Amplitude Range Analysis of Otolithic Organ Responses

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Abstract: Benign paroxysmal positioning vertigo is easily diagnosed with the Dix-Hallpike maneuver. It is an ideal clinical condition in which to study the electrical response of the inner ear with electrocochleography techniques. Responses can be recorded during head tilt in roll and in pitch. With this technique we found that the amplitude range and scaling behavior of recorded raw data for the baseline resting position versus the stimulus position was statistically different in both patients and normal subjects. This can be demonstrated in the visual format of box plots. This technique promises to become a valuable addition to electrical examination techniques of the inner ear.

Key Words: benign paroxysmal positioning vertigo; box-plot analysis; electrocochleography; electrootolithography; otolithic organ

We have gained experience in examining the otolithic organ with what we call *electro-otolithography* [1]. In this technique, which is similar to extratympanic electrocochleography, an electrode is placed in the tympanic recess. The subject's head is tilted in roll and in pitch to stimulate the otolithic organ. Generally, roll is conceded mainly to stimulate the utriculus, whereas pitch mainly stimulates the sacculus. Then responses are averaged. However, the principle of this averaging is different, as we do not employ multiple stimuli; instead, we stimulate once only. Because the vestibular organ shows rhythmicity, the responses that are averaged are phase-locked to a harmonic of an individual response frequency.

Electrootolithography is useful in the hands of experienced audiologists who have the ability to detect the window of activity within the evolving time-series signal on a monitor. What is needed is a reductionist technique that can display the averaged (region-of-interest) signal in real time. Unfortunately, modern equipment does not provide this facility. The quality of recordings also can vary, as the chosen averaging frequency might not be exactly in tune with a harmonic of an individual response frequency. This will cause the signal to fade in and out. In addition, averaging is not phase-locked to the maximum amplitude of the response; therefore, the signal varies in strength.

To overcome these problems and with the aim of developing a robust signal-processing method for routine clinical evaluation, we investigated several different statistical methods. Initially, we applied a range of fractal methods using physical wavelet analysis for the examination of two types of signals (baseline resting position and head tilting) to establish first that the signals were different and, second, that this difference was statistically significant [2,3]. Ultimately, the raw electrode data were displayed in the visual format of box plots. Our aim was to perform data acquisition and analysis that can show at a glance, as in reading an audiogram, whether a response differs from the norm. Therefore, this study reports on box-plot analysis of raw collected data.

METHOD

Thirty-six subjects took part in this study. Twelve were normal subjects (7 women, aged 45.2 ± 14.2 yr; 5 men, aged 33.8 ± 16.3 yr) free of any ear disorder and particularly free of any balance disturbances during the

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last 12 months. Twenty-four patients (16 women, aged 54.2 ± 10.1 yr; 8 men, aged 54 ± 13.5 yr) had benign paroxysmal positioning vertigo, clinically diagnosed with the Dix-Hallpike maneuver. In three patients, benign positioning vertigo was part of Ménière's disease. Ten patients had normal hearing levels; the majority had a symmetrical mild sensorineural hearing loss sloping toward the high frequencies. The electrocochleograms were normal except in those suffering from Ménière's disease. Generally, we observed a vestibular pattern of voltage changes during raised intracranial pressure [4]. Brainstem audiometry showed normal tracings and latencies in all these subjects, and none suggested retrocochlear pathology. Four patients of this group could be reassessed after a successful repositioning maneuver. One additional 62-year-old man was included in this study. An acoustical neuroma had been removed from his left ear 6 months before this investigation.

For recording, the active electrode remained in the tympanic recess after electrocochleography; the reference electrode was fixed on the ear lobe, and the common ground electrode was fixed just beneath the frontal hairline. The active electrode was secured with tapes on the pinna so as to avoid movement during head tilting.

We examined all subjects while they sat comfortably at the edge of the examination table. After obtaining a baseline response, we tested subjects in roll (ipsilateral head tilt to the electrode side and contralateral head tilt away from the electrode side, stimulating the utriculus) and in pitch (forward head tilt and backward head tilt, stimulating the sacculus). Head tilting was swift but not forceful. Each recording took approximately 3–5 seconds.

Several responses also were obtained from subjects subjected to the sound of a tuning fork (512 Hz) held in front of the external ear canal, after clenching the teeth and shaking the head. We tested four normal subjects on a tilt table so as to avoid possible contamination by the semicircular canals, and in four patients we recorded responses after a head tilt lasting 10 seconds.

