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Recommendations for measuring the Electrically-Evoked Compound Action Potential in Children with Cochlear Nerve Deficiency

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Abstract

Objective: This study reports a method for measuring the electrically-evoked compound action potential (eCAP) in children with cochlear nerve deficiency (CND).

Design: This method was developed based on experience with 50 children with CND who were Cochlear® Nucleus™ cochlear implant (CI) users.

Results: This method includes three recommended steps conducted with recommended stimulating and recording parameters: initial screen, pulse phase duration optimization, and eCAP threshold determination (i.e., identifying the lowest stimulation level that can evoke an eCAP). Compared to the manufacturer-default parameters, the recommended parameters used in this method yielded a higher success rate for measuring the eCAP in children with CND.

Conclusions: The eCAP can be measured successfully in children with CND using recommended parameters. This specific method is suitable for measuring the eCAP in children

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with CND in clinical settings. However, it is not suitable for intra-operative eCAP recordings due to the extensive testing time required.

Keywords

cochlear implant; cochlear nerve deficiency; electrically evoked auditory compound action potentials; speech processor programming

INTRODUCTION

Cochlear nerve deficiency (CND) refers to a small (hypoplastic) or absent (aplastic) cochlear nerve (CN) as revealed by results of a high-resolution magnetic resonance imaging (MRI) scan. It is estimated to be present in 10 – 19% of children with congenital sensorineural hearing loss (e.g. McClay et al., 2008; Teagle et al., 2010), and can occur in up to 50% of children with single-sided deafness (SSD) (Nakano et al., 2013). The pathogenesis of CND is believed to be due to arrested inner ear development during embryogenesis (Jackler et al., 1987). The inner ear develops from ectoderm – the germ layer of the embryo that forms the entire nervous system. CND can occur as a part of the overall abnormality of ectoderm differentiation. As a result, around 50 – 60% of children with CND have other neurological deficits in addition to hearing loss (Birman et al., 2016; Huang et al., 2010). These comorbidities often result in developmental delays that limit the child's ability to provide reliable behavioral responses, which makes cochlear implant clinical management extremely challenging.

Due to advances in imaging techniques and expansion in cochlear implant (CI) candidacy criteria, the number of children with CND who receive CIs at a young age has increased. This new clinical trend, along with the lack of an evidence-based clinical practice for managing implanted children with CND, creates a tremendous challenge for clinicians who manage this unique patient population. In current practice, clinicians often use default parameters suggested by the CI programming software and increase the amount of charge per electrode by manipulating various parameters. A period of watchful waiting ensues to determine if the child can tolerate and/or will respond to auditory stimulation using those settings. This method, while rational, requires multiple clinical appointments, prolonged periods of observation for progress in auditory skills and speech and language development, and may ultimately yield inappropriate CI programming settings.

Delays in providing sufficient auditory input have lasting detrimental effects on communication skill development and overall cognitive function in children (e.g. Ching et al., 2013; Conway et al., 2010; Pierson et al., 2007). In addition, providing appropriate CI program settings at an early post-implant stage is essential for identifying a subgroup of children with CND whose CN deficiencies preclude benefit from their CIs. For these patients, a timely transition to alternative intervention strategies (e.g., auditory brainstem implantation and/or visual communication) is crucial to achieve maximum potential in communication skill development. Therefore, there is an urgent need to identify and develop objective clinical tools that can be used to assist in the programming process of these patients.

In the absence of reliable behavioral responses, electrophysiological measures are the most promising tool for clinicians due to their objective nature. The electrically-evoked compound action potential (eCAP) is a near-field recorded neural response generated by electrically-stimulated CN fibers that can be recorded using intra-cochlear CI electrodes via a “reverse” telemetry capability incorporated in current CIs. Its presence depends on the existence of sufficient CN fibers responding synchronously to electrical stimulation delivered by the CI. Its amplitude is weighted by responses generated by CN fibers near the stimulating and recording electrodes (Abbas et al., 2006; Miller et al., 2008; Hughes & Stille, 2010). Therefore, the eCAP offers opportunities to assess CI function as well as neural responsiveness at the level of the cochlea. Compared with other electrophysiological measures, the eCAP offers several advantages that make it an ideal tool for testing children in clinical settings. First, measuring the eCAP requires minimal patient cooperation due to its relatively large amplitude. Second, the eCAP is not affected by the patient’s arousal status or developmental changes in the central auditory system due to its peripheral neural origin. This results in very good test-retest reliability (Brown et al., 2010). Finally, the eCAP can be measured using standard programming equipment and software that are provided by CI manufacturers, minimizing financial costs for clinics.

In CI recipients with typical anatomy, it has been shown that stimuli presented at the level of eCAP threshold (i.e., the lowest stimulation level that can evoke an eCAP) are always audible to CI users (Brown et al., 1998; Abbas et al., 1999; Hughes et al., 2000; Franck & Norton, 2001; Thai-Van et al., 2001; Gordon et al., 2002, 2004; Smoorenburg et al., 2002; Eisen & Franck, 2004; Han et al., 2005; McKay et al., 2005; Potts et al., 2007; Wolfe & Kasulis, 2008; Holstad et al., 2009; Jeon et al., 2010). Thus, the eCAP threshold can provide an initial estimation of audible programming levels when present.

Prolonged pulse-phase durations and high stimulation levels are often used in implanted children with CND as a combined result of the lack of guidance for selecting these parameters, the absence of reliable behavioral responses, and the overall poor responsiveness of these patients to electrical stimulation of the CI (Teagle et al., 2010; Buchman et al., 2011). Both of these manipulations substantially increase the likelihood of electrical artifact contamination on eCAP responses, making measuring the eCAP in these patients challenging. The current manufacturer-default parameters usually work well for measuring the eCAP in CI users with non-amorphous anatomy. However, in children with CND they often result in recording traces that are contaminated by electrical artifact and can be easily misinterpreted. This technical difficulty has limited the usefulness of the eCAP in children with CND.

