Original Article

Optimizing the Measurement of 0.5–kHz Cubic Distortion Product Otoacoustic Emission

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BACKGROUND: The measurement of low-frequency cubic distortion product otoacoustic emission, for example, 0.5-kHz cubic distortion product otoacoustic emission, is often severely affected by background noise, and currently 0.5-kHz cubic distortion product otoacoustic emission is not commonly applicable in clinical setting.

METHODS: The fundamental part of current study was the optimization of recording technology to reduce noise interference with the measurement of 0.5-kHz cubic distortion product otoacoustic emission and to establish the response patterns of cubic distortion product otoacoustic emission across speech frequencies from 0.5 to 8kHz in the presence of normal hearing and noise-induced hearing loss.

RESULTS: After a series of optimization, a clinically applicable technology of measuring 0.5-kHz cubic distortion product otoacoustic emission was successfully completed via animal model. Cubic distortion product otoacoustic emission was recorded in 6 guinea pigs across speech frequencies from 0.5 to 8kHz before and after exposure to white bandnoise between 0.5 and 2 kHz. After noise exposure, significant reduction in the signal-to-noise ratio of cubic distortion product otoacoustic emission was found at 0.5 and 2 kHz, indicating our recording technology was sensitive and accurate. Other interesting finding was the reduction in cubic distortion product otoacoustic emission-signal-to-noise ratio at 4 and 6 kHz although the reduction was not statistically significant probably because of short exposure time. The result implied that the damaging effect induced by low-frequency noise exposure might spread upward to high-frequency region.

CONCLUSIONS: Our recording technology was stable and reliable and had the great potentiality to be used in clinical setting.

KEYWORDS: 0.5-kHz cDPOAE, low-frequency noise exposure, noise-nduced hearing loss (NIHL)

INTRODUCTION

Noise-induced hearing loss (NIHL) is becoming increasingly common in our community. Distortion product otoacoustic emissions (DPOAEs) are often adopted in clinical setting to evaluate hearing functions. Distortion product otoacoustic emissions depend on the electro-mechanical activity of outer hair cells (OHCs). When ear receives 2 simultaneous pure-tone stimuli (primary tone-burst F1 and secondary tone-burst F2), OHCs generate a few nonlinear DPOAEs.[1] The frequencies of the first and the second primary tones are defined as f_1 and f_2, respectively, (with $f_1 < f_2$). The frequencies of DPOAEs (f_{DP}) are mathematically associated with primary-tone

frequencies. Of all the nonlinear DPOAEs, the one with the biggest magnitude is called cubic DPOAE (cDPOAE) whose frequency is calculated as $f_{DP} = 2f_1 - f_2$. The magnitude of cDPOAE is often defined as signal-to-noise ratio (SNR).[2-4]

Cubic DPOAE is produced near f_2 area on basilar membrane (BM) and launched at f_{DP} region. Then cDPOAE is transmitted backward along BM, through middle ear, and into external ear canal where it is recorded by microphone, and then cDPOAE-SNR is positively correlated with the function of OHCs.[5-8]

Cubic DPOAE is an objective test of cochlear function, and the response pattern of cDPOAE provides an overview of hearing function from low to high frequency.[9] However, when f_2 is lower than or equal to 0.5 kHz, for example, 0.5-kHz cDPOAE is often interrupted by background noise; here, 0.5 kHz indicates the frequency of the secondary primary tone-burst (f_2).[10-14] At present, 0.5-kHz cDPOAE and the response pattern of cDPOAE are not commonly available in clinics.

There were only a few reports about the measurement of 0.5-kHz cDPOAE, and SNR was very small because of noise interruption.[15-17] The measurement of 0.55-kHz cDPOAE was attempted in human, and if SNR $\geq$ 6 dB sound pressure level (SPL) was taken as acceptable criteria, successful recording rate was very low as a result of noise disturbance.[18] So noise interference is an issue in the measurement of 0.5-kHz cDPOAE which needs to be addressed urgently.

