A Comparison of Distortion Product Otoacoustic Emission Properties in Ménière's Disease Patients and Normal-Hearing Participants

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Objectives: Postmortem examination of temporal bones of Ménière's disease patients consistently show dilated endolymphatic spaces of the inner ear, for which the term endolymphatic hydrops has been coined. During the past decade, magnetic resonance imaging techniques for the inner ear appeared, advancing the diagnosis of Ménière's disease. They require, however, a field-strength of at least 3 T, are costly and not universally available. Alternative, noninvasive, cost-effective tests with high sensitivity and specifity for endolymphatic hydrops are desirable. In this study, we test the suitability of distortion product otoacoustic emissions (DPOAEs) for endolymphatic hydrops detection. Previous measurements of the commonly recorded cubic DPOAEs mainly register cochlear hearing loss and are not specific for Ménière's disease. Simultaneous recordings of cubic and quadratic DPOAEs might be more suitable to detect endolymphatic hydrops, because both DPOAE orders react differently to changes of the cochlear operating point as they might occur in Ménière's disease patients.

Design: Cubic and quadratic DPOAEs were recorded in normal-hearing participants (N = 45) and in the affected and unaffected ears of patients with a diagnosis of definite Ménière's disease (N = 32). First, to assess the integrity of DPOAE-generating mechanisms, cubic DPOAE-grams were obtained with primary tone frequencies f_2 between 1 and 8 kHz with primary tone levels l_1 = 60 dB SPL and l_2 = 50 dB SPL, and a fixed primary tone frequency ratio of 1.22. Then, cubic and quadratic DPOAEs were simultaneously recorded with primary tone levels $l_1 = l_2$ = 65 dB SPL and at primary tone frequencies f_2 = 4 and 5 kHz, where f_1 was successively varied such that the ratio f_2/f_1 ranged between 1.1 and 1.6 in 0.04 steps while quadratic and cubic DPOAE levels were extracted from the same recording.

Results: Cubic DPOAEs were significantly reduced in the affected ears of Ménière's disease patients, and slightly reduced in the unaffected ears of Ménière's disease patients, relative to the ears of normal-hearing participants. In contrast, no significant changes could be seen in quadratic DPOAEs across the ears of normal-hearing participants and Ménière's disease patients.

Conclusions: We could identify a relatively good preservation of quadratic DPOAE levels in relation to a reduction of cubic DPOAE levels as a potential noninvasive diagnostic approach in the early stage of suspected Ménière's disease. Future studies validating the differential diagnostic power of this parameter in control groups with nonhydropic forms of hearing loss are warranted.

Key words: Cochlea, Endolymphatic hydrops, Operating point.

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INTRODUCTION

Ménière's disease (MD) is a chronic disease of the auditory and vestibular periphery affecting about 50/100,000 in the general population (review: Sajjadi & Paparella 2008), with reports of up to 500/100,000 (Havia et al. 2005). Patients suffer from episodes of vertigo, (low-frequency) hearing loss and tinnitus, often accompanied by a feeling of aural fullness (Monsell et al. 1995). Postmortem examination of temporal bones of MD patients consistently show dilated endolymphatic spaces of the inner ear, for which the term endolymphatic hydrops (ELH) has been coined (review: Schuknecht 1976; Foster & Breeze 2013). It has been suggested that ELH is the cause of the symptoms MD patients show, but to date the precise role of ELH within the disease process has not been identified (Merchant et al. 2005; Berlinger 2011).