Over the last four years, we have worked with 50 implanted children with CND nationally and internationally, for both research and clinical care purposes, and developed a method for measuring the eCAP in this unique patient population. This perspective paper reports this newly developed method with the hope that it can be used to obtain useful information from some children with CND who cannot be tested otherwise.

METHOD

General Introduction

Measuring the eCAP in children with CNL requires independent adjustment of a variety of stimulating and recording parameters. Only parameters adjusted in this new method are discussed. In addition, at the time of development, only the Advanced Neural Response Telemetry (NRT) function implemented in the Custom Sound EP commercial software (Cochlear Ltd, Macquarie, NSW, Australia) allowed for these adjustments. Therefore, this method was developed based on experiences of working with Cochlear® Nucleus™ CI users with Freedom (Nucleus 24RE) or newer internal devices, and cannot necessarily be extrapolated to recipients of other devices at this time.

Subjects

There were 50 children with CNL included in this work. Eighteen were female and 32 were male. They ranged in age at test between 1.6 to 17.2 years. All children were implanted with a Cochlear® Nucleus™ device (Cochlear Ltd., Macquarie, NSW, Australia) with an internal electrode array of 24RE[CA], CI512, or CI522. Their clinical diagnosis of CNL was based on results of MRI scans interpreted by the implanting surgeon.

Forty-two out of 50 children were recruited and tested for research studies that were approved by the local Biomedical Institutional Review Board. They received payment for their participation and written informed consents were obtained from legal guardians prior to participation. For the other eight children, legal guardians' permission was obtained for the researcher (SH) to provide recommendation and expertise to clinicians while they tested patients clinically for eCAP measures.

Recommended Parameters

Recommended Parameters—The recommended stimulating parameters of this method include the pulse phase duration and the probe rate. The recommended recording parameters used in this method include the recording electrode location, the amplifier gain, and the number of sweeps averaged for each eCAP response. Details of these parameters are described below.

Stimulating Parameters—Also called pulse width in the Custom Sound programming software, pulse phase duration interacts with stimulation level to increase or decrease the amount of electrical charge delivered by the CI electrode. The auditory percept that results from increasing electrical charge is loudness growth. Compared to “typical” CI patients, children with CNL require higher electrical charge to generate behavioral and eCAP responses (Buchman et al., 2011; He et al., 2018). Due to the voltage compliance limits, increasing pulse phase duration is typically needed to deliver sufficient electrical charge in children with CNL. Therefore, the pulse phase duration is typically the first parameter to be adjusted for individual children with CNL. The pulse phase duration typically used to evoke an eCAP in children with CNL ranges from 25 to 100 μ s/phase. Minimizing artifact contamination is extremely challenging for pulse phase durations that are longer than 88 or 100 μ s/phase.

Probe rate is the frequency of stimulation used to elicit the eCAP. The amount of neural adaptation to single pulses is minimal for probe rates of 15 Hz or lower (Clay & Brown, 2007). In addition, CN fibers in children with CND have prolonged refractory recovery time (He et al., 2018). Therefore, a slow probe rate is necessary to successfully evoke an eCAP in children with CND. In this method, a probe rate of 15 Hz or lower is recommended for measuring the eCAP in these patients. Panel (a) and (b) of Figure 1 shows representative traces recorded in one child with CND (CND3) using a probe rate of 80 Hz and a probe rate of 15 Hz, respectively. These traces were evoked with a biphasic pulse with a pulse phase duration of 50 μ s/phase presented at a stimulation level of 200 CL. All other stimulating and recording parameters used to measure these two traces were the same. Whereas the eCAP could not be identified for the trace elicited using the manufacturer-default probe rate (i.e., 80 Hz), it was recorded when a slower probe rate (i.e., 15 Hz) was used. For some patients with severe deficiency in the CN, a probe rate of 5 or even 2 Hz is needed in order to elicit an eCAP. Among 50 patients involved in this study, four patients required a probe rate slower than 15 Hz for eCAP recording.

Recording Parameters—Figure 2 depicts traces recorded at electrode 9 in one child with CND (CND4). Traces shown in panel (a) were recorded with a recording active electrode that was two electrodes away from the stimulating electrodes in the *apical* direction (manufacturer-default). In comparison, traces shown in panel (b) were recorded with a recording active electrode that was two electrodes away from the stimulating electrodes in the *basal* direction. All other stimulating and recording parameters used to record traces shown in these two panels were the same. It is apparent that traces shown in panel (a) do not include an identifiable eCAP. In contrast, the eCAP could be identified for all traces shown in panel (b). These data clearly indicate that the recording active electrode location is one important parameter for successfully measuring the eCAP in children with CND.

