Effects of stimulus intensity on low-frequency toneburst cochlear microphonic waveforms

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Abstract

This study investigates changes in amplitude and delays in low-frequency toneburst cochlear microphonic (CM) waveforms recorded at the ear canal in response to different stimulus intensities. Ten volunteers aged 20-30 were recruited. Low-frequency CM waveforms at 500 Hz in response to a 14-ms toneburst were recorded from an ear canal electrode using electrocochleography techniques. The data was statistically analyzed in order to confirm whether the differences were significant in the effects of stimulus intensity on the amplitudes and delays of the low-frequency CM waveforms. Electromagnetic interference artifacts can jeopardize CM measurements but such artifacts can be avoided. The CM waveforms can be recorded at the ear canal in response to a toneburst which is longer than that used in ABR measurements. The CM waveforms thus recorded are robust, and the amplitude of CM waveforms is intensity-dependent. In contrast, the delay of CM waveforms is intensity-independent, which is different from neural responses as their delay or latency is intensity-dependent. These findings may be useful for development of the application of CM measurement as a supplementary approach to otoacoustic emission (OAE) measurement in the clinic which is severely affected by background acoustic noise. The development of the application in the assessment of low-frequency cochlear function may become possible if a further series of studies can verify the feasibility, but it is not meant to be a substitute for audiometry or OAE measurements. The measurement of detection threshold of CM waveform responses using growth function approach may become possible in the clinic. The intensity-independent nature of CMs with regards to delay measurements may also become an impacting factor for differential diagnoses and for designing new research studies.

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Introduction

Besides subjective measurements, objective measurements are also important for hearing assessment in the clinic.[1] Audiometry is a subjective measurement. This measurement relies on the ability of a patient to provide subjective responses, and therefore, relies on a patient's subjective judgment as to whether the test sound is heard. In the clinic, audiometry plays an important role in hearing assessment. Some other measurements such as otoacoustic emissions (OAEs), cochlear microphonics (CMs) and auditory brainstem responses (ABRs) are objective, and do not rely on the tester's subjective judgment.[2-8] While objective measurements cannot completely substitute for audiometry, they are important tools for the clinicians. That is why OAE measurements are now frequently used in the clinic because they are often needed for further assessment of cochlear function and also for further assessment of various hearing disorders.

However, there are limitations associated with OAE measurements. At low frequencies, OAEs are difficult to measure due to a high noise floor. The high noise floor either conceals the OAE signal or results in a high detection threshold.[9,10] The detection threshold is the minimal stimulus intensity at which a measurement system can detect a given type of response. Even if a high detection threshold can be utilized in the clinic, its measurement is very challenging because the measurement of high detection thresholds requires high stimulus intensities. The latter can result in false OAEs, which can be elicited from a dead cochlea.[11] In addition, the results of low-frequency OAEs can vary greatly. For example, response amplitudes in lower frequency distortion product OAEs and those in higher frequency distortion product OAEs differ significantly.[12]

Despite these hurdles, obtaining a measurement at low frequencies is essential. For instance, the low frequency of 500 Hz is included in tuning fork tests, pure tone average tests, and toneburst-ABR tests.[13,14] In addition, we have addressed high frequency CMs in two recent articles in 2012.[15,16] Therefore, we focus on the low-frequency CM in this report by extending our attention to one more factor, intensity dependence.

CM measurements may be considered as a supplementary approach to OAE measurements in assessing low-frequency cochlear function. Aside from OAEs, CMs can also be used for assessing cochlear conditions as hair cells are involved in generation of both CMs and OAEs.[6] CM measurements do not have the same limitations that OAE measurements have. For example, acoustic noise will not jeopardize CM measurements, as CMs are electrical signals.[17,18]

Based on the information and reasons above, this study explores the possibility of using low-frequency toneburst evoked CM waveforms as a supplementary approach to OAE measurements in the clinic by investigating the effects of intensity on such CMs such as their amplitudes and delays.

CM measurements have gradually become a feasible tool in assessing cochlear functions in the clinic including low frequency functions. CM measurements have undergone a long history of development. Wever and Bray recorded CMs but they thought these recorded waves were neural responses.[19] Adrian later suggested that these recorded waves were cochlear responses instead.[20] More information on post-1931 developments can be found in Dallos' book.[21] Subsequently, CM measurements became a feasible option for assessing human cochlear conditions in the clinic. The term electrocochleography was adopted to encompass assessment techniques such as CM measurements.[22]

Fully utilizing CM measurements in the clinic will require substantial research endeavors. The exploration of various applications for using CM measurements has been attempted in the past.[5] For example, in 1999, an electrode was placed on the tympanic membrane under local anesthesia to record CMs from human ears in response to a speaker in a free field.[23] Low-frequency CMs in response to a short toneburst (5 ms) were recorded, and a detection threshold at 20 dB nHL was observed.[23] In 2003, an insert earphone with an ear canal recording electrode was used in human ears to record low-frequency CMs in response to a longer toneburst (14 ms). The reporters found that at higher intensities the CMs recorded at the ear canal were robust although the amplitude was smaller than the response signals recorded at the tympanic membrane.[24] Later, the recordability of robust CMs using ear canal electrodes in human ears in response to a longer toneburst at high intensities was confirmed by investigators in this field.[25] Furthermore, measurement of CMs with a recording electrode at the mastoid was also attempted by multiple researchers.[25-27] These results were positive, although the response signals were smaller than those measured with an ear canal recording electrode. The difference between responses measured at the mastoid and at the ear canal was statistically significant. A recent study on human subjects showed that the detection threshold of low-frequency CMs could be achieved even at 0 dB HL (with an average at 10 dB HL) using a mastoid electrode and speaker-generated stimulations.[27] Furthermore, CMs recorded with the electrodes placed at three locations (the ear canal, the concha, and the mastoid) from the same human subjects were compared, providing a description of CM measurements with a concha recording electrode.[18]

Despite the information gained from these studies, there is still insufficient amount of solid data to support the possibility of using CMs as a supplementary method to OAE measurements in the clinic in assessment of the cochlear function.[28] Therefore, prior to the conclusion that ear-canal measured CM waveforms at low frequencies can be used as a supplementary approach to OAE measurements in the clinic, a series of studies should be performed to explore the possibility for such an application. The series of such studies may include place-specific CM responses, low-frequency cochlear function, effect of stimulus intensity on CM responses, etc.

