 0.1 cm^3 coupler connected to a Brüel & Kjær type 2636 half inch microphone. The probe microphone signal was amplified (20 dB), passed a custom made 1.5 kHz high pass filter and was subsequently displayed on a dynamic spectrum analyzer (R9211A Advantest). The noise floor in the 4.5 kHz region averaged to approximately 0 dB SPL. The probe microphone signal was also routed via a SRS dual channel low pass filter (SR640) to a lock-in amplifier (SRS, model SR830 DSP). The lock-in amplifier displayed the amplitude and phase of the DPOAE. It was referenced to an electronic $2f_1$-f_2 -distortion product derived from the original primaries. The production of this reference electronic $2f_1$-f_2 signal was performed by two multipliers (AD532JH) in series with subsequent filtering and amplification of the signal.

Through the exposed round window membrane, the tip of a double-barreled micropipette was inserted into scala tympani. The double-barreled micropipettes were drawn from borosilicate glass (1.5/0.84 mm diameter per barrel) and the tips were bevelled (Narishige EG-40). Tip diameters were around 30-35 µm per barrel, which is a compromise between a low enough flow resistance for fluid injection and tip smallness. One barrel of the pipette was used to measure inner ear pressure and DC potential (WPI 900A micropressure system). Through the other barrel, artificial perilymph (Salt and DeMott, 1998) was injected with a constant flow rate, by applying a controlable pneumatic pressure to the barrel end (WPI PV830 Pneumatic PicoPump). The injected volume

was measured as the displacement of the fluid meniscus in the pipette, for which the inner diameter is precisely known (0.84 mm). The fluid injection rate was calculated as the total injected volume divided by the total injection time. As injection and/or aspiration time and repetition rate were controlled with a precision electronic timer (Stanford DG 535), subsequent pressure profiles could be averaged to improve the sensitivity of the measuring method. Different volume manipulations were performed, all with a rate of 50 nl/s; injection of artificial perilymph during 10 s, aspiration of perilymph during 10 s and alternate injection and aspiration both lasting 10 s. Measurement series consisted typically of 20 repetitions with a period duration of 50 s for injection or aspiration only and of 20 s for alternate injection and aspiration. During an experiment National Instruments LabVIEW® was used for data acquisition with a storage rate of 2/s. The recorded output signals were amplitude and phase of the $2f_1$-f_2 -DPOAE, DC potential and inner ear pressure. The latter was stored after low pass filtering with a cut-off frequency of 5 Hz. Averaging of relevant portions of the obtained recordings and correction of pressure recordings for small linear drift were performed off-line with an appropriate software package.

Results

Succesful experiments were performed in all guinea pigs (n=8). In 6 guinea pigs, after prolonged experiments on one ear, the physical condition allowed further experiments on the other ear. Repeated sequences of injection (n=8), aspiration (n=8) and alternate injection and aspiration (n=6) were carried out, all with a rate of 50 nl/s.

The mean steady state inner ear pressure measured prior to manipulation of perilymph volume was around 200 Pa. The $2f_1$-f_2 -DPOAE amplitude in the different guinea pigs and different ears prior to the experiments, covered a wide range: 12-26 dB SPL.

In figure 1a the averaged recorded inner ear pressure, $2f_1$-f_2 -amplitude and -phase changes during and after injection of 0.5 µl of artificial perilymph are shown. At the start of injection the mean pressure increased to an approximately 520 Pa higher stable level within seconds. After 10 s, when injection was stopped, the pressure immediately dropped, returning to its initial value within approximately 20 s.

The mean $2f_1$-f_2 -amplitude showed a typical similar pattern with a small observable time lag. Almost directly after the start of injection the $2f_1$-f_2 -amplitude also increased to reach a maximum value of about 0.75 dB above its initial value at the end of the injection period. When the injection was instantaneously terminated, the amplitude dropped and returned to slightly above its initial level. This pattern was consistently observed in all individual experiments. The mean $2f_1$-f_2 -phase change showed a similar typical course as the inner ear pressure and $2f_1$-f_2 -amplitude, and reversibly changed by almost 3 degrees.