Gadolinium-enhanced inner-ear magnetic resonance imaging (MRI) in MD patients with intratympanically injected contrast agents has been demonstrated to enable the separate visualization of endolymphatic and perilymphatic spaces in humans (Zou et al. 2005), and therefore the detection of ELH (Nakashima et al. 2007) as a method of ascertaining the diagnosis (Gürkov et al. 2011, 2012). It requires, however, a field-strength of at least 3 T, is costly and not universally available. Before cochlear MRI became available, tone burst electrocochleography measurements were the only available method to detect at least a surrogate of ELH or its underlying cause (review: Ferraro & Durrant 2006): Summating potential amplitudes, normalized with the corresponding compound action potential amplitudes can indicate changes in the symmetry of BM movements (review: Ferraro & Durrant 2006). It was suggested that ELH can dislocate the BM from its normal resting position, which will therefore give rise to increased summating potentials. In MD diagnostics, a summating potential/compound action potential ratio of more than 0.5 is considered abnormal and thus an indication for MD. Electrocochleography is a quick and inexpensive procedure and has been reported to be of at least equal sensitivity for the detection of cochlear ELH compared with inner-ear MRI (Hornibrook et al. 2015), but requires transtympanic positioning of recording electrodes for optimum signal to noise ratios, which is not tolerated by some patients.

As a consequence, noninvasive, cost-effective tests with high sensitivity and specifity for ELH are desirable. In this study, we therefore examine the suitability of otoacoustic emissions (OAEs) for ELH detection.

OAEs are sounds produced by the inner ear which can be measured with sensitive microphones in the ear canal. They result from the cochlea's active, nonlinear processing of sound and occur spontaneously, or can be evoked with acoustic or electrical stimulation (see Shera 2004 for review). Ample evidence is available in the literature demonstrating that OAEs are physiologically vulnerable and therefore reflect cochlear integrity (Probst et al. 1987; Hauser et al. 1991; Reshef et al. 1993; Gorga et al. 1997).

OAEs are products of cochlear nonlinearities, predominantly generated in the outer hair cells (Kemp 1979, 1980; Wilson

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1980; Siegel et al. 1982; Zurek et al. 1982; Brown et al. 1989; Verpy et al. 2008). Most cochlear nonlinearities can be reasonably approximated with a sigmoidal Boltzmann function and represent the transfer function of for example, the outer hair cell (OHC) mechano-electrical transducer (Santos-Sacchi 1993). Active, nonlinear properties of the cochlea produce several even and odd orders of distortion product otoacoustic emissions (DPOAEs) when supplied with the sum of two sinusoidal acoustic stimuli. The levels of the two most prominent DPOAEs in humans, the quadratic (f_2–f_1) and cubic ($2f_1$–f_2) DPOAEs reflect different symmetric and antisymmetric properties of the cochlear transfer function: cubic DPOAEs are largest when the gain of the cochlear amplifier is maximized, whereas quadratic DPOAEs are largest when the cochlear transfer function saturates (Bian & Chen 2008). The levels of quadratic and cubic DPOAEs can be estimated by the absolute value of the second or third derivative of the Boltzmann function, respectively (Frank et al. 1996, 1997; Lukashkin & Russell 2005; Abel et al. 2009). When the operating point (OP) is close to the inflection point (i.e., the point of the maximum slope) of the transfer function, cubic DPOAEs will show maximum levels. When the OP is shifted away from the inflection point (toward saturation), quadratic DPOAE levels grow larger while cubic DPOAE levels decrease (Drexl et al. 2012). It has been shown that electrically or acoustically induced shifts of the OP indeed result in changes of cubic and quadratic DPOAE levels as predicted by a Boltzmann simulation (Frank & Kössl 1996, 1997; Abel et al. 2009). It has been suggested that ELH leads, due to the increased endolymphatic volume and, presumably, consequent displacement of the basilar membrane, to changed resting positions of the organ of Corti and thus the OP of the OHC transfer functions (Brown & Gibson 2011; Brown et al. 2013).

Experimental induction of ELH in animal models (e.g., by injection of artificial endolymph) causes typical changes of cubic and quadratic DPOAEs as predicted from OP shifts (Sirjani et al. 2004). Since a similar DPOAE behavior can be expected in MD patients, given that ELH indeed causes OP shifts, several attempts have been made to find correlations between the presence of ELH and cubic DPOAE measurements (Rotter et al. 2008; Avan et al. 2011; Brown & Gibson 2011). Cubic DPOAE mainly serve to register the cochlear hearing loss these patients present with, and MD patients are often not distinguishable from patients with comparable hearing impairments not related to MD (Harris & Probst 1992; Pérez et al. 1997; Fetterman 2001; de Kleine et al. 2002).

