

An efficient test protocol for identification of a limited, sensitive frequency test range for early detection of ototoxicity

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Abstract—A primary focus of research at the National Center for Rehabilitative Auditory Research (NCRAR) has been to develop methodology for rapid and efficient early detection of ototoxicity. It has been shown that an individualized, limited frequency range can be identified, which is sensitive to early ototoxic changes in the auditory system. In this study, a rapid identification protocol for identifying the uppermost target frequency within this sensitive range of ototoxicity (SRO) was investigated. In 36 of 42 ears, the target frequency found with the rapid identification protocol was the same as that found with the full-frequency baseline testing. Where differences occurred, target frequencies obtained by the two methods did not differ by more than one-half octave. This rapid identification protocol results in considerable time savings in ototoxicity monitoring, which will result in the capability to include more patients in a monitoring program.

Key words: *ototoxicity, rapid identification protocol, sensitive range of ototoxicity (SRO), uppermost target frequency.*

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INTRODUCTION

The National Institute on Deafness and Other Communication Disorders (NIDCD) reports that more than 28 million individuals in the United States have hearing loss of a sufficient degree as to impose a communication disorder [1,2]. A leading cause of sensorineural hearing loss arises from therapeutic treatment with drugs having ototoxic potential, especially the aminoglycoside (AMG) antibiotics and the chemotherapeutic agent cisplatin (CDDP) [3]. The effects on hearing may be highly individualized, depending on the patient's baseline hearing sensitivity, but commonly are seen initially in the highest frequencies within an individual's hearing range. Those patients with preexisting hearing loss are at an increased risk for additional hearing impairment from ototoxicity [4]. Even low doses of cisplatin have been shown to increase hearing loss in this patient population. As treatments continue, the hearing loss progresses from the individual's highest frequency range into the lower frequencies where the effect on communication is most damaging and the resulting impact on quality of life may be dramatic. Hearing loss caused by ototoxic drugs is usually irreversible. Consequently, establishing a routine test protocol for early detection of hearing loss caused by therapeutic ototoxic drug treatment is imperative.

The need for audiometric testing to identify early changes in hearing thresholds resulting from drug therapy

is widely recognized. Life-threatening conditions may require treatment with highly ototoxic agents, and the risk of hearing loss may well be unavoidable. In many cases, however, alternative drugs, reduced dosages, or altered treatment regimens are options if ototoxicity is detected early in the treatment period. Prospective monitoring of high-frequency auditory function enables the physician to weigh the merits of alternative treatment before the loss of hearing sensitivity progresses into the speech communication range. Conversely, the absence of evidence for ototoxicity can justify continued or more aggressive treatment. Monitoring hearing threshold changes can also alert the family and the patient to be aware of the potential for hearing loss and, if needed, early amplification assistance.

The test procedures currently used to perform ototoxicity monitoring are time-consuming and labor-intensive. The establishment of protocols to achieve sensitive and reliable early detection of ototoxicity in a short time would allow routine clinical monitoring to be expanded to a greater number of patients. The development of such clinically efficient monitoring techniques significantly could reduce the number of patients who suffer from disabling hearing losses and could require expensive, avoidable rehabilitation, allowing patients to retain a better quality of life.

The development of protocols for rapid and efficient early detection of ototoxicity is a primary focus of efforts at the National Center for Rehabilitative Auditory Research (NCRAR). The data from an ongoing multisite study based out of this laboratory have shown certain reliable characteristics of hearing loss caused by ototoxic agents. Specifically, initial changes in thresholds have been shown to occur in the high-frequency range when high-frequency sensitivity is present. In addition, most ototoxic hearing loss occurs initially in a small range of frequencies, and thresholds tend to be more stable at frequencies where baseline thresholds are >100 dB sound pressure level (SPL) [5–7].

These initial findings led to the development of national ototoxicity monitoring guidelines [5–8]. Subsequently, a retrospective analysis of data more specifically identified a limited but sensitive frequency range that might be useful in developing a more rapid monitoring method for early detection of ototoxicity [9]. In that study, baseline testing was performed in the routine clinical test range 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz and in the range 9, 10, 11.2, 12.5, 14, 16, 18, and 20 kHz [9]. A target, or reference, frequency was identified from this