In this report, we do not intend to address place-specific CM responses but intend to report the effects of stimulus intensity on low-frequency toneburst cochlear microphonic waveforms, which is just one in the series of such a line of studies.

Materials and Methods

Subjects

Ten human volunteer subjects aged 20-30 were recruited into the study as one group. The subjects were healthy and reported no hearing problems within the last five years. Otoscopy and tympanometry were conducted to exclude abnormalities in the external and middle ear. Participants were required to have a hearing threshold of ≤20 dB HL at 500, 1000, 2000, and 4000 Hz in air-conducted pure tone audiometry. They were also required to have an air-bone gap of ≤10 dB for all these audiometric frequencies. Recruitment of subjects and the procedures of the study were conducted according to the human subject protocol approved by the University Ethics Committee Institutional Review Board.

Measurement of cochlear microphonic waveforms

The stimuli were created using parameters set up by procedures in the Bio-logic Navigator Pro Auditory Evoked Potential System software (Natus Medical Incorporated, San Carlos, CA, USA). The system and stimulus intensity were calibrated in accordance with ANSI S3.6-2004 standards.[29] A 500 Hz toneburst for measuring CM waveforms was formulated. The toneburst was relatively long with a total duration of 14 ms, consisting of a 2 ms rise-time, a 10 ms plateau-time, and a 2 ms fall-time. The stimulus signals during rise and fall times were gated by the Blackman function. Such a toneburst is much longer than the toneburst used in standard toneburst ABR measurements. A longer toneburst and rise-fall time minimize the possibility of evoking prominent waves of ABR. CM waveforms which have a minimal possibility of being contaminated by ABR waves facilitate a more accurate data analysis. The recording settings were similar to those that were previously reported:[11,18,30-32] 100-2000 Hz filtering with a slope of 2 poles, 100,000x gain, 23.8 μV artifact rejection feature on, 27.7/s stimulation rate to minimize 60 Hz artifacts, 10k/s sampling rate, 2000 sweeps, 20 ms epoch, correction of 0.8 ms acoustic transmission time through a sound delivery tube, and a sampling rate higher than the Nyquist frequency to avoid sampling alias.

The toneburst was presented in a single polarity, and rarefaction polarity was selected. Intensity levels were set at 80, 60, 40, 30, 20, and 10 dB nHL. The recording electrode (inverting or '-' electrode) was placed in the ear canal at the ipsilateral side, with the reference (non-inverting or '+' electrode) at the forehead and the common (ground or 'G' electrode) on the contralateral side. The ear canal electrode was a foam insert plug wrapped with gold foil (Tip-trode). The electrodes were appropriately placed so that the impedance between the electrodes was below five kilohms. To avoid cross-talk transmissions of electromagnetic interference signals from the stimulus pathway to the recording electrodes and their leads, the earphone and its wires were shielded with Mμ-metal material. To test the effectiveness of the shielding, the sound delivery tube was clamped to block acoustic stimulations to serve as a negative control test. In addition, when the sound delivery tube was not clamped, a delay was observed when monitoring potential artifact contaminations, ensuring that the recorded waveform was not an artifact. In case of artifacts, no latency would be observed.

The latency (which is equivalent to delay, as termed for this article) is the time period between the onset of stimulation (or of a given wave within the stimulus waveforms) and the appearance (onset) of the CM waveform (or of a given response wave to that same given stimulus wave). For the sinusoidal signal, the latency can be expressed as a phase shift. The 20 ms epoch is long enough to enclose both the evoked CM waveforms in response to the 14 ms toneburst and any latency or delay. If no latency is observed, then a possible contamination artifact might have occurred, and the measurement system would be inspected to exclude the potential artifact.

Data analysis

The data sets (CM waveforms) were collected from each subject in the group. The amplitude and latency (or delay) of the CM waveforms were measured based on a previous report,[28] which is described as follows. The amplitude of the CM waveforms was obtained by transformation of the responses from the time domain into the frequency spectrum via FFT. The magnitude located at 500 Hz in the spectrum appeared prominent and was defined as the amplitude of the CM waveforms. Amplitudes for the CM waveforms were analyzed in response to different stimulus intensities, resulting in growth functions showing CM amplitudes as a function of stimulus intensity. The latency (or delay) was also analyzed against stimulus intensities. The latency here again as described above is the time period between the onset of stimulation (or of a given wave within the stimulus waveforms) and the appearance (onset) of the CM waveform (or of a given response wave to that same given stimulus wave). The peaks of the CM waveforms near a certain time point were used for the purpose of this analysis. We selected a late peak at around 11 ms for all measures as a criterion for analysis because the peaks at this approximate temporal location have three features: stable, clear, and sensitive (*i.e.*, still noticeable at low stimulus intensities). These three features may be due to the fact that the peaks of the CM waveforms at around 11 ms were more robust than those at the beginning of the toneburst which were still at the rise time period and also than those at the end of the toneburst which were at fall time. The peak at 11 ms is also more stable because two other prior peaks were just after transition from rise time to plateau. Furthermore, should the period of the delay change as a result of varying stimulus intensities, the temporal location of the peaks of these late CM waveforms would change or shift. Therefore, because we analyzed these late CM waveforms as a function of stimulus intensity, we use the term *delay* to describe the time where a given wave peak is located along the x-scale (Figure 1).