In figure 1, the curve along which the pressure reached a stable higher level has an exponential shape. To determine whether the $2f_1$-f_2 -amplitude curve has the same rise and fall time as the pressure curve, proper fits were obtained with the simple exponential function (figure 1b):

$$a \exp(- t/ \tau) + c$$

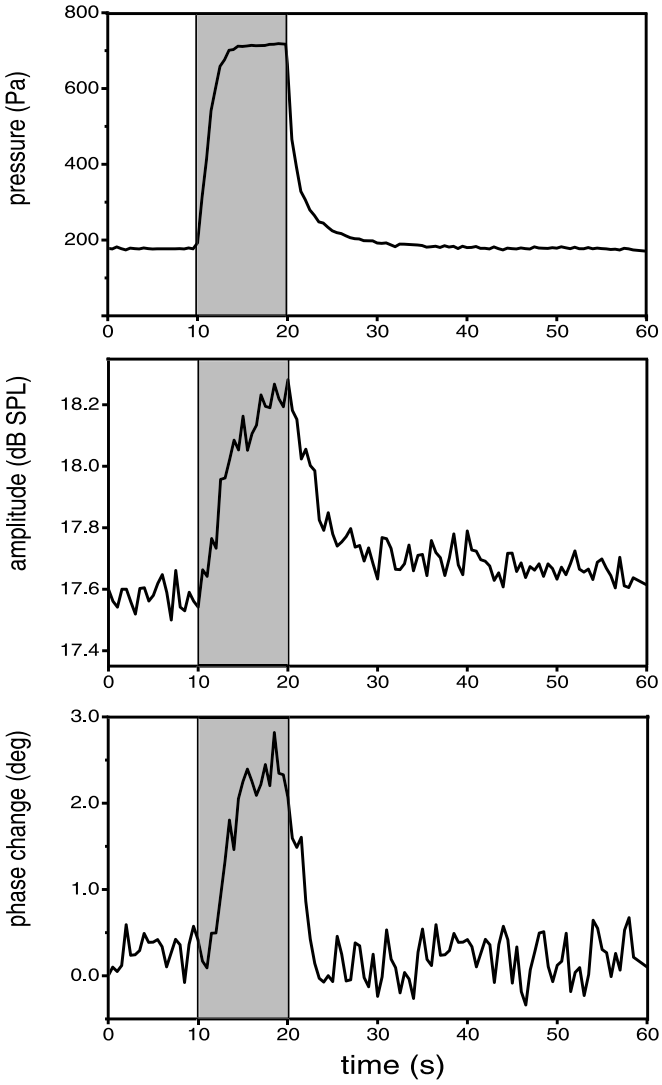

Figure 1a: Averaged changes (n=8) in inner ear pressure (upper panel), $2f_1$-f_2 -amplitude (middle panel) and $2f_1$-f_2 -phase (lower panel) during and after injection of 0.5 µl of artificial perilymph into scala tympani. The grey area depicts the injection period.

The inner ear pressure recovery curves in figure 1c and 2b needed an extra term in the formula for a proper fit:

$$a \exp(- t/ \tau) / [1 + b \{1 – \exp(- t/ \tau)\}]$$

According to Wit et al. (1999), time constants τ were calculated from the fits. The mean time constant showed a marked difference; $\tau = 0.95$ for pressure increase vs $\tau = 2.94$ for $2f_1$-f_2-amplitude increase (figure 1b). Only a small part of this difference can be explained by delay in the $2f_1$-f_2 generating mechanism and in the measuring equipment: a sudden change in the f_1-amplitude was followed by $2f_1$-f_2 amplitude change with a time constant of 0.18 s. This was measured in an ad-