Our first research goal was to optimize recording technology to control and reduce background noise so that 0.5-kHz cDPOAE could be recorded successfully. The second research goal was to establish the response pattern of cDPOAE across speech frequencies from 0.5 to 8 kHz in the presence of normal hearing and NIHL.

Guinea pig had been used to investigate the effect of noise exposure on hearing function.[19-21] Cubic DPOAE recorded in guinea pig was

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MAIN POINTS

- Cubic distortion product otoacoustic emission (cDPOAE) of 0.5 kHz was often overlapped by low-frequency noise coming from the subject itself. Numerous endeavors had been attempted before; however, acceptable cDPOAE signal had not been achieved. Our major optimization method was the usage of pass-filter technique to remove most of the low-frequency noise and maximize cDPOAE signal.
- The major contribution of current research was the successful recording of 0.5-kHz cDPOAE with the signal-to-noise ratio above 10 dB and averaging times of 8. Result showed this recording technology could improve the measurability of 0.5-kHz cDPOAE without any significant interruption of the major characteristics of the evoked cDPOAE. These results were applicable in the clinical setting.
- From a technical standpoint, the successful animal experimental protocols in which all details had been proved might be a useful template for future translation to human research. The current study has added more valuable information to the literature on the topics of low-frequency hearing test and provided more reliable recording technology that could be used in clinical settings.

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usually greater than that measured in human;[22] however, the difference was less obvious and predictable when the levels of primary tone-bursts were in the range of low to moderate SPL which were similar to that used in clinical setting.[19,20,23] Thus, guinea pig model is appropriate for human cochlear investigation.[24-26]

METHODS

Animals

Six guinea pigs with normal hearing as estimated by the presence of Preyer's reflex were used in our study. Animals were ~2 months old and weighed from 250 to 300 g. The animals were from the same strain, and they were genetically identical. All animal procedures were reviewed and approved by University Animal Care and Use Committee. The protocol number is 201. All experimental methods were performed in accordance with the relevant guideline and regulation.

Otoscopy was performed under surgical microscope to ensure ear canal clean of debris and cerumen that could obstruct probe tube and interfere with the measurement of cDPOAE. Tympanic membrane was also examined to make sure that the membrane color and shape were normal.

Instruments

The lab computer used in experiment had an embedded controller (National instrument, NI, PXI-8108 Core 2 Duo 2.53 GHz Controller, etc.), a 16-bit digital Input/output board (NI, PXI-6221), and a 24-bit digital Input/output board (NI, PXI-4461). The instruments used to deliver stimuli included a 2-channel audio amplifier (Tucker-Davis Technologies Stereo Amp & Power Supply), 2-channel equalizer, and 2-speaker acoustic system. A stainless steel nosepiece transmitted the stimuli generated by speakers into animal ear canal. The instruments used to collect cDPOAE included a probe-tube microphone (Knowles Electret Condenser, FG-23329-P07), a Mic. Bias Box, and a Mic. Amplifier (Etymotic ER10C).

Band-pass filter was set in Labview Signal Express (National Instruments, version 8.5) and was used to generate white band noise between 0.5 and 2 kHz. The noise level was set at 5 Vrms (root mean square voltage) so that the noise output was equal to 120 dB SPL.

Calibration

The system was calibrated to ensure that auditory stimuli presented to animal ear were at the set level. System calibration included 3 parts, the calibration of reference microphone, the calibration of probe tube, and in-ear calibration. The reference microphone was a Larson-Davis 1/4″ microphone (#377B10) which had a very flat frequency response (LD2530: ±1 dB 0.02-50 kHz, ±3 dB 0.02-100 kHz).

