Article published online: 2023-03-14

Wideband Acoustic Reflex Measurement

M. Patrick Feeney, Ph.D.,[1,2] Kim S. Schairer, Ph.D.,[3,4] and Daniel B. Putterman, Au.D.[1,2]

ABSTRACT

Acoustic reflex thresholds (ART) obtained using pure-tone probe stimuli as part of a traditional immittance test battery can be used to evaluate site of lesion and provide a cross-check with behavioral results. ARTs obtained as part of a wideband acoustic immittance (WAI) test battery using a click as the probe stimulus can be used in the same way with the added benefit that they may provide lower ARTs than those obtained using a pure-tone probe. Another benefit of the WAI ART test is that it can be completed without requiring a hermetic seal or pressurizing the ear canal. A new adaptive method of obtaining ARTs using WAI techniques may cut test time in half, thus making this an attractive option for future clinical use. More advanced uses of WAI ART tests include the measurement of AR growth functions. These may be used to investigate the possible effects of synaptopathy related to high levels of noise exposure and possible auditory deficits related to ototoxicity.

KEYWORDS: wideband acoustic immittance, acoustic reflex thresholds, absorbance, noise-induced synaptopathy

THE ACOUSTIC STAPEDIUS REFLEX

Metz[1] demonstrated that the acoustic stapedius reflex (AR) caused by an intense sound in one ear could be detected in the opposite ear by measuring impedance changes in the ear canal. Low-frequency middle ear impedance increases during the reflex due to the contraction of the

[1]VA Portland Health Care System, National Center for Rehabilitative Auditory Research, Portland, Oregon; [2]Department of Otolaryngology, Head and Neck Surgery, Oregon Health & Science University, Portland, Oregon; [3]Hearing and Balance Research Program, James H. Quillen VA Medical Center, Mountain Home, Tennessee; [4]Department of Audiology & Speech Language Pathology, East Tennessee State University, Johnson City, Tennessee.

Address for correspondence: M. Patrick Feeney, Ph.D., National Center for Rehabilitative Auditory Research (NCRAR), VA Portland Health Care System, 3710 SW US Veterans Hospital Road/P5, Portland, OR 97239 (e-mail: Patrick.Feeney@va.gov).

Assessment of Middle Ear Function Using Wideband Acoustic Immittance: Current Practices and Future Prospects; Guest Editor, Hammam AlMakadma, Ph.D., Au.D.

Semin Hear 2023;44:84–92.

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA
DOI: https://doi.org/10.1055/s-0043-1763296.
ISSN 0734-0451.

stapedius muscle, which stiffens the ossicular chain. The AR threshold (ART) is the lowest level of the activator that can elicit a measurable change in middle ear impedance. It is a bilateral response such that when an activator is presented to one ear, the AR occurs in both ears. Therefore, the AR may be measured by detecting changes in impedance in the same ear as the activator (ipsilateral AR) or in the opposite ear from the activator (contralateral AR). The main ipsilateral reflex arc involves the cochlea on the side of the activator stimulus, VIIIth nerve, ventral cochlear nucleus (VCN), medial superior olivary (MSO) complex, the motor nucleus of the facial nerve (MN VII), and VIIth nerve, which causes the stapedius muscle to contract if the level of the activator stimulus is at the level of the ART or higher. The main contralateral reflex arc includes the cochlea, VIIIth nerve, and the VCN on the side of the activator, and the MSO, MN VII, VIIth nerve, and stapedius muscle on the contralateral side. As the intensity of the eliciting stimulus increases, the amplitude of the AR response increases as, to a lesser extent, does the width of the impedance shift in the frequency domain.[2] Current clinical middle ear testing systems can be used to detect both the contralateral and ipsilateral ARTs.[3] These clinical systems typically measure the change in a probe tone (e.g., 226 or 1,000 Hz) to calculate changes in middle ear admittance, the inverse of impedance. Clinical tests are done at tympanometric peak pressure (TPP) at which point the pressure in the middle ear and ear canal are the same, and admittance of the probe tone into the middle ear is maximized for detecting the AR.

