MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 3814-3824
DOI: 10.12659/MSM.895291

Received: 2015.07.09
Accepted: 2015.08.11
Published: 2015.12.07

Comparison of 3 ABR Methods for Diagnosis of Retrocochlear Hearing Impairment

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ADF 1 **Krzysztof M. Kochanek**
CDEF 1 **Lech Śliwa**
D 2 **Marek Gołębiowski**
BC 1 **Adam Piłka**
G 1 **Henryk Skarżyński**

1 Department of Experimental Audiology, Institute of Physiology and Pathology of Hearing, Warsaw, Poland
2 Department of Clinical Radiology, Warsaw Medical University, Warsaw, Poland

Corresponding Author: Lech Śliwa, e-mail: l.sliwa@ifps.org.pl
Source of support: Partial funding for this project was provided by Polish grant No. NN 403 136 439 from the Ministry of Science and Higher Education

Background: The purpose of this study was to compare the effectiveness of methods for screening for retrocochlear pathologies based on auditory evoked brainstem responses (ABRs). The study compared the sensitivity, specificity, and effectiveness of these 3 techniques.

Material/Methods: The methods were: (i) standard ABR utilizing click-evoked responses, (ii) stacked ABR based on derived-band responses, and (iii) ABRs evoked by tone-pips (ABR TP). The methods were tested on patients with retrocochlear pathologies confirmed by MRI-Gd, normal-hearing subjects, and patients with cochlear hearing loss. The system and software used in the tests was NavPro AEP v.6.2.0 (BioLogic – Natus). Prior to testing, all subjects were given comprehensive audiologic and otologic examinations, including MR imaging. Sensitivity and specificity functions and predictive values of methods were determined.

Results: The stacked ABR method as realized in the NavPro system exhibited high sensitivity but specificity was very low, due to the high variability of stacked ABR amplitudes. The standard ABR method had good specificity, but low sensitivity in cases of small tumors (below 1 cm in diameter). Best sensitivity and specificity was obtained with the ABR TP method.

Conclusions: The stacked ABR method allows small acoustic tumors to be detected, but produces high percentage of false positive results. The ABR TP method offers good sensitivity and specificity, and relatively high predictive value. The best option would be to use a two-stage screening, consisting of a standard ABR in the first stage and an ABR TP test in the second.

MeSH Keywords: **Early Detection of Cancer • Evoked Potentials, Auditory, Brain Stem • Hearing Disorders**

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/895291

4918 4 6 45

Background

Modern otoneurosurgical techniques and methods of radiotherapy (such as the use of γ-rays, the 'gamma knife') make it possible to remove small acoustic neuromas without affecting hearing thresholds, even when the patient's hearing sensitivity is normal [1–5]. However, to effectively use these techniques, one must detect acoustic neuromas or tumors of the cerebellopontine angle at a very early phase, when their size does not exceed 1 cm in diameter. For this reason, the key issue is to use screening methods with high sensitivity and specificity, and diagnostic methods that allow for early detection. Electrophysiological methods satisfy these requirements, and are often based on recording auditory brainstem responses (ABRs) or using magnetic resonance imaging with gadolinium (MRI-Gd). The latter is considered the gold standard in diagnosis of acoustic neuroma [6].

Because of the increased accessibility of MRI examinations and its high sensitivity for diagnosis of small acoustic neuromas, some researchers have in recent years developed the view that to detect small acoustic neuromas (smaller than 1 cm) one may give up ABR testing altogether and rely only on MRI [7]. However, taking economic considerations into account, many authors still believe that a combination of ABR and MRI methods remains a better option [6,8–10]

At the same time, clinical symptoms in retrocochlear pathologies are not very specific, so it is difficult to accept that one should directly refer all patients with a suspected retrocochlear pathology for an MRI examination – because MRIs are much more costly than ABR tests (in Polish conditions approximately 6 times more expensive). Such a process would lead to a large number of false-negatives, low predictive value, and significantly increased diagnostic cost. Additionally, one cannot overlook the problem of claustrophobia in some patients, who are reluctant to subject themselves to MRI examination. On this basis, it still seems reasonable to adopt a two-stage procedure in which all patients suspected of having a retrocochlear pathology are first subjected to an ABR examination and then followed up with an MRI examination at a second stage if necessary [2,10–12]. Obviously, the ABR method used must satisfy the criteria for an efficient screening method: it must have high sensitivity and specificity, and be inexpensive and easy to apply on a large scale.

In the case of acoustic neuromas and tumors exceeding 1 cm, the standard ABR method (ABR STD), which relies on click-evoked responses, has very high sensitivity (over 95%) and high specificity [10,13]. However, if the size of the tumor is less than 1 cm, sensitivity of the ABR STD method drops quickly, according to some authors to 85%, or even to 63% [7,11,14]. Because of this limitation, researchers have for many years been seeking an ABR method which, with appropriate stimulus and analysis, might give enough sensitivity to detect small tumors.

One successful approach has come from the investigations of Don, who has developed the so-called *stacked ABR* method. Its most important feature is very high sensitivity in detecting small tumors, comparable to that of the MRI method [15–18] The method is based on the recording and registration of so-called *derived band* responses that originate from narrow segments of the basilar membrane, and which can be obtained by applying a masking technique employing high-pass filtered noise. Such an approach provides an integrated response, the stacked ABR, which represents activity of the whole cochlea as generated by nearly all auditory nerve fibers. Deterioration of transmission through any group of fibers (e.g., that resulting from pressure from an acoustic neuroma) significantly decreases the amplitude of the integrated response. However, popularity of the stacked ABR method is limited by the fact that it is more troublesome and time-consuming than a standard ABR examination, and because the availability of commercial ABR-measuring devices equipped with a stacked ABR option is poor. Yet another disadvantage of the method is that it is based on measuring wave V amplitudes, which have high variability and low repeatability [19,20]. The result is that the stacked ABR method, despite its obvious advantages, is very rarely used in clinical practice.

An attempt to replace the time-consuming registration of derived-band responses used in the stacked ABR method by much more easily obtained responses evoked by tone-bursts was undertaken by Philibert and co-workers [21]. Although tone-burst stimuli are not as often used as click stimuli, their usefulness in electrophysiology is well documented [22–25]. The comparison done by Philibert showed that the basic characteristics of the stacked ABR waveforms are similar, regardless of whether one uses the derived-band technique or responses evoked by tone-bursts. This conclusion applies to both normal ears and ears with sensorineural impairments. However, in the approaches used by both Don and Philibert, [15,21], the responses must be analyzed using the Stacked-ABR software, which is implemented in only one commercially-available device produced by Bio-Logic – Natus [26].