Thus, exploiting the different behavior of simultaneously recorded cubic and quadratic DPOAE to changed OPs might represent a more suitable approach to detect pathologies associated with ELH.

There is also evidence from animal models that ELH leads to inner hair cell (IHC) and OHC loss (Megerian et al. 2008). OHC loss and an associated decrease in cochlear gain should impair the generation of both cubic and quadratic DPOAEs and lead to reduced levels of both DPOAE orders, but the presence of notches in DPOAE growth functions can also lead to differential changes in both DPOAE orders (Mills et al. 1993; Lukashkin et al. 2002). In addition, it is also feasible that OP shifts contribute to reduced DPOAE levels in MD patients in comparison to normal-hearing participants.

In this study, we therefore simultaneously recorded cubic and quadratic OAEs in normal-hearing participants and in the affected and unaffected ears of MD patients at different f_2/f_1 ratios to ensure that best ratios for both DPOAE orders were included in the measurements.

MATERIALS AND METHODS

A total of 77 patients was screened, and OAEs were analyzed in 32 patients with definite MD (according to the criteria reported in Monsell et al. 1995). Patients were enrolled when they had unilateral disease, two or more definitive episodes of vertigo with hearing loss, tinnitus, aural fullness, and no history of middle ear or neurological disorders. In 22 MD patients, the diagnosis of certain MD was confirmed by MRI of ELH (Nakashima et al. 2016). Forty five participants with normal hearing were also included in this study.

All experiments were approved by the ethics committee of the University Hospital of the Ludwig-Maximilians-University Munich, Germany, in agreement with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and all participants gave their written informed consent. Recordings were either carried out in a sound-attenuated chamber (averaged noise floor between 1 and 8 kHz: 28.8 ± 4.8 dB SPL) or in a quiet examination room fitted with a sound-attenuated door (averaged noise floor between 1 and 8 kHz: 24.8 ± 5.5 dB SPL). Audiometric (at 0.5, 1, 2, 3, 4, and 6 kHz) and tympanometric data were assessed for both groups. MD patients with a four-frequency (0.5, 1, 2, and 3 kHz) average hearing threshold of more than 40 dB HL were excluded from the study, as were healthy participants with average hearing thresholds of more than 20 dB HL. Participants in both groups were also excluded when otoscopic or tympanometric assessment gave abnormal results. Tympanometric results were considered normal when the peak admittance was found to be between −150 and +25 daPa with peak levels between 0.2 and 1.5 millimhos. Before measurements, the ear canals of the participants were inspected by an otolaryngologist and cerumen was removed, if necessary. Participants were seated in a comfortable recliner during measurements and were advised to remain as still and quiet as possible during measurements. DPOAEs were recorded with an Etymotic Research ER-10C DPOAE probe system (Etymōtic Research, Inc., Elk Grove Village, IL). Signal generation and data acquisition were carried out with a Fireface UC 24-bit external sound card (RME, Audio AG, Haimhausen, Germany), run at a sampling rate of 44.1 kHz with a buffer size of 512 bits. The recorded signal was amplified 30 dB by the soundcard's microphone preamplifier, the built-in preamplifier of the ER-10C probe system was set to a gain of 0. The sound card was controlled by scripts written in MatLab 7.5 (MathWorks, Natick, MA). The SoundMexPro sound application (HörTech, Oldenburg, Germany) was employed to use low-latency multi-channel Audio Stream Input/Output (ASIO) interfacing in Matlab. ER10C-14A Foam eartips (Etymōtic Research, Inc., Elk Grove Village, IL) were used to seal the probe into the ear canal of the participants. All analysis, statistics, and visualization were carried out in MatLab.