The sensitivity of reference microphone was determined by calibration with a pistonphone. In brief, the levels of pistonphone output (dB SPL) and gain of B&K microphone amplifier (dB) were selected, the sampling rate and number of spectrum averages at 20 kHz and 1, respectively, were set, and the calibration was run. In the calibration procedure, there was no need to specify the frequency of the pistonphone tone because it was automatically detected from the measured power spectrum. Since the SNR of the measurement was very high, it was only necessary to average one response.

The calibration of probe tube was conducted within acoustic assembly to calculate the relationship between the SPL at the end of probe tube and the voltage output of acoustic assembly microphone. This calibration was made by measuring the SPL near the tip of probe tube with reference microphone while simultaneously measuring the voltage output of acoustic assembly microphone. The probe-tube calibration was performed by holding reference microphone at a very short distance from the end of probe tube using a calibration coupler. The probe tube calibration used the ratio of the output of acoustic assembly microphone to the output of reference microphone, so the SPL of acoustic stimuli used for calibration was cancelled out.

In brief, in probe-tube calibration, a chirp (a brief sound that contained all frequencies throughout the range to be calibrated) was produced as stimulus by one of the earphone speakers. The stimulus frequency resolution step of calibration was 50 Hz, calibration sampling rate was 100 kHz, attenuation of calibration stimulus from full scale was 30 dB, and the number of averages of response signals was 256. The outputs of acoustic assembly microphone and reference microphone were measured simultaneously. Then, calibration software could compute the ratio of the voltage output of acoustic-assembly microphone to the SPL at the end of probe tube.

Finally, in-ear calibration was performed right before the measurement of cDPOAE. In brief, chirp was always selected as calibration stimulus, frequency resolution step of calibration was was set to 50 Hz, calibration sampling rate was set to 10 kHz, attenuation of calibration stimulus from full scale was set to 30 dB, the number of average of response signal was set to 128 and then the in-ear calibration was run. In-ear calibration involved computing the ratio of the voltage applied to earphone speakers to the SPL at the end of probe tube (near animal tympanic membrane).

Measurement of Cubic Distortion Product Otoacoustic Emission
Eaton-Peabody Laboratories Cochlear Function Test Suite (CFTS) was used to record cDPOAE. Cochlear Function Test Suite was a free software provided by the Massachusetts Eye and Ear Infirmary (USA). The experimental procedure was similar to that in previous reports.[27,28]

Cubic DPOAE was measured before and after band noise exposure at f_2 of 0.5, 2, 4, 6, and 8 kHz, respectively, as these frequencies were in the range of human speech. Animals were exposed to white band noise at 120 dB SPL for 2 hours. In each animal, the average of 2 ears' measurements was adopted as the final level in statistical analysis.

Surgical-plane anesthesia was reached with intramuscular injection of a mixture of ketamine and dex-domitor (ketamine 40 mg/kg and dex-domitor 0.15 mg/kg). If needed, a maintenance dose of the mixture was given every 1 hour. Animal was placed on its side into a customized foam bed to make sure that animal position was stable during recording procedure. And the foam bed was placed on a warm water pad to maintain the animal's temperature at 37°C. During the experiment, the animal's temperature was monitored with a digital rectal probe thermometer.

Optimization of the Measurement of 0.5-kHz Cubic Distortion Product Otoacoustic Emission
Background noise usually included 3 sources: instrumentational, environmental noise, plus the one coming from subject itself.

Because of the stationary property of instrumentational and environmental noise, increasing synchronous averaging times could improve SNR.[29] Thus, increasing averaging times was adopted in our study to minimize the disturbance of instrumentational and environmental noise, but the averaging times in our experiment were only 8, as increasing averaging times were time-consuming and could cause discomfort to subject. Our averaging times are acceptable in clinical setting.

