Comparison of Auditory Brainstem Response Results in Normal-Hearing Patients With and Without Tinnitus

Helga M. Kehrle, MD, MSc; Ronaldo C. Granjeiro, MD, MSc; André L. L. Sampaio, MD, PhD; Roberta Bezerra, MD, PhD; Vanessa F. Almeida, PhD; Carlos A. Oliveira, MD, PhD

Objective: To evaluate electrophysiologically the auditory nerve and the auditory brainstem function of patients with tinnitus and normal-hearing thresholds using the auditory brainstem response (ABR).

Design: Case-control study.

Setting: Ambulatory section of the Department of Otolaryngology, Hospital de Base de Brasília.

Patients: Thirty-seven individuals with tinnitus and 38 without tinnitus, with ages ranging from 20 to 45 years and pure-tone thresholds of 25 dB or better at frequencies between 500 and 8000 Hz.

Main Outcome Measures: We compared the latencies of waves I, III, and V; the interpeak intervals I-III, III-V, and I-V; the interaural latency difference (wave V); and the V/I amplitude ratio between the 2 groups.

Results: Among the 37 patients in the study group, abnormal results were found in 16 (43%) in at least 1 of the 8 parameters evaluated. When we analyzed the latencies, although the values were on average in the normal range used in the present study, the tinnitus group presented a significant prolongation of the latencies of waves I, III, and V when compared with the control group. Furthermore, we found the interpeak I-III, III-V, and I-V values to be within the normal limits, but the interpeak III-V value was significantly (P= .003) enlarged in the study group compared with the control group. The V/I amplitude ratio found in the tinnitus group was within normal limits; however, a significant (P=.004) difference was found when the 2 groups were compared. The averages of the interaural latency difference (wave V) did not show significant differences in relation to the control group.

Conclusions: We conclude that, although the averages obtained in several analyzed parameters were within normal limits, the ABR results from the patients with and without tinnitus and normal hearing are different, suggesting that ABR might contribute to the workup of these patients. Our data show that there are changes in the central pathways in the study group. The meaning of these changes must be further investigated.

Tinnitus on ABR are not common in the clinical literature. In studies of patients with tinnitus, for example, ABR has shown quantitative increases in latency and poor reproducibility. However, these reports did not state whether increases in tinnitus latencies were greater than those associated with sex, age, or hearing loss.

The present study was designed to determine if significant differences exist in ABR parameters when patients with and without tinnitus and with normal hearing were matched as closely as possible for age and sex. A secondary aim of the investigation was an attempt to supplement and thereby extend our knowledge of the nature and origins of tinnitus in normal listeners.

### METHODS

#### STUDY PARTICIPANTS

The study group with tinnitus had 37 patients aged 20 to 45 years (mean, 36 years; SD, 7.2 years) with normal-hearing sensitivity in the conventional audiometric range and normal impedance audiometry. Normal sensitivity was defined as less than a 25-dB hearing level at each frequency examined in the range of 0.25 to 8 kHz. To avoid inclusion of individuals with audiograms that displayed minor dips, frequencies of 3 and 6 kHz were also tested. A type A response in the impedance audiometry was defined as normal. The control group had 38 patients without tinnitus and with normal hearing, age and sex matched to the study group. These patients were randomly selected during a routine otorhinolaryngologic examination, a general investigation of the clinic’s patients with and without tinnitus.

 Patients in the study group, 16 (43%) showed abnormal values in the absolute latency of wave I; 7 (12%) had abnormal latencies of waves III and V, and 10 (16%) had abnormal latencies of waves III and V. The amplitude ratio between waves V and I and the interaural relation of the latency of wave V were also studied. We used the normal pattern described by Hall in 1992. The prevalence of normal and abnormal results for each parameter measured was calculated for each patient group.

#### APPARATUS AND PROCEDURE

After a detailed physical examination that included a complete otorhinolaryngologic examination, a general investigation that consisted of a complete blood test, conventional audiometry (GSI-16 audiometer with telephones and TDH-50P earphones; Grason-Stadler Inc, Milford, New Hampshire), and impedance audiometry was performed in all patients. The ABR recordings were obtained at the initial 12 milliseconds using Amplaid MK-15 (Milan, Italy) equipment with the patient lying supine in a silent electrically shielded room. Surface electrodes were applied to the scalp: the active electrode was placed on the forehead, the reference electrode was placed on the mastoid of the tested ear, and the ground electrode was placed on the contralateral mastoid. A total of 1000 to 2000 alternating polarity clicks between 2 and 4 kHz at 80-dB hearing level were delivered for each test at a repetition rate of 12 clicks per second through the earphones. The click duration was 100 microseconds. Contralateral masking was used at a 50-dB hearing level. Artifact rejection and a fine impulse response real-time digital filter with a 40-dB octave attenuation and linear phase shift response were applied to every ABR evoked by the click stimuli. The responses were recorded differentially between the vertex electrode and the contralateral and ipsilateral mastoid electrode, with the contralateral mastoid electrode serving as the ground. The responses were filtered (100-2500 Hz) and computer averaged.