Stimuli were presented with duration of 0.5 second including a rise/fall time of 2 msec with a repetition rate of 1.5 Hz. Sound pressure levels were chosen between 50 and 65 dB SPL, and frequencies were set between 1 and 8 kHz. Stimulus presentation and concurrent DPOAE recording was repeated between 16 and 32 times depending on the number of rejected noisy averages. Recordings were rejected when the averaged noise floor surrounding the DPOAE spectral line exceeded sound pressure levels of −5

dB SPL. The noise floor was estimated by averaging the magnitudes of three spectral lines above and three below the actual OAE frequency spectral line. The recording stopped when 32 repetitions were recorded, or when at least 16 valid averages with a signal to noise ratio equal to or exceeding 6 dB were recorded, depending on whichever occurred earlier. Averaged data points not reaching a signal to noise ratio of 6 dB after 32 repetitions were not used for later calculation of interparticipant mean values. These procedures kept the contamination of the signal with artifacts caused by swallowing, coughing etc. to a minimum.

Recorded signals were averaged in the time domain to reduce random noise, windowed with a Hann window, and then analyzed with a Fast Fourier Transform, where Fast Fourier Transform size was equal to the length of the recorded signal. The spectral magnitudes of the cubic and quadratic DPOAEs $2f_1–f_2$ and $f_2–f_1$, respectively, were then extracted from the real part of the spectrum.

Calibration of the sound system was carried out in situ, that is, stimuli were calibrated for constant sound pressure at the probe tip, not at the tympanic membrane, with the known drawback of sound pressure levels deviations due to standing waves at frequencies higher than 3 kHz (Siegel 1994). Please refer to Drexl et al. (2012) for details of the calibration procedure.

The following recording protocol was carried out in all participants:

1. To assess the integrity of the DPOAE-generating mechanisms, DPOAE-grams were recorded: With a fixed f_2/f_1 ratio of 1.22, cubic DPOAEs, $2f_1–f_2$, were evoked with f_2 set to frequencies between 1 and 8 kHz and levels were set to l_1 = 60 dB SPL, l_2 = 50 dB SPL.
2. Cubic and quadratic DPOAEs, $2f_1–f_2$ and $f_2–f_1$, were simultaneously recorded, while f_2 was held constant at 4 and 5 kHz, and f_1 was changed so that the f_2/f_1 ratio changed from 1.1 to 1.6 in 0.04 steps, levels were set to l_1 = 65 dB SPL, l_2 = 65 dB SPL in normal-hearing participants, as well as in the affected and the unaffected ear of MD patients at fixed f_2 frequencies of 4 and 5 kHz. As best ratios for cubic and quadratic DPOAEs are quite different (Bian & Chen 2008; Drexl et al. 2012), varying the f_2/f_1 ratios ensured that the individual best ratio was included in the recordings.

All statistical analysis was carried out with MatLab. Ratio and frequency curves were tested in separate, two-factor, mixed design analysis of variances for influences of f_2 frequency or f_2/f_1 ratio (13 and 10 values, respectively) and the ear condition (normal hearing, MD affected, MD nonaffected), followed by a posthoc analysis. The interaction of these parameters was also tested. p values of the posthoc analysis were adjusted for multiple comparisons according to the Holm-Bonferroni correction.

RESULTS

DPOAE-Grams

Cubic DPOAE-grams of normal-hearing participants (Fig. 1) were comparable with the results of similar measurements available in the literature (Moulin 2000; Drexl et al. 2012): they showed distinct level minima for DPOAEs evoked with f_2 frequencies in the region around 3kHz, followed by a recovery of DPOAE levels around f_2 frequencies of about 5 kHz. DPOAE-grams of the affected and unaffected ears of MD patients