Three methods were adopted to reduce environmental noise: a sound-proof box with an appropriate noise-rejection threshold, a rubber immittance tip fitted onto the nosepiece of acoustic assembly, and the shielding of acoustic assembly. Cubic DPOAE was recorded inside the sound-proof box. The level of environmental noise inside the sound-proof box during recording procedure was estimated at about 11-dB SPL. A rubber immittance tip was fitted onto the nosepiece of acoustic assembly. The tip was like a sealing ring used to seal ear canal and reduce environmental noise. Acoustic assembly was painted with CuPro-Cote conductive copper-bearing paint for 3 times, and these paints were electromagnetic shielding which could prevent acoustic assembly from picking up environmental noise.

However, it was difficult to deal with the noise coming from subject itself. Subject-noise, for example, respiratory sound, cardiovascular murmur, swallowing, snoring, and teeth grinding, were usually of low frequency. The measurement of low-frequency cDPOAE, such as 0.5-kHz cDPOAE, was mostly interfered by subject noise.[30-32]

Fortunately, low-frequency noise could be controlled and reduced by digital filtering technique.[31,33] Based upon this concept, an optimal pass-filter technique was adopted in our research to reduce the low-frequency noise coming from the subject itself and to maximize 0.5-kHz cDPOAE-SNR. And this digital filtering technique was our important optimization method to reduce subject noise.

In brief, cDPOAE was recorded by probe-tube microphone. The microphone's output was amplified by ER10C (Etymotic Research) which was then connected to the lab computer. Digital pass filter was setup by LabView Signal Express, raw signal of cDPOAE was put through the filter to remove unwanted noise, and then the "pure=" signal was analyzed by CFTS. In this way, low-frequency noise coming from animal itself were controlled and reduced, and 0.5-kHz cDPOAE-SNR was optimized and maximized. Other optimization methods included the adjustment of input/output parameters, for example, the f_2/f_1 ratio was set at 1.22 to evoke the most robust cDPOAE.

Calculation of Cubic Distortion Product Otoacoustic Emission-Signal-to-Noise Ratio
The level of F2 stimulus ranged from 40- to 60-dB SPL. When F2 level was ≤60-dB SPL, the recorded cDPOAE was considered as real response from OHCs, when F2 level was >60-dB SPL, the recorded signal was taken as artifact. When F2 level reached 60-dB SPL (F1 = F2 + 10 = 70-dB SPL), amplitude of cDPOAE plateaued. Cubic DPOAE-SNR was calculated as cDPOAE plateau value minus noise-floor level.[34]

Statistical Analysis
Based on G-Power analysis, when the sample size was 6, the effect size was in the range of 0.8-0.9, thus sufficient statistical power was

available to detect the difference between and within groups if such difference existed. Also, it was common to have a sample size of 6 ears in previous animal experiments.[35,36-38]

Repeated measure of analysis of variance along with Bonferroni correction was used to compare cDPOAE-SNR before and after noise exposure, with $P < .05$ adopted as an indication of statistical significance.

RESULTS

Successful Recording of 0.5-kHz Cubic Distortion Product Otoacoustic Emission After Optimization

Cubic DPOAE measured at f_2 of 0.5 kHz was expressed as 0.5-kHz cDPOAE; however, f_{DP} of cDPOAE itself was 0.34 kHz. Many cut-off values of low- and high-frequency pass filter were attempted covering the range from 0 to 0.68 kHz. For each value of low-frequency pass filter, high-frequency pass filters were varied so that a better and strong cDPOAE signal could be achieved. After a series of experiments, it was found out that when low-frequency pass filter was set at 0.17 kHz and high-frequency pass filter was set at 0.51 kHz, the magnitude of 0.5-kHz cDPOAE was maximal. Our technique was optimal in the sense that the pass filters were set according to the value of f_{DP}, low-frequency pass filter was set at $f_{DP} - 1/2\, f_{DP}$, and high-frequency pass filter was set at $f_{DP} + 1/2\, f_{DP}$.

Figure 1 and 2 show the measurements of 0.5-kHz cDPOAE before and after optimization, respectively. Before optimization, 0.5-kHz cDPOAE-SNR was unstable, and in some animals, 0.5-kHz cDPOAE could not be recorded at all. After optimization, 0.5-kHz cDPOAE-SNR

was greatly improved. The SNR in Figure 2 was more obvious and stable than that in Figure 1.