Figure 1 shows our recording setup. We have built a breakout box connected to an existing interface unit (Navigator; Biologic, Chicago, IL). The breakout box collected raw data and diverted them to a new data acquisition system for further processing of the incoming signals. Initially, we used physical wavelet analysis for data classification after acquisition [4]. We found that plotting voltage change and time from the electrodes were equally efficient. We chose the visual format of box plots to read the analyzed data. We digitized raw data from the electrodes and plotted as voltage amplitude versus time using a medically rated analog-to-digital converter. Normally, we recorded the baseline and four head-tilt positions, and we displayed individual box plots for comparison. Box plots provided a statistical summary of the roll and pitch motion from our patients. We displayed ratios for the utriculus and sacculus to classify the shape of the data distribution. Box plots are useful in exploratory data analysis when two or more data sets are being compared. Visually, the box plots show the median, quartiles, cutoffs, and minimum-maximum values.

Median

The median value splits a data set into two sets. The median is the pivot point above which and below which an equal number of values appear. If the array has equal numbers of values, the median is the average of the two middle numbers.

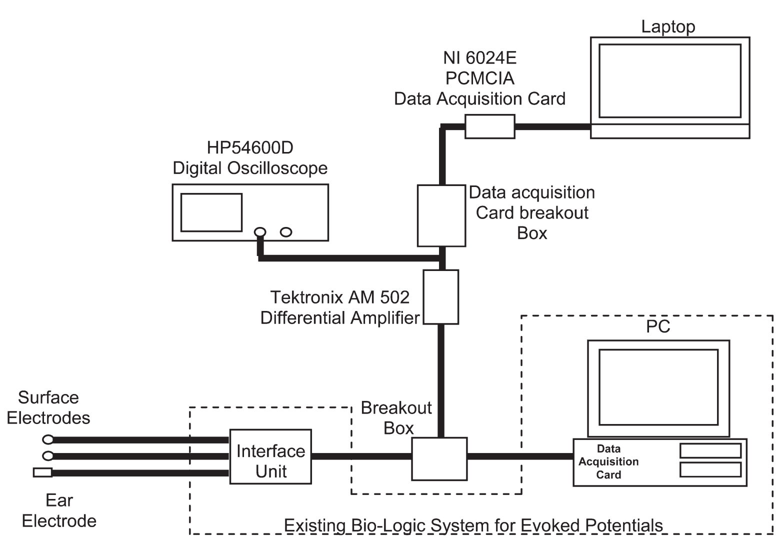

Figure 1. Data collection setup.

Quartiles

As their name implies, quartiles subdivide a data array into one-quarter intervals. Q1 is the value below which 25% of the data are found. Q3 is the value above which 25% of the data are found. Q2 is the median. Q1 is the median of the lower one-half of the data. If the data array is an odd number, Q1 includes the median; Q1 is known as the twenty-fifth percentile. Q3 is the median of the upper one-half of the data. If the data array is an odd number, Q3 includes the median; Q3 is known as the seventy-fifth percentile.

Interquartile Range

Q3 − Q1 describes the variation in the array.

Rules:

$$\begin{aligned} \text{cutoff1} &= Q1 - 1.5*(Q3 - Q1) \\ \text{cutoff2} &= Q3 + 1.5*(Q3 - Q1) \end{aligned} \qquad \text{(Equation 1)}$$

Minimum: The explicit value in the array that is just above cutoff 1.

Maximum: The explicit value in the array that is just below cutoff 2.

Classification: A ratio between the seventy-fifth and twenty-fifth percentiles is used:

$$Q3 - Q1 = Q_m \qquad \text{(Equation 2)}$$

This specifies the set descriptor for each paired movement:

$$\frac{\text{contralateral } Q_m}{\text{ipsilateral } Q_m} \approx \text{utriculus} \qquad \text{(Equation 3)}$$

$$\frac{\text{backward } Q_m}{\text{forward } Q_m} \approx \text{sacculus} \qquad \text{(Equation 4)}$$

This method presents statistical information showing the median, twenty-fifth, and seventy-fifth percentiles shown as the top and bottom of the boxes with error bars showing the cutoffs and minimum-maximum values (SigmaPlot version 8.02). We were particularly interested in the Q_m values (seventy-fifth through twenty-fifth percentiles) of the amplitude range of each response (size of the box in the box-plot analysis). The Q_m values were used for statistical analysis (Student's *t*-test) and ultimately led to a new coefficient describing the response of the utriculus and the sacculus.

RESULTS

Table 1 gives a numerical data description of the scaling behavior in head resting versus ipsilateral and forward head tilt in a subject without vestibulocochlear symptoms. These figures show the signal amplitude versus time. A clear difference between resting and stimulus position is seen (see Table 1). Although the differences are quite obvious, they might not be a suitable format for clinicians.

Table 1. Comparison Between Head-Resting Controls and Two Stimulus Positions

Condition	Range
Head resting, control 1	0.54
Head resting, control 2	0.53
Ipsilateral tilt, stimulus 1	1.26
Forward tilt, stimulus 2	0.90

Note: Comparison between head-resting controls and two stimulus positions quantified by examining the data range for the signal amplitude (voltage) versus time based on physical wavelet analysis. Note that other methods of statistical data analysis of the electrode signal can also be used for numerical classification.