WIDEBAND ACOUSTIC REFLEX THRESHOLD TESTS

Feeney and Keefe[2] were the first to report on using wideband (WB) acoustic immittance (WAI) to measure the contralateral ART. WB chirps with duration of 40 ms were used as the WAI probe stimulus and 1,000 or 2,000 Hz contralateral tones were used as the activator. The study demonstrated that the AR could be measured using this technology and that the ART appeared to be as much as 8 dB lower using the WAI method compared to a standard clinical admittance method using a 226-Hz probe tone. The same WAI method was used by Feeney and Keefe[4] but with a contralateral white noise reflex activator. Average ARTs from seven subjects were approximately 18 dB lower with the WAI method compared to the clinical method. Subsequent studies using similar methods also reported lower ARTs with the WAI method compared to the clinical method for both ipsilateral and contralateral ARTs.[5,6] Schairer et al[7] used a WB click as the WAI probe stimulus at ambient pressure with an automated system to measure ipsilateral ARTs for 1,000 and 2,000 Hz tones or broadband noise (BBN) activators. ARTs with these stimuli were 2.2 to 9.4 dB below clinical ARTs depending on the activator stimulus. This was promising because a method that provides for lower reflex thresholds would allow for the procedure to be conducted with lower activator levels thus reducing the sound exposures to patients. It would also potentially allow for ARTs to be measured in individuals for whom the traditional method results in absent reflex thresholds, thus providing more information about the patient's peripheral and brainstem auditory system and possibly avoiding over referral for absent reflex thresholds.

An automated WAI method for assessing ARTs in adults and infants at ambient pressure and at TPP was reported by Keefe et al[8] and modified in Keefe et al.[9] WB ARTs were obtained using a computer-controlled Interacoustics AT235 tympanometer. An Interacoustics Titan probe assembly with two receivers was used to generate the acoustic stimuli. One receiver generated the WB probe clicks (250–8,000 Hz). The other receiver allowed higher levels to generate reflex activator signals for the ipsilateral AR test. In that study, BBN or tones were used as the activator stimuli. For the ipsilateral test, there was a sequence of four activator pulses alternating with five WB probe clicks. The analysis buffer for each click was 1,024 samples (46.4 ms) and each activator pulse was 116 ms. The total stimulus duration for the four activators and five clicks was 790 ms, which was followed by 790 ms of silence for the middle ear response to return to baseline prior to the next set of stimuli for a total of 1,580 ms (Fig. 1). There were two presentations

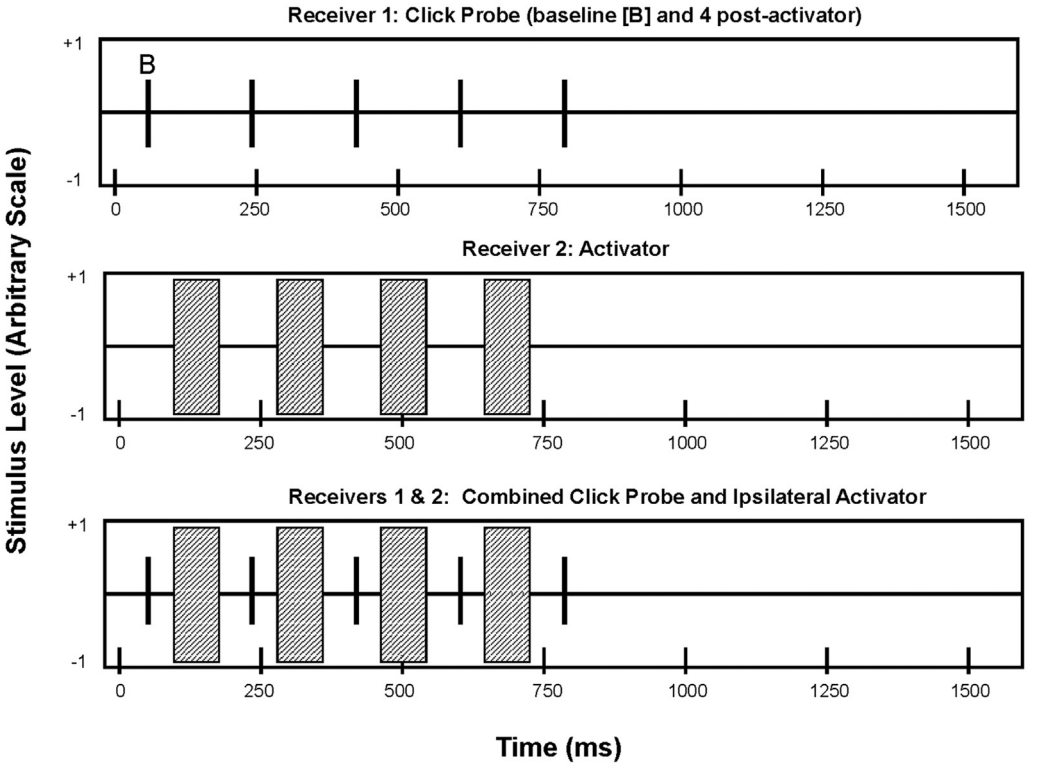

Figure 1 Cartoon of the ipsilateral wideband acoustic reflex stimulus waveform for the method described in Keefe et al.[8] The top panel shows a series of 5 wideband probe clicks presented every ~200 ms. The BBN activator pulses (middle panel) were selected from a sampled white-noise signal that was low-pass filtered at 8,000 Hz and had a duration of 116 ms. The overall waveform (bottom panel) had a duration of 1,580 ms with the stimuli presented in the initial 790 ms.