The results achieved by Don and Philibert have encouraged other authors to develop their own methods of stimulation and analysis, free of the drawbacks of the Stacked-ABR method, but which could still provide early detection of small retrocochlear lesions in different groups of auditory nerve fibers [27–30]. As this paper will attempt to show, there are reasons to believe that one satisfactory approach is a method developed by Kochanek et al. [29] called the ABR TP technique. The method is based on registration of responses evoked by Gaussian-shaped tone-pips with frequencies of 1000, 2000,

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

and 4000 Hz. The rise and fall times of these pips are twice as long as those used in standard ABRs for objectively evaluating hearing threshold: for tone pips of 1000 and 2000 Hz, the rise/fall times are 4 ms while at 4000 Hz the figure is 2 ms. The longer rise times mean that the stimulus bandwidth is approximately halved, which improves frequency specificity and the ability to detect retrocochlear lesions.

Results of studies by many authors [31–38] have shown that the increase in rise/fall time of a tone-pip leads to the reduction of wave V amplitude and increase in its latency. This is because the auditory nerve impulses generated by such extended stimuli are averaged over a longer time, and effectiveness of averaging is poorer than in the case of a shorter rise time. This can be explained by a decrease in synchrony of the averaged neural impulses, which in an extreme case may lead to total disappearance of the averaged response – despite the fact that the nerve potentials are still generated in auditory neurons. Then, considering the effectiveness of the averaging process, we may say that the responses to a tone-pip of a longer rise/fall time are poorly synchronized with the stimulus, compared to those evoked by a stimulus of shorter rise/fall times. It makes these responses weaker, as far as response amplitude is concerned, and more sensitive to different factors, such as reduction of stimulus intensity or retrocochlear pathology.

In summary, using tone pips with relatively long rise/fall times ensures, on the one hand, adequate frequency specificity of the response, and, on the other hand, makes it more sensitive to disturbance of synchronization in the auditory nerve caused by the presence of a neuroma or other pathology.

Until recently, direct comparison of the three methods, evaluating their sensitivity, specificity, and predictive values, has not been done. From reports published so far, it is known that both the stacked ABR and ABR TP methods have greater sensitivity than the standard ABR STD method in detecting small acoustic neuromas. Preliminary results comparing the specificity and selectivity of the three methods have shown that the stacked ABR method offered very high sensitivity, approaching 100% [39]. At the same time, however, it yielded the greatest number of false-positives, which made its specificity much lower than that of the other two methods. A full assessment requires a comparative study on the same group of patients. In this way, it is possible to directly compare the clinical usefulness of each method for detecting retrocochlear impairments.

The aim of the study was to compare the sensitivity and specificity of three ABR-based methods for early detection of retrocochlear impairments. Ideally, the comparison should lead to the development of an optimal procedure for screening for these pathologies.

The three ABR methods evaluated were:

- Method 1: ABR STD, the standard ABR method which makes use of click stimuli;
- Method 2: stacked ABR, the method developed by Don from the House Ear Institute and based on derived-band responses;
- Method 3: ABR TP, the original method developed by Kochanek and co-workers based on responses evoked by tone pips with relatively long rise/fall times.

Material and Methods

Material

The study was carried out on material consisting of 152 persons. The starting point for the study was an evaluation of the results of magnetic resonance imaging (MRI) with gadolinium (GT1W MR images) by 3 independent expert radiologists. On this basis, the examined subjects were divided into 2 groups:

(I) Group NR: 123 persons (246 ears) without retrocochlear impairments consisting of 62 men and 61 women aged between 19 and 66 years (mean 36 years).

(II) Group R: 29 patients with retrocochlear hearing loss, 14 men and 15 women aged 22 to 66 years (mean 44 years). Among them there were 22 cases of unilateral acoustic neuroma of size ranging from 2 mm in diameter to 20×17 mm (13 small and 9 medium or large size) and 7 patients with unilateral neurovascular conflicts.

The subjects gave written informed consent prior to participation in the study. The research procedures were approved by the Ethics Committee of the Institute of Physiology and Pathology of Hearing, Poland. Among the subjects in group NR, there were 47 persons with normal hearing, volunteers recruited from employees of the Institute of Physiology and Pathology of Hearing, and 76 patients admitted to the Institute for diagnostic examinations aimed at excluding possible retrocochlear pathology. In this latter group, the majority reported tinnitus, episodes of vertigo, or balance disorders. In 76% of cases, hearing thresholds were no higher than 20 dB HL; in the others, hearing thresholds were elevated but did not exceed 50 dB HL over the frequency range 0.25–8 kHz. Average hearing thresholds in both groups are listed in Table 1 and illustrated in Figure 1.

According to the guidelines for the stacked ABR method by BioLogic [26], and to comply with the conditions required for the ABR STD and ABR TP methods, we excluded from both groups cases of:

(i) conductive hearing loss,

(ii) sensorineural hearing loss greater than 50 dB HL,

(iii) steeply sloping audiograms, and

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 1. Average values of hearing thresholds in the investigated groups of subjects.

Frequency (Hz)		125	250	500	1000	2000	4000	8000
PTA Threshold Mean ±SD (dB HL)	NR	14.4±8.0	11.8±7.3	10.85±7.1	10.2±7.8	12.1±8.8	17.1±12.0	22.0±16.7
	R	16.8±10.1	14.6±11.0	15.0±11.5	15.8±13.7	17.7±15.0	22.7±17.2	29.3±23.3

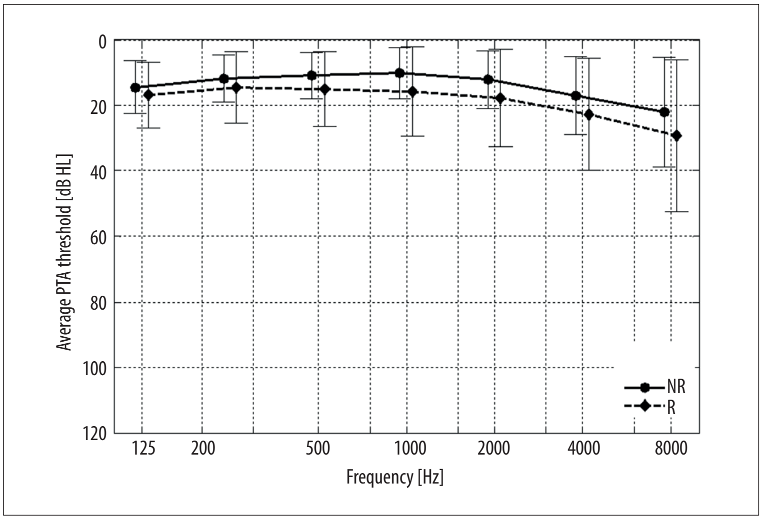

Figure 1. Average values of hearing thresholds (both ears) in the examined groups of subjects. NR: group without retrocochlear impairments (continuous line); R: patients with retrocochlear pathologies (broken line); whiskers denote standard deviation.