Instead of a numerical data description, a visual format, such as box plots, provides the same statistics. This is a suitable format for clinicians who can see at a glance, as in reading an audiogram, whether a response is diverse from the norm (Fig. 2).

Figure 3 shows the interquartile range analysis in a normal subject, comparing ipsilateral with contralateral and forward head tilt with backward head tilt. The upper one-half of the diagram contains the digitized raw data. The lower one-half of the diagram contains the interquartile range analyses, displayed in box plots.

In normal subjects, we typically found that the interquartile range coefficient (Q_m) of ipsilateral head tilt was always larger than the interquartile range coefficient of contralateral head tilt, representing the response of the utriculus. Similarly, we found that the interquartile range coefficient of forward head tilt tended to be equal to or larger than the interquartile range coefficient of backward head tilt, representing the response of the sacculus.

This relationship could be expressed in a new ratio between the Q_m coefficients (Equation 2). The ratio was

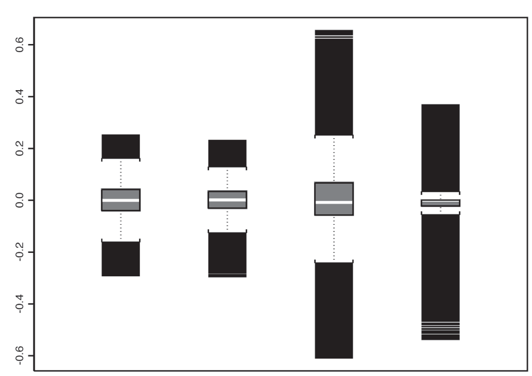

Figure 2. Left to right: box plot of raw data for both head-resting controls, followed by ipsilateral tilt, then forward tilt.

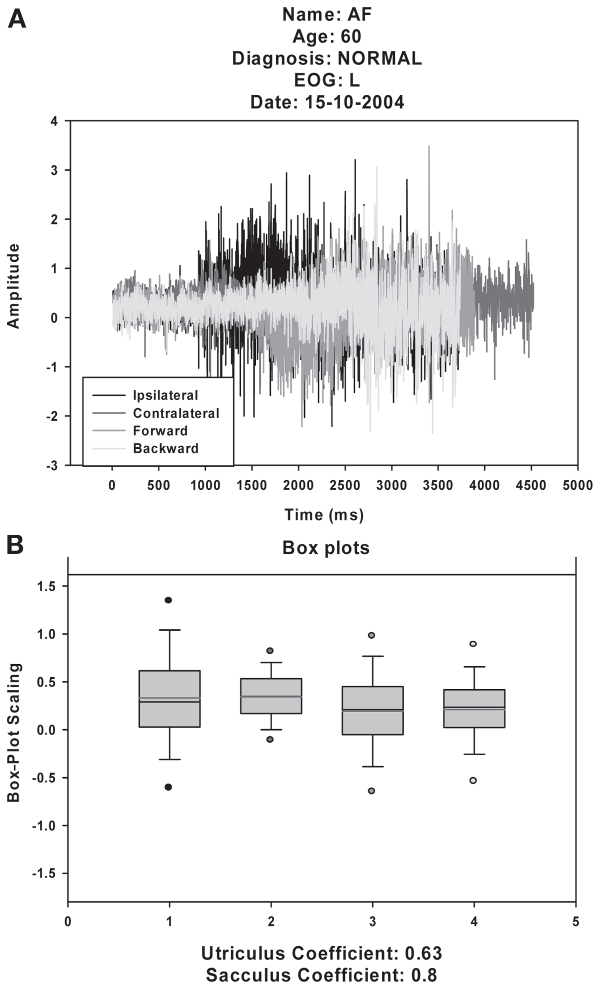

Figure 3. Recordings of a normal subject. (A) Digitized raw data. (B) The analyses in box plots. Typically, ipsilateral and forward head tilt show larger box plots than do contralateral and backward head tilt. (*EOG* = electrootolithography; *L* = left.)