ditional experiment. The mean time constants for pressure and $2f_1$-f_2-amplitude recovery after termination of injection were 1.27 and 2.88 s respectively (figure 1c).
In figure 2a the averaged recorded inner ear pressure, $2f_1$-f_2-amplitude and -phase changes during and after aspiration of 0.5 µl of artificial perilymph are shown. At the start of aspiration the mean pressure decreased immediately, reaching a maximum decrease of approximately 680 Pa at the end of injection. No stable pressure level was reached within the 10 s aspiration period. When the aspiration was stopped, the pressure immediately increased, returning to its initial value within roughly 20 s.
Again, the mean $2f_1$-f_2-amplitude showed a typical similar pattern with a small observable time lag with respect to the pressure change. With aspiration the $2f_1$-f_2-amplitude also decreased to reach a maximum decrease of about 0.9 dB below its initial value at the end of the 10 s aspiration period. When the aspiration stopped, the amplitude again increased to its original level within approximately 20 seconds. This pattern was consistently observed in all performed experiments. The $2f_1$-f_2-phase change was in the order of a few degrees and did not show a typical course in the individual experiments which can also be seen in the mean $2f_1$-f_2-phase change. Because no stable inner ear pressure level was reached during aspiration, no time constants for the corresponding parts of the curves were derived. For the pressure and $2f_1$-f_2-amplitude recovery curves, after termination of aspiration, τ was 2.25 and 4.41 s respectively (figure 2b). These time constants are larger than for recovery after injection, as shown in figure 1c.
In figure 3, the averaged results of the alternate injection and aspiration experiments are summarized.

Discussion

The major finding of this study is that large changes in overall inner ear pressure give only small changes in $2f_1$-f_2 -amplitude and -phase. This is in contrast with previous experiments, in which an acute endolymphatic hydrops of about 1 µl was created by injection of artificial endolymph into scala media in the guinea pig (1.65 nl/s) and the inner ear pressure level increased by only 22 Pa with a maximum decrease in $2f_1$-f_2 -amplitude of 2.6 dB. In the same series of experiments a larger and more rapid induction of acute endolymphatic hydrops resulted in an inner ear pressure increase of 100 Pa, with a $2f_1$-f_2 -amplitude drop of 12 dB (Valk et al., 2004). Thus, the larger changes of $2f_1$-f_2 -amplitude (and phase) observed in these earlier experiments can not primarily be the result of a changing overall inner ear pressure, because the present experiments show that the influence of pressure on the $2f_1$-f_2 generating mechanism is only small. This conclusion is supported by the finding of Salt and DeMott (2002) that large pressure changes, induced by injection of artificial perilymph into scala tympani, created virtually no endolymph movement or change of the endocochlear potential (EP), unless a fluid outlet was created in scala vestibuli (in the latter situation significant EP changes occurred). This leads to the conclusion that in our earlier endolymphatic hydrops experiments it is somehow the increased endolymph volume itself and not merely the increased inner ear pressure that is responsible for the changes in cochlear function measured by low-level DPOAEs.

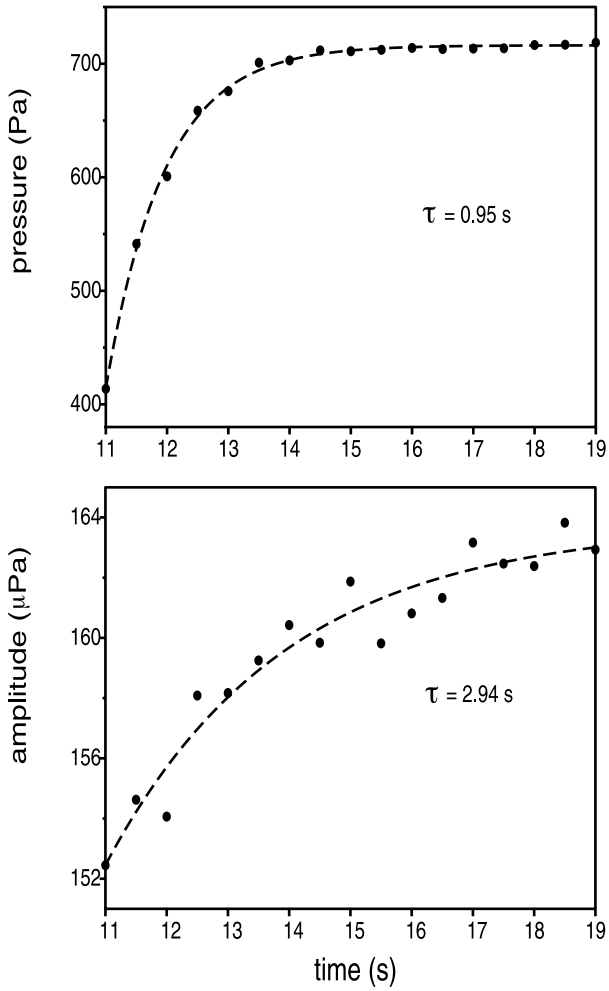

Figure 1b: The shape of the mean inner ear pressure (upper panel) and $2f_1$-f_2 -amplitude (lower panel) curves during injection of artificial perilymph into scala tympani (time axis corresponds with figure 1a). The recordings (solid circles) are both fitted (dashed line) with a single exponential function, yielding different time constants (τ).