(iv) interaural audiometric threshold differences greater than ±10 dB (the difference between average values calculated over the frequency range 0.5–8 kHz).

Experiment design

In all ABR examinations, we used the system for registration and analysis of auditory evoked potentials AEP NavPro v. 6.2.0 (BioLogic – Natus) which was equipped with hardware and software suitable for applying the stacked ABR method. The stimuli were presented through ER2 BioLogic broadband earphones. Non-disposable silver electrodes were placed at C_Z, M_L (left mastoid), and M_R (right mastoid), as recommended. The tests were carried out in acoustic chambers.

In the stacked ABR method, we used the measuring procedure described in the literature [15–18,26] for implementation in the AEP NavPro system. In the NavPro system, most of the measurements are performed automatically, so there is no option for the user to modify the parameters or interfere with the procedure (such as interrupting the measurement cycle or repeating a single registration). The number of sweeps is determined by the system based on signal to noise ratio, and the averaging process is continued until the residual noise level reaches approx. 20 nV rms; it requires between 1900 and 9720 sweeps (mean approx. 6900) for each trace. Control by the user is limited to maintaining a low level of noise by minimizing disturbances, and correcting waveform fitting (when the stacked ABR response is created by summing derived-band responses). The result of a test (positive or negative) is determined automatically based on the stacked ABR wave V amplitude (*A*) and/or interaural amplitude difference (IAD) after comparing them with normative values. Normative values are taken to be 800 nV (males) and 875 nV (females), with the normative relative interaural amplitude difference equal to 10% (both genders).

During registration of signals in the stacked ABR method, care was taken to comply with the requirements laid down by the system manufacturer, in particular, maintaining an adequately low level of EEG background noise and eliminating other artifacts such as sensorimotor potentials. To this end, patients were seated in a comfortable, semi-reclining position, and instructed to keep their eyes closed and not to move during the tests (many fell asleep after a few minutes). In cases of excessive noise and/or myogenic artifacts, the protocol was repeated.

Examinations started with the ABR STD test; in cases where we observed excessive disturbance and noise (due to patient fatigue or restlessness) the tests were postponed to the following day, otherwise, we continued with registration of stacked ABRs, and then ABRs evoked by tone pips (the ABR TP method). Registrations of auditory evoked potentials were performed once in every subject.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 2. Normative values of latencies in the ABR STD and ABR TP methods.

Parameter of wave V	Method			
	ABR STD	ABR TP		
		1000 Hz	2000 Hz	4000 Hz
LV [ms]	6.2	8.70	8.14	7.18
IT5 [ms]	0.2	0.24	0.24	0.24

In measurements with the ABR STD method, we used a click stimulus of alternating polarity presented through TDH 39 (Telephonics) earphones at a level of 90 dB nHL with a repetition rate of 31/s. The amplifier bandwidth was 100–1500 Hz, amplification 100 000 times, and analysis time 20 ms. The number of sweeps required for each averaged response was between 512 and 1024 (average approximately 750 sweeps); 2 traces were registered for each ear to control repeatability of the response. We measured the latencies of waves I, III, and V and the inter-peak time intervals I–III and III–V; interaurally, we measured latency differences of wave V and other inter-peak time intervals. If the wave V interaural latency difference and/or the interaural difference in inter-peak time intervals exceeded 0.2 ms, the result was considered abnormal. The upper normal limit for wave V latency was assumed to be 6.2 ms.

In the ABR TP method, we used tone pips of Gaussian envelope (no plateau), whose rise and fall times were equal to 4 periods at 1000 Hz and 8 periods at 2000 and 4000 Hz. The stimuli had alternating polarity, a repetition rate of 31/s, and were presented through TDH 39 (Telephonics) earphones. The amplifier bandwidth, amplification, and analysis time were the same as those used in the ABR STD method. However, the number of sweeps required to obtain a well-averaged response was greater, ranging from approximately 800 to 1500 (average 1550 sweeps). Two traces were registered for each stimulus in order to control repeatability of the response. In the tone-pip evoked responses we analyzed morphology of the waveforms; latency of wave V, L_V; and the interaural latency difference of wave V (IT5). The upper limits of norms for wave V latency are presented in Table 2 [40]. Responses in which 1 of these values exceeded the norm were considered abnormal [28,40].

Analyses

Waveforms of evoked potentials recorded with ABR STD and ABR TP were analyzed by 3 independent experts. The person who evaluated the results had no information about assessments made by the other experts. In a few cases of diverging opinions, the experts met to agree on the assessment.

Statistical analyses were performed with Statistica v.7.1–10.2 (StatSoft Inc., Tulsa, OK, USA) and Matlab (The MathWorks, Natick, MA, USA). For statistical analysis, we used descriptive statistics (scatter plots, *t*-tests), generalized linear regression, nonparametric statistics (Kolmogorov-Smirnov 2-sample test), and ROC analysis for assessing screening test effectiveness. Generally, we used a confidence level of $p=0.05$.

Results

To illustrate the usefulness of each method for early diagnosis of retrocochlear impairment, examples of test results are presented in Figures 2 and 3. These results were obtained from the 3 ABR-based methods in otologically normal males (Figure 2) and in patients with confirmed retrocochlear pathologies (Figure 3).

In Figure 2, retrocochlear processes were excluded by MRI-Gd examination. In both cases, results of examination with ABR STD and ABR TP were normal (negative). Interestingly, however, the result of examination with the stacked ABR method was abnormal (positive) in both subjects. In the first case, (*a*), the stacked ABR wave V amplitude was below the limit of the norm, and in the second case, (*b*), despite a high stacked ABR wave V amplitude, the result of the test was abnormal (positive) because of an excessively high interaural amplitude difference (IAD >10%).