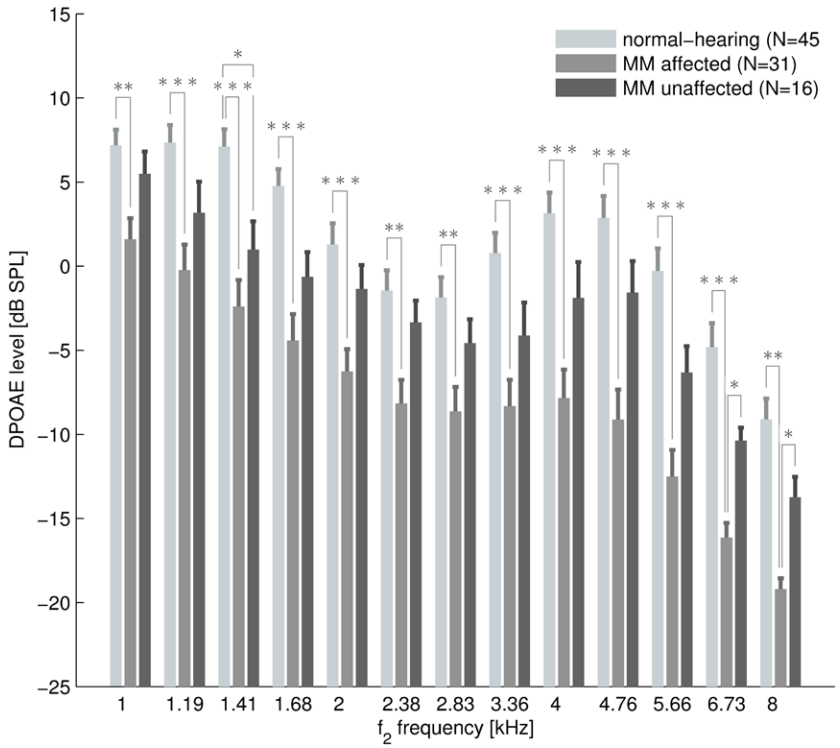

Fig. 1. DPOAE-grams of normal-hearing ears, and of the affected and unaffected ears of MD patients with f_2 frequencies between 1 and 8 kHz in quarter-octave steps, primary tone levels l_1 and l_2.were 60 and 50 dB SPL, respectively. Bars represent means; error bars give the SE of the mean. Brackets indicate significant differences between pairs (post hoc analysis; *, **, ***p values smaller than 0.05, 0.01, and 0.001, respectively. p values were corrected for multiple comparisons. DPOAE indicates distortion product otoacoustic emission; MD, Ménière's disease.

(Fig. 1) shared the same qualitative features, albeit at reduced DPOAE levels. Statistical analysis revealed that there was an overall effect of the ear condition ($F_{2, 95} = 18.15$, $p < 0.001$) and of the f_2 frequency ($F_{12,1140} = 34.10$, $p < 0.001$) on cubic DPOAE level. There was no significant interaction effect between ear condition and f_2 frequency ($F_{24, 1140} = 1.44$, $p = 0.079$). Only the affected ears of MD patients showed significant differences to normal-hearing participants at all tested frequencies. Significant differences between ears of normal-hearing participants and the nonaffected ears of MD patients, and the affected and unaffected ears of MD patients were only seen at a few frequencies (see Fig. 1 for results of the posthoc analysis, p values adjusted according to the Holm-Bonferroni method).

Cubic and Quadratic DPOAEs as a Function of f_2/f_1 Ratio

Ears of Normal-Hearing Participants • In normal-hearing participants, cubic DPOAEs typically show a distinct maximum at f_2/f_1 ratios of about 1.2 (Bian & Chen 2008). Here, the mean best ratio was also 1.2 at f_2 frequencies of 4 and 5 kHz, respectively (Fig. 2A, B). The picture is quite different for quadratic DPOAEs in normal-hearing participants. As already reported (Bian & Chen 2008), quadratic DPOAE amplitudes as a function of f_2/f_1 ratio do not show a distinct peak. In this study, quadratic DPOAE levels at both f_2 frequencies showed maximum values at the smallest f_2/f_1 ratio tested (1.1) and decreased steadily from there (Fig. 2C, D). Taken together, quadratic and cubic DPOAEs produced a specific pattern in normal-hearing participants: The cubic DPOAE levels at both f_2 frequencies clearly exceeded the quadratic DPOAE amplitude with increasing f_2/f_1 ratios of up to about 1.35, where quadratic and cubic amplitudes were almost equal. With f_2/f_1 ratios greater than this, quadratic DPOAE amplitudes remained equal-level or even exceeded cubic DPOAE levels