of the 1,580-ms stimulus set for each activator level. In an automated procedure, the activators increased in 5-dB steps for 10 levels, which varied in level for each stimulus type (BBN or tones) but ranged between 44 and 89 dB SPL for adults with a maximum level of 13 dB lower for infants. To calculate reflex threshold, the shifts in complex sound spectra induced by the activator, measured in the ear canal, were compared between the baseline click and subsequent clicks for spectra that attained a >6 dB signal-to-noise ratio. Correlated shifts in the complex signal spectra were expected if the shifts were due to the AR rather than random noise, and thus detecting these correlated shifts increased test reliability. Correlations were calculated between the six pairs of complex spectra for the four click-difference responses in each set and statistical significance was required for the shifts to be considered an AR response for either of the 1,580-ms stimulus sets at a given presentation level.[8]

This general method of detecting a reflex threshold was incorporated in the reflex threshold method of Keefe et al.[9] The stimulus configuration and timing were the same as in Keefe et al,[8] as was the use of 10 activator levels. Fig. 2 shows the absorbance as a function of activator presentation for one ear with an ipsilateral BBN activator for activator levels from 0 dB SPL (baseline) to 80 dB SPL. For the highest activator level, the absorbance was approximately 10% lower at 500 Hz and 3% higher at 1,000 Hz. The shift in absorbance from baseline across frequency as a function of activator level is plotted in Fig. 3 for the same conditions and ear

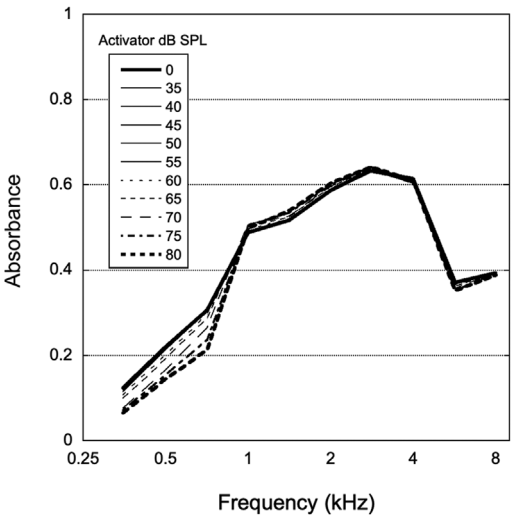

Figure 2 Absorbance as a function of activator presentation level for one ear with an ipsilateral BBN activator for activator levels from 0 dB SPL (baseline) to 80 dB SPL.

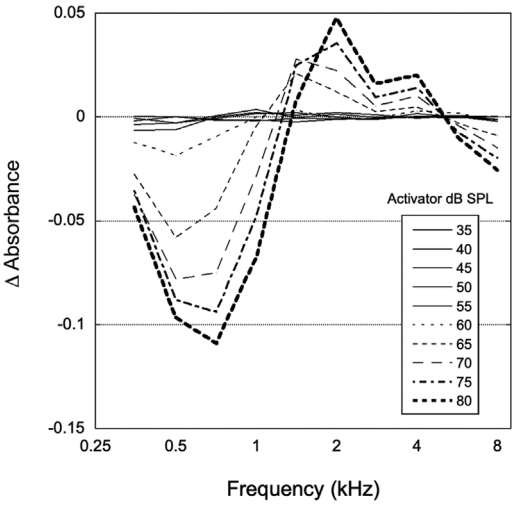

Figure 3 The change in absorbance from baseline across frequency as a function of activator level for the same ear and conditions as Fig. 2.

as Fig. 2. Reflex threshold was calculated as 60 dB SPL for this case. Keefe et al[9] calculated reflex threshold using changes in absorbed power rather than absorbance with similar results. They also used the correlations between the shifts at each activator level to further refine the estimate of ART. Feeney et al[10] reported that in adults with normal hearing, this WB method resulted in ARTs for BBN that averaged 12.3 dB lower than the traditional clinical method with a 226-Hz probe tone.