baseline test as the highest frequency where the threshold was ≤ 100 dB SPL. This frequency, termed the “uppermost target frequency,” was also the frequency that showed the greatest number of initial threshold changes during treatment with ototoxic drugs. Frequencies where baseline thresholds exceeded 100 dB SPL showed little or no change during ototoxic drug administration. Subsequent analysis showed that fewer initial threshold changes occurred below the target frequency with the fewest changes occurring between the fourth and fifth frequencies below the target frequency. These data led to the identification of an individualized sensitive range of ototoxicity (SRO) as the five frequencies below and including the target frequency [9]. Based on retrospective data analysis of all ears that were detected for ototoxicity with the use of full-frequency testing (0.2 to 20.0 kHz), 84 percent of AMG ears and 94 percent of CDDP ears would have been detected just as early if only the SRO frequencies had been monitored. These findings supported previous observations that a high rate (90 percent) of early detection of ototoxicity is possible within a restricted frequency range for each individual [5–7].

These findings were based on retrospective data and showed the feasibility of identifying a shortened test range of audiometric frequencies that is sensitive to individual ototoxicity effects. To investigate the use of a limited frequency range prospectively in a patient population, three Veterans Affairs medical centers and two university hospitals are currently acquiring data from an ongoing study. The goal of this study is to verify the usefulness of the limited SRO in patients who are currently receiving AMG antibiotics, CDDP, or carboplatin. To date, evaluations have been performed on 221 patients (mean age is 58.9 years), including 34 patients on control drugs. Preliminary findings suggest that approximately 80 percent of patients who exhibit ototoxicity-related hearing loss as detected by the full-frequency baseline testing are identified just as early by testing the five frequencies in the SRO customized to the individual patient. Furthermore, adding two frequencies to the SRO (seven-frequency range) improves the detection rate to 83 percent.

The prospective data just mentioned strongly support the feasibility of testing within a limited, individualized frequency range as a reliable, efficient, and sensitive method of early detection of ototoxic effects. For this technique to be expeditiously administered, a method for rapidly determining each individual’s SRO needs to be developed. Currently, full-frequency baseline testing is

required to identify the uppermost target frequency in the SRO, which can involve testing behavioral thresholds at as many as 16 frequencies per ear. Such full-frequency behavioral testing is a labor-intensive protocol. In addition, it is a demanding procedure for ill patients to undergo. If a patient's SRO could be determined with a shorter testing protocol, baseline test times could be significantly reduced. Therefore, the purpose of this study was to evaluate a technique to rapidly identify the individualized SRO as defined by the uppermost target frequency (highest frequency with threshold ≤ 100 dB SPL), plus the four test frequencies immediately below the target [9].

METHODS

Subjects

Subjects included 21 hospitalized male patients (42 ears) ranging in age from 33 to 79 years (mean = 57 years) who were not receiving any medications with known ototoxic potential.

Instrumentation

A certified audiologist conducted all testing in a double-walled, sound-treated booth. Bilateral pure tone thresholds were obtained for all participants.

A Virtual Corporation Model 320 audiometer was used for all audiometric testing. Earphones were Koss Pro/4X Plus, which were modified, as described in Fausti et al. to improve the signal-to-noise ratio for high-frequency testing [10]. This earphone was used to test frequencies from 2 to 20 kHz, and a flat-plate coupler was used for calibration as described in Fausti et al. [11].

Procedures

Each subject completed all testing within a single test session. Otoscopy was conducted at the beginning of the session to confirm the appearance of unoccluded ear canals. Two audiometric tests were administered during the session. These tests were termed the "rapid identification" and "full baseline" protocols and are described in the subsequent paragraphs. The rapid identification protocol was administered first to simulate the actual condition of using the rapid procedure without first familiarizing the subject with lower frequency testing. Subsequently, hearing thresholds were obtained at all frequencies 2 kHz and above (2, 3, 4, 6, 8, 9, 10, 11.2,

12.5, 14, 16, 18, and 20 kHz) in the full baseline testing protocol. Note that the test frequencies above 8 kHz were separated by approximately one-sixth octave steps.

Rapid Identification Protocol

The rapid identification protocol is an algorithm developed to identify the uppermost target frequency of the SRO. The uppermost target frequency is specified as the highest frequency where a threshold could be obtained at or below 100 dB SPL. The initial test level for the rapid identification protocol was 95 dB SPL. Pure-tone presentation started at 20 kHz and moved to consecutively lower frequencies until an initial response was obtained. The algorithm then moved to a 100 dB SPL presentation level beginning at the frequency above, and adjacent to, the initial response frequency. If the first 100 dB SPL presented no response, the initial response frequency at 95 dB SPL was considered the uppermost target frequency. If a response occurred at the first 100 dB SPL presentation, the next higher frequency was tested at 100 dB SPL, and this frequency progression is continued until there was no response. In that case, the highest frequency at which the subject responded to the 100 dB SPL pure tone was considered the uppermost target frequency.