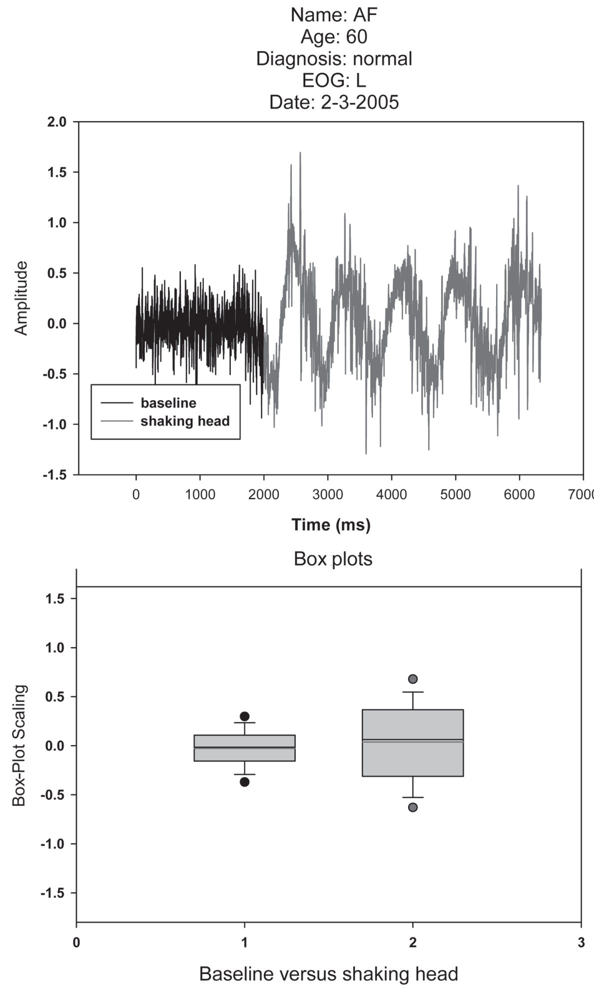

Figure 4. Head shaking reveals major artifacts, which affect the size of the box plot, here compared with the baseline. These recordings should be discarded for analysis. (*EOG* = electrootolithography; *L* = left.)

obtained by dividing Q_m of contralateral tilt by the Q_m of ipsilateral tilt, representing the response of the utriculus (Equation 3). Equally, the ratio representing the sacculus was obtained by dividing the Q_m of backward head tilt by the Q_m of forward head tilt (Equation 4).

In normal subjects, the ratio coefficient for the utriculus was 0.8 ± 0.15, and for the sacculus it was 0.9 ± 0.15. Taking into consideration the standard deviation, we expected that 95% of subjects would score between 0.5 and 1.1 for the response of the utriculus and between 0.6 and 1.2 for the sacculus.

Recordings during head shaking are shown in Figure 4. The marked regression from the zero line creating artifacts affects the size of the box plots. These artifacts should be discarded before the final analysis, and most likely they are the result of an electrode movement in the tympanic recess.

Recordings in resting position during teeth clenching showed an immediate and obvious response (Fig. 5). Here we expected recording of muscle potentials. Note that these recordings have been conducted under extreme and nonphysiological conditions to test the responsivity of the method.

Figure 6 compares resting position with the presentation of a 512-Hz tuning fork to the test ear. The box plot during this sound stimulus was larger than in resting position without stimulus. The difference was obvious and showed that this technique will record inner-ear responses, although the recordings look very much like microphonics.

To reduce interference from muscle activity or a disturbance from a moving electrode in the tympanic recess—or even contamination by the semicircular canals—we performed recordings using a tilt table while subjects

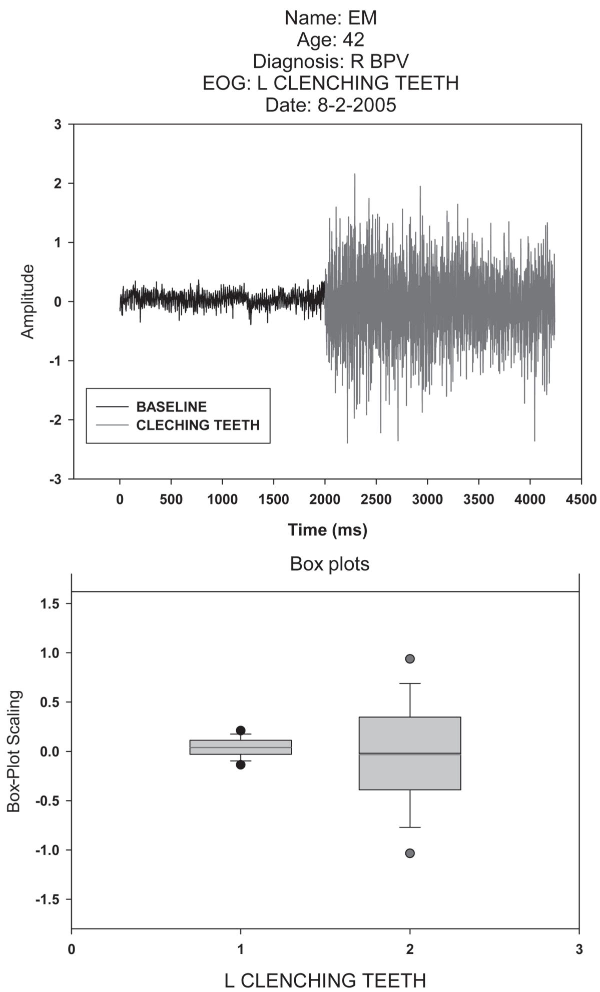

Figure 5. Clenching the teeth demonstrates an immediate response, which is most likely due to muscle activity. (*R BPV*= right benign paroxysmal vertigo; *EOG* = electrootolithography; *L* = left.)