Schairer et al[11] presented an adaptive method for calculating the ART using the basic WB ART method of Keefe et al[9] with the same equipment used in that study. Schairer et al obtained WB ARTs at ambient pressure and at TPP using an automated adaptive procedure based on the reflex response for each activator presentation. As in Keefe et al,[9] at each activator level, five probe clicks were interleaved with four activator pulses (Fig. 1). The ART was detected based on two criteria as described by Keefe et al.[9] The change in the power absorbed by the middle ear between the initial pre-activator click and the four post-activator clicks was measured from 200 to 2,400 Hz in half octave steps. If the cumulative shift in absorbed power summed across that frequency band exceeded 0.7 dB between the initial click and the final post-activator click with an expected low-frequency decrease in absorbed power, this was taken as an indication that an AR had occurred. Secondly, the spectrum of the shift in absorbed power had to be significantly correlated for at least two post-activator clicks within each five-probe—four-activator sequence, which indicated a physiological response rather than noise.

If the AR was judged to occur based on these criteria, the stimulus level was decreased to 10 dB; if not, the level was increased in 5-dB steps and the procedure repeated until the AR was judged to be present again in an ascending run. The starting presentation level for an ART run was 80 dB SPL for pure-tone activators and 60 dB SPL for a BBN activator. The maximum presentation level was 105 dB SPL for pure-tone activator and 90 dB SPL for the BBN activator. The ART was defined as the lowest activator level for which the AR was present on two ascending runs. A test in which the ART was not present at the maximum presentation level was defined as an absent ART. A test that was terminated after 20 trials without establishing threshold was also documented as an absent ART.

Schairer et al[11] obtained ipsilateral and contralateral ARTs from 78 ears of 39 adults with normal hearing using the adaptive WB

method in comparison with the manual adaptive clinical method with a 226-Hz probe tone. The AR activator stimuli were pure tones at 500, 1,000, and 2,000 Hz and BBN. The mean number of trials across conditions to obtain an ART with the WB adaptive method was 9.6 and the mean test duration for each activator condition was 14 seconds. This compares with 31.6 seconds for a WB ART using the 10 fixed-level ascending research procedure described by Keefe et al,[9] in which trials occurred at 10 ascending levels with a repetition at each level for a total of 20 trials per activator condition. Further research is needed in clinical settings, but this automated method is promising for obtaining a rapid WB ART for clinical applications.

WB ACOUSTIC REFLEX GROWTH FUNCTIONS: MEASURES OF NOISE-INDUCED SYNAPTOPATHY

In addition to calculating the ART, the WB ART method described by Keefe et al[9] has proven useful for systematically evaluating acoustic reflex growth functions (ARGFs) over the increasing levels of stimulus presentation. Fig. 4 shows the ARGF for the same ear and stimulus conditions as Figs. 2 and 3. In the study by Keefe et al, the ARGF was used to determine the ART when the cumulative shift in absorbed power scalar between the initial click and the final post-activator click measured from 200 to 2,400 Hz exceeded a 0.7 dB cutoff. In Fig. 4, the cumulative change in absorbed power in dB is plotted as a function of BBN activator level. The criterion shift in absorbed power considered to be an AR is 0.7 dB[9] indicated by the dashed line in the figure. At levels below 60 dB SPL, the change in absorbed power is well below the 0.7-dB criterion point, and the function is relatively flat with increasing activator level from 35 to 55 dB SPL. However, once the ART is reached (60 dB SPL in this ear), responses at higher activator levels all exceed the ART criterion and increase with activator level up to the maximum level of 80 dB SPL. In addition to being used for the detection of ARTs, ARGFs may provide additional information for assessing auditory function.

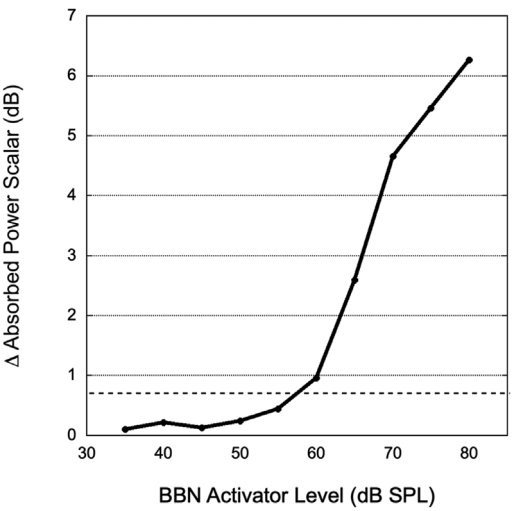

Figure 4 The cumulative change in absorbed power scalar in dB from 200 to 2,400 Hz as a function of BBN activator level for the same ear and conditions as Figs. 2 and 3. The criterion change in absorbed power to be considered an AR is 0.7 dB indicated by the dashed line.[9] The reflex threshold was 60 dB SPL.