The development of the CN is dependent on the neurotrophic factors secreted by hair cells located in the cochlear duct (Rubel & Fritzsch, 2002). Vestibulocochlear nerve fibers die without these neurotrophic factors (Lefebvre & Leprince, 1990; Torres & Giraldez, 1998). As mentioned previously, the proposed pathogenesis of the CND is the arrested inner ear development during embryogenesis (Jackler et al., 1987). The amount of damage in the CN (i.e., the amount of surviving CN fibers) in patients with CND depends on the time point at which the inner ear development is interrupted, with poorer neural survival for earlier interruptions. Due to the “base-to-apex” sequence of cochlear duct development (Arnold & Lang, 2001; Jeffery & Spoor, 2004; Yasuda et al., 2007) and cochlear hair cell maturation (Rubel, 1978; Lavigne-Rebillard & Pujol, 1988), CN fibers located at the base of the cochlea are likely to have less damage (better neural survival) than those located at more apical locations in children with CND. This theoretical possibility is supported by results of our previous study (He et al., 2018). Specifically, the likelihood of measuring the eCAP in children with CND reduces as the stimulating CI electrode site moves from the base to the apex of the cochlea, with many apical CI electrodes showing no measurable eCAP (He et al., 2018). These results support the idea that children with CND have better neural survival at the base than the apex of the cochlea because the presence of the eCAP depends on the availability of sufficient CN fibers responding synchronously to electrical stimulation. CN

fibers near the recording electrode are important contributors to the eCAP (Abbas et al, 2006; Miller et al., 2008; Hughes & Stille, 2010). Therefore, the recording active electrode that is two electrodes away from the stimulating electrode in the *basal* direction is more appropriate for children with CND. In Cochlear® devices, electrodes 1 and 2 are located at the most basal end of the electrode array. Therefore, the recording active electrode has to be in the apical direction when stimulating these two electrode for eCAP recordings.

Amplifier gain and the number of sweeps averaged for each eCAP response are closely associated with each other. These two parameters typically need to be adjusted when pulse phase durations of 50 μ s/phase or longer are used to evoke the eCAP in order to minimize the likelihood of electrical artifact contamination. The system gain of 40 dB can be used for pulses with prolonged phase durations (i.e., 50 μ s/phase) in order to avoid saturating the recording amplifier. Empirical observations of the eCAP recordings suggest that the number of averaged sweeps should be doubled (i.e., 100 sweeps) when the system gain is set at 40 dB. Figure 3 demonstrates the effect of adjusting the system gain and the number of averaged sweeps on traces recorded in one child with CND (CND5). Solid lines indicate traces recorded with a system gain of 50 dB and 50 averaged sweeps/trace. Dark grey, dashed lines indicate traces recorded with a system gain of 40 dB and 100 averaged sweeps/trace. These traces were recorded at the C level measured for each electrode tested. All other stimulating and recording parameters used to record these traces were the same. Panel (a) shows eCAP responses recorded at electrodes 1–15 using these two sets of recording parameters. These results suggest that using these two sets of parameters yields similar eCAP results. Results of Mann-Whitney U test revealed no statistical significant difference in peak latency or amplitude between eCAPs measured using these two sets of parameters ($p>0.05$). Panels (b) and (c) show traces recorded for electrodes 16–22. It is clear that traces shown in both panels (b) and (c) are contaminated by electrical artifact but to a different degree. Traces recorded using a system gain of 50 dB [panel (b)] contained larger artifact contaminations than those shown in panel (c), making it difficult to determine the presence/absence of an eCAP response for these traces. In comparison, eCAPs could be identified for traces recorded using a system gain of 40 dB and 100 averaged sweeps/trace [panel (c)] due to the reduced electrical artifact contamination. Overall, these results show that using the system gain of 40 dB and 100 averaged sweeps/trace preserves the required signal quality for eCAP recordings and increases the likelihood of eCAP identification due to reduced effects of amplifier saturation.

Manufacturer-Default Parameters vs Recommended Parameters—The

manufacturer-default parameters for measuring the eCAP in the Advanced NRT function (v. 5.1) include a pulse phase duration of 25 μ s/phase, an interphase gap of 7 μ s, a probe rate of 80 Hz, a system gain of 50 dB, 50 sweeps for each averaged response, and a recording active electrode located two electrodes away in an apical direction from the stimulating electrode.

Figure 4 shows traces recorded at 10 electrode locations in one child with CND using three different sets of parameters. Traces shown in panel (a) were recorded using the manufacturer-default parameters at the compliance voltage limit for each CI electrode. Results shown in panels (b) and (c) were recorded at longer pulse phase durations (50 or 75 μ s/phase) and higher electrical charge per unit phase than those shown in panel (a).

Specifically, traces were recorded at the maximum comfortable level for electrodes 1, 2, 6 and 7 and at the compliance voltage limits for other electrodes. All other parameters used were kept the same for results shown in panels (a) and (b). In contrast, traces shown in panel (c) were recorded using the recommended parameters, including a probe rate of 15 Hz, a system gain of 40 dB, 100 sweeps for each averaged response, and a recording active electrode located two electrodes away in a basal direction from the stimulating electrode. The eCAP could not be identified for any traces shown in panel (a) due to either the lack of neural response (i.e., results recorded at electrodes 1, 7, 11, 12, 16, 17 and 22) or electrical artifact contaminations (i.e., results recorded at electrodes 2, 6, and 21). Increasing the amount of electrical charge through increasing the pulse phase duration and the stimulation level without modifying other parameters resulted in identifiable eCAPs for electrodes 1, 2, 6 and 7. The eCAP could be identified for results recorded at an additional two electrodes (i.e., electrodes 11 and 12) using the recommended parameters. In addition, the amount of artifact contamination on traces recorded at electrodes 16, 17, 21 and 22 using the recommended parameters was dramatically reduced compared to those recorded using the default parameters (traces shown in both panels [(a) and (b)], which makes it relatively easy to determine the presence/absence of the eCAP for these traces. For this subject, measuring the eCAP was attempted at higher charge levels by increasing the pulse phase duration up to 100 μ s/phase for electrodes 16, 17, 21 or 22. No identifiable eCAP was recorded for these electrodes.