Full Baseline Protocol

Following testing with the rapid identification protocol, subjects were tested with the full baseline protocol to obtain thresholds at all test frequencies. Testing started at 2 kHz and progressed to consecutively higher test frequencies through 20 kHz. Hearing thresholds were determined at each frequency, and the highest frequency with a threshold of ≤ 100 dB SPL was identified as the uppermost target frequency of the SRO. The uppermost target frequencies determined with this procedure were then compared to the uppermost target frequencies found with the rapid identification protocol.

RESULTS

Figure 1 displays the mean pure tone thresholds in decibels SPL at the test frequencies for each ear of the participating patients. Note that the average hearing loss in this population increases by approximately 20 dB/octave within the two octaves from 2 kHz to 8 kHz commonly recognized as the mid to upper speech frequencies. The high frequency slope is only slightly

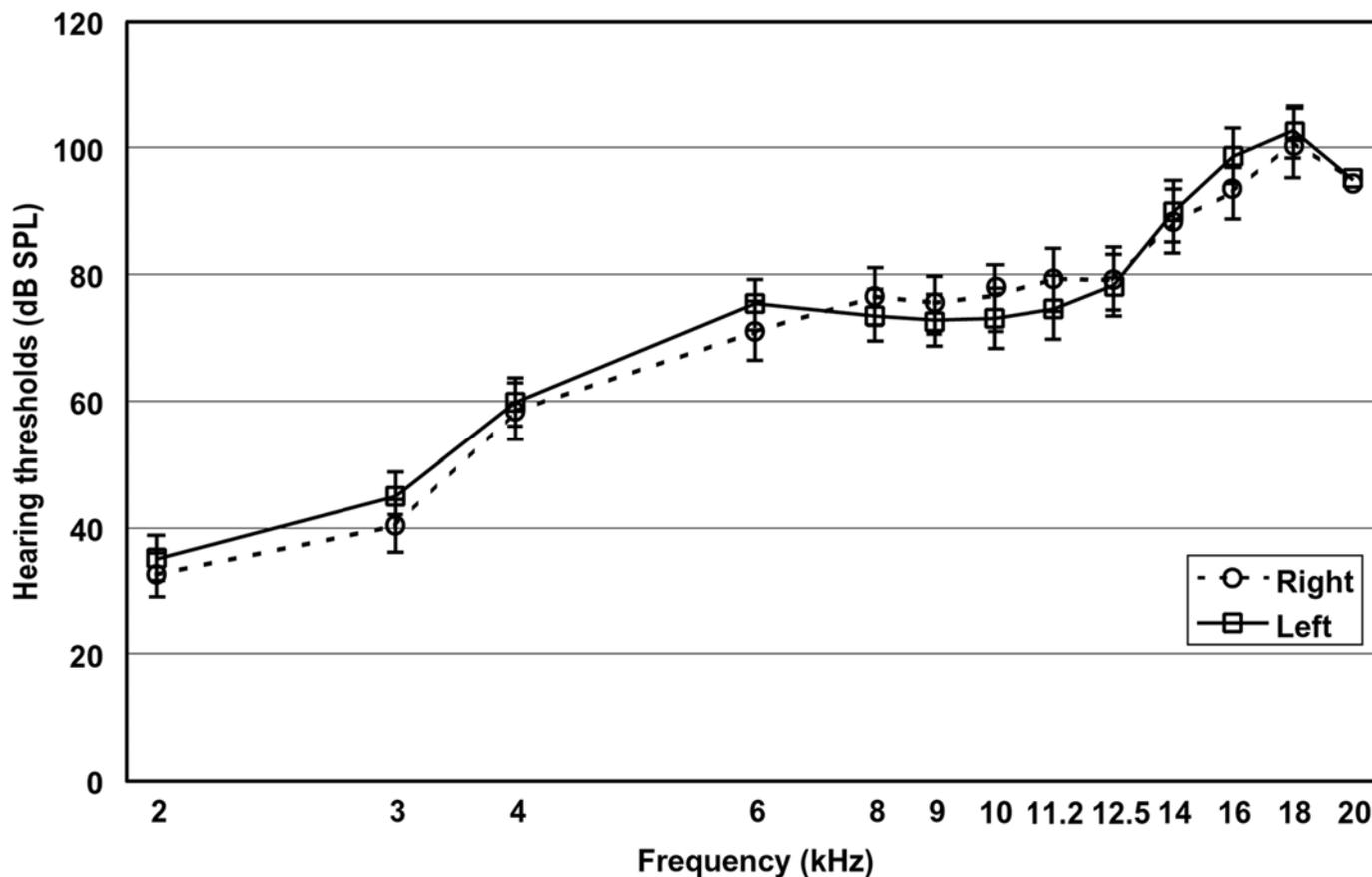


Figure 1.
Average thresholds and standard errors for each ear by frequency.