Figure 3 shows examples of tests done with the 3 ABR methods in patients with radiologically-confirmed small (<1 cm in diameter) acoustic neuroma. In patient *a*, the result of the ABR STD method was normal (negative), but results obtained with the ABR TP and stacked ABR methods were both abnormal (positive). In patient *b*, results were abnormal in all 3 methods, but in this patient (a male), stacked ABR wave V amplitudes in both ears were normal (greater than 800 nV) and only the interaural amplitude difference (IAD=42%) exceeded the norm.

These examples indicate that the stacked ABR method might not be a reliable tool for assessing retrocochlear pathologies because of apparent random variability of stacked ABR amplitude observed in both normal-hearing and pathologic ears.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System]
[ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica]
[Chemical Abstracts/CAS] [Index Copernicus]

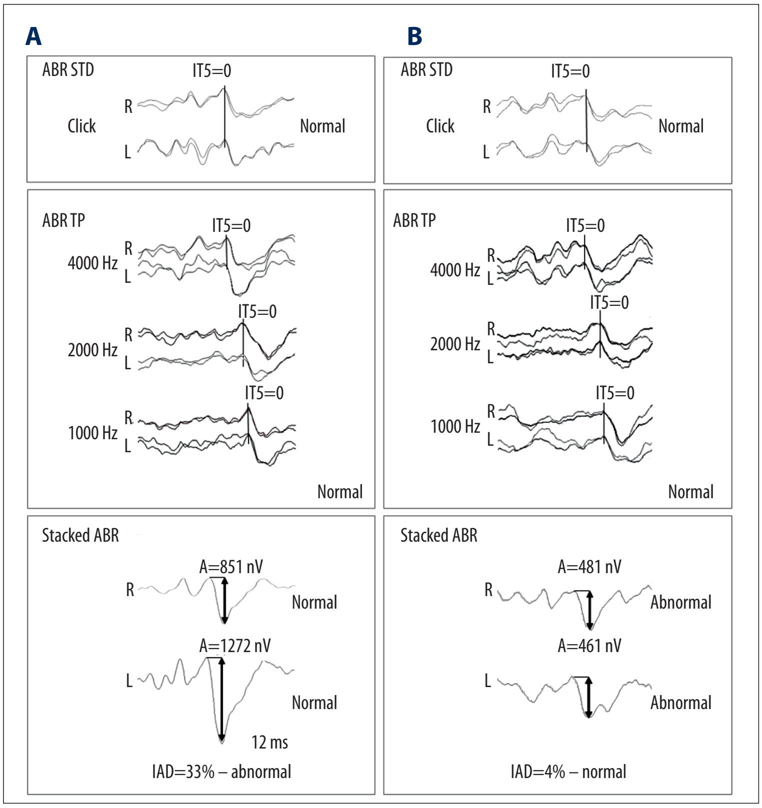

Figure 2. Example of ABR waveforms registered in the ABR STD, ABR TP, and stacked ABR methods (top to bottom) in 2 male normal-hearing subjects (columns). (**A**) Normal ABR STD; normal ABR TP; normal stacked ABR amplitudes; normal amplitude but abnormal (excessive) interaural amplitude difference. (**B**) Normal ABR STD; normal ABR TP; abnormal (too low) stacked ABR amplitude.

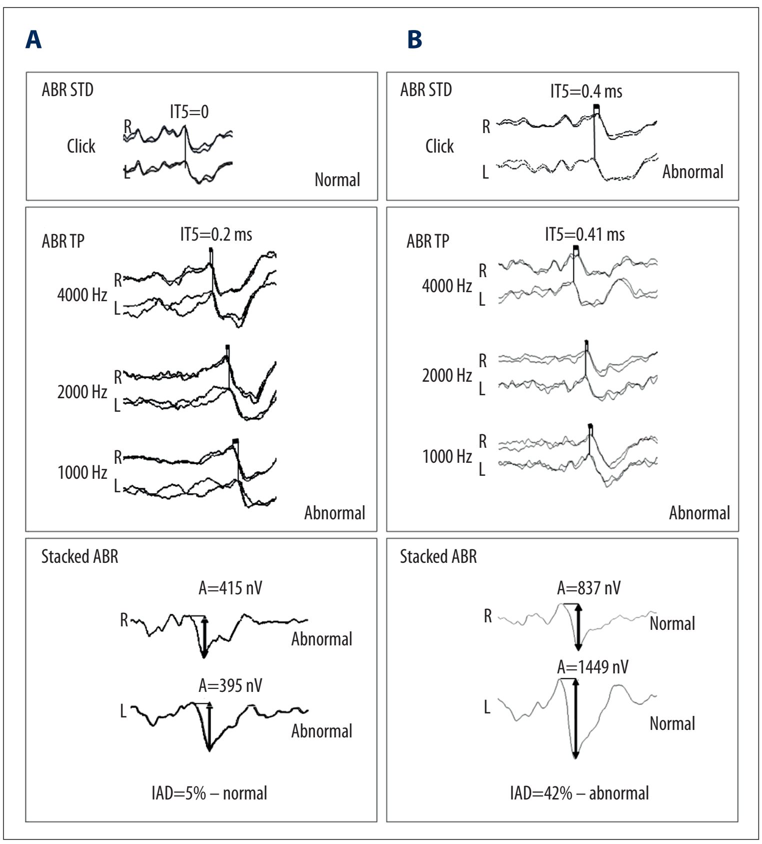

Figure 3. Examples of ABR waveforms registered with the ABR STD, ABR TP, and stacked ABR methods (top to bottom) in 2 male patients with neuromas of the VII–VIII nerve complex in the left ear (columns). (**A**) Normal ABR STD, abnormal ABR TP (excessive interaural latency difference at 1000 Hz); abnormal amplitude in stacked ABR. (**B**) Abnormal ABR STD; abnormal ABR TP; normal stacked ABR amplitude but abnormal interaural amplitude difference.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System]
[ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica]
[Chemical Abstracts/CAS] [Index Copernicus]

Table 3. Test results and sensitivity, specificity, and positive predictive value of three ABR methods.