As can be seen in figures 1a, 2a and 3, the $2f_1$-f_2-DPOAE amplitude directly follows the changes in inner ear pressure. When inner ear pressure is increased by injection of artificial perilymph (to 720 Pa), the $2f_1$-f_2-amplitude also increases. The other way round, when inner ear pressure is decreased by aspiration of perilymph (to –500 Pa), the $2f_1$-f_2–amplitude also decreases. At first sight the direction and magnitude of the $2f_1$-f_2-amplitude changes can be explained by the model predictions of Büki et al. (2002). These authors show that, as a consequence of a changing stiffness of the oval window, inner ear pressure increase causes a small increase of DPOAE-amplitude for frequencies above 2 kHz (their figures 8 and 9). In the case of aspiration of perilymph the Büki (Zwislocki)-model (2002) will predict a decrease of DPOAE-amplitude, followed by an increase, because if the stapes moves inwards through its zero position the oval window compliance first increases, whereafter it decreases again (Ivarsson and Pedersen, 1977). This predicted $2f_1$-f_2 -amplitude change was not observed: the amplitude simply followed inner ear pressure.

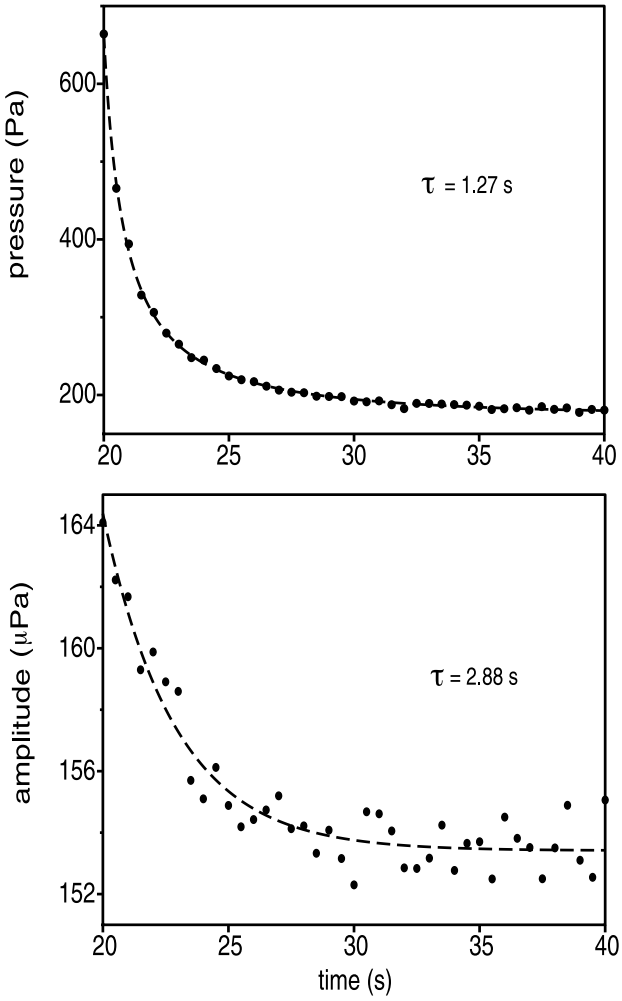

Figure 1c: The shape of the mean inner ear pressure (upper panel) and $2f_1$-f_2 -amplitude (lower panel) recovery directly after injection of artificial perilymph into scala tympani (time axis corresponds with figure 1a). The recordings (solid circles) are fitted (dashed line) by exponential functions, yielding different time constants (τ).