Each ear was tested individually, and the parameters studied were the absolute latency of waves I, III, and V and the intervals between the different waves (interpeak latencies [IPLs]) I-III, I-V, and III-V. The amplitude ratio between waves V and I and the interaural relation of the latency of wave V were also studied. We used the normal pattern described by Hall in 1992. The prevalence of normal and abnormal results for each parameter measured was calculated for each patient group.

### STATISTICAL ANALYSIS AND COMPARISONS

The study group with tinnitus and the control group were compared. The prevalence of normal and abnormal results for each parameter measured was calculated for each patient group.

**Table 1** gives the results of the 8 ABR parameters evaluated in the control group. All individual values in all control patients were within the normal limits. Of the 37 patients in the study group, 16 (43%) showed abnormalities in at least 1 of the 8 ABR parameters evaluated compared with the normal values adopted in our electrophysiology laboratory. The mean (SD) absolute values of the latencies of waves I, III, and V in the study and control groups are given in **Table 2**. Eight ears in the study group (13%) showed abnormal values in the absolute latency of wave I; 7 (12%) and 10 (16%) had abnormal latencies of waves III and

### RESULTS

**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD), ms</th>
<th>Range, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wave I</td>
<td>1.46 (0.10)</td>
<td>1.24-1.68</td>
</tr>
<tr>
<td>Wave III</td>
<td>3.65 (0.11)</td>
<td>3.41-3.94</td>
</tr>
<tr>
<td>Wave V</td>
<td>5.41 (0.17)</td>
<td>5.14-5.81</td>
</tr>
<tr>
<td>Interpeak I-III</td>
<td>2.19 (0.11)</td>
<td>2.00-2.45</td>
</tr>
<tr>
<td>Interpeak III-V</td>
<td>1.74 (0.15)</td>
<td>1.40-2.07</td>
</tr>
<tr>
<td>Interpeak V-V</td>
<td>3.95 (0.19)</td>
<td>3.65-4.36</td>
</tr>
<tr>
<td>Amplitude ratio VI</td>
<td>2.19 (0.11)</td>
<td>2.00-2.45</td>
</tr>
<tr>
<td>Interaural difference V</td>
<td>0.13 (0.09)</td>
<td>0.00-0.29</td>
</tr>
</tbody>
</table>

©2008 American Medical Association. All rights reserved.
A statistically significant prolongation was found in the latencies of waves I, III, and V in the study group compared with the control group ($P < .001$).

Table 3 gives the mean (SD) absolute values of latencies of interpeaks I-III, III-V, and I-V in the study and control groups. Of the 61 ears tested in the study group, 4 (7%) showed abnormal values for the interpeak I-III, 2 (3%) for the interpeak III-V, and 2 (3%) for the interpeak I-V. A statistically significant enlargement was found for the interpeak III-V in the study group compared with the control group ($P = .003$). No difference between the groups was found regarding interpeaks I-III and I-V.

The mean (SD) V/I amplitude ratio was 1.64 (0.81) in the study group and 1.21 (0.9) in the control group. Only 1 ear (2%) in the study group showed an abnormal result for this ABR parameter. A statistically significant enhancement was found in the amplitude ratio in the study group compared with the control group ($P = .004$).

The interaural difference of the latency of wave V was calculated individually for patients with bilateral and unilateral tinnitus. The mean (SD) interaural differences of this latency in the bilateral and unilateral tinnitus groups were 0.11 (0.11) and 0.18 (0.16) millisecond, respectively. Only 1 of 24 patients with bilateral tinnitus (4%) showed an abnormal value for the interaural difference of this latency. Two of 13 patients (15%) in the unilateral tinnitus group showed an abnormal interaural difference in the latency of wave V. No significant difference was found between the 2 tinnitus subgroups and the control group, and the $P$ values were .35 and .20 for the bilateral and unilateral tinnitus subgroups, respectively.

### Table 2. Wave Latencies in the Study and Control Groups

<table>
<thead>
<tr>
<th>Wave</th>
<th>Study Group Latency</th>
<th>Control Group Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD), ms</td>
<td>Range, ms</td>
</tr>
<tr>
<td>I</td>
<td>1.58 (0.12)</td>
<td>1.30-1.92</td>
</tr>
<tr>
<td>III</td>
<td>3.76 (0.16)</td>
<td>3.46-4.22</td>
</tr>
<tr>
<td>V</td>
<td>5.59 (0.21)</td>
<td>5.09-6.14</td>
</tr>
</tbody>
</table>

$P < .001$ for all differences between groups.