Research Goal 2—Establishment of Response Patterns of Cubic Distortion Product Otoacoustic Emission in the Presence of Normal Hearing and Noise-Induced Hearing Loss

The overall response of an auditory test across all tested frequencies is called response pattern. In Figure 3, cDPOAE-SNR was plotted as function of f_2 of 0.5, 2, 4, 6, and 8 kHz to establish the response pattern of cDPOAE.

The response pattern of cDPOAE before noise exposure showed that the lowest SNR of cDPOAE was at 0.5 kHz and the highest was at 6 kHz. With the increment of f_2, cDPOAE-SNR had a tendency to increase. After noise exposure, reduction in SNR was observed at 0.5 and 2 kHz as compared to that before noise exposure. The response pattern before noise exposure reflected the standard characteristics of normal cochlea, and the change in response pattern after exposure provided a general estimation of hearing loss across all tested frequencies.

Figure 3 shows the difference in cDPOAE-SNR before and after noise exposure, indicating that band-noise exposure could cause significant reduction in cDPOAE-SNR at 0.5 and 2 kHz, $P < .05$; this implied our recording technology is sensitive and accurate.

Another interesting finding was that exposure to white band noise between 0.5 and and 2 kHz could produce hearing losses at higher frequencies, such as at 4 and 6 kHz; however, the reduction in cDPOAE-SNR at 4 and 6 kHz was not statistically significant, probably because of short exposure time.
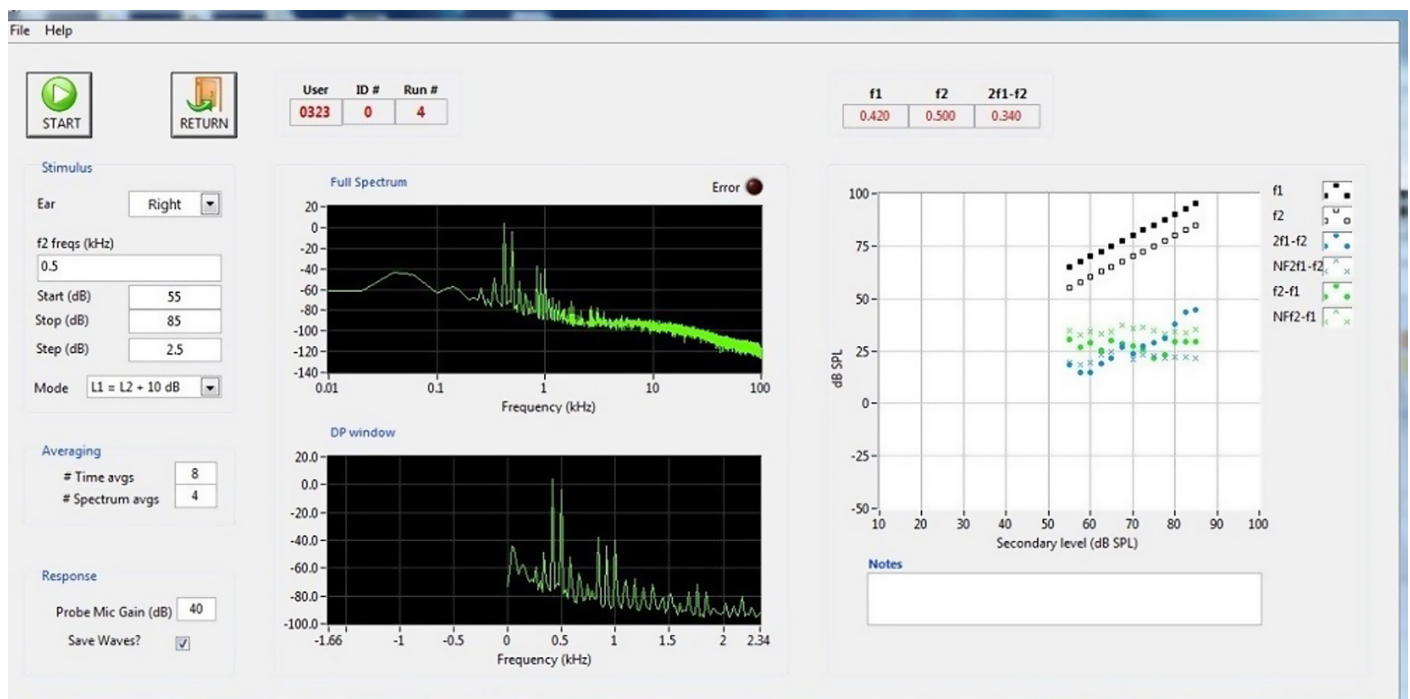