Method	No of ears		Test results				Test characteristics					
	Retro	No Retro	*TP*	*FN*	*TN*	*FP*	*SEN*	*SEN* conf. interval	*SPE*	*SPE* conf. interval	*PPV*	*PPV* conf. interval
Stacked ABR	29	265	28	1	68	197	96.6%	89.3%, 100.0%	25.7%	21.2%, 29.9%	12.4%	10.7%, 13.1%
ABR STD	29	265	13	16	260	5	44.8%	31.0%, 58.6%	98.1%	96.6%, 99.2%	72.2%	50.0%, 89.5%
ABR TP	29	265	26	3	237	28	89.7%	79.3%, 96.6%	89.4%	86.4%, 92.5%	48.1%	39.0%, 58.3%

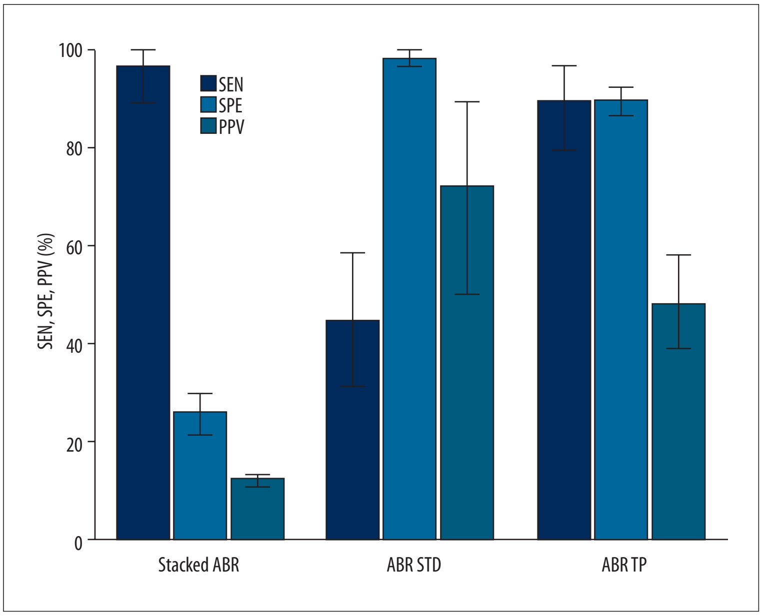

Figure 4. Sensitivity (SEN), specificity (SPE), and positive predictive value (PPV) of 3 ABR-based tests. Whiskers denote confidence intervals.

Table 3 shows results of the three ABR methods applied in the two groups of 148 subjects (*N*=296 ears). Numbers indicate positive results (true positive, *TP*, and false positive, *FP*), and negative results (true negative, *TN*, and false negative, *FN*). Also shown are calculated values of sensitivity, *SEN*, specificity, *SPE*, and positive predictive value, *PPV*=*TP*/(*TP*+*FP*) of each method. The same data are plotted in graphical form in Figure 4.

In assessing the stacked ABR method, we applied normative values of stacked wave V amplitude as assumed in the AEP NavPro system (800 nV for males and 875 nV for females). The supplementary criterion based on interaural amplitude difference IAD (IAD <10% for the norm) was not taken into account. Because of limited sample size, the values of sensitivity and specificity carry uncertainty. Confidence intervals shown in the table are based on the assumption that the number of *TP* and *TN* results are independent random variables that follow a binomial distribution, with probability of success equal to *SEN* and *SPE*, respectively, and the number of trials is equal to the number of ears with and without pathology, respectively. We assumed confidence levels of 0.05 and 0.95 [41]. In a similar way, one may estimate the interval of uncertainty for positive predictive value (*PPV*).

One can see that the stacked ABR method gives the highest sensitivity (well over 90%). Unfortunately, this sensitivity is obtained at the expense of specificity, which is extremely low, and therefore the positive predictive value is also low. This is due, among other things, to the significant variability of stacked ABR amplitudes (illustrated in the examples of Figures 2, 3), which leads to a large number of false positives.

Detailed analysis of the results shows that the performance of the other two ABR methods depends on the kind of retrocochlear pathology and the size of the acoustic neuroma. Unfortunately, the number of acoustic neuromas in the examined population was too low to reliably determine an exact relationship between the tumor size and the test result. Nevertheless, it is clear that ABR TP has an advantage over ABR STD. All false negatives in ABR STD pertain to cases of

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 4. Comparison of the stacked ABR method using two different normative values of wave V. Stacked ABR(1) – conventional values (assumed in Nav-Pro system); stacked ABR(2) – modified normative values.

Method	No of examined ears in groups		Test results				Test characteristics					
	Retro	No Retro	*TP*	*FN*	*TN*	*FP*	*SEN*	*SEN* conf. interval	*SPE*	*SPE* conf. interval	*PPV*	*PPV* conf. interval
Stacked ABR(1)	29	265	28	1	68	197	96.6%	89.3%, 100.0%	25.7%	21.2%, 29.9%	12.4%	10.7%, 13.1%
Stacked ABR(2)	29	265	21	8	102	163	72.4%	57.1%, 85.7%	38.5%	33.3%, 43.2%	11.4%	9.3%, 13.0%

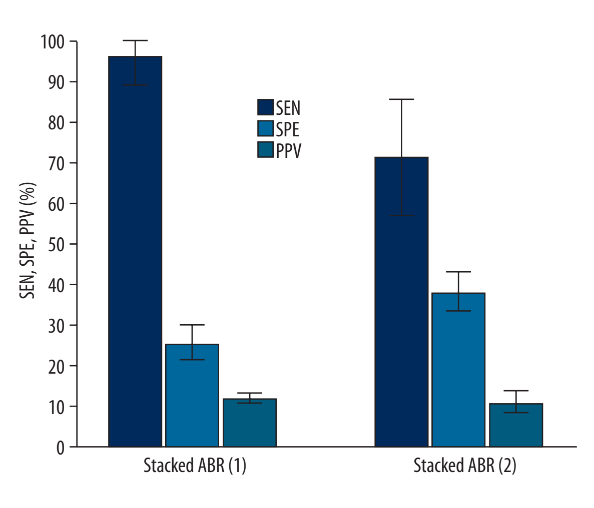

Figure 5. Comparison of stacked ABR method for different normative values of wave V amplitude. Stacked ABR (1): conventional values (assumed in Nav-Pro system). Stacked ABR (2): modified normative values. Whiskers denote confidence intervals.