The CM data were pooled together for statistical analysis. The analysis was performed using the SPSS statistical package for Windows (version 14.0; SPSS Inc., Chicago, IL, USA). The means among variables were analyzed and compared statistically with ANOVA methods, *e.g.*, repeated measures. The significance was considered at $P<0.05$.

Results

Cochlear microphonic waveforms: signal or artifact

Figure 1 shows a typical sample of CM waveforms recorded at the ear canal. The *CM* trace was recorded with the sound tube un-clamped (*tube open*). The bottom trace was recorded with the sound *tube clamped*. When the tube was clamped, the earphone was still on as the electrical current to the insert earphone was not turned off. The *CM* trace shows that with sound tube un-clamped, low-frequency CM waveforms can be recorded at the ear canal in response to a toneburst.

The response was robust, and the CM waveforms mimicked the sinusoidal waveforms of the stimulus toneburst. The period between the peaks of each cycle was 2 ms, indicating that the response is a 500 Hz signal. A delay also appeared after the onset of the stimulation and before the appearance of the CM waveforms. On the bottom trace, with the sound tube clamped, no sound was delivered to the ear canal. A flat trace was recorded, indicating that no CM waveforms were detected.

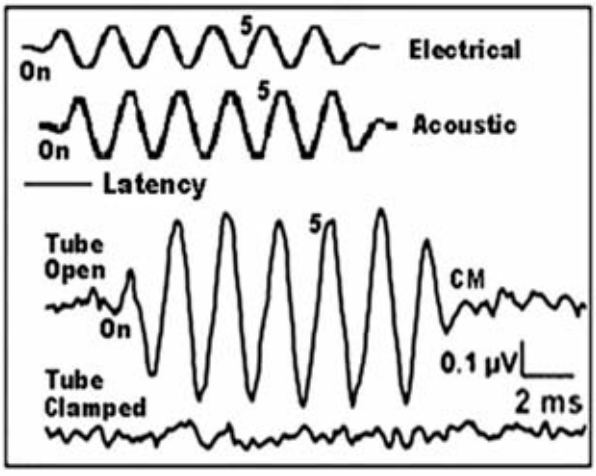

Figure 1. Cochlear microphonic (CM) waveforms. *CM (Tube Open)*: A sinusoidal waveform, which was recorded at the ear canal in response to a 14-ms 500-Hz toneburst at an intensity of 80 dB nHL. A latency existed after onset of electrical and *acoustic* stimulation (*On*). After the latency, the CM waveform appeared (*On*) and mimicked the waveform of a sinusoidal toneburst stimulus, *i.e.*, at different time point. Bottom trace (*Tube Clamped*): A flat trace, which was recorded with the sound delivery tube clamped. No sinusoidal waveform was recorded. Relative time course and delay (equivalent to latency) can be observed by the appearance of wave 5 as labeled.

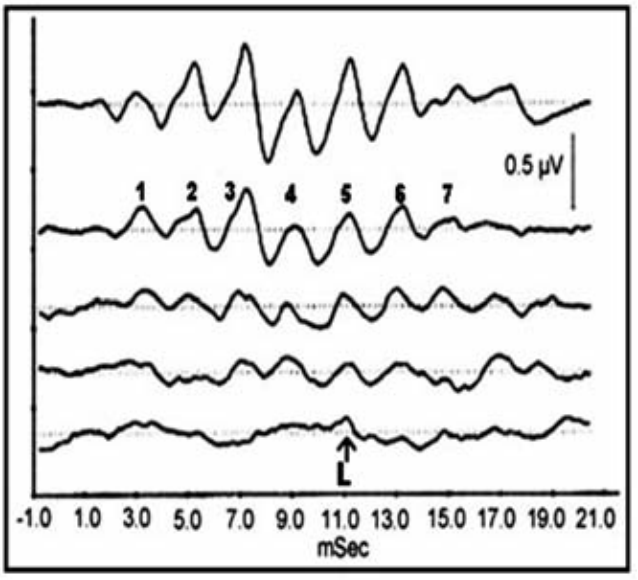

Figure 2. A family of cochlear microphonic (CM) waveforms. The waveforms were recorded in response to a 500-Hz 14-ms toneburst at the intensities of 60, 40, 30, 20, and 10 dB nHL, respectively from top to bottom. Of 7 waves as labeled, wave 5 of the CM waveforms at around 11 ms is still noticeable in the bottom trace (L with an arrow).

Effects of stimulus intensity on cochlear microphonic waveforms

Figure 2 shows the general behavior of CM waveforms as a function of stimulus intensity. A family of CM waveforms was recorded with stimulus intensity decremented from 60 dB nHL to 10 dB nHL. The amplitude and the delay of the waveforms as well as their possible changes can be observed. The amplitudes of the CM waveforms seem to decrease with a decrement in intensity. The resulting CM waveforms were still obvious at a 20 dB nHL stimulus level, as shown in the second to last trace. As to the delay, as described in the *Materials and Methods* section (*Data analysis*), the peak of the CM waveforms in each trace does not seem to shift substantially along the horizontal axis (time) as a function of stimulus intensity, which is especially reflected by observing the peak at around 11 ms for every CM waveform trace (Figure 2, labeled with an L and an arrow on wave 5). The temporal locations for these peaks seem to appear relatively constant and aligned vertically along the time point around 11 ms for all CM waveform traces recorded in response to different intensities.