greater: approximately 25 dB in a little more than an octave from 9 kHz to 20 kHz. The number of threshold responses decreased as frequency increased beyond 10 kHz so that the average thresholds reported on this figure at the highest frequencies include a progressively smaller number of ears. Only two ears (one patient) showed measurable thresholds at 20 kHz.

The uppermost target frequencies for each patient were then compared between protocols (rapid identification and full baseline). Six patients exhibited a different target frequency in only one ear with the two protocols. As shown in **Figure 2**, each of the procedures identified the same uppermost target frequency for 36 of the 42 test ears (85.7 percent). Four ears (9.5 percent) revealed a one test-frequency difference in the uppermost target frequencies. One ear (4.2 percent) yielded a two test-frequency difference and one ear (2.4 percent) revealed a three test-frequency difference.

We would like to point out here that there were differences in the step size of the test frequencies above and below 8 kHz. Above 8 kHz test frequencies approximated one-sixth octave steps while standard audiometric frequencies (octave and mid octave) were tested below 8 kHz. Thus, a one-frequency difference above 8 kHz was smaller than a one-frequency difference in the standard audiometric frequency range. Of the six ears that demonstrated differences in the uppermost target frequencies, four of those differences occurred in the range above 8 kHz, where three of the four ears showed a difference of only one test frequency (i.e., one-sixth octave) and one ear showed a difference of three test frequencies (one-half octave). The remaining two ears that demonstrated differences between the two procedures included frequencies at the upper boundary of the standard audiometric range. One of those ears identified 6 kHz as the uppermost target frequency with the rapid identification protocol, while 9 kHz was the

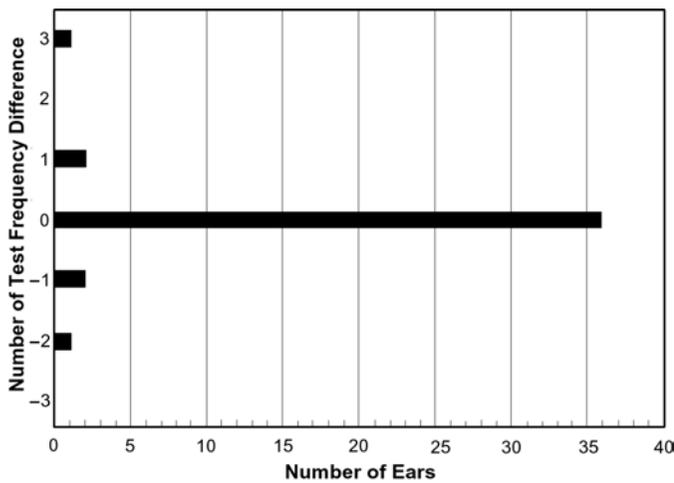


Figure 2.

Number of ears showing lower (negative numbers), no difference, and higher (positive numbers) target frequencies for rapid identification protocol compared to full baseline protocol. Differences are expressed as number of test frequencies.

uppermost target frequency or the same ear with the use of the full baseline protocol (a three test-frequency difference amounting to approximately a half octave). In the other ear, a one test-frequency difference (one-sixth octave) was found between 9 kHz (rapid identification) and 8 kHz (full baseline).

Figure 3 displays the distribution of uppermost target frequencies for the 42 ears (21 patients) as identified by the rapid identification protocol. In this group of patients not currently receiving ototoxic drug therapy, the most often identified uppermost target frequency was

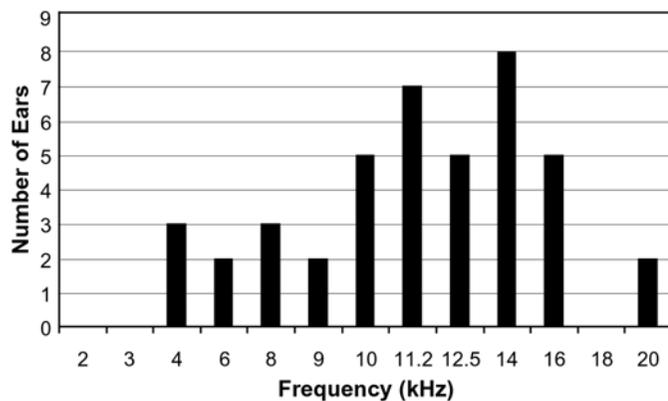


Figure 3.