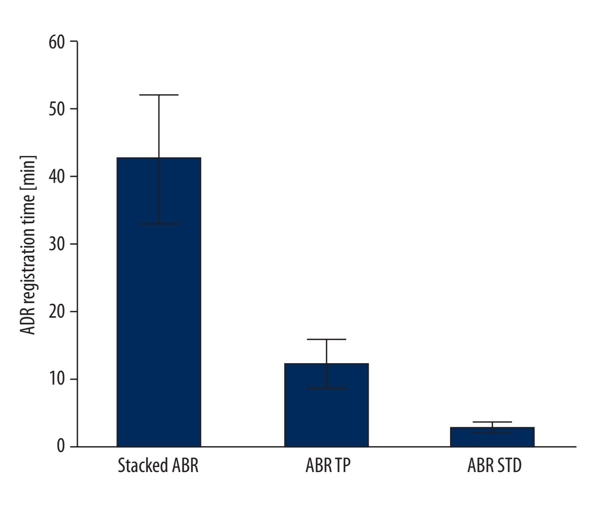

Figure 6. Time for ABR recording in the 3 methods. Whiskers denote standard deviations.

small tumors (all below 1 cm), but all of them were positive in the ABR TP method. Indeed, we observed that in all cases of tumors, irrespective of their size, the ABR TP test results were positive.

Both the ABR STD and ABR TP methods exhibited worse sensitivity in cases of neuro-vascular conflict. Over 70% of these ears tested positive in the ABR TP method, but the ABR STD method gave much poorer results – about 60% of these ears tested negative (i.e., false negatives).

The stacked ABR method applied with standard normative values of stacked ABR amplitude (the values assumed in the system) had very high sensitivity (above 90%), but its specificity was extremely low, much lower than either of the other 2 methods. This makes its usefulness questionable. One might suspect that the normative values for stacked ABR amplitude, as given by the system manufacturer, were too high, and an improvement in effectiveness might come from modifying the normative values. Table 4 presents test results and characteristics obtained for modified normative values – 700 nV for males and 750 nV for females – derived from previous experiments by the authors. Comparison of the 2 sorts of stacked ABR tests is also illustrated in Figure 5.

As one can see, in this case sensitivity drops to about 70% and specificity remains very low (well below 50%, which is still unsatisfactory). Consequently, the positive predictive value of the method is almost the same as that obtained with the previous normative values. Such a low PPV value means that 80–90% of positive results are false positives. Consequently, if one applied such a screening test, the number of cases referred to MRI examination would be 10 times more than the actual number of pathologies, leading to a substantial increase in the cost of diagnosis, and casting doubt on any screening test based on such a method (instead, it might be better to do an MRI examination on all patients suspected of retrocochlear pathology, as suggested by some authors [7].

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Considering the practicality of each method for clinical use, it is of interest to compare the test duration of all 3 methods. Figure 6 plots the examination times of the stacked ABR, ABR TP, and ABR STD methods. The times pertain only to the period of registration; preparation time (e.g., electrode montage and system start-up) is not taken into account.

Discussion

The assessment of the sensitivity and specificity of the stacked ABR method, based on our investigations and presented here, differs from the analyses published by the original authors of the method [15–18]. In their investigations, the reported sensitivity and specificity were much better, and ROC analysis showed much greater effectiveness (area under the curve above 0.9). However, one must take into account that those investigations were carried out in a controlled, research environment, with the use of dedicated instrumentation and software originally created by Don and co-workers. In this way, one might expect very good stability and repeatability. For example, as shown in [18], the scatter of stacked ABR amplitude was reasonably low, and one could easily differentiate between normal and pathology. Our investigation generated a much greater variability of stacked ABR amplitude, and more closely overlapping amplitude distributions for the normal and pathology groups. Another factor that might have contributed to higher sensitivity/specificity values in the work by Don and coworkers was that the reference groups were recruited from normal-hearing, experienced, and cooperative volunteer subjects, who were compared with patients with diagnosed pathology. The situation changes when we deal with a population of actual patients; many have physiological or psychological deficits, for whom lengthy electrophysiological tests are difficult to withstand, and for whom high levels of stimulus and masker noise cause irritation and fatigue. Even in a group without retrocochlear pathology, we can expect more disturbances and instability in ABR waveforms, and this strongly affects the ABR amplitude. On the other hand, there is no evidence that the working parameters of hardware and realization of software algorithms in the commercial AEP Nav-Pro system are identical to those originally used by the method's authors. In particular, a key parameter is the level of residual noise that remains after the averaging process is terminated (in theory, it should not exceed 20 nV rms). This level is measured and displayed by the system, but there is no way of verifying the correctness of this value, nor can one increase the number of sweeps over the fixed maximum (9000 sweeps) to improve the S/N ratio.

Nonetheless, the investigations performed in this study confirmed the notion, evident from our previous works, that one can obtain high sensitivity and specificity using methods based on the morphology and latency of auditory evoked responses. The standard method based on click-evoked responses (ABR STD) has very high specificity – in our case well over 90% (as it generates a small number of false positives) – but its sensitivity is unsatisfactory. Unfortunately, in cases of small tumors one can barely notice abnormalities in click-evoked ABRs [27,42–44]. Much better results can be obtained using the method based on ABRs evoked by appropriately specified tone-pips (ABR TP). Previous reports by the authors have shown that it can provide very high sensitivity and satisfactory specificity [28,40]. This finding has been confirmed by the present investigation.

Yet another advantage of the ABR STD and ABR TP methods is the short time needed for examination. The first method needs only 4 recordings of ABRs evoked by clicks (recordings are repeated twice in each ear); the second requires 12 recordings (at 3 frequencies, twice for each ear), and the number of sweeps is relatively low. In the stacked ABR method, one must record 12 waveforms, and the registrations usually take much longer because of a lower stimulus level and the presence of masker noise. Consequently, the number of sweeps is much greater (up to 9000) and the whole procedure is several times longer.

We might consider the option of combining the ABR STD and ABR TP methods. The proposed strategy of testing for retrocochlear pathologies would then be as follows: first, one applies the standard ABR, which is simple, quick, and has high specificity. If the result of this test is abnormal (positive), the patient would be referred to MRI examination to confirm the diagnosis. Negative results would be followed up at a second stage using the ABR TP method, which is more sensitive than the ABR STD. Normal (negative) results of both tests would justify not proceeding to an MRI examination and instead referring the patient to clinical observation.