Figure 5 depicts traces elicited by a biphasic pulse with a pulse phase duration of 50 μ s/phase presented at the C level measured for each CI electrode in one child with CND (CND2). Panel (a) shows traces recorded using the manufacturer-default parameters (except for the pulse phase duration). Panel (b) shows eCAPs recorded at all 22 electrodes using the recommended parameters, including a probe rate of 15 Hz, a system gain of 40 dB, 100 sweeps for each averaged response, and a recording active electrode located two electrodes away in a basal direction from the stimulating electrode. For each electrode location, traces shown in these two panels were evoked using the same stimulation levels. For this patient, using the default parameters yielded identifiable eCAPs for electrodes 1–4. The eCAP could not be identified for any of other traces, potentially due to the electrical artifact contamination and the poor neural responsiveness. In contrast, eCAPs could be identified for all traces recorded at all 22 electrode locations using the recommended parameters. Overall, these results indicate that use of the recommended parameters leads to a higher success rate of recording eCAPs in children with CND compared to the manufacturer-default parameters.

For each of the first 25 subjects tested in this study, measuring the eCAP was attempted using both the default parameters and the recommended parameters (described in detail below) at multiple electrode locations across the electrode array. The stimulation level used for this within-subject comparison was either the maximum comfortable level (i.e., C level) or the electrode compliance voltage limit. Using the default parameters, the eCAP was recorded at 92 out of 245 (37.50%) electrodes tested. Using the recommended parameters, the eCAP was recorded at 407 out of 468 (86.97%) electrodes tested. There were only three subjects where the eCAP was recorded at each electrode tested using both the default and the recommended parameters. The eCAP could not be identified for traces recorded at any electrodes tested using the default parameters in nine subjects due to either the absence of

the neural response or the electrical artifact contamination. Using the recommended parameters, the eCAP was recorded from all 22 electrodes in four of these nine subjects. For the other five subjects, the number of electrodes with an identifiable eCAP recorded using the recommended parameters ranged from 7 to 17. For the other 11 subjects, the success rate of recording the eCAP using the default parameters at all electrode locations tested in each subject ranged from 11.11% to 85.71% (mean: 38.93%, SD: 22.35%). The *increase* in the success rate of measuring the eCAP at the same set of electrode locations tested with the recommended parameters in each subject ranges from 13.64% to 88.89% (mean: 56.59%, SD: 27.33).

Recommended Steps

The eCAP is measured using the Advanced NRT function implemented in the Custom Sound EP commercial software (Cochlear Ltd, Macquarie, NSW, Australia) via a sound processor interfaced with a programming pod. For any children with CND who have not been previously tested for the eCAP, the following three steps are recommended after checking impedances for all CI electrodes.

Step 1: Initial Screen—The purpose of the initial screen is to identify the potential range of pulse phase durations that can be used to elicit the eCAP at different CI electrodes across the electrode array for individual children with CND.

It is recommended to use the pulse phase duration of 50 μ s/phase for this step. Set a probe rate of 15 Hz, a system gain of 40 dB and 100 averaged sweeps/recorded traces for electrodes 3, 6, 9, 12, 15, 18, and 21 with the recording active electrode two electrodes away in the basal direction from the stimulating electrode. The stimulus can be presented at the maximum comfortable level (C level) that is measured for each CI electrode if patients can provide reliable behavioral responses. Otherwise, it is recommended to present the biphasic pulse at 150 CL as the initial, estimated starting point. No sign of discomfort was observed in any of the 50 patients assessed using this stimulation level. However, it can cause facial stimulation in some cases, so vigilant attention to signs of facial twitch is recommended. Figure 6 shows a screen shot of a NRT series created in Custom Sound EP (v.5.1) with the recommended parameters. In this case, the stimulating electrode (i.e., Probe Active Electrode) is electrode 9. Traces are recorded at electrode 7 (i.e., Recording Active Electrode).

Stimulation level should be increased when no measurable eCAP is recorded. Small step size increments (< 5 CL) should be used, and the patient should be closely observed for any signs of discomfort after each increment. Testing should be immediately stopped when signs of discomfort and/or facial stimulation are observed.

Step 2: Optimize Pulse Phase Duration—In cases where the eCAP cannot be recorded within the voltage compliance limit during the initial screen, the pulse phase duration should be increased from 50 to 62 μ s/phase, and the initial stimulation level can be decreased from 150 to 139 CL for patients who cannot provide any behavioral responses. The amount of charge per unit phase (nC) is comparable between a pulse with a pulse phase duration of 50 μ s/phase presented at 150 CL and a pulse with a pulse phase duration of 62

μs/phase presented at 139 CL. Conversion from clinical levels to charges per unit for the Nucleus™ Freedom or newer internal devices can be computed using an equation of the form:

$$n \text{ C} = 0.0175 * 100^{\wedge} (C \text{ L} / 255) * \text{pulse phase duration in } \mu\text{s} / 1000 \quad (1)$$

Attempts at measuring the eCAP need to be repeated following similar steps and using similar stimulating and recording parameters as those used in the initial screen. If the eCAP still cannot be evoked at the C level or the highest stimulation level that does not cause any discomfort or facial stimulation, further increases in the pulse phase duration can be attempted (i.e., 75, 88, or even 100 μs/phase) with the initial stimulation level adjusted accordingly. The patient should, of course, be continuously monitored. In addition, smaller steps in stimulation level increments should be used for longer pulse phase durations. The process can be repeated until the longest pulse phase duration is attempted within the voltage compliance limit. In cases where recorded traces are contaminated by electrical artifact at one pulse phase duration, further increasing pulse phase duration is not necessary.

It should be pointed out that increasing the pulse phase duration allows for sending more electrical charge to CN fibers, which improves the likelihood of eliciting an eCAP. However, this practice does not necessarily lead to improved eCAP morphology because the neural membrane of auditory neurons is a leaky integrator (Loeb et al., 1983). As a result, pulses with longer phase durations are less effective than short-duration pulses to activate CN fibers (Loeb et al., 1983; Parkins & Colombo, 1987; Shepherd & Javel, 1999), which may lead to poorer eCAP morphology in some cases.