High noise exposure in animals has been shown to result in cochlear synaptopathy, the loss of synaptic connections between inner hair cells and auditory nerve fibers. Noise exposure can result in as much as 50% cochlear synaptopathy without causing any loss of cochlear hair cells.[12] Electrophysiological measures such as wave I of the auditory brainstem response (ABR) have been shown to be sensitive to synaptopathy in animal models.[12–15] However, the results of Bourien et al[16] suggest that because the ABR is an onset response, ABR wave I is dominated by high spontaneous rate (SR)/low threshold auditory nerve fibers and low SR/high threshold fibers have a limited contribution. Given that animal models demonstrate that low SR auditory nerve fibers are the most vulnerable to cochlear synaptopathy,[13,17] ABR wave I amplitude may lack sensitivity as a measure of noise or age-related synaptopathy. Because the subset of auditory-nerve fibers with high thresholds and low SRs is predominantly affected in synaptopathy, audiometric thresholds, which are dependent on high SR fibers, are relatively insensitive to this type of neural degeneration. The AR might be a sensitive measure of synaptopathy[18–20] because low-SR fibers appear to be an important element in

evoking the AR.[21,22] In ears with synaptopathy, the AR may have a higher threshold of activation and suppressed growth function compared to normal controls. Thus, ARGFs are a potential candidate for a future noninvasive clinical test for synaptopathy.

Wojtczak et al[23] reported low WB AR magnitude in human adults aged 25 to 63 years with noise-induced tinnitus and up to a mild hearing loss, even after statistically adjusting for pure-tone thresholds. They suggested that this may represent noise-induced synaptopathy. Bramhall et al[24] compared contralateral ARGFs for a BBN activator in 57 young veterans and 35 non-veteran controls, aged 19 to 35 years, with normal audiograms and a history of high or medium levels of noise exposure (veterans) compared with low noise exposure (non-veteran controls). There were 35 veterans in the high-noise group and 22 veterans in the medium-noise group. They used the 10-level WB AR method of Keefe et al[9] to obtain ARGFs for a BBN activator ranging from 55 to 100 dB SPL in five dB steps. Model results suggested a reduction in mean AR magnitude for the veteran high-noise group compared to the non-veteran control group that increased with activator level. This is illustrated in Fig. 5 which shows hypothetical mean ARGFs for a normal control hearing group without noise exposure (solid line) and a group of subjects with synaptopathy (lower dashed line). Based on the above findings, the group with synaptopathy is hypothesized to have a reduced ARGF compared to normal controls. Bramhall et al reported that there was a maximum relative decrease in AR magnitude of 25% for the highest-level activator in that study compared to controls. This contrast was not statistically significant because the confidence interval overlapped zero. However, the parameter estimate showing a reduction in AR magnitude for Veterans with high-noise exposure is consistent with the reduction in AR strength observed in a mouse model of noise-induced synaptopathy.[20]

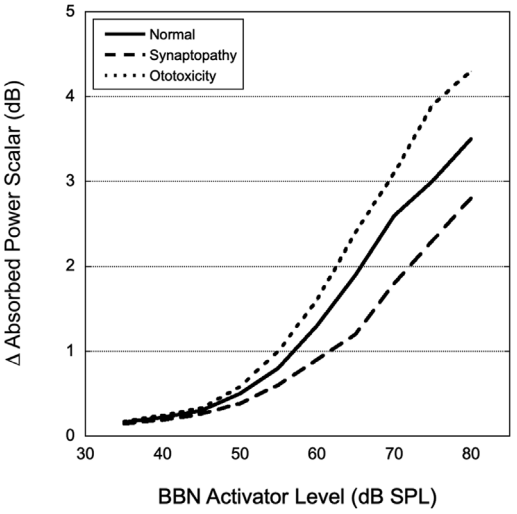

Figure 5 Hypothetical mean acoustic reflex growth functions for three groups: normal hearing (solid line), synaptopathy (dashed line), and ototoxicity (dotted line) based on the data of Bramhall et al[24] and Westman et al.[25]