Running the 2 tests in series, according to the above strategy, may significantly increase sensitivity, as expressed by the following formula [45]:

$$SEN = 1 - (1 - SEN_1)(1 - SEN_2).$$

At the same time, the effective specificity is slightly reduced, but it remains relatively high if both tests have sufficient specificity:

$$SPE = SPE_1 \cdot SPE_{2,}$$

where SEN_1 and SEN_2 denote sensitivities of the first and second tests, and SPE_1 and SPE_2 denote their specificities.

The above formulae are valid, however, when the tests are carried out in a large population, and true values of sensitivity/specificity are known. Taking into account the results obtained

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

in the examined group presented in Table 2, one might expect that combined strategy of ABR STD and ABR TP would give an effective sensitivity of 94.3% and a specificity of 87.7%. In reality, in our study, we could hardly obtain any improvement in sensitivity applying the 2-stage strategy compared to the application of the ABR TP method only. Sensitivity and specificity values are loaded with uncertainly (Figure 4). Besides, in this particular group of patients, all positive cases detected with ABR STD method also tested positive in the ABR TP method. Nevertheless, the 2-stage strategy is still worth using, because a number of pathologies are detected already in the first stage, so it is not necessary to use the ABR TP method, which is slightly more complicated and time-consuming. In conclusion, using the combination of ABR methods, one may expect a significant reduction in cost of diagnosis in comparison with a strategy that refers all patients with suspected retrocochlear lesions to MRI examination.

Conclusions

The advantages of methods based on assessment of latencies of auditory brainstem responses – ABR STD and ABR TP – are:
- high sensitivity (in the case of the ABR TP method);
- very good specificity (especially for the ABR STD method);
- relatively high positive predictive value (*PPV*);
- availability of instrumentation (any evoked response test system that allows appropriate tone pips to be generated);
- uncomplicated measuring procedure, short measurement time (less than 10 min for bilateral examination), and no overly loud stimulus noise.

A clear disadvantage of the method is that the results must be interpreted visually, which calls for adequate qualifications and experience of the audiologist performing the tests.

The advantage of the stacked ABR method consists in its very high sensitivity (when one applies settings recommended by the manufacturer); however, the disadvantage is very low specificity. An automatic measuring process and an automatic decision about the outcome of the test are also advantages, which avoid errors made by the audiologist. Nevertheless, the stacked ABR method as implemented in the AEP NavPro system has several serious disadvantages, including:
- significant variability and instability of test results;
- sensitivity to disturbing phenomena (e.g., patient condition, noise, and spurious physiological potentials);
- very low specificity and very low positive predictive value.

Other disadvantages that one must take into account are:
- limited availability of instrumentation (presently only 1 system implementing this method);
- long measurement time (approximately 40–60 min for bilateral examination);
- various factors that may increase discomfort for the patient (e.g., long time in a fixed position, appreciable acoustic level of the stimulus, and high level of masking noise).

The results presented above show that the stacked ABR method, in its present version, is not yet an optimal clinical tool for screening for retrocochlear pathologies.

At the same time, the results obtained from the other 2 ABR-based methods indicate that a practical solution for screening for retrocochlear pathologies is to apply ABR STD and ABR TP in series.

Acknowledgements

The authors are indebted to Prof. John D. Durrant, Pittsburgh University, for his valuable comments and criticism.

References:

1. Attias J, Nageris B, Ralph J et al: Hearing preservation using combined monitoring of extra-tympanic electrocochleography and auditory brainstem responses during acoustic neuroma surgery. Int J Audiol, 1998; 47(4): 178–84
2. Bush ML, Shinn JB, Young AB, Jones RO: Long-term hearing results in gamma knife radiosurgery for acoustic neuromas. Laryngoscope, 2008; 118(6): 1019–22
3. Lasak JM, Klish D, Kryzer TC et al: Gamma knife radiosurgery for vestibular schwannoma: early hearing outcomes and evaluation of the cochlear dose. Otol Neurotol, 2008; 29(8): 1179–86
4. Timmer FC, Hanssens PE, van Haren AE et al: Gamma knife radiosurgery for vestibular schwannomas: results of hearing preservation in relation to the cochlear radiation dose. Laryngoscope, 2009; 119(6): 1076–81
5. Yamakami I, Yoshinori H, Saeki N et al: Hearing preservation and intraoperative auditory brainstem response and cochlear nerve compound action potential monitoring in the removal of small acoustic neurinoma via the retrosigmoid approach. J Neurol Neurosurg Psychiatry, 2009; 80(2): 218–27
6. Fortnum H, O'Neill C, Taylor R et al: The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost effectiveness and natural history. Health Technol Assess, 2009; 13(18): iii–iv, ix–xi, 1–154
7. Cueva RA: Auditory brainstem response versus magnetic resonance imaging for the evaluation of asymmetric sensorineural hearing loss. Laryngoscope, 2004; 114(10): 1686–92
8. Murphy MR, Selesnick SH: Cost-effective diagnosis of acoustic neuromas: a philosophical, macroeconomic, and technological decision. Otolaryngol Head Neck Surg, 2002; 127(4): 253–59
9. Robinette MS, Bauch CD, Olsen WO, Cevette MJ: Auditory brainstem response and magnetic resonance imaging for acoustic neuromas: costs by prevalence. Arch Otolaryngol Head Neck Surg, 2000; 126(8): 963–66
10. Rupa V, Job A, George M, Rajshekhar V: Cost-effective initial screening for vestibular schwannoma: auditory brainstem response or magnetic resonance imaging? Otolaryngol Head Neck Surg, 2003; 128(6): 823–28
11. Ruckenstein MJ, Cueva RA, Morrison DH, Press G: A prospective study of ABR and MRI in the screening for vestibular schwannomas. Am J Otol, 1996; 17: 317–20
12. Bozorg Grayeli A, Refass A, Smail M et al: Diagnostic value of auditory brainstem responses in cerebellopontine angle tumours. Acta Otolaryngol, 2008; 128(10): 1096–100

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System]
[ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica]
[Chemical Abstracts/CAS] [Index Copernicus]