In cases where the eCAP is recorded at 50 μs/phase, reducing pulse phase duration (i.e., 25 or 37 μs/phase) is recommended in order to identify the potential optimal pulse phase duration to be used in the programming map. Assuming the presence of the eCAP to both stimuli and the range between eCAP threshold and the C level is not too narrow for the short pulse, the short pulse is preferred because it is more effective in activating the CN than the long pulse. Other benefits of using short pulses include lesser charge requirements which results in improved battery life.

Step 3: Determine eCAP thresholds—The eCAP threshold can provide an estimation for stimulation level that is audible to the patient and thresholds measured from multiple electrodes across the electrode array may be helpful in determining the overall contour of the programming map (Hughes et al., 2000; Brown et al., 2000; Smoorenburg et al., 2002; Franck & Norton, 2001). Unfortunately, the association between eCAP threshold and behavioral T (i.e., the lowest stimulation level that patients can detect) or C levels in children with CND remains unknown. As a result, the eCAP threshold does not provide specific information about where the T or C levels should be set for individual electrodes in the programming map. Behavioral testing continues to be the gold standard for creating programs with the Cochlear Custom Sound software.

Determine the Presence/Absence of the eCAP

Accurately determining the presence/absence of the eCAP is crucial for results measured in each step listed above. Identifying a no-response trace is comparably easy because it shows as a relatively flat line without any identifiable response peaks. Conversely, determining traces that are contaminated by electrical artifact can be challenging. The method that we have been using to address this issue is to reverse the polarity of the stimulus that is used to evoke the eCAP. The underlying assumption/principle of this method is that changing pulse polarity leads to flipping the polarity of electrical artifact but does not affect the polarity of the neural response (i.e., the eCAP). Specifically, the anodic-leading biphasic pulse is used to evoke the eCAP in addition to the cathodic-leading biphasic pulse. Electrical artifact contamination can be determined if recorded traces to the anodic and the cathodic pulse show a reversed polarity. It should be pointed out that the anodic-leading stimulus is more effective in activating auditory nerve fibers than the cathodic-leading stimulus in human CI users (Macherey et al., 2008; Undurraga et al., 2010; Undurraga et al., 2012; Undurraga et al., 2013; Hughes et al., 2017; Hughes et al., 2018; Luo et al., 2019). Even though the neural response polarity is not affected by the stimulus polarity, eCAPs evoked by the anodic-leading stimulus have larger amplitudes and shorter latencies than those evoked by the cathodic-leading stimulus (Macherey et al., 2008; Undurraga et al., 2010; Hughes et al., 2017; Hughes et al., 2018; Luo et al., 2019).

Panel (a) of Figure 7 shows the polarity effect on the eCAP recorded at electrode 10 in one child with CND (CND6). Panel (b) of Figure 7 shows a successful example of using the method of changing pulse polarity to identify artifact contamination for traces recorded at electrode 5 of one child with CND (CND7). In both panels, the solid and the dashed line represent the traces evoked by the cathodic-leading and the anodic-leading biphasic pulses, respectively. It is apparent that the eCAP evoked by the anodic-leading stimulus is larger in amplitude and shorter in latency than that evoked by the cathodic-leading stimulus [panel (a)], which is consistent with the literature. Despite these differences, eCAPs elicited using different pulse polarities show the same response polarity (i.e., a negative trough followed by a positive peak). In contrast, the upper trace shown in panel (b) follows a decreasing exponential decay function and the lower trace in panel (b) follows an increasing exponential decay function. In this case, changing pulse polarity resulted in the reversed polarity in recorded traces. Therefore, these traces were contaminated by electrical artifact with no identifiable eCAP response.

Even though the method of changing pulse phase polarity works reasonably well for identifying artifact-contaminated traces for many patients, it can lead to inconclusive results in some cases. Figure 8 shows the trace in response to the cathodic stimulus (solid line) and the trace evoked by the anodic stimulus (dashed line) at electrode 9 in one patient (CND8). In this case, both traces follow an increasing exponential decay function with the same response polarity. Therefore, the possibility that the recorded traces contain eCAP responses with only the positive peak recorded (Abbas et al., 1999) cannot be excluded. However, the trace evoked by the anodic-leading stimulus is smaller in amplitude than that evoked by the cathodic-leading stimulus, which is inconsistent with the well-established pulse polarity effect on the eCAP. Therefore, the method of changing pulse phase polarity did not yield

conclusive results for differentiating between the eCAP and electrical artifact contamination in this case. Further studies are warranted in order to identify a better method to address this issue.

CLINICAL APPLICATIONS

The method recommended here can be used to measure the eCAP in children with CND in clinical settings. Due to the slow probe rate used in this recommended method, it is not suitable for intraoperative eCAP recording. Collection of the responses at this slow rate will effectively triple, or more, the amount of time needed to collect responses using default parameters of Auto-NRT. An extended clinic visit, or repeated visits, may be required.