Figure 1. The recording of 0.5-kHz cDPOAE before optimization. In figure 1 and 2, the left part showed the parameters of stimulus and averaging times. The middle section was spectrum display, the top graph was full spectrum, the bottom was a small range centered on the frequency of $2f_1$-f_2. The right panel showed the measured SPL of F1, F2, 2F1-F2, 2F1-F2 noise floor, F2-F1, F2-F1 noise floor as function of F2 stimulus level. In figure 1, when F2 stimulus level was equal to or low than 60 SPL, the cDPOAE was overwhelmed by background noise, the SNR was very low and meaningless; please note that when F2 stimulus level was higher than 60 SPL, cDPOAE was considered as artifact. cDPOAE, cubic distortion product otoacoustic emission; SPL, sound pressure level.
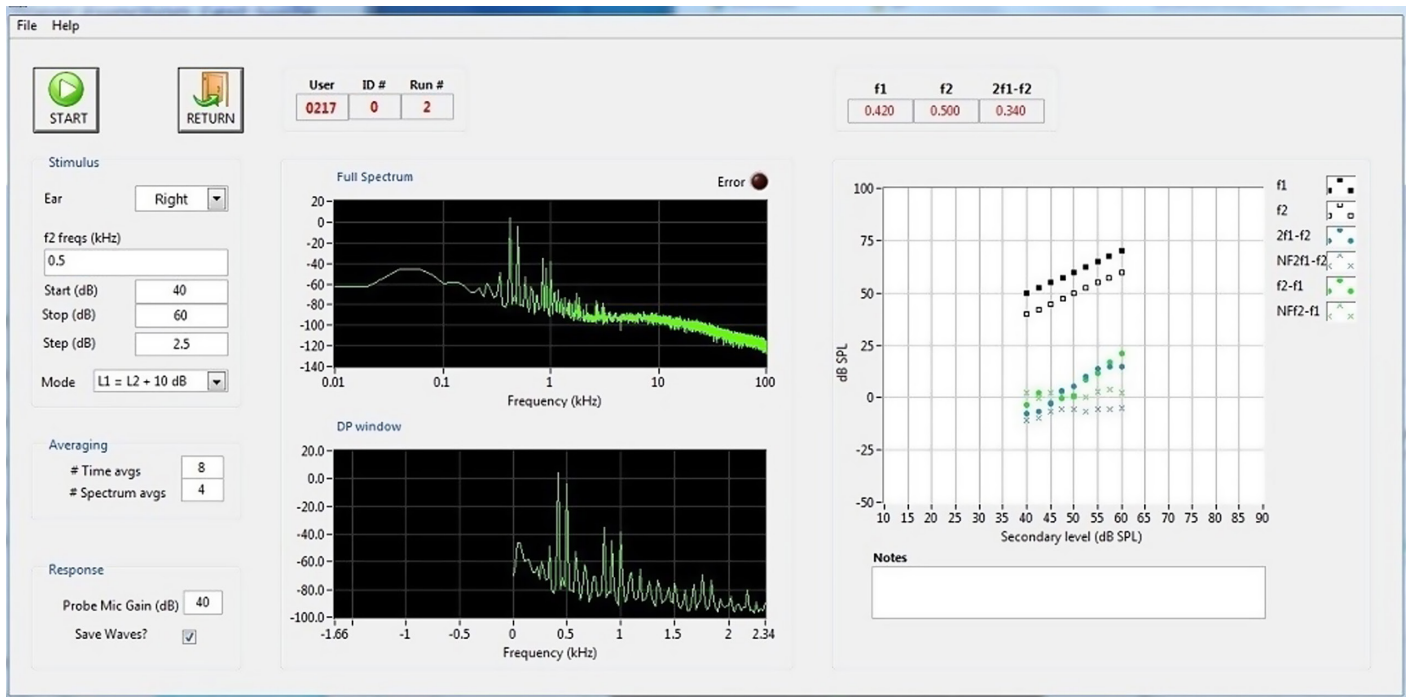
Figure 2. The recording of 0.5-kHz cDPOAE after optimization. The cDPOAE-SNR increased gradually with the growth of F2 stimulus level and reached the maximum plateau when F2 stimulus level was 60 SPL. The comparison between figure 1 and 2 showed that background noise reduced and SNR became distinct and stable after optimization. cDPOAE, cubic distortion product otoacoustic emission; SNR, signal-to-noise ratio; SPL, sound pressure level.