Ears of MD Patients • In both affected and unaffected ears of MD patients cubic DPOAE levels had, very similar to normal-hearing participants, a distinct maximum at a f_2/f_1 ratio of about 1.2 at both f_2 frequencies, but maximum levels amplitudes were reduced by about 10 and 5 dB, respectively, in comparison to healthy ears (Fig. 2A, B). Quadratic DPOAEs of the affected and unaffected ears of MD patients resembled their counterparts in normal-hearing participants more closely and showed similar characteristics: quadratic DPOAE levels at both f_2 frequencies tended to decrease with increasing f_2/f_1 ratios, and with f_2/f_1 ratios exceeding 1.4, quadratic and cubic amplitudes were about iso-level.

For cubic DPOAEs, at $f_2 = 4$ kHz, there was no overall effect of the ear condition ($F_{2, 46} = 2.3$, $p = 0.112$), but there was an

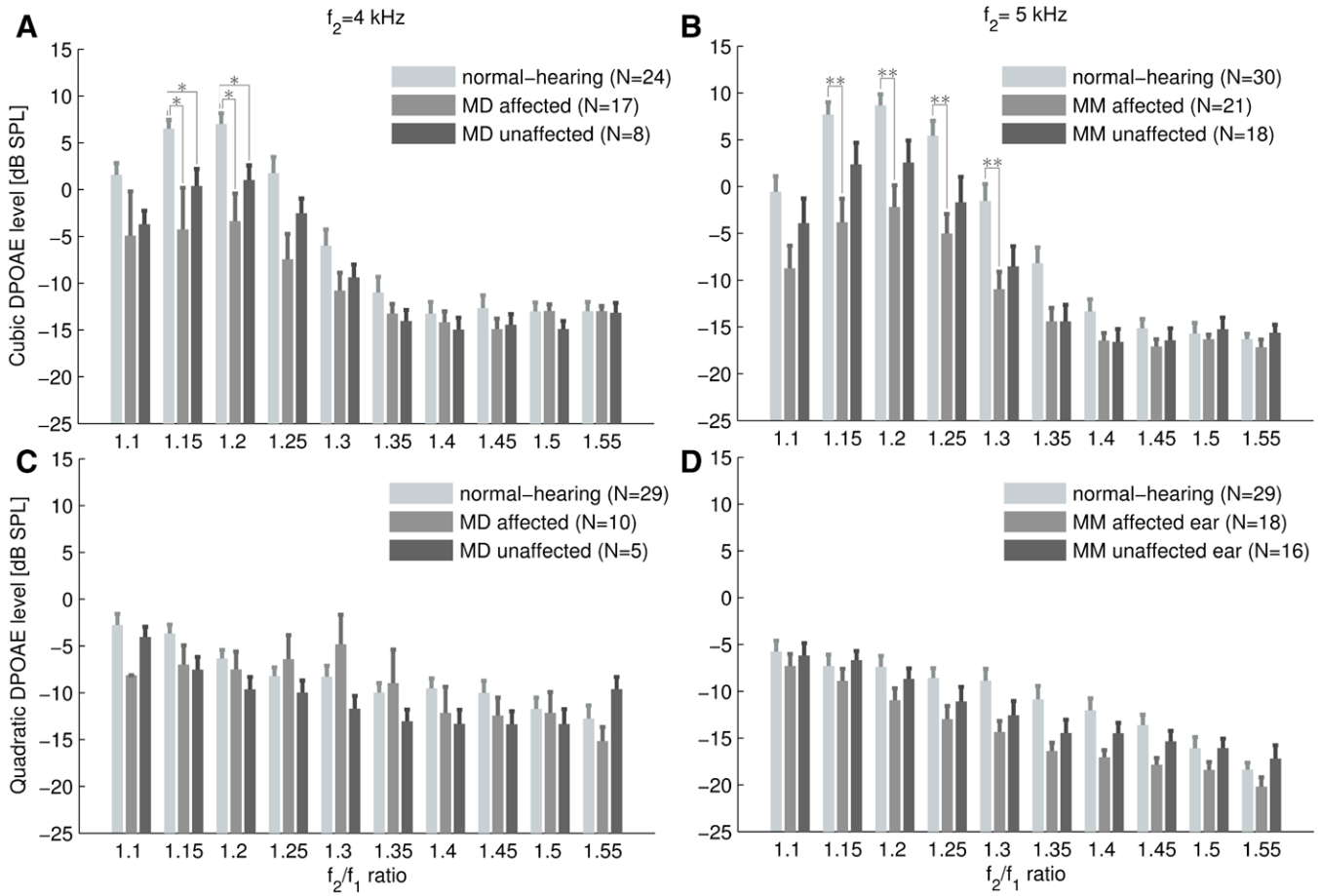

Fig. 2. Cubic (A, B) and quadratic (C, D) DPOAE levels as function of f_2/f_1 ratio between 1.1 and 1.55 of normal-hearing ears, and of the affected and unaffected ears of MD patients at $f_2 = 4$ kHz (A, C) and $f_2 = 5$ kHz (B, D). Bars represent means; error bars give the SE of the mean. Brackets indicate significant differences between pairs (post hoc analysis; *, **p values smaller than 0.05, and 0.01, respectively. p values were corrected for multiple comparisons. DPOAE indicates distortion product otoacoustic emission; MD, Ménière's disease.