WB ACOUSTIC REFLEX GROWTH FUNCTIONS: A MEASURE OF OTOTOXICITY

Westman et al[25] examined the effect of aminoglycoside ototoxicity on ARGFs. Aminoglycosides are a class of broad-spectrum antibiotics that when administered intravenously (IV) are trafficked across the stria vascularis into endolymph and absorbed into inner and outer hair cells.[26] The hair cells may be particularly susceptible to ototoxic damage due to their unusually high metabolic rate and slow drug clearance, and they have historically been considered the primary target of aminoglycoside ototoxicity.[27,28] In addition to damaging cochlear hair cells, recent evidence suggests aminoglycosides may cause cochlear synaptopathy and/or damage to neural mechanisms in higher auditory brainstem structures. Several rodent studies have identified the inner hair cell ribbon synapse as the primary target of ototoxic damage, with synaptopathy observed prior to hair cell damage.[29–31] Moreover, Xu et al[32] suggested that gentamicin damages areas of the brainstem simultaneously or prior to the cochlea after observing a decrease in cross-sectional area of cochlear nucleus neurons 1 day after administration.

Aminoglycosides can also affect the medial olivocochlear (MOC) efferent system, a descending corticofugal pathway that modulates cochlear outer hair cell function. The MOC reflex is activated by sound in either the ipsilateral or contralateral ear and inhibits the outer hair cells'

ability to amplify motion in the organ of Corti.[33] In humans, the function of the MOC reflex likely relates to improved hearing in noise.[34] Avan et al[35] found that gentamicin affected the MOC in guinea pigs, causing a lack of suppression of the outer hair cells that resulted in increased amplitude of otoacoustic emissions, a measurement of outer hair cell function.

Westman et al[25] hypothesized that patients with cystic fibrosis (CF) who were treated with IV aminoglycosides for respiratory infections would have reduced ARGFs due to ototoxicity-induced synaptopathy similar to the results for Veterans with presumed noise-induced synaptopathy reported by Bramhall et al.[24] Westman et al examined ipsilateral BBN ARGFs at ambient pressure using the method of Keefe et al[9] in four groups of subjects with normal audiometric thresholds (250–8,000 Hz). Subjects with CF formed three groups that were classified by lifetime IV-aminoglycoside exposure according to their cumulative life-time dose of aminoglycosides weighted by the frequency of dosing.[36] Of the 42 CF participants with IV-aminoglycoside exposure, the median number of cumulative doses was 40. Subjects were divided into a low IV-aminoglycoside group with 40 or fewer doses and a high IV-aminoglycoside group with over 40 doses. An additional 15 subjects with CF who had no recorded IV-aminoglycoside exposure formed a third CF group. A fourth group consisted of 29 control subjects without CF and with no history of IV-aminoglycosides exposure who were age and sex matched to the CF subgroups. The mean ages of each group ranged from 25 to 31 years and were approximately 60% males per group.

There were no significant differences between groups in mean ART. The BBN ARGFs were examined across the increasing activator levels. The growth function for the high IV AG group was greater than for the other three groups. However, a one-way analysis of variance was conducted to evaluate group differences for the average cumulative reflex power shift, and this difference was not found to be significant. Next the average ARGFs were analyzed relative to each participant's ART, thus eliminating the part of the growth function that fell below ART for each participant. A general linear model analysis was performed to examine the effect of ear on the average reflex growth from ART across level for the four groups. The effect of group was significant and Bonferroni post hoc testing revealed that both the high and low IV-aminoglycoside groups showed significantly greater absorbed power shifts than controls. This pattern is illustrated in the hypothetical mean data in Fig. 5 comparing the normal control group to the ototoxicity group. The ARGF for the ototoxicity group (dotted line) is progressively greater in magnitude than that for the normal control group. An additional analysis by Westman et al[25] showed that there were no significant group mean differences for transient otoacoustic emission levels, suggesting that outer hair cell differences between groups were not responsible for the findings.

These results caused Westman et al[25] to reject the initial hypothesis that high IV AG exposure may cause cochlear synaptopathy leading to shallow ARGFs. In fact, just the opposite occurred with higher exposure to IV AGs resulting in increased growth functions compared to controls. Westman et al postulated that increased reflex magnitude could be a sign of central gain, whereby the auditory system responds to peripheral damage with central hyperactivity. This has been proposed as a mechanism for central tinnitus and hyperacusis.[37] Furthermore, animal studies have demonstrated ototoxic damage to the VCN[32] after gentamicin exposure, which may lead to increased central gain affecting the reflex arc.[38] The CF patients with aminoglycoside exposure in Westman et al may have had several sites affected by ototoxicity, with increased central gain predominating. Additional study is needed to evaluate these effects including functional tests of speech perception in noise, for which a deficit is expected in the case of synaptopathy, and controlling for outer hair call function between groups with otoacoustic emissions.