DISCUSSION

Significance of the Optimization of Recording Rechnology

Because of noise interruption, it was difficult to record low-frequency cDPOAE, or cDPOAE-SNR was very small and unstable. The level of background noise is high at low f_2, and the noise level tends to decrease with the increment of f_2. For example, when f_2 is equal to or below 1 kHz, the noise level is about at least 18 dB higher than that when f_2 is 8.0 kHz.[39-41] Thus, the diagnostic value of cDPOAE was poor when f_2 is equal to or below 1 kHz; in clinical setting, cDPOAE is useful only when f_2 ranges from 2 to 8 kHz.[42]

And the performance of cDPOAE was poor at low frequency in terms of the correlation between cDPOAE and behavioral hearing threshold (BHT). Larger discrepancy of the correlation was noted at low frequency as compared to that at high frequency.[43] The correlation between cDPOAE and BHT at high frequency was strong. On the other hand, the association between cDPOAE and BHT at low frequency was weak and not reliable.[16,44] In a word, BHT could be predicted by cDPOAE at high frequency but could not be predicted by cDPOAE at low frequency. At present, 0.5-kHz cDPOAE is not commonly available for patients.

Before our optimization, the characteristics of cDPOAE have not been thoroughly examined across the speech frequency range
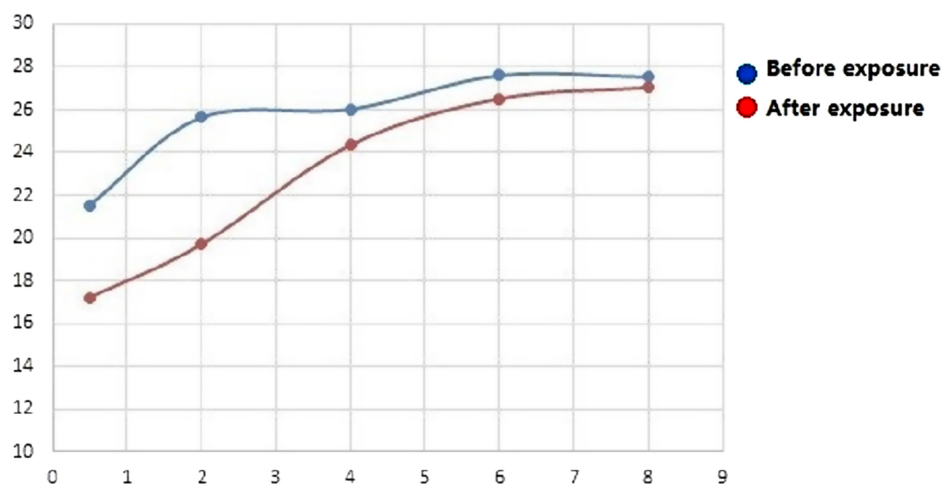