Furthermore, if it is the overall stiffness of the stapes-oval window-system that governs the behaviour of the $2f_1$-f_2 -amplitude, it is expected that this amplitude follows stiffness changes instantaneously. This was not measured: the time constant for the $2f_1$-f_2 -amplitude change was 1 to 2 seconds larger than the time constant for pressure change. This difference can not be covered by the delay in the $2f_1$-f_2 generation mechanism and the measuring equipment, because this was measured to be only 0.18 s. It is imaginable that a delayed change in cochlear potentials is the cause of the difference in τ-values, but in experiments by Salt and DeMott (1999) the endocochlear potential followed a transient pressure stimulus with a delay smaller than 0.1 s. So, the mechanism for the delay in $2f_1$-f_2 -amplitude change following inner ear pressure change remains to be elucidated.

In guinea pigs, hydrostatic pressure in the inner ear fluids is in the order of 200 Pa (2 cm H_2O) and has physiological variations in the range of -100 to 700 Pa. Böhmer did not observe a consistent

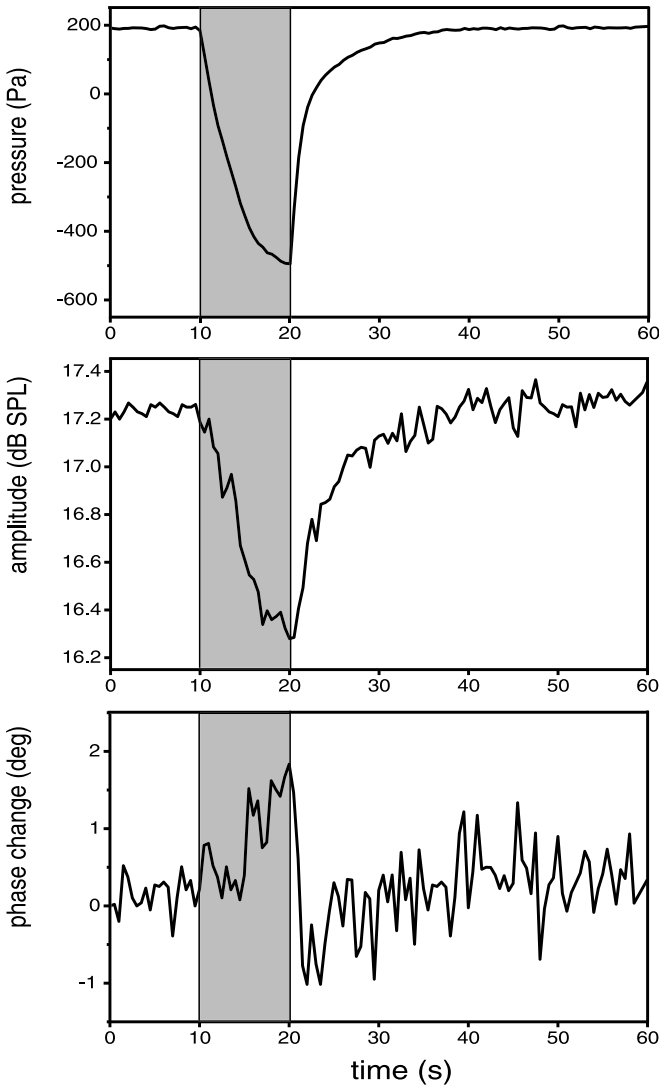

Figure 2a: Averaged changes (n=8) in inner ear pressure (upper panel), $2f_1$-f_2 -amplitude (middle panel), and $2f_1$-f_2 -phase (lower panel) during and after aspiration of 0.5 µl of perilymph. The grey area depicts the aspiration period.

effect on tresholds of compound action potentials (CAPs) when hydrostatic pressure was changed in this physiological range (Böhmer, 1993). Nor were pressure differences detected between endolymph and perilymph during a variety of manipulations, including posture change, osmotic dehydration and cochlear perforation (Böhmer, 1993). These results are in accordance with our finding that large inner ear pressure variation hardly affects its functioning. To investigate the relation between inner ear pressure and otoacoustic emissions, Chang et al. (1995) recorded click-evoked otoacoustic emissions at different perilymphatic pressures in guinea pigs. Actual inner ear pressures were not measured in this experiment, but "pressure loadings" of 10, 20 and 30 cm H_2O gave reductions in the amplitude of click-evoked OAEs of 0.9, 2.5 and 3.7 dB respectively. Amplitudes returned to normal after removal of the excess pressure. The "pressure loading" will have