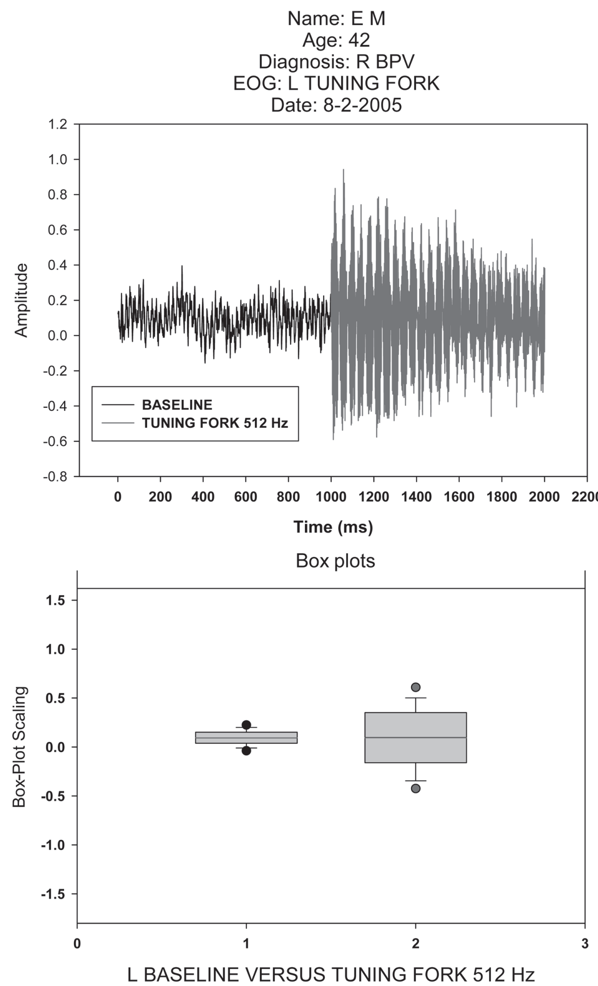

Figure 6. The presentation of a tuning fork to the test ear shows a strong response, suggesting that this technique is suitable for recording inner-ear responses. (*R BPV*= right benign paroxysmal vertigo; *EOG* = electrootolithography; *L* = left.)

were completely relaxed. The table was tilted 10 degrees per second. These results compared well with those obtained from a subject sitting at the edge of an examination table and swiftly tilting the head (Fig. 7). Also here, we observed that boxes of ipsilateral head tilt were larger than boxes of contralateral head tilt. Equally, boxes of forward head tilt were larger than boxes of backward head tilt. This suggested that interference from muscle activity or contamination by the semicircular canals can possibly be ignored; when using a tilt table, they could be avoided.

We usually performed recordings over a period of 3–5 seconds while swiftly tilting the head. Figure 8 shows the response after a static tilt for 10 seconds before recording. These results were different from the swift head tilt recording. The interquartile range calculation (Equations 3 and 4) showed a reversed pattern, where contralateral tilt and backward tilt now showed a larger interquartile range. We believe that the reversed pattern was most likely due to adaptation phenomena or that responses came from different areas of the maculae. Because patients generally—and particularly the elderly—had problems in holding the head in a tilted position and more artifacts were seen, we no longer use this method.

The recordings of a patient after the removal of an acoustical neuroma from the left ear are shown in Figure 9. Here, the response of the vestibular organ appeared to be silent. The baseline recordings showed regular fluctuations. These fluctuations had a frequency of 72 cycles per minute and coincided with the patient's pulse. The frequency of these fluctuations and the strength of the response seemingly remained during stimulation in roll and in pitch. We also observed more