Distribution of uppermost target frequencies identified by rapid identification protocol.

14 kHz. The uppermost target frequencies fell within the routine clinical test range (2 to 8 kHz) in only 8 (19 percent) of the 42 ears (six patients) further justifying the need for high frequency (>8 kHz) threshold testing.

DISCUSSION

A focus of efforts at the NCRAR is to develop methodology for rapid and efficient early detection of ototoxicity. Thus far, data from both the retrospective study and the preliminary prospective data suggest that identifying and testing a small range of frequencies for each patient would provide sensitive early detection capability [9]. The current study demonstrates that an uppermost target frequency for a limited frequency range can be determined for each individual with a rapid and efficient protocol. In this study, the rapid identification protocol identified the same uppermost target frequency as the full baseline test protocol in 87 percent of patients. In addition, the six ears that showed a difference in the uppermost target frequency identified by the two procedures had no consistent trend for the rapid identification protocol to over- or underestimate; three of the target frequencies were higher with rapid identification and three were lower. Those results suggest that the rapid identification protocol is an accurate method to determine the optimal test frequencies for early detection of ototoxicity.

Where a difference was found in target frequencies between these two methods, it is important to note that the actual frequency difference was small. Frequency steps employed in the frequency range above 8 kHz approximate one-sixth octave intervals. For those patients receiving therapeutic treatment with ototoxic drugs who are older and/or have greater preexisting hearing loss than the current group (mean age was 57 years), target frequencies most likely will be found more often at or below 8 kHz.

This laboratory is currently exploring the advantages of testing one-sixth octave steps in the frequency test range below 8 kHz. Smaller frequency steps in the routine clinical frequency range would make fine threshold structure within the SRO available for monitoring for those patients showing little or no high-frequency hearing sensitivity. Use of smaller frequency steps could provide increased sensitivity for early detection of ototoxicity at frequencies within the speech range that are not included in routine clinical threshold testing. Early

detection would permit intervention before the effect on communication becomes debilitating.

This study also supports the necessity for threshold testing to include the highest frequencies that an individual can hear, since the majority of uppermost target frequencies were identified within the upper-frequency range. Although these higher frequencies are outside the normal-speech frequency range, they can provide early warning information that may permit intervention before the speech frequencies are affected.

The rapid identification protocol makes it possible to extend behavioral ototoxicity monitoring to a greater number of patients. This is because ill patients who are unable to tolerate longer procedures may be better able to withstand a shortened testing procedure. In the NCRAR laboratory, the rapid identification protocol can be completed in less than one-third the time usually needed to complete baseline testing. Hence, the time savings for the audiologist and the diminished test fatigue for the patients makes it practical to extend hospital ototoxicity monitoring programs to a greater number of patients.

An area of additional study is the use of objective audiometric tests for ototoxicity detection and monitoring for those patients who are unable to provide reliable responses to behavioral threshold tests. For example, otoacoustic emissions tests as well as early auditory-evoked potentials show considerable promise as means of early detection of changes that occur in the auditory system because of ototoxic drug therapy [12–14]. It will be important to identify strategies for increasing the speed with which some of these tests can produce reliable and sensitive results to make such a protocol feasible for ongoing ototoxicity monitoring. The concept of identifying and monitoring only the individualized SRO may be adaptable to both evoked potential and otoacoustic testing. The use of reliable test procedures that are sensitive to ototoxicity as well as being time-efficient will enable the practical implementation of ototoxicity monitoring programs in a greater number of hospitals. Such procedures will also allow the early identification of ototoxic change in patients regardless of their ability to provide reliable behavioral responses.

In the current study, emphasis was placed on the comparison of the rapid identification protocol with the full baseline protocol to determine whether sensitivity and reliability can be maintained with the more time-efficient procedure for early detection of ototoxicity. These results show that ototoxicity can be detected with the

rapid protocol in the majority of patients at the highest frequencies well before it invades the important frequencies understanding speech. Future investigations will explore such issues as cost-benefit studies and quality-of-life studies resulting from use of the abbreviated early detection method.

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