### Table 3. Interpeak Latencies in the Study and Control Groups

<table>
<thead>
<tr>
<th>Interpeak</th>
<th>Study Group Latency</th>
<th>Control Group Latency</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD), ms</td>
<td>Range, ms</td>
<td></td>
</tr>
<tr>
<td>I-III</td>
<td>2.17 (0.17)</td>
<td>1.57-2.45</td>
<td>.30</td>
</tr>
<tr>
<td>III-V</td>
<td>1.82 (0.16)</td>
<td>1.49-2.16</td>
<td>.003</td>
</tr>
<tr>
<td>I-V</td>
<td>3.99 (0.21)</td>
<td>3.49-4.37</td>
<td>.21</td>
</tr>
</tbody>
</table>

V, respectively. A statistically significant prolongation was found in the latencies of waves I, III, and V in the study group compared with the control group ($P < .001$).

### Table 3. Interpeak Latencies in the Study and Control Groups

**COMMENT**

Tinnitus is a common and persistent symptom. The pathogenesis and site of origin have yet to be clearly established. Tinnitus is often a feature of primary ear disease usually associated with hearing loss, but it may also occur in patients with normal hearing. Our study focused on the latter group. The lack of scientific evidence to prove that tinnitus arises from cochlear damage in normal-hearing patients has encouraged us to investigate whether patients with tinnitus show changes in the central pathways.

Jastreboff remarks that tinnitus is the result of aberrant activity within the auditory system, interpreted as sound. Attempts have been made to understand tinnitus and to investigate its background by means of electrophysiologic methods.

One such method is ABR. Shulman and Seitz reported ABR abnormalities in some tinnitus cases, usually changes in the morphologic features of ABR waveforms, indicating a central origin of the tinnitus. Cassvan et al reported that the abnormality of the I-III, III-V, or I-V IPLs occurred in many patients with tinnitus. However, in those reports, most patients experienced vertigo as well as tinnitus.

Maurizi et al reported an increase in the wave I latency in ears with tinnitus that had residual inhibition. This abnormality had a tendency to decrease after ipsilateral masking. In ears with no residual inhibition, an increase of wave V latency was observed.

Lemaire and Beutter studied a large group of patients with tinnitus. The latency of wave I was significantly increased in ears with tinnitus that had residual inhibition. The abnormality had a tendency to decrease after ipsilateral masking. In ears with no residual inhibition, an increase of wave V latency was observed.

Ikner and Hassen compared patients with tinnitus with patients without tinnitus. Female patients with tinnitus and normal hearing had a significant prolongation of wave I. In patients who were matched regarding the stapedius reflex and hearing thresholds, the tinnitus population had prolonged latencies for waves I, III, and V and a prolonged III-V IPL.
The relationship between ABR activity and tinnitus is probably inconsistently reported for a variety of reasons, including differences in the origin of the tinnitus, ABR recording methods, and sometimes the selection criteria of the control groups. In our study, we tried to eliminate these biases by selecting a homogeneous group of normal-hearing patients with and without tinnitus who were age and sex matched.

In contrast to the studies mentioned herein and to the present study, Barnea et al. found normal ABR results in all 17 patients with tinnitus enrolled in their study compared with 19 patients without tinnitus. McKee and Stephens reported normal ABR latencies in all 18 normal-hearing patients with tinnitus in their study. All these methods for evaluating tinnitus have used an evoking stimulus. It has been proposed that tinnitus is caused by abnormal spontaneous hyperactivity in the auditory pathways analogous to epilepsy and that the absence of extreme values in the ABR parameters in patients with tinnitus might be owing to the masking effect of the stimulus masking the abnormal activity in the central pathways, therefore changing the expected ABR results. In the present study, we found wave latencies I, III, and V significantly prolonged in the study group compared with the control group, a finding that is partially in agreement with the studies by Maurizi et al. and Lemaire and Beutter and totally in agreement with the studies of Ikner and Hassen and Rosenhall and Axelson. A prolongation of wave 1, parallel to a lengthening of the latter ABR waves, occurs in ears with cochlear hearing loss and has been reported since 1977. Our patients possibly had sensorineural hearing loss at frequencies greater than 8000 Hz, which were not tested. In patients with tinnitus, a prolongation of wave I that also affects the late ABR waves is seen in ears with normal hearing. The method used in this study to evaluate cochlear status (conventional audiogram) might not have been sufficiently sensitive for assessing all aspects of cochlear functioning. This lies in the fact that many commonly encountered hearing losses initially affect the high frequencies that were not evaluated in this study.