The amplitude of the CM waveforms can be re-examined. In the last trace in response to a 10 dB nHL stimulus level, although the response signal becomes weak, the response waveform peak still seem noticeable at around 11 ms in reference to the other CM waveforms which are responding to higher stimulus levels (Figure 2, L with an arrow and wave 5).

Delay of the cochlear microphonic waveforms as a function of stimulus intensity

Besides the growth function of CM waveforms as shown in Figure 2, the delay of the late CM waveform at around 11 ms as a function of stimulus intensity is shown in Figure 3. The means of the delay of the CM waveform were plotted as group data with standard error bars against the different toneburst intensities. As described above, the wave peaks of the CM responses at around 11 ms were selected as the analyzing peaks because these wave peaks were more stable, constant, and robust than those at the beginning of the waveforms. For example, in Figure 2, these peaks still seem noticeable at an intensity of 10 dB nHL. As shown in the intensity-delay function (Figure 3), the change in the delay due to the change in toneburst intensity is not-significant ($P>0.05$).

Average growth function of cochlear microphonic waveforms

Figure 4A shows a growth function for the CM waveforms as a function of stimulus intensity plotted semi-logarithmically. The function shows an increase in output (*e.g.*, amplitude of CM waveforms) in response to an increase in input (*e.g.*, intensity of tonebursts). The means of the CM waveform amplitudes are plotted as group data with standard error bars against the different toneburst intensities. The change in amplitude in response to different intensities is statistically significant ($P<0.05$). Therefore, as a result, this growth function is intensity-dependent, unlike the *delay* of the CM waveforms, which is intensity-independent. The same data in Figure 4A are plotted in Figure 4B but on a logarithm scale, which more clearly shows the nonlinear cochlear functions.

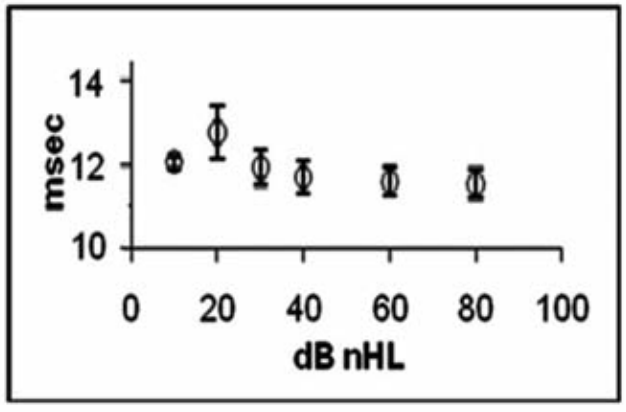

Figure 3. The delay of cochlear microphonic (CM) waveforms as a function of toneburst intensity. The effect of stimulus intensity on the latency of CM waveforms is shown. The stimulus intensities are labeled along the horizontal axis. The means of the delay of the late CM waveforms at around 11 ms with standard error bars are plotted against the different toneburst intensities. As described in *Materials and Methods* section, the chosen peak of the late CM waveforms is located temporally at around 11 ms (Figure 2, wave 5 with an L and an arrow). The change in delays due to a change in toneburst intensities is not-significant ($P>0.05$, ANOVA, repeated measures, n=10).

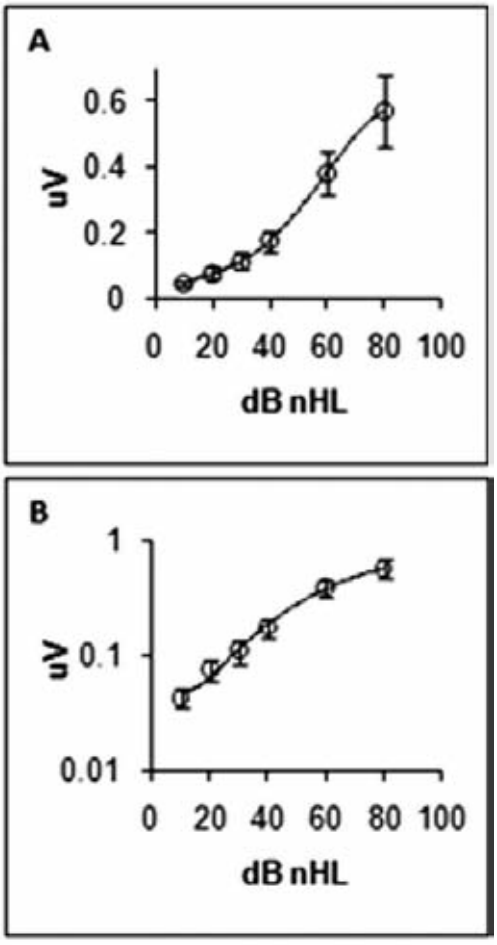

Figure 4. Average growth function of the cochlear microphonic (CM) waveforms as a function of toneburst intensity. The effect of stimulus intensity on the amplitude of CM waveforms is shown (A: semi-logarithmically; B: logarithmically. The intensities are labeled along the horizontal axis. The means of the amplitudes of the CM wave 5 at around 11 ms (as shown in Figure 2) with standard error bars are plotted against the different toneburst intensities. The change in the amplitude due to changes in toneburst intensities is significant ($P<0.05$, ANOVA, repeated measures, n=10).