Figure 3. The response pattern of cDPOAE before and after noise exposure. The response pattern before noise exposure showed the lowest cDPOAE-SNR was at 0.5 kHz, the highest was at 6 kHz, and with the increment of tested frequency, cDPOAE-SNR had a tendency to increase, the response pattern before noise exposure may represent the standard characteristics of normal cDPOAE. The response pattern after noise exposure showed, significant reduction in the cDPOAE-SNR was observed at 0.5 and 2-kHz; reduction was also observed at 4 and 6 kHz, but not statistically significant.

(including 0.5 kHz) due to the fact that the measurement of low-frequency cDPOAE is often deteriorated by background noise. The significance of current study was that stable 0.5-kHz cDPOAE can be successfully measured after our optimization of recording technology, and the technology used in the study can provide valuable information for its future clinical application.

Extensive Cochlear Damage Induced by Low-Frequency Noise Exposure

In the study, cDPOAE-SNR measured before noise exposure was used as baseline level and then animals were exposed to low-frequency band noise, and significant reduction in cDPOAE-SNR was observed at 0.5 and 2 kHz, respectively, after noise exposure. Furthermore, decrease in cDPOAE-SNR at 4 and 6 kHz was also noticed after noise exposure. These findings suggested that exposure of low-frequency band noise could cause damage to the corresponding partition in cochlea''s BM, and the damage effect might spread upward to high-frequency region.

The Mechanism About the Reduction in Cubic Distortion Product Otoacoustic Emission-Signal-to-Noise Ratio After Noise Exposures

Cubic DPOAE is generated by OHCs. It is expected that cDPOAE-SNR will decrease after noise exposure; however, the mechanism underlying the reduction in cDPOAE-SNR is complex. Exposure to noise of high SPL could induce damage and or death of OHCs, so the number of functioning OHCs became smaller after exposure, and cDPOAE-SNR fell down correspondingly. On the other hand, the remaining functioning OHCs might be less efficient in energy transduction with respect to the transformation between mechanical and electrical energy, and less efficient in energy transduction of OHCs could also lead to the reduction in cDPOAE-SNR.[45,46]

Some research indicated that noise exposure could cause abnormal change in potassium gating system, also resulting in less-efficient energy transduction of OHCs.[46,47] However, the detailed mechanism about noise-induced damage of OHCs remains unclear.

Response pattern of Cubic Distortion Product Otoacoustic Emission

Response pattern of cDPOAE was the plot of cDPOAE-SNR as function of tested f_2. From the response pattern of cDPOAE before noise exposure, it was noted that cDPOAE-SNR had a tendency to rise when the tested frequencies increased. There might be 2 explanations for this finding, the first explanation was that low-frequency cDPOAE-SNR was easily interrupted by severe background noise so that the cDPOAE-SNR was small, whereas the interruption was mild at high frequency, and the cDPOAE-SNR became large. The second explanation was that the auditory acuity of guinea pig was better at high frequency than that at low frequency. In guinea pig, the most appropriate frequency range of hearing was between 4 and 20 kHz; thus, the cDPOAE-SNR recorded at appropriate frequency range (above 4 kHz) was larger than that recorded at the less appropriate frequency range (e.g., 0.5 kHz).[48]

The response pattern of cDPOAE provided an overview of OHCs function across the tested frequencies. The comparison of response patterns before and after noise exposures could be very useful for the estimation of hearing loss.

The limitation of current study was that no human experiment was carried out. In future, we will do experiment to translate the result of animal study to clinical setting.

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