The presence of the eCAP measured using our recommended method provides supporting evidence for device integrity and the presence of functional CN fibers near stimulating and recording CI electrodes. In addition, these eCAP results may provide useful information about the pulse phase duration and the stimulation level that can be used for an individual CI electrode in the programming map. Finally, eCAP results may provide limited prediction and a better understanding of CI outcomes for individual children with CND. Specifically, the presence of the eCAP depends on the availability of sufficient CN fibers that can fire synchronously. Although the mere presence of the eCAP does not provide any predictions of CI outcomes for individual patients, the absence of the eCAP in children with CND is known to be associated with poor CI outcomes (Teagle et al., 2010; Buchman et al., 2011). Among 50 children with CND included in this work, the eCAP was not recorded at any CI electrodes in five patients. Three out of these five children showed only sound awareness with their devices and the other two children did not receive any observable benefit from their CIs. None of these five children developed sufficient auditory skills needed to support speech perception or spoken language development. These five children either received an auditory brainstem implant in the opposite ear or eventually stopped using their CIs. This experience is consistent with previously published results (Teagle et al., 2010; Buchman et al., 2011)

LIMITATIONS

This method can be used in children with CND to assess the presence/absence of the eCAP at individual electrodes, and to provide a general idea about the audible stimulation level by measuring eCAP threshold. However, results obtained following the method recommended here **do not** provide conclusive information about the appropriate pulse rate, or the T or C levels for individual electrodes. In addition, it remains unknown whether CI electrodes with absent eCAPs, or those that were contaminated by electrical artifact, should be included as functional channels in the programming map. Further studies are warranted. Finally, compared to those recorded in CI children with non-amorphous anatomy, eCAPs recorded at many CI electrodes in children with CND show prolonged peak latency and increased response width. Correctly identifying and differentiating the eCAP from electrical artifact requires experience and expertise from clinicians. The built-in peak-identifying function of the NRT typically cannot be used to identify the eCAP for children with CND due to its atypical morphology.

CONCLUSIONS

This recommended method can be used to measure the eCAP in children with CND in clinical settings. However, the required testing time is relatively long due to the slow pulse rate used in this method. Therefore, it is not suitable for intra-operative eCAP recordings. Successfully measuring the eCAP in individual patients requires adjusting and optimizing many stimulating and recording parameters. Results of eCAP responses measured using our recommended method may provide limited, yet useful information for making clinical decisions in programming parameter selection for this unique patient population.

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REFERENCES

- Abbas PJ, Brown CJ, Shalloo JK, et al. (1999). Summary of results using the nucleus CI24M implant to record the electrically evoked compound action potential. *Ear Hear*, 20, 45–59. [PubMed: 10037065]
- Abbas PJ, Brown CJ, & Etler CP (2006). Utility of electrically evoked potentials in cochlear implant users In: Waltzman S, Roland T. (Eds.), *Cochlear Implants*, second Ed. Thieme Publisher, New York.
- Arnold WH, & Lang T (2001). Development of the membranous labyrinth of human embryos and fetuses using computer aided 3D-reconstruction. *Ann Anat*, 183, 61–66. [PubMed: 11206984]
- Brown CJ, Abbas PJ, & Gantz B (1998). Preliminary experience with Neural Response Telemetry in the Nucleus CI24M cochlear implant. *Am J Otol*, 19, 320–327. [PubMed: 9596182]
- Brown CJ, Abbas PJ, Etler CP, et al. (2010). Effects of long-term use of a cochlear implant on the electrically evoked compound action potential. *J Am Acad Audiol*, 21, 5–15. [PubMed: 20085195]
- Brown CJ, Hughes ML, Luk B, et al. (2000). The relationship between EAP and EABR thresholds and levels used to program the nucleus 24 speech processor: data from adults. *Ear Hear*, 21, 151–163. [PubMed: 10777022]
- Birman CS, Powell HRF, Gibson WPR, et al. (2016). Cochlear implant outcomes in cochlea nerve aplasia and hypoplasia. *Otol Neurotol*, 37, 438–445. [PubMed: 27050647]
- Buchman CA, Teagle HFB, Roush PA, et al. (2011). Cochlear implantation in children with labyrinthine anomalies and cochlear nerve deficiency: implication for auditory brainstem implantation. *Laryngoscope*, 121, 1979–1988. [PubMed: 22024855]
- Clay KM, & Brown CJ (2007). Adaptation of the electrically evoked compound action potential (ECAP) recorded from Nucleus CI24 cochlear implant users. *Ear Hear*, 28, 850–861. [PubMed: 17982371]
- Ching TY, Dillon H, Marnane V, et al. (2013). Outcomes of early- and late-identified children at 3 years of age: findings from a prospective population-based study. *Ear Hear*, 34, 535–552. [PubMed: 23462376]
- Conway CM, Pisoni DB, & Kronenberger WG (2010). The importance of sound for cognitive sequencing abilities: the auditory scaffolding hypothesis. *Curr Dir Psychol Sci*, 18, 275–279.
- Eisen MD, & Franck KH (2004). Electrically evoked compound action potential amplitude growth functions and HiResolution programming levels in pediatric CII implant users. *Ear Hear*, 25, 528–538. [PubMed: 15604914]