Individual growth function of cochlear microphonic waveforms: potential nonlinearity

Figure 5 shows the exact same plot as shown in Figure 4B but is only based on the data from an individual subject. This separate plot is presented not because non-linearity is not shown in Figure 4B but because individual data may appear differently from group data, and the group data as shown in Figure 4B may be affected by averaging process. For example, if there were some unknown changes in amplitude during growth with intensity in individual data, the changes might not occur at the same segment along the growth function in the data among all the subjects tested; and the averaging process might overlap different segments among all data points in the group so that unknown changes might not be revealed. To avoid such a possibility and to reveal the potential unknown changes, if any, during nonlinear growth course, plotting the growth function measured from an individual subject may be interesting. In Figure 5, the growth function from individual data is plotted, and the nonlinearity is also clearly shown. Some changes or slight difference are shown in Figure 5 when compared to the averaged data in Figure 4B. For example, the slope of the growth function seems somewhat steeper during the lower stimulus intensities, and the appearance of saturation at the higher intensities seems more obviously. However, the patterns between the average and individual growth functions are not substantially different from each other.

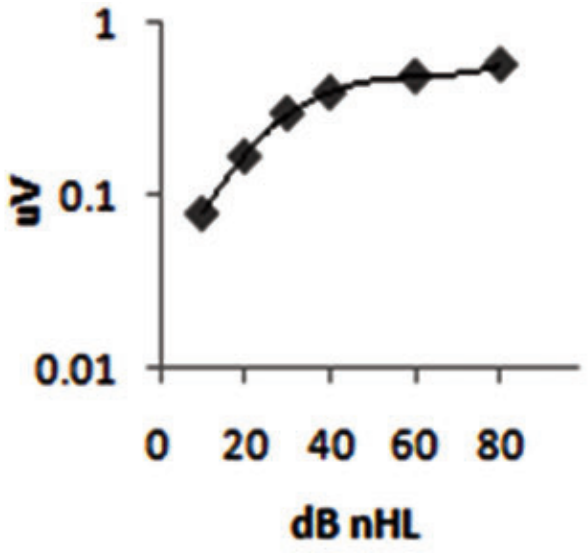

Figure 5. Individual growth function of the cochlear microphonic waveforms as a function of toneburst intensity. The plot is the same as the one as shown in Figure 4B but is only based on data from one subject.

Discussion

Growth function of cochlear microphonic waveforms

The average growth function of CM waveforms is shown in Figure 4. The amplitude is increased with stimulus intensity. Growth of the amplitude of CM waveforms with intensity is understandable because it is consistent with general behaviors in the physiology kingdom. As described in the results, the process of averaging and analysis might obscure the nonlinearity in the growth function if it existed. As such, individual growth functions of the CM waveforms were plotted in Figure 5. The nonlinearity of the growth functions seem to exist to a certain extent. It is not surprising that nonlinearity exists because the cochlear function is nonlinear in nature in response to the change of stimulus intensity. This is consistent with the results reported previously by other investigators.[33,34] In addition, the growth function approach may be used to measure detection threshold, which will be further discussed later in the subsection titled *Detection threshold*.

Independence of stimulus intensity in delay measurement

CM measurements are not new, but the study of the behavior of the delay of relatively long toneburst CM waveforms as a function of intensity for clinical application is relatively new as we have not identified reports with great detail on this topic, especially when using an ear canal electrode to perform the measurement.

The latency or delay occurred before the appearance of the CM waveforms and after the onset of the stimulation (Figure 1, tube open; Figure 2, a family of traces). This suggests that the recorded waveform was not an artifact of electromagnetic interference. CMs are known as the summation of alternating transduction currents generated by a population of hair cells, especially by outer hair cells.[35-38] As a physiological response, the sinusoidal CM waveforms occur after a latency or delay but does not occur instantaneously at the same time as the onset of the input of electrical current to an earphone.[5,18,24] The latency (or delay) analyzed in this study is based on a single frequency. Therefore, only one individual latency (*i.e.*, one frequency) was involved, as opposed to a group latency (*e.g.*, not for one frequency but for a group of multiple frequencies). Analysis of a single frequency with an individual latency avoids complexity in analysis, interpretation, and discussions, especially during the early stages of this series of studies.

Attention could also be paid to the delay of the CM waveforms when different intensities are presented. The intensity-delay function in the measurements of CM waveforms appears differently from that in ABR measurements. In our study, as described in the *Materials and Methods* section, the change in the delay (equivalent to latency) was analyzed by examining the CM waveform peaks at around 11 ms. The results in Figure 3 show that the delay of those peaks did not significantly change in temporal location due to a change in intensities, indicating that the delay is intensity-independent. If the delay were intensity-dependent, the temporal location of the peaks would shift as a function of stimulus intensity.

This finding is consistent with the physiological features of hair cells. Once stimulation reaches the hair cells, the hair cells generate CMs almost instantaneously without any discernible latency or delay, regardless of any change in stimulus intensities.[21,35-37,39] This intensity-independent behavior of responses is different from neural responses. For neural responses, *e.g.*, ABRs, the latency (or delay) is prominently intensity-dependent, and this is reflected in their level-latency function curves.[40]

Although the change in amplitude with intensity analyzed as an overall result by ANOVA repeated measures is not significant, the change in delay due to a great change in intensity between the individual pair of means may result in some significance. As such, by observing the results in Figure 3, the largest possible change in delay is between the data at 60 and at 20 dB nHL, which is a 40 dB change in intensity. However, the change in CM delay between this pair is still not significant. Although not statistically significant, we believe the reason is potentially due to statistical power (small change, sample size, and data variation), and the trend of the change still exists, and the amount of change is small even if the change is significant. These features are consistent with a previous study in which a small change in latency (~0.36 ms) was found due to change in intensity (60 dB *vs* 30 dB SL).[41]

They explained that the change in latency is because at low intensity the recorded response is from more apical cochlea.[41] The more the shift towards the apical cochlea, the closer the peak of traveling wave towards the characteristic frequency location, and the more *active* cochlear mechanism is involved. This is also consistent with a recent finding that the measured CMs are not associated with the *passive* basilar membrane traveling described by von Bekesy in cadavers.[42] Lack of association with passive mechanisms suggests an association with an active mechanism, and the active mechanism suggests an activity of hair cells close to the characteristic frequency location.