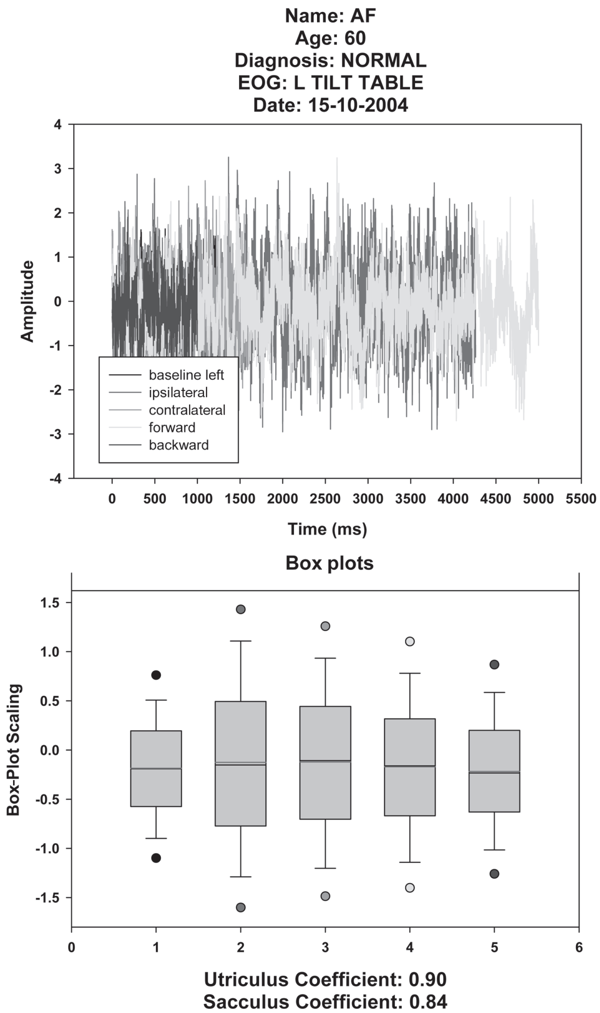

Figure 7. Tilt-table recordings show a pattern comparable to that of a swift head tilt, suggesting that contamination from the semicircular canals can possibly be ignored. (*EOG* = electrootolithography; *L* = left.)

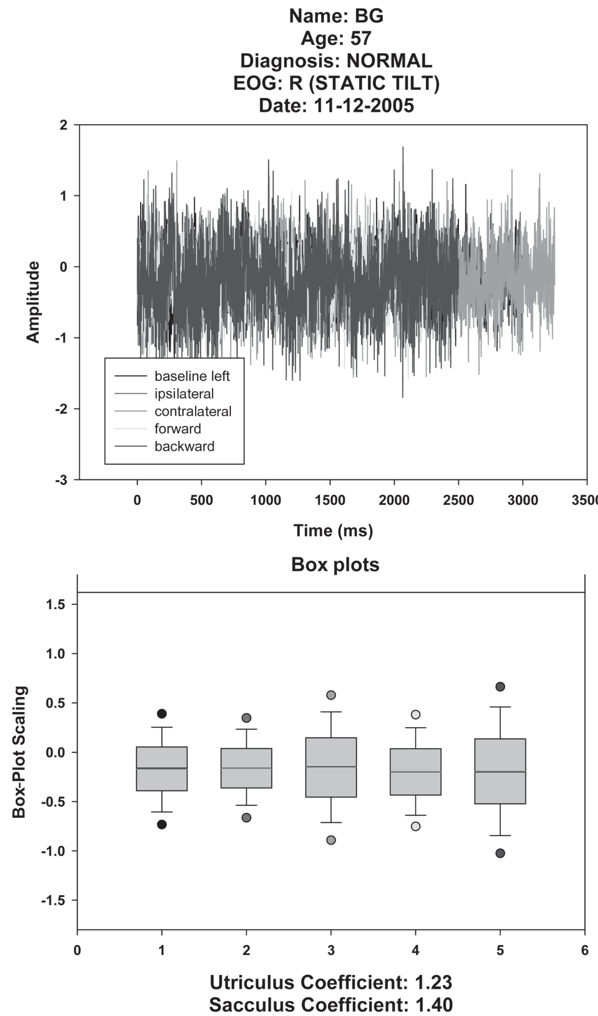

Figure 8. Tilting the head for the 10 seconds and then recording shows a reversed pattern of the box plots, possibly due to adaptation phenomena. (*EOG* = electrootolithography; *R* = right.)

artifacts, possibly due to the movement of the electrode in the tympanic recess.

Figure 10 shows the response of a patient with benign paroxysmal positioning vertigo before canalith repositioning and before the otolithic organ had recovered. The Dix-Hallpike maneuver was positive for the right ear. This reversed pattern of the box sizes was typical for benign paroxysmal positioning vertigo. In this case, the contralateral box was larger than the ipsilateral box, rendering a coefficient above 1.1 and suggesting a deficit in the right utriculus.

After a successful repositioning maneuver, that patient no longer had a balance problem, and box sizes returned to a normal pattern (i.e., the ipsilateral interquartile range was larger than the contralateral), and the coefficient returned to normal; equally, the coefficient of the sacculus response remained within normal limits (Fig. 11).

DISCUSSION

Short-lived positioning attacks of vertigo are generally conceded to result from movement of dislodged, gravity-sensitive otoconia that somehow found their way into a semicircular canal. The diagnosis is clinical and easily made with the Dix-Hallpike maneuver. The Dix-Hallpike maneuver is also suitable for reviewing the treatment outcome after canalith repositioning.

Benign paroxysmal positioning vertigo, therefore, is an ideal clinical condition in which to study the electrical response of the inner ear before and after treatment and to compare responses with normal subjects.