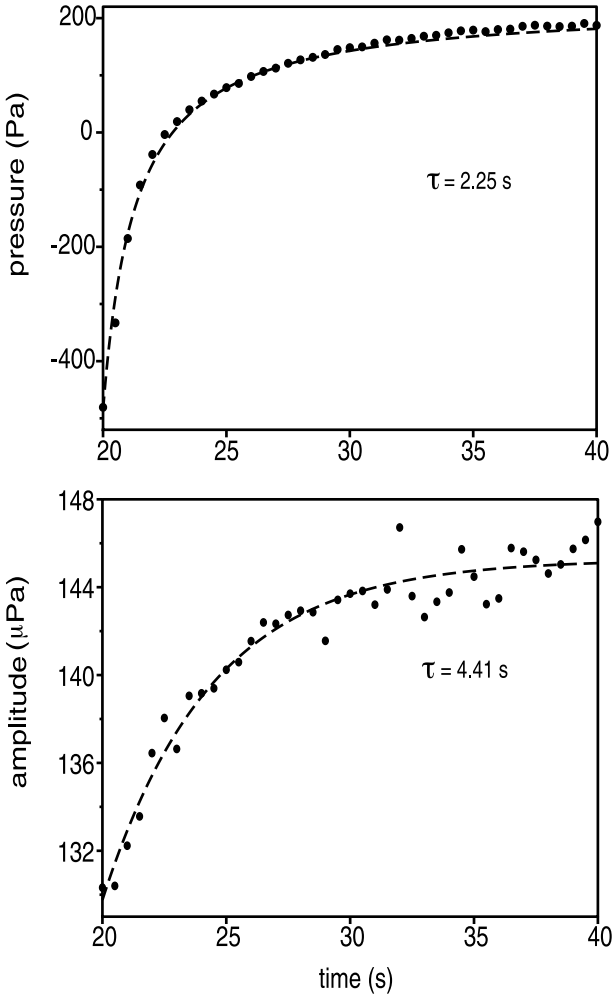

Figure 2b: The shape of the mean inner ear pressure (upper panel) and $2f_1$-f_2 -amplitude (lower panel) recovery directly after aspiration of perilymph out of scala tympani (time axis corresponds with figure 2a). The recordings (solid circles) are fitted (dashed line) by exponential functions, yielding different time constants (τ).

caused an outflow of perilymph through the cochlear aqueduct (Carlborg and Farmer, 1983; Suzuki et al., 1994). In this situation the actual inner ear pressure increase is smaller than the pressure value of the "loading", measured at theinjection pipette entrance, because of the large flow resistance of the micropipette tip (20-30 µm diameter).

An increased perilymphatic pressure, or perilymph hypertension, results in an outbulging round window membrane and is considered a precursor to perilymphatic fistulas (Paparella et al., 1987). In experimentally created perilymphatic fistulas in the guinea pig, inner ear pressure immediately dropped, whereas the compound action potentials remained unchanged (Böhmer, 1990). Kokesh et al. (1994) found a 18.8 dB depressed $2f_1$-f_2 -DPOAE on average across all frequencies and stimulus levels that were applied, immediately after a round window perilymphatic fistula had been made. Assuming that inner ear pressure drops in the presence of perilymphatic fistulas, this condition resembles the situation in the present experiments in which perilymph was aspirated. In