- Franck KH, & Norton SJ (2001). Estimation of psychophysical levels using the electrically evoked compound action potential measured using the neural response telemetry capabilities of Cochlear Corporation's CI24M device. *Ear Hear*, 22, 289–299. [PubMed: 11527036]
- Gordon KA, Ebinger KA, Gilden JE, et al. (2002). Neural response telemetry in 12- and 24-month-old children. *Ann Otol Rhinol Laryngol*, 119, 42–48.
- Gordon KA, Papsin BC, & Harrison RV (2004). Toward a battery of behavioral and objective measures to achieve optimal cochlear implant stimulation levels in children. *Ear Hear*, 25, 447–463. [PubMed: 15599192]
- Han DM, Chen XQ, Zhao XT, et al. (2005). Comparison between neural response imaging thresholds, electrically evoked auditory reflex thresholds and most comfortable loudness levels in CII bionic ear users with HiResolution sound processing strategies. *Acta Otolaryngol*, 125, 732–735. [PubMed: 16012035]
- He S, Shamsavarani BS, McFayden TC, et al. (2018). Responsiveness of the electrically stimulated cochlear nerve in children with cochlear nerve deficiency. *Ear Hear*, 39, 238–250. [PubMed: 28678078]
- Holstad BA, Sonneveldt VG, Fears BT, et al. (2009). Relation of electrically evoked compound action potential thresholds to behavioral T- and C-levels in children with cochlear implants. *Ear Hear*, 30, 115–27. [PubMed: 19125034]
- Hughes ML, Brown CJ, Abbas PJ, et al. (2000). Comparison of ECAP thresholds with MAP levels in the nucleus 24 cochlear implant: data from children. *Ear Hear*, 21, 164–174. [PubMed: 10777023]
- Hughes ML, Choi S, & Glickman E (2018). What can stimulus polarity and interphase gap tell us about auditory nerve function in cochlear-implant recipients? *Hear Res*, 359, 50–63. [PubMed: 29307495]
- Hughes ML, Goehring JL, & Baudhuin JL (2017). Effects of stimulus polarity and artifact reduction method on the electrically evoked compound action potential. *Ear Hear*, 38, 332–343. [PubMed: 28045836]
- Hughes ML, & Stille LJ (2010). Effect of stimulus and recording parameters on spatial spread of excitation and masking patterns obtained with the electrically evoked compound action potential in cochlear implants. *Ear Hear*, 31, 679–692. [PubMed: 20505513]
- Huang BY, Roche JP, Buchman CA, et al. (2010). Brain stem and inner ear abnormalities in children with auditory neuropathy spectrum disorder and cochlear nerve deficiency. *AJNR Am Neuroradiol*, 31, 1972–1979.
- Jackler RK, Luxford WM, House WF (1987). Congenital malformations of the inner ear: a classification based on embryogenesis. *Laryngoscope*, 97, 2–14. [PubMed: 3821363]
- Jeffery N, & Spoor F (2004). Prenatal growth and development of the modern human labyrinth. *J Anat*, 204, 71–92. [PubMed: 15032915]
- Jeon EK, Brown CJ, Etler CP, et al. (2010). Comparison of electrically evoked compound action potential thresholds and loudness estimates for the stimuli used to program the Advanced Bionics cochlear implant. *J Am Acad Audiol*, 21, 16–27. [PubMed: 20085196]
- Lavigne-Rebillard M, & Pujol R (1988). Hair cell innervation in the fetal human cochlea. *Acta Otolaryngol*, 105, 398–402. [PubMed: 3400441]
- Lefebvre P, & Leprince P (1990). Neuronotropic effects of developing otic vesicle on cochlea-vestibular neurons: evidence for nerve growth factor involvement. *Brain Res*, 507, 254–260. [PubMed: 2337765]
- Loeb GE, White MW, & Jenkins WM (1983). Biophysical considerations in electrical stimulation of the auditory nervous system. *Ann NY Acad Sci*, 405, 123–136. [PubMed: 6575638]
- Luo JF, Xu L, Chao XH, et al. (2019). The effects of *GJB2* or *SLC26A4* gene mutations on neural response of the electrically-stimulated auditory nerve in children. *Ear Hear*, (Accepted).
- Macherey O, Carlyon RP, van Wieringen A, et al. (2008). Higher sensitivity of human cochlear nerve fibers to positive electrical currents. *J Assoc Res Otolaryngol*, 9, 241–251. [PubMed: 18288537]
- McClay JE, Booth TN, Parry DA, et al. (2008). Evaluation of pediatric sensorineural hearing loss with magnetic resonance imaging. *Arch Otolaryngol Head Neck Surg*, 134, 945–952. [PubMed: 18794439]

- McKay CM, Fewster L, & Dawson P (2005). A different method to using neural response telemetry for automated cochlear implant processor programming. *Ear Hear*, 26, 38S–44S. [PubMed: 16082266]
- Miller CA, Brown CJ, Abbas PJ, et al. (2008). The clinical application of potentials evoked from the peripheral auditory system. *Hear Res*, 242, 184–197. [PubMed: 18515023]
- Nakano A, Arimoto Y, Matsunaga T (2013). Cochlear nerve deficiency and associated clinical features in patients with bilateral and unilateral hearing loss. *Otol Neurotol*, 34, 554–558. [PubMed: 23449441]
- Parkins CW, & Colombo J (1987). Auditory-nerve single-neuron thresholds to electrical stimulation from scala tympani electrodes. *Hear Res*, 31, 267–286. [PubMed: 3436853]
- Pierson SK, Caudle SE, Krull KR, et al. (2007). Cognition in children with sensorineural hearing loss: etiologic considerations. *Laryngoscope*, 117, 1661–1665. [PubMed: 17690618]
- Potts LG, Skinner MW, Gotter BD, et al. (2007). Relation between neural response telemetry thresholds, T- and C-levels, and loudness judgements in 12 adult nucleus 24 cochlear implant recipients. *Ear Hear*, 28, 495–511. [PubMed: 17609612]
- Rubel ER (1978). Ontogeny of structure and function in the vertebrate auditory system In: Johnson M (Ed). *Handbook of Sensory Physiology. Development of sensory systems*. New York: Springer, 135–257.
- Rubel EW, & Fritzsch B (2002). Auditory system development: primary auditory neurons and their targets. *Annu Rev Neurosci*, 25, 51–101. [PubMed: 12052904]
- Shepherd RK, & Javel E (1999). Electrical stimulation of the auditory nerve: II. Effect of stimulus waveshape on single fibre response properties. *Hear Res*, 130, 171–188. [PubMed: 10320107]
- Smootenburg GF, Willeboer C, & van Dijk JE (2002). Speech perception in Nucleus CI24M cochlear implant users with processor settings based on electrically evoked compound action potential thresholds. *Audiol Neurotol*, 7, 335–347.
- Teagle HF, Roush PA, Woodard JS, et al. (2010). Cochlear implantation in children with auditory neuropathy spectrum disorder. *Ear Hear*, 31, 325–335. [PubMed: 20090530]
- Thai-Van H, Chanal JM, Coudert C, et al. (2001). Relationship between NRT measurements and behavioral levels in children with the Nucleus 24 cochlear implant array over time: preliminary report. *Int J Pediatr Otorhinolaryngol*, 58, 153–162. [PubMed: 11278024]
- Torres M, & Giraldez F (1998). The development of the vertebrate inner ear. *Mech Dev*, 71, 5–21. [PubMed: 9507049]
- Undurraga JA, Carlyon RP, Wouters J, et al. (2013). The polarity sensitivity of the electrically stimulated human cochlear nerve measured at the level of the brainstem. *J Assoc Res Otolaryngol*, 14, 359–377. [PubMed: 23479187]
- Undurraga JA, Carlyon RP, Macherey O, et al. (2012). Spread of excitation varies for different electrode pulse shapes and stimulation modes in cochlear implants. *Hear Res*, 290, 21–36. [PubMed: 22583921]
- Undurraga JA, van Wieringen A, Carlyon RP, et al. (2010). Polarity effects on neural responses of the electrically stimulated cochlear nerve at different cochlear sites. *Hear Res*, 269, 146–161. [PubMed: 20600739]
- Wolfe J, & Kasulis H (2008). Relationships among objective measures and speech perception in adult users of the HiResolution bionic ear. *Cochlear Implant Int*, 9, 70–81.
- Yasuda M, Yamada S, Uwabe C, et al. (2007). Three-dimensional analysis of inner ear development in human embryos. *Anat Sci Int*, 82, 156–163. [PubMed: 17867342]