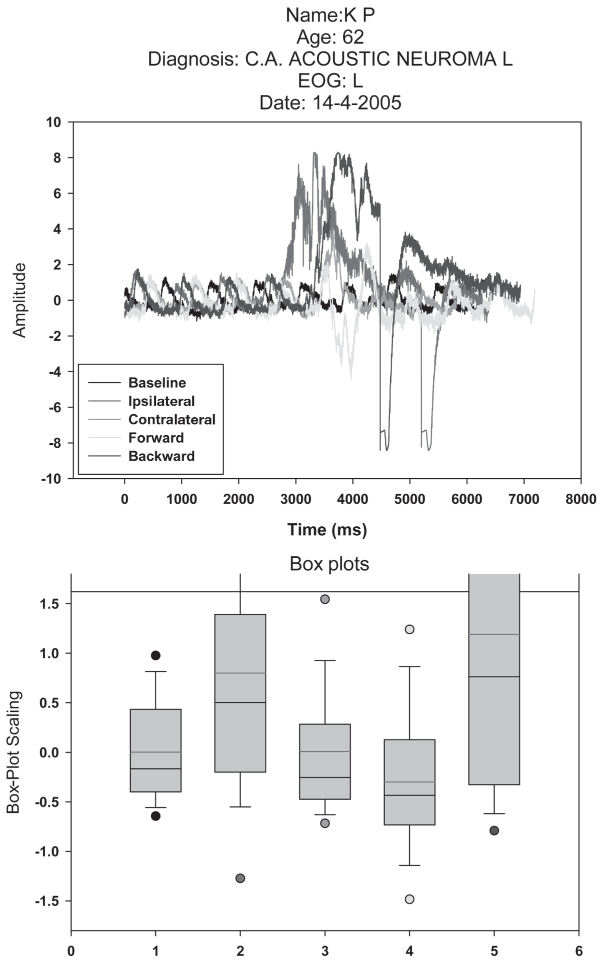

Figure 9. After removal of an acoustic neuroma, only artifacts can be demonstrated. Box plots also show a marked digression of the median (lower bar in the box) from the mean (upper bar in the box). The baseline recordings show a sinusoidal pattern at a frequency of 72 per minute, which coincided with the patient's pulse. (*C.A.* = condition after; *EOG* = electrootolithography; *L* = left.)

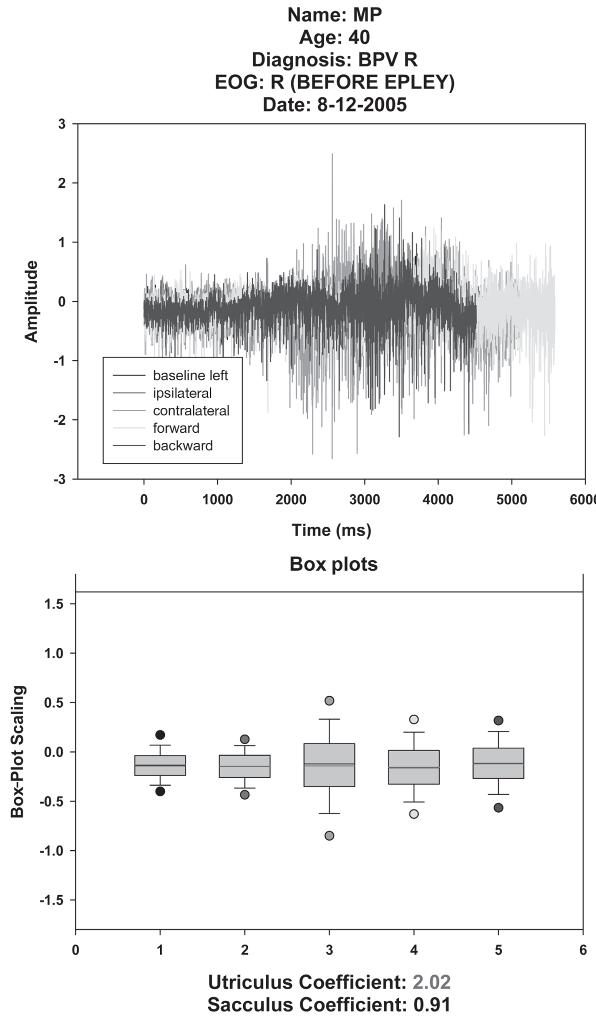

Figure 10. Box-plot analysis in a subject with benign paroxysmal positioning vertigo (*BPV*) before a repositioning maneuver. The contralateral interquartile range ratio is larger than the ipsilateral interquartile range ratio, suggesting a deficit in the right utriculus. (*R* = right; *EOG* = electrootolithography; *L* = left.)

Amplitude range analysis compares well with electrootolithography. In electrootolithography, we find in normal subjects with swift ipsilateral head tilt and forward head tilt a smaller summating potential/action potential (SP/AP) ratio than with contralateral head tilt and backward head tilt. The smaller SP/AP ratio is likely due to increased activity of the vestibular nerve giving a larger AP voltage and resulting in a smaller SP/AP ratio. In amplitude range analysis, we would consequently expect larger interquartile ranges due to an increased vestibular nerve response.