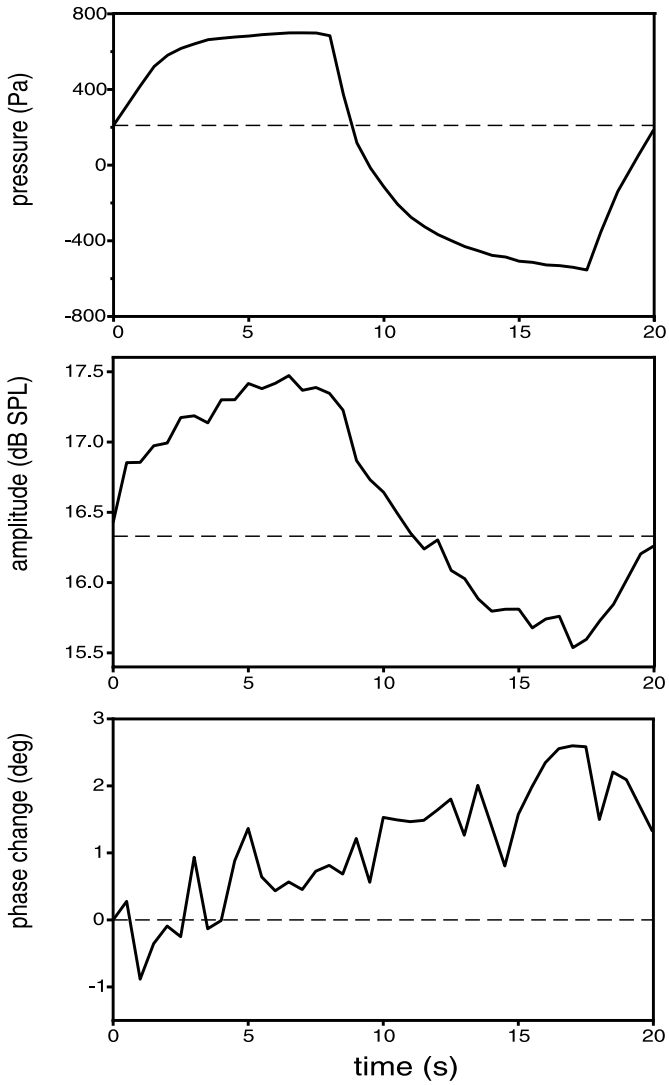

Figure 3: Averaged changes (n=6) in inner ear pressure (upper panel), $2f_1$-f_2 -amplitude (middle panel) and $2f_1$-f_2 -phase (lower panel) during alternate injection (10 s) and aspiration (10 s), both with a rate of 50 nl/s. The inner ear pressure and $2f_1$-f_2 -amplitude prior to manipulation of perilymph volume were 210 Pa and 16.3 dB SPL respectively. Aspiration period in this figure is roughly from 7.5 to 17.5 s.

these experiments a negative inner ear pressure was accompanied by a relatively mild drop in $2f_1$-f_2 -DPOAE amplitude. When aspiration was terminated, the inner ear pressure and $2f_1$-f_2 –amplitude returned to their initial values, underlining the recovering properties of the inner ear.

Time constants were derived for all inner ear pressure curves. The difference between time constants for pressure recovery after an increased or after a decreased inner ear pressure is striking. It is well documented that the round and oval window position is related to time constants for inner ear pressure recovery (Ivarsson and Pedersen, 1977; Feijen et al., 2002; Wit et al., 2003). In the performed experiments, the cochlear windows are moving outwards when inner ear pressure is increased, whereas the windows are moving inwards when inner ear pressure is decreased. The time constant τ depends on R and C, in which R is the cochlear aqueduct's flow resistance and C is the

sum of compliances of the cochlear windows (Wit et al., 2003). It is plausible that an outward moving round window reduces the cochlear aqueduct's flow resistance by stretching of the attached meshwork (Feijen et al., 2002; Wit et al., 2003). This is in accordance with the observation that smaller time constants were found after increased inner pressure levels than during recovery after decreased inner ear pressure levels.

As the inner ear is continually exposed to pressure fluctuations at infrasonic frequencies from external and internal sources, cochlear fluid movements could play a role in fluid homeostasis in the normal state and in fluid disturbances in pathological states. Salt and DeMott (1999) demonstrated that cochlear fluid movements induced by an alternating pressure stimulus at 0.1 to 10 Hz resulted in substantial endocochlear potential changes and small longitudinal movements of endolymph. Likewise, the cochlear microphonics (CM) response followed the dynamics of the stimulus. In our experiments in which a sequential alternate perilymphatic injection and aspiration was executed, a similar infrasonic frequency (0.05 Hz) of pressure disturbance was created. Characteristically, the $2f_1$-f_2 -amplitude followed the dynamics of pressure disturbances (figure 3). This observation is in agreement with the results of Salt and DeMott (1999).

In conclusion, DPOAEs as a measure of cochlear function almost directly follow the dynamics of acute changes in inner ear pressure. However, large changes in overall inner ear pressure give only small changes in $2f_1$-f_2 -amplitude. These findings can be of value in gaining insight into the pathophysiological mechanisms in pathological pressure changes, like in Menière's disease or perilymphatic fistulas.

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