The explanation that supports the latency prolongation as a shift of the excitation on the basilar membrane from the basilar turn to another place, which is more distant from the oval window, is not valid in the patients with tinnitus and normal hearing. Oliveira performed light microscopic techniques on postmortem temporal bone and found 37% with normal histologic aspects and 23% with endolymphatic hydrops. He postulated a change in the fluid homeostasis, leading to tinnitus and later to endolymphatic hydrops and hearing loss because of this change. It is more likely that the latency prolongation reflects a slowing of the synaptic processes in the organ of Corti or decreased neural conduction velocity in the first auditory neuron.

In our study, we found prolonged III-V IPL in the study group compared with the control group, concurring with the studies of Ikner and Hassen and Rosenhall and Axelson. An increased latency of the III-V IPL usually reflects an increased neural conduction time in the brainstem.

The study of the wave's amplitudes is less used in clinical practice than the absolute latencies and IPLs in the detection of brainstem auditory pathway problems because the amplitudes are extremely variable. The analysis of the V/I amplitude ratio is considered by some authors to be one of the most important parameters in ABR recording. For this reason, we decided to evaluate the amplitude ratio instead of the individual amplitude of the waves in this study. This ABR parameter was not previously considered in other studies. We found a statistically significant enhancement in this ratio in the study group compared with the control group. This isolated finding cannot support any conclusion. Auditory brainstem response should be analyzed with all parameters together. Other investigations should be performed to better understand this finding.

The role of the evaluation of the interaural difference of the latency of wave V in the diagnosis of cochlear and retrocochlear diseases has been pointed out by Hood. This parameter has not been used in ABR studies of patients with tinnitus. In our study, we found no statistically significant difference between the 2 tinnitus subgroups and the control group. On the other hand, 3 patients showed abnormality in this ABR parameter; thus, indicating that additional studies should be performed to better investigate this parameter in the tinnitus population. Again, the presence of an abnormality in only 1 parameter evaluated does not lead to a specific site of alteration.

The total prevalence of abnormalities in the ABR parameters in our study was 47%. It is reported in the literature that 31% to 40% of patients with tinnitus and normal hearing or slight hearing loss have abnormalities in the ABR parameters. However, these figures represent the compilation of 8 parameters and include patients with abnormalities of 1 or more of these parameters, which tends to increase the total prevalence of the abnormalities seen in this group of patients.

Even though 53% of the patients with tinnitus had ABR within the normal limits, when we analyzed the latencies, we found that the study group presented a significant prolongation of the latencies of waves I, III, and V when compared with the control group and an enlargement for the interpeak III-V and an enhancement of the V/I amplitude ratio, showing that even within the normal limits the ABR parameters in both groups are different. To distinguish patients with normal hearing and tinnitus from patients with normal hearing and no tinnitus using ABR certainly demands a tightening of the criteria for normalcy, but this would have to be done with many more patients to allow statistical validation of new criteria for normalcy.

In conclusion, 2 patterns of abnormalities were found in the present study and in some previous reports. One is a prolongation of wave 1 and late ABR waves, signaling a peripheral lesion in the auditory system. The other is the lengthening of the III-V IPL, indicating a dysfunction in the brainstem, thus indicating probably more than 1 site for the origin of tinnitus or the initial cochlear dysfunction, leading to brainstem abnormality that enhances the symptom. Additional studies should clarify these possibilities. Moreover, whether there are different sensitivities in the central pathways toward the cochlear dysfunction should also be investigated. Finally, al-
though the averages obtained in several analyzed parameters remained within normal limits, the ABR results from patients with and without tinnitus with normal hearing are different, suggesting that ABR might contribute to the workup of these patients. Nevertheless, other studies must be performed to investigate the meaning of the differences found in the present study.

Submitted for Publication: January 18, 2007; final revision received September 24, 2007; accepted October 2, 2007.

Correspondence: Helga M. Kehrle, MD, MSc, Department of Otolaryngology, Hospital de Base de Brasília, SQSW 306, Bloco A, Ap 208, Bairro Sudoeste, Brasília DF 70673-431, Brazil (helgak1@terra.com.br).

Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kehrle, Sampaio, Almeida, and Oliveira. Acquisition of data: Kehrle, Granjeiro, and Oliveira. Analysis and interpretation of data: Kehrle, Granjeiro, Sampaio, Bezerra, Almeida, and Oliveira. Drafting of the manuscript: Kehrle and Almeida. Critical revision of the manuscript for important intellectual content: Kehrle, Granjeiro, Sampaio, and Oliveira. Administrative, technical, and material support: Kehrle, Granjeiro, Sampaio, Almeida, and Oliveira. Study supervision: Kehrle, Sampaio, Bezerra, Almeida, and Oliveira.

Financial Disclosure: None reported.

REFERENCES