Frequency following responses and cochlear microphonic waveforms

A comparison and differentiation between frequency following responses (FFRs) and CM waveforms has never been an easy task because no clear discussion of this issue has been identified in the literature.[43-46] However, our attempt here is to explore a way to address this issue. CM waveforms and FFRs share at least three common features to result in the uneasy task as mentioned above.[46,47] The first is that both of them are electrical signals. The second is that both responses have the same behavior, *i.e.* mimicking the stimulus waveforms by being phase-locked to the stimulus. The third is that the signals of both can be recorded by surface electrodes.

However, they also differ in several ways, by which we may use to meet the challenge of the uneasy task and to differentiate which of the two is recorded. The differences can be considered at least in four major aspects: origin of the cells, location of the sources, latency of the responses, and intensity dependence of the latency. As for the origin of the cells, the CM waveforms are generated by outer hair cells, while the FFRs are generated by neurons.

As for the location of the source, the CM waveforms are from the cochlea, while FFRs are from the auditory nervous system.[47] The location of the source for FFRs has been considered to be complex and be from multiple stages along the long pathway of the whole auditory system. For example, the FFR can be either permanently abolished by sectioning the eighth nerve or reversibly abolished by cooling the cochlear nucleus.[47] Latency studies using click-evoked responses indicate that the onset of the FFR corresponds with early waves IV and V.[48] Some investigators have found that the FFR originates at the level of the brainstem,[49] or from the level near the inferior colliculi.[50] Other investigators have even considered that FFRs come from the cochlea (*i.e.*, CMs) or is severely contaminated by CMs.[43-46]

As for the latency of responses, FFRs have a long latency after the vibration reaches the hair cells because time is required for the signal to be relayed through one or multiple synapses. For example, FFRs in humans can have a latency of 8.2 ms and is consistent with a response source at the level of the midbrain.[45] The latency of the FFR can also be around 6 ms when the toneburst intensity is 30 dB above the FFR threshold.[48] Additionally, in stacked ABRs, wave V in response to a short 500-Hz toneburst is near 9 ms, and wave I is near 5 ms.[51] However, CM waveforms occur instantaneously without any delay once the vibration reaches the hair cells. Although time is needed for the signal to be transmitted from the ear canal to the cochlea and additionally from the stapes to the hair cells along the basilar membrane, CM waveforms appear much earlier than FFRs.

As for the intensity dependence of the latency, the latency of FFRs is intensity dependent, *i.e.*, their latency changes with intensity.[45,48] For example, a great change in the latency of FFRs was observed as a function of intensity, up to about a 4-ms to 5-ms difference to a 30 dB change in intensity, *e.g.* between 30 dB to 60 dB SL.[41,52] In contrast, our results indicate that the delay (equivalent to latency) of CM waveforms is basically intensity independent, *i.e.*, its delay (*i.e.* its latency) does not seem to change substantially with intensity. This is reflected in the latency-equivalent delay of the CM waveforms as a function of time as shown in our result and in Figure 3. The peaks of the waveforms stay relatively constant as a function of intensity. A small change in latency due to change in intensity between 30 dB and 60 dB has been reported in the past.[41] Such a small change around 0.36 ms was observed as well in our result as shown in Figure 3 between 30 dB and 60 dB nHL although not significant. This amount of change (0.36 ms) is almost the same as that reported by Picton,[41] and is more than 10 fold smaller than the change in FFRs (*i.e.*, 4 ms to 5 ms). Therefore, it is not convincing to say that the waves shown in Figure 3 are FFRs.

Types of cochlear microphonics

Traditionally, CMs measured in the clinic are typically a signal in response to a transient click stimulus.[5,53-55] The CMs thus measured are shown in an electrodcochleogram usually together with but earlier than summating potentials (SP) and action potentials (APs). The latter are used to facilitate recognition of APs or for calculating the SP/AP ratio.[5,54] The CMs thus recorded generally indicate that the cochlea is functioning.

Including the click-evoked CMs, three types of CMs have been typically measured as reported in the literature based on the difference in stimulus paradigms. For example, the CMs can be evoked by a click, by a short toneburst (*e.g.*, <5 ms), and by a relatively long toneburst (*e.g.*, >14 ms). These three paradigms, and thus evoked CMs, have been previously discussed and addressed.[16] Based on this previous report, only a couple of period cycles appear in a click-evoked CM, which is represented by ringing of the basilar membrane and represents activities associated with many frequencies.[56,57] Compared to click-evoked CMs, a short toneburst evoked CM contains more periods of cycles and represents fewer frequencies, and therefore, is more frequency specific.

However, the CM evoked by a relatively long toneburst appears to have many more waves than either the click or the short toneburst evoked CMs, and therefore, is the most frequency specific of the three types of CMs. In addition, improvements upon the analysis of the amplitude and delay of a given wave can be facilitated because of the availability of a sufficient number of periods of cycles and stabilized waves of the CMs during the plateau period which is in the middle segment of the whole length of the relatively long trace with multiple waves.[56,57] A stable plateau can be as long as 10 ms between the rising time and falling time. The amplitudes of the waves within the plateau are relatively constant and have reached a maximum level already, as shown in Figure 1 and 2. The multiple stable and maximal CMs during the plateau facilitates a more accurate extraction of the value of the amplitudes and delays from the data.