SUMMARY

The WB ART method results in lower ARTs than the traditional clinical method, especially for BBN. This is promising because lower ARTs would allow for the procedure to be conducted with lower activator levels thus reducing the sound exposures to patients. It

would also potentially allow ARTs to be measured in individuals for whom the traditional method results in absent ARTs, thus providing more information about the patient's peripheral and brainstem auditory system. The adaptive WB ART method of Schairer et al[11] holds promise for eventual clinical use of the method to quickly obtain automated ARTs. The ART method of Keefe et al[9] may be used to measure ARGFs for the exploration of noise-induced synaptopathy and auditory deficits caused by ototoxic drugs. Additional study is needed to evaluate WB ARTs and ARGFs for these and other causes of auditory dysfunction.

CONFLICT OF INTEREST
None declared.

ACKNOWLEDGMENTS
This work was supported by the Department of Veterans Affairs Rehabilitation Research and Development (RR&D) Service through a center award to the National Center for Rehabilitative Auditory Research (C2361-C), and a Research Enhancement Award Program, Hearing and Balance Research Program (C9221-F).

DISCLAIMER
The content of this manuscript does not represent the views of the U.S. government or the Department of Veterans Affairs.

REFERENCES

1. Metz O. Threshold of reflex contractions of muscles of middle ear and recruitment of loudness. AMA Arch Otolaryngol 1952;55(05):536–543
2. Feeney MP, Keefe DH. Acoustic reflex detection using wide-band acoustic reflectance, admittance, and power measurements. J Speech Lang Hear Res 1999;42(05):1029–1041
3. Feeney MP, Schairer KS. Acoustic stapedius reflex measurements. In: Katz J, Chasin M, English KM, Hood LJ, Tillery KL, eds. Handbook of Clinical Audiology. 7th ed. Baltimore, MD: Lippincott, Williams and Wilkins; 2015:165–186
4. Feeney MP, Keefe DH. Estimating the acoustic reflex threshold from wideband measures of reflectance, admittance, and power. Ear Hear 2001;22 (04):316–332
5. Feeney MP, Keefe DH, Marryott LP. Contralateral acoustic reflex thresholds for tonal activators using wideband energy reflectance and admittance. J Speech Lang Hear Res 2003;46(01): 128–136
6. Feeney MP, Keefe DH, Sanford CA. Wideband reflectance measures of the ipsilateral acoustic stapedius reflex threshold. Ear Hear 2004;25(05): 421–430
7. Schairer KS, Ellison JC, Fitzpatrick D, Keefe DH. Wideband ipsilateral measurements of middle-ear muscle reflex thresholds in children and adults. J Acoust Soc Am 2007;121(06):3607–3616
8. Keefe DH, Fitzpatrick D, Liu YW, Sanford CA, Gorga MP. Wideband acoustic-reflex test in a test battery to predict middle-ear dysfunction. Hear Res 2010;263(1-2):52–65
9. Keefe DH, Feeney MP, Hunter LL, Fitzpatrick DF. Aural acoustic stapedius-muscle reflex threshold procedures to test human infants and adults. J Assoc Res Otolaryngol 2017;18(01):65–88
10. Feeney MP, Keefe DH, Hunter LL, et al. Normative wideband reflectance, equivalent admittance at the tympanic membrane, and acoustic stapedius reflex threshold in adults. Ear Hear 2017;38(03): e142–e160
11. Schairer KS, Putterman DB, Keefe DH, et al. Automated adaptive wideband acoustic reflex threshold estimation in normal-hearing adults. Ear Hear 2022;43(02):370–378
12. Kujawa SG, Liberman MC. Adding insult to injury: cochlear nerve degeneration after "temporary" noise-induced hearing loss. J Neurosci 2009; 29(45):14077–14085
13. Furman AC, Kujawa SG, Liberman MC. Noise-induced cochlear neuropathy is selective for fibers with low spontaneous rates. J Neurophysiol 2013; 110(03):577–586
14. Sergeyenko Y, Lall K, Liberman MC, Kujawa SG. Age-related cochlear synaptopathy: an early-onset contributor to auditory functional decline. J Neurosci 2013;33(34):13686–13694
15. Fernandez KA, Jeffers PW, Lall K, Liberman MC, Kujawa SG. Aging after noise exposure: acceleration of cochlear synaptopathy in "recovered" ears. J Neurosci 2015;35(19):7509–7520
16. Bourien J, Tang Y, Batrel C, et al. Contribution of auditory nerve fibers to compound action potential of the auditory nerve. J Neurophysiol 2014;112(05): 1025–1039
17. Schmiedt RA, Mills JH, Boettcher FA. Age-related loss of activity of auditory-nerve fibers. J Neurophysiol 1996;76(04):2799–2803
18. Shaheen LA, Valero MD, Liberman MC. Towards a diagnosis of cochlear neuropathy with envelope following responses. J Assoc Res Otolaryngol 2015; 16(06):727–745