13. Chandrasekhar SS, Brackmann DE, Devgan KK: Utility of auditory brainstem response audiometry in diagnosis of acoustic neuromas. Am J Otol, 1995; 16(1): 63–67
14. Schmidt RJ, Sataloff RT, Newman J et al: The sensitivity of auditory brainstem response testing for the diagnosis of acoustic neuromas. Arch Otolaryngol Head Neck Surg, 2001; 127(1): 19–22
15. Don M, Masuda A, Nelson R, Brackmann D: Successful detection of small acoustic tumors using the stacked derived-band auditory brain stem response amplitude. Am J Otol, 1997; 18: 608–21
16. Don M, Kwong B: ABR: Differential diagnosis. In: Katz J (ed.), Handbook of Clinical Audiology 5th ed. Baltimore: Lippincott Williams & Wilkins, 2002; 274–79
17. Don M: Auditory brainstem response testing in acoustic neuroma diagnosis. Curr Opin Otolaryngol Head Neck Surg, 2002; 10: 376–81
18. Don M, Kwong B, Tanaka C et al: The stacked ABR: a sensitive and specific screening tool for detecting small acoustic tumors. Audiol Neurootol, 2005; 10(5): 274–90
19. Schwartz DM, Berry GA: Normative aspects of the ABR. In: Jacobson ET (ed.), The Auditory Brainstem Response. London: Taylor & Francis, 1985; 65–70
20. Picton TW: Auditory brainstem responses. Picks along the way. In: Human auditory evoked potentials. San Diego: Plural Publishing, 2011; 214–84
21. Philibert B, Durrant JD, Ferber-Viart C et al: Stacked tone-burst-evoked auditory brainstem response (ABR): preliminary findings. Int J Audiol, 2003; 42(2): 71–81
22. Gorga MP, Johnson TA, Kaminski JR et al: Using a combination of click- and tone burst-evoked auditory brain stem response measurements to estimate pure-tone thresholds. Ear Hear, 2006; 27(1): 60–74
23. Vander Werff KR, Prieve BA, Georgantas LM: Infant air and bone conduction tone burst auditory brain stem responses for classification of hearing loss and the relationship to behavioral thresholds. Ear Hear, 2009; 30(3): 350–68
24. Jedrzejczak WW, Smurzynski J, Blinowska KJ: Origin of suppression of otoacoustic emissions evoked by two-tone bursts. Hear Res, 2008; 235(1–2): 80–89
25. Jedrzejczak WW, Kochanek K, Trzaskowski B et al: Tone-burst and click-evoked otoacoustic emissions in subjects with hearing loss above 0.25, 0.5, and 1 kHz. Ear Hear, 2012; 33(6): 757–67
26. Bio-logic Systems Corp. Stacked ABR and CHAMP Data Collection; in AEP Systems User's and Service Manual, 590-AEPUM1 Rev C, 2005; 175–86
27. Kochanek K, Tacikowska G, Pierchała K et al: Usefulness of auditory brainstem potentials in diagnosis of retrocochlear hearing impairments. Polish Journal of Otolaryngology, 1998; 52(1): 68–75
28. Kochanek K. [Fundamentals of method utilizing ABRs evoked by tone pips in early diagnosis of retrocochlear hearing impairments.] Otorynolaryngologia, 2006; Supplement 1: 30–31 [in Polish]
29. Bush ML, Jones RO, Shinn JB: Auditory brainstem response threshold differences in patients with vestibular schwannoma: a new diagnostic index. Ear Nose Throat J, 2008; 87(8): 458–62
30. Dort JC, Cook EF, Watson C et al: Power spectrum auditory brainstem response: novel approach to the evaluation of patients with unilateral auditory symptoms. Otolaryngol Head Neck Surg, 2009; 38(1): 59–66
31. Anderson DJ, Rose JE, Hind JE, Brugge JF: Temporal position of discharges in single auditory nerve fibers within the cycle of a sine-wave stimulus. Frequency and intensity effects. J Acoust Soc Am, 1971; 49: 1131–39
32. Antonelli A, Grandori F: Some aspects of the auditory nerve responses evoked by tone bursts. Br J Audiol, 1984; 18: 117–26
33. Barth CD, Burkard R: Effects of noise burst rise time and level on the human brainstem auditory evoked response. Audiology, 1993; 32: 225–33
34. Beattie RC, Moretti M, Warren V: Effects of rise-fall time, frequency, and intensity on the early/middle evoked response. J Speech Hear Disord, 1984; 49: 114–27
35. Burkard R: Effects of noise burst rise time and level on the gerbil brainstem auditory evoked response. Audiology, 1991; 30: 47–58
36. Gerull G, Mrowiński D, Jansen T, Anft D: Auditory brainstem responses to single-slope stimuli. Scand Audiol, 1987; 16: 227–35
37. Hecox K, Deegan D: Rise-fall time effects on the brainstem auditory evoked response. Mechanisms. J Acoust Soc Am, 1983; 73: 2109–16
38. Kodera K, Marsh R, Suzuki M, Suzuki J: Portions of tone pips contributing to frequency-selective auditory brain stem responses. Audiology, 1983; 22: 209–18
39. Kochanek K, Gołębiewski M, Śliwa L et al: Comparison of three ABR-based methods in diagnosis of retrocochlear hearing loss: preliminary results. XXII IERASG Symposium 2011; Available from: URL: *http://www.ierasg.ifps.org.pl/files/ p.101*
40. Orkan-Łęcka E: [Clinical usability of auditory brainstem potentials evoked with tone pips in diagnosis of sensorineural hearing impairments – PhD Thesis.] Medical University of Warsaw, 2006, Warsaw, Poland [in Polish]
41. Heckerling PS: Confidence in diagnostic testing. J Gen Int Med, 1988; 3: 604–6
42. Gordon ML, Cohen NL: Efficacy of auditory brainstem response as a screening test for small acoustic neuromas. Am J Otol, 1995; 16(2): 136–39
43. Møller AR: Diagnosis of acoustic tumors. Am J Otol, 2000; 21(1): 151–52
44. Schmidt RJ, Sataloff RT, Newman J et al: The sensitivity of auditory brainstem response testing for the diagnosis of acoustic neuromas. Arch Otolaryngol Head Neck Surg, 2001; 127(1): 19–22
45. Hyde ML, Davison MJ, Alberti PW: Auditory test strategy. In: Jacobson JT, Northen JL (eds.), Diagnostic Audiology. Boston: Allyn & Bacon, 1997

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System]
[ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica]
[Chemical Abstracts/CAS] [Index Copernicus]