overall effect of the f_2/f_1 ratio ($F_{9, 414} = 27.12$, $p < 0.001$) on DPOAE level. There was also a significant interaction effect between ear condition and f_2/f_1 ratio ($F_{18,414} = 2.79$, $p < 0.001$), A posthoc analysis revealed statistical differences between normal-hearing ears and unaffected and affected MD ears at f_2/f_1 ratios between 1.15 and 1,2, respectively, but not between unaffected and affected MD ears.

For cubic DPOAEs at $f_2 = 5$ kHz, an overall effect of the ear condition ($F_{2,66} = 6.37$, $p = 0.003$) could be found, and there was on overall effect of the f_2/f_1 ratio ($F_{9,594} = 60.77$, $p < 0.001$) on cubic DPOAE level. There was also a significant interaction effect between ear condition and f_2/f_1 ratio ($F_{18,594} = 44.50$, $p < 0.001$). A posthoc analysis revealed statistical differences between normal-hearing and affected MD ears at f_2/f_1 ratios between 1.1 and 1.3.

In quadratic DPOAEs, at $f_2 = 4$ kHz, an overall effect of the f_2/f_1 ratio was found ($F_{9,369} = 13.56$, $p < 0.001$) and there was also a significant interaction between ear condition and f_2/f_1 ratio ($F_{18,369} = 44.50$; $p < 0.001$), but no overall effect of the ear condition ($F_{2,41} = 1.10$; $p = 0.340$) on quadratic DPOAE levels.

At $f_2 = 5$ kHz, there was no overall effect of the f_2/f_1 ratio on quadratic DPOAE levels ($F_{2,60} = 3.13$; $p = 0.051$) and no interaction between ear condition and f_2/f_1 ratio ($F_{18,540} = 1.16$). There was a significant overall effect of f_2/f_1 ratio on DPOAE levels ($F_{9,540} = 26.15$, $p < 0.001$). At both f_2 frequencies, posthoc analyses revealed no significant differences.