Actually, measuring long CM waveforms is not new because their measurement from animals was reported as early as in the 1930s.[19,20] Later, they were measured from humans as well, for example, using a tympanic membrane electrode,[7] using an ear canal electrode at both low and high intensities before 2003,[24] at high intensities,[25] and using a mastoid electrode and speaker-generated stimulations,[27] although rarely using a canal electrode with an insert earphone.

Differential diagnosis

Independence of stimulus intensity in delay measurement of CM waveforms may become an impacting factor for the differential diagnosis. This seems to be a relatively new area in the field of audiology; however, speculation in this new area will promote its extension and expansion in applications.

First, in patients with auditory neuropathy, measurable CMs support the diagnosis because measurable CMs indicate that cochlea is functional; the outer hair cells are not substantially affected; and poor speech perception is not due to poor cochlear function but due to poor neural function because of dys-synchrony. In addition, there is a second

consideration. A measurable response phase-locked with the stimulus can also support the diagnosis if the latency or delay of the response is independent of stimulus intensity. The responses which are independent of stimulus intensity in latency measurement are not congruous with the feature of an FFR. FFRs as a neural response will not be able to be measured in auditory neuropathy, even though auditory neuropathy patients usually have normal outer hair cells.

Second, besides the independence of stimulus intensity in the delay measurement of CM waveforms, the growth function in low frequencies may be used to monitor the change of the number of hair cells in a longitudinal study or a clinical follow-up. The growth function of neural responses has been considered for use in assessing the number of neurons in the auditory nerve.[58-60] For example, a narrower dynamic range may indicate a limited number of functional neurons. The growth function may be used to assess the number of hair cells as well. For example, the pure tone hearing threshold may not be affected when a number of hair cells have already been lost. However, we may hypothesize that the amplitude and growth function of CM waveforms may change before any change in the hearing threshold is detected, and low-frequency CMs may also relate better to low-frequency hearing.

Third, the independence of stimulus intensity in delay measurement for CM waveforms may be used to assist in ensuring whether the FFR is obtained from neural source. Independence of stimulus intensity in delay measurement may indicate that the FFR is severely contaminated by CMs. The contamination will affect the accuracy of the application of the FFR measurement. Recently, using FFRs as an approach in the assessment of various nervous systems including auditory systems and speech ability is rising.[61-64] The FFR is known to be more prominent in lower frequencies than in higher frequencies. Assessing speech perception using FFRs may become attractive as lower frequencies are more associated with the sounds needed to produce vowels, and vowels are one of main components in speech.[62]

Fourth, the opposite is also true, as the feature of independence of stimulus intensity in delay measurement of CM waveforms may be used to assist in ensuring that the CMs are not severely contaminated by FFRs. Contamination by FFRs will affect the accuracy of the electrocochleography application of the CMs. Recently, attention has been paid to rekindle the application of the (ECochG).[5,24,25,27] The ECochG includes CMs, and low-frequency FFRs may be mistaken as low-frequency CMs.

Detection threshold via subjective *versus* via objective measurement

Measurement of CM detection threshold may be achievement using the measurement of growth function of CM waveforms. CM detection threshold, if achievable, is completely different from regular hearing threshold measured using audiogram. Audiograms are a subjective measurement requiring testers to respond based on their subjective judgment of whether or not they hear the testing sound, while CMs and OAEs are objective measurements which do not require subjects to perform subjective judgment and behavioral response. In the clinic, the measurement of hearing threshold subjectively by using an audiogram approach is practical, but the measurement of detection threshold objectively by using OAEs is not practical as of today. This is due to the limitations which are associated with OAE measurement, *e.g.*, background acoustic noise. However, being able to objectively measure the detection threshold is one of the major expectations in the clinic.

This study shows that the CM waveform may still be recognized at low stimulus intensities. Therefore, measurement by using the CM approach may provide an opportunity to measure detection threshold objectively. The CM detection threshold is not the same value as that in the hearing threshold. However, the CM detection threshold may be correlated with hearing threshold, and as such, the CM detection threshold may be used to estimate the hearing threshold.

There may be many ways to measure detection threshold using CM waveforms. For example, a comparison of measures between stimulus on (sound tube opened) and stimulus off (sound delivery tube clamped) can be performed to obtain the signal to noise ratio. The signal is the response when the tube is opened (*e.g.*, 10 dB, 20 dB nHL, etc.), and the noise is the electrical background noise when the tube is clamped. Software can be developed to compare (in real time during signal averaging) the two measures between stimulus on and off until a statistical significance is reached within a reasonable time period. If the significance cannot be achieved within that period, a next higher stimulus intensity can be selected and the test can be continued.

Exploration of potential application in adults *versus* in children

To test the CM waveform approach on children is highly expected as background acoustic noise encountered in children is much higher than in adults during OAE measurement. If the measurement of CM waveforms can benefit diagnosis in the clinic, it may be appropriate to test the efficacy of the approach first on adults before children. Data thus obtained from adults is usually more accurate than that obtained from children as adults are more cooperative and produce less background noise than children, *e.g.*, from muscles, etc. In fact, even on adults, using CM waveforms to assess low-frequency cochlear function is still a new approach and has not been fully explored. Moreover, the availability of more accurate data from adults will be of high value for the interpretation of the data recorded from a child which may be compromised by background noise. Therefore, research using the CM waveform approach on adults first should be a reasonable plan for this line of study.