Figure 1.

Traces evoked using different probe rates recorded at electrode 11 in CND3. All other stimulating and recording parameters used to measure these traces were the same. Subject number, the electrode location, the pulse phase duration (PPD) and the stimulation level used to evoke these traces are indicated in each panel. The upward and downward triangle indicate the trough and peak of the eCAP identified for the trace shown in panel (b).

Figure 2.

Traces measured using different recording electrodes at electrode 9 in CND4. Stimulation levels used to evoke these traces are indicated in this figure. Subject number, the electrode location and the pulse phase duration (PPD) used to evoke these traces are indicated in each panel. The upward and downward triangles indicate the troughs and peaks of eCAPs identified for traces shown in panel (b).

Figure 3.

Traces recorded at all 22 electrode locations in CND5 using different system gains and numbers of sweeps for the averaged response. Electrode number is indicated for each trace. Troughs and peaks of identified eCAPs in panel (c) are indicated using upward and downward triangles, respectively.

Figure 4.

Traces recorded at ten electrode locations using three different settings in one child with CND. Each panel shows results recorded using one setting. Traces shown in panel (a) were elicited using a biphasic pulse with a pulse phase duration of 25 $\mu\text{s}/\text{phase}$. Black and dark grey dashed lines shown in panels (b) and (c) indicate traces evoked by a biphasic pulse with a pulse phase duration of 50 $\mu\text{s}/\text{phase}$ and a biphasic pulse with a pulse phase duration of 75 $\mu\text{s}/\text{phase}$, respectively. Electrode number and stimulation level (in CL) are indicated for each trace. Troughs and peaks of identified eCAPs are indicated using upward and downward triangles, respectively.

Figure 5.

Traces recorded at all 22 electrode locations using two different settings in CND2. Electrode numbers are labelled for these traces in both panels. Troughs and peaks of identified eCAPs are indicated using upward and downward triangles, respectively. It should be pointed out that peaks of eCAPs recorded at electrodes 3 and 4 shown in panel (a) could not be accurately identified due to electrical artifact contamination. Therefore, they are not labelled.

EP Insert measurement(s) based on default measurement

Quick Definition Basic Parameter Set Advanced Parameter Set Stimulate Only

Probe

Probe Active Electrode 9

Probe Indifferent Electrode MP1

Probe Current Level 150

Probe Pulse Width [μs] 50

Probe Rate [Hz] 15

Masker

Masker Active Electrode 9

Masker Indifferent Electrode MP1

Masker Current Level 160

Masker Pulse Width [μs] 50

Number of Maskers 1

Masker Rate [Hz] 100

Masker Probe Interval [μs] 400

Recording

Recording Active Electrode 7

Recording Indifferent Electrode MP2

Gain [dB] 40

Delay [μs] 122

Artefact Cancellation Technique Forward M

Artefact Reduction Off

Averaging

Number of Sweeps 100

Measurement Window [μs] 1600

Effective Sample Rate [kHz] 20

Offset

A Offset -2

Auto correct

1 of 1 Measurement(s) valid.

OK Cancel

Figure 6.

A screen shot of a NRT series created in Custom Sound EP (v.5.1) with recommended parameters for initial screen.

Figure 7.

Traces in response to the cathodic-leading (solid line) and the anodic-leading (dashed line) biphasic pulse recorded at electrode in CND6 (panel [a]) and at electrode 14 in CND7 (panel [b]). The pulse phase duration (PPD) and stimulation level (in CL) used to evoke these traces are indicated in each panel.

Figure 8. Traces in response to the cathodic-leading (solid line) and the anodic-leading (dashed line) biphasic pulse recorded at electrode 9 in CND8. The pulse phase duration (PPD) and stimulation level (in CL) used to evoke these traces are indicated in the lower right corner.