DISCUSSION

The experiments in the present study are based on the hypothesis that in MD patients, the presence of ELH leads to shifts of cochlear transfer function OPs which change the relation between cubic and quadratic DPOAE levels when compared with normal-hearing participants: In particular, OP shifts away from the point of inflection of the cochlear transfer function increase the quadratic DPOAEs, and decrease cubic DPOAE. Therefore, if ELH shifts the OP away from its typical resting position near the point of inflection, quadratic DPOAEs should be increased. We could not confirm that quadratic DPOAEs at given primary tone frequencies and levels are significantly larger in MD patients compared with normal-hearing participants. Averaged quadratic DPOAE levels in the affected ear of MD patients are slightly (but not statistically significant) reduced and cubic DPOAE levels in the affected ear of MD patients are significantly reduced relative to normal-hearing participants. A comparison of simultaneously evoked cubic and quadratic DPOAEs reveals the real nature of DPOAE generation changes in MD patients: OHC function impairment should affect cubic and quadratic DPOAE generation, albeit by different amounts due to the different growth function characteristics (Bian & Chen 2008), if we accept that the sources for the nonlinear distortion component for both cubic and quadratic DPOAEs are near the f_2 representation and thus the same. It has been shown that manipulations affecting OHC motility (Frank & Kössl 1996) can indeed decrease cubic and quadratic DPOAEs, explained by a linearization of the cochlear transfer function, but at certain time points differential changes of cubic and quadratic DPOAEs occur, explained by OP shifts. Removing a dominant source of cochlear nonlinearity (Verpy et al. 2008) results in complete loss of DPOAEs, regardless the order. In the case of OHC impairment, the typical DPOAE pattern seen by simultaneously evoking quadratic and cubic DPOAE should simply be shifted to lower levels, but in the presence of notches in DPOAE growth functions differential changes can also occur (Mills et al. 1993; Lukashkin et al. 2002). Notches in human DPOAE growth functions are not as consistently found as in rodents, but can sometimes be observed (Whitehead 1998).

In our results, quadratic DPOAE levels are fairly conserved across experimental groups and are only slightly reduced, whereas cubic DPOAE levels are significantly reduced in the affected ears of MD patients, compared with normal-hearing participants. This seemingly paradoxical behavior can be explained by assuming that reductions of quadratic DPOAE levels caused by OHC impairment are, at least in part, compensated by an enhancement of quadratic DPOAE amplitudes caused by the suggested OP shift related to ELH or its underlying mechanism in MD patients. In addition, a more global sensitivity change might also cause differential alterations of cubic and quadratric DPOAEs in the presence of DPOAE growth function notches. Also, the slopes of quadratic DPOAE growth functions in humans (but also in rodents) are typically shallower than of cubic DPOAEs (Frank & Kössl 1996; Lukashkin et al. 2002; Bian & Chen 2008), and, as a consequence, are less sensitive to gain changes. Alternatively, ELH or its underlying mechanism might also induce changes of DPOAE fine structure. While the most prominent differences across experimental groups in our results occurred near the optimum ratio for DPOAE generation, it has been shown that the DPOAE reflection component is relatively small compared with the distortion component in the range of the primary tone levels we used (Mauermann & Kollmeier 2004), rendering a major contribution from fine structure changes unlikely.

While significant differences were found between affected ears of MD patients with ears of normal-hearing participants, there were only few stimulus configurations where statistically significant differences between unaffected and affected ears of MD patients existed. Our patient population consisted of patients with unilateral MD, defined as the absence of audiovestibular symptoms and functional deficits in the contralateral ear. However, recent evidence from inner-ear MRI studies has shown that the prevalence of bilateral ELH in patients with unilateral MD may be as high as 65% (Pyykkö et al. 2013), offering a possible explanation for the observed effects. In summary, we could identify the relatively good preservation of quadratic DPOAEs in relation to a significant reduction of cubic DPOAE levels in the affected ears of MD patients as a potential noninvasive diagnostic approach in the early stage of suspected MD. Future studies validating the differential diagnostic power of this parameter in control groups with nonhydropic forms of hearing loss are now warranted.

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The authors Krause and Gürkov contributed equally to this study.

M.D. designed and performed experiments, analyzed data, and wrote the article; E.K. and R.G. designed experiments and wrote the article.

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