Polarity of the stimulus and the randomization of the stimulus presentation

Polarity of the stimulus and the randomization of the stimulus presentation may affect the measurement of CM waveforms. Stimulus can be setup to start pushing the tympanic membrane first or pulling the tympanic membrane first, which are thought to be of different polarities and termed condensation and rarefaction polarity respectively. For the polarity, during our studies which have recently reported,[15,16,18] we have considered the potential effect of different polarities on the results and tested the effect. The amplitude of the responses was somewhat different in response to different polarities if a click was used because a click has only one polarity, either rarefaction or condensation (data not shown) without any opposite polarity followed within the same stimulus trace. For this study, by using a relatively long toneburst, no significant effect was observed due to different polarity on the conclusions of how the intensity affects the change of amplitude and latency or delays. Lack of such effect can be thought due to using the relatively long toneburst which has both polarities and has a sufficient number of waves to allow the effect of both polarities to be included together in one analysis which covers a peak to trough correspondent to both polarities. For the randomization, our order of presentation was related to the intensity. We tested the randomization of the order of the presentation. For a small step such as a 5 dB change, the order of the presentation may affect the amplitude result between the data from two adjacent intensities. With a larger step such as 10 or 20 dB intervals, the effect of intensity on the conclusion related to the amplitude and the latency or delay was not found.

Potential effects of age and canal volume on cochlear microphonic measurement

Like OAE measurement, age and canal volume can also potentially

affect the results of CM measurement. These issues in the CM measurement can be regarded to be and treated the same way as those in the OAE measurement. We were concerned about these issues. Therefore, to avoid these potential effects for this study, we narrowed the population of the subjects to a small age range between 20 to 30 years old, which has also provided us with a relatively small variation in canal volume. Even if there are small effects due to these effects, our study is more of a relative comparison of multiple data points from the same individuals (intra-subjects or within-group) instead of a comparison of the data between different individuals (inter-subjects or between-group). So the comparison is performed between the data obtained from the same canals, and the effects of canal volume on this study of CM measurement can be neglected or minimized.

Limited use of cochlear microphonic measurement in the clinic

CM measurements may have limited use in the clinic. For example, this is mentioned by previous investigators in 2006.[65] It is very appropriate and reasonable that they felt that CMs presented limited clinical use because they observed the existence of CMs in subjects with hearing loss and also in subjects with no OAEs measured. They also showed two interesting correlations: compound action potential (CAP) with CMs (in their Figure 3B) and CAPs with OAEs (in their Figure 4). Combining these two correlations may logically and reasonably lead to a third correlation, *i.e.*, CMs with OAEs, to a certain extent, although this third correlation was not directly performed. Since 2006, more studies have been done to explore potential clinical application of CMs, and are reflected in quite a few post-2006 references cited in this current report. Our study is one of these studies and it explores some potential CM behaviors which may facilitate the clinical use of CMs. For example, the potential applications are described in several subsections above: *Differential diagnosis*, *Exploration of potential application in adult* versus *in children*, *Detecting threshold via subjective* versus *via objective measurement*, and *Frequency following responses and cochlear microphonic waveforms*. Thus the process of rekindling the application of CM measurements has been started.[66]

Magnitude of the recording and proximity of the recording electrodes to the hair cells

It is critical to select the location of a recording electrode from which the CMs are measured. As such, this issue has been investigated by various investigators. It is acknowledged that Wever and Bray first recorded the CM but they claimed it to be a neural response.[19] Later, Adrian suggested that the CM originated in the cochlea.[20] Dallos' book can be referred to for further details.[21] With the advancement of technology in the past several decades, the electrode has been placed further away from the hair cells and from inside the cochlea, to outside the cochlea, to the round window niche or promontory area, to the outside of the middle ear, to the tympanic membrane, to the external ear canal, and eventually to outside the ear canal, *i.e.*, the concha.[5,18] Such an achievement in the migration of the electrode placement seems to be resulted from a better understanding of how to obtain a clearer recording from weaker signals using a remote electrode and how to analyze and interpret such response signals thus recorded. Through these achievements, a non-invasive approach may become feasible in the clinic. It is obvious that the closer the electrode to the hair cells, the stronger CM recordings will be. There is no doubt that, in the clinic, the trans-tympanic electrode is the best site to obtain the strongest CM recordings, so as to be considered the *gold standard* technique.[65] For a number of our projects on CMs, we have obtained and identified relevant data which indicate that the response magnitude changes by four fold between those measurements obtained using a trans-tympanic and those using a tympanic electrode, by two fold between those using a tympanic and those using a canal electrode, and by a non-significant amount between those using a canal and those using a concha electrode. Therefore, the magnitude decreases by a total of eight fold from use of the trans-tympanic to the canal or concha electrode. However, studies have shown that a clear CM waveform which can be utilized can still be measured by a canal or concha electrode. The migration of recording electrode away from stronger signal measurements has been motivated by the ability to perform less invasive and more convenient measurements as well as the ability to measure weak signal more accurately due to the advancement of technology.

Conclusions

In this report, we do not intend to address place-specific CM responses but intend to report on the effects of stimulus intensity on low-frequency toneburst evoked CM waveforms, which is just one of the series of such studies in this area. The reported findings may be useful for the development of the application of CM measurements as a supplementary approach to OAE measurement in the clinic. The development of the application of CM measurements in the assessment of low-frequency cochlear function may become possible if a further series of studies can verify its feasibility, but it is not meant to be a substitute for audiometry or OAE measurements. Through this development, the measurement of CM detection threshold using a growth function approach may become possible in the clinic. The independence of stimulus intensity in delay measurement of CM waveforms may become an interesting factor for differential diagnosis and for designing new research studies.

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