19. Valero MD, Hancock KE, Liberman MC. The middle ear muscle reflex in the diagnosis of cochlear neuropathy. Hear Res 2016;332:29–38
20. Valero MD, Hancock KE, Maison SF, Liberman MC. Effects of cochlear synaptopathy on middle-ear muscle reflexes in unanesthetized mice. Hear Res 2018;363:109–118
21. Liberman MC, Kiang NY. Single-neuron labeling and chronic cochlear pathology. IV. Stereocilia damage and alterations in rate- and phase-level functions. Hear Res 1984;16(01):75–90
22. Kobler JB, Guinan JJ Jr, Vacher SR, Norris BE. Acoustic reflex frequency selectivity in single stapedius motoneurons of the cat. J Neurophysiol 1992;68(03):807–817
23. Wojtczak M, Beim JA, Oxenham AJ. Weak middle-ear-muscle reflex in humans with noise-induced tinnitus and normal hearing may reflect cochlear synaptopathy. eNeuro 2017;4 (06):4
24. Bramhall NF, Reavis KM, Feeney MP, Kampel SD. The impacts of noise exposure on the middle ear muscle reflex in a veteran population. Am J Audiol 2022;31(01):126–142
25. Westman MR, Putterman DB, Garinis AC, Hunter LL, Feeney MP. Wideband acoustic reflex growth in adults with cystic fibrosis. Am J Audiol 2021;30(3S):825–833
26. Li H, Steyger PS. Systemic aminoglycosides are trafficked via endolymph into cochlear hair cells. Sci Rep 2011;1:159
27. Mulheran M, Degg C, Burr S, Morgan DW, Stableforth DE. Occurrence and risk of cochleotoxicity in cystic fibrosis patients receiving repeated high-dose aminoglycoside therapy. Antimicrob Agents Chemother 2001;45(09):2502–2509
28. Cheng AG, Johnston PR, Luz J, et al. Sensorineural hearing loss in patients with cystic fibrosis. Otolaryngol Head Neck Surg 2009;141(01):86–90
29. Liu K, Jiang X, Shi C, et al. Cochlear inner hair cell ribbon synapse is the primary target of ototoxic aminoglycoside stimuli. Mol Neurobiol 2013;48 (03):647–654
30. Li S, Hang L, Ma Y. FGF22 protects hearing function from gentamycin ototoxicity by maintaining ribbon synapse number. Hear Res 2016; 332:39–45
31. Ishikawa M, García-Mateo N, Čusak A, et al. Lower ototoxicity and absence of hidden hearing loss point to gentamicin C1a and apramycin as promising antibiotics for clinical use. Sci Rep 2019; 9(01):2410
32. Xu M, Hu HT, Jin Z, et al. Ototoxicity on cochlear nucleus neurons following systemic application of gentamicin. Acta Otolaryngol 2009; 129(07):745–748
33. Liberman MC, Guinan JJ Jr. Feedback control of the auditory periphery: anti-masking effects of middle ear muscles vs. olivocochlear efferents. J Commun Disord 1998;31(06):471–482, quiz 483, 553
34. Lima da Costa D, Erre JP, Pehourq F, Aran JM. Aminoglycoside ototoxicity and the medial efferent system: II. Comparison of acute effects of different antibiotics. Audiology 1998;37(03):162–173
35. Avan P, Erre JP, da Costa DL, Aran JM, Popelár J. The efferent-mediated suppression of otoacoustic emissions in awake guinea pigs and its reversible blockage by gentamicin. Exp Brain Res 1996;109 (01):9–16
36. Garinis AC, Cross CP, Srikanth P, et al. The cumulative effects of intravenous antibiotic treatments on hearing in patients with cystic fibrosis. J Cyst Fibros 2017;16(03):401–409
37. Noreña AJ. An integrative model of tinnitus based on a central gain controlling neural sensitivity. Neurosci Biobehav Rev 2011;35(05):1089–1109
38. Cao XJ, Lin L, Sugden AU, Connors BW, Oertel D. Nitric oxide-mediated plasticity of interconnections between t-stellate cells of the ventral cochlear nucleus generate positive feedback and constitute a central gain control in the auditory system. J Neurosci 2019;39(31):6095–6107