In contralateral head tilt and backward head tilt, possibly owing to inhibition, cross-striolar or commissural, response of the vestibular nerve is comparatively reduced. This will lead to a larger SP/AP ratio. In amplitude range analysis, interquartile ranges will consequently be smaller, owing to a reduced vestibular nerve response.

Our results are consistent with the clinical presentation of symptoms but also give us additional information based on the unique anatomical arrangement of hair cells in the otolithic organ [5]. The utriculus is divided by the reversal line of the striola into a medial portion and a lateral portion of the macula, and the hair cells have opposite polarization, with the kinocilia facing each other (Fig. 12). Thus, an ipsilateral tilt (bending hairs toward the kinocilia) appears mainly to stimulate the medial portion of the macula utriculi, and contralateral tilt stimulates mainly the lateral portion of the macula utriculi.

A coefficient above 1.1 thus suggests a deficit in the

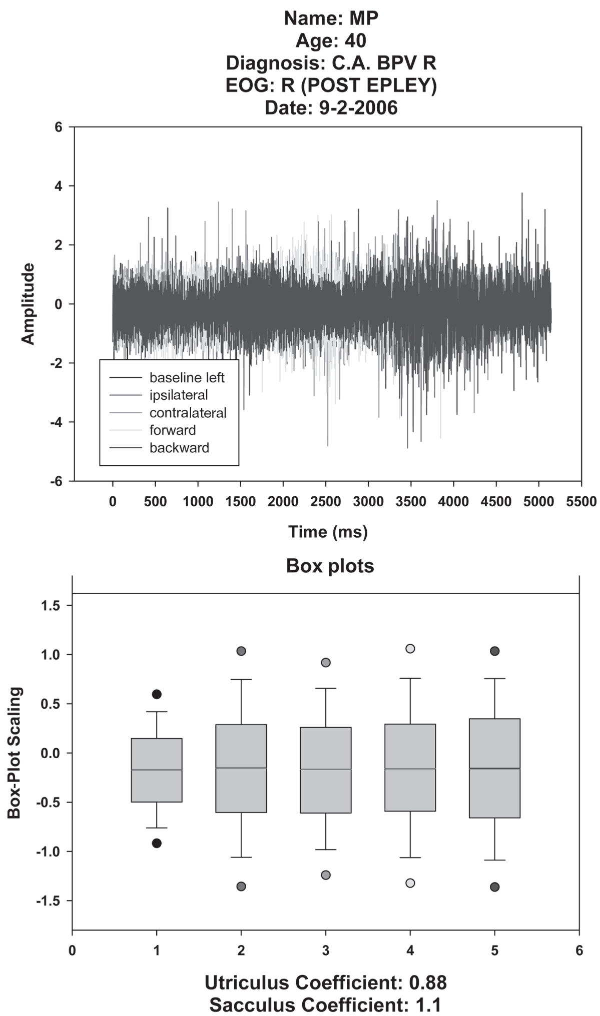

Figure 11. Box-plot analysis after a successful repositioning maneuver. The coefficient ratio of the utriculus has returned to normal, and the coefficient ratio of the sacculus has remained within normal limits. (*C.A.* = condition after; *BPV* = benign paroxysmal vertigo; *EOG* = electrootolithography; *R* = right.)

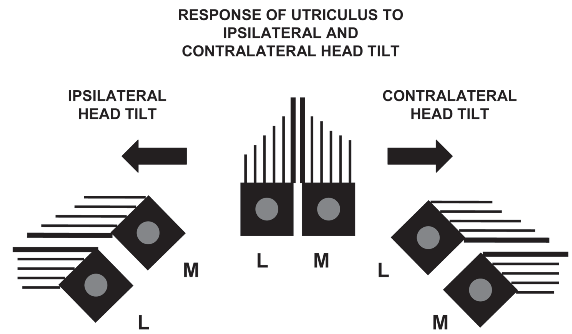

Figure 12. Hair cells of the macula utriculi are separated by the reversal line of the striola, and the hair cells have polarization opposite, with the kinocilia facing one another. Ipsilateral head tilt mainly stimulates the medial macula utriculi, whereas contralateral head tilt will mainly stimulate the lateral macula utriculi. (L = lateral portion of macula utriculi; M = medial portion of macula utriculi.)

medial portion of the macula utriculi, owing to a relatively larger response of the lateral portion, whereas a coefficient below 0.5 indicates a deficit in the lateral portion of the macula utriculi, owing to a relatively larger response of the medial portion. Because a deficit can equally affect both the medial and the lateral portions of the utriculus, a normal coefficient could possibly be seen. However, in that case, an interaural difference in the size of the boxes is to be expected.

In the sacculus, we can distinguish between an anterior portion and a posterior portion of the macula, and the polarization of the hair cells along the reversal line of the striola is opposite that of the utriculus (Fig. 13). Thus, forward head tilt will mainly stimulate the anterior portion of the macula sacculi, and backward head tilt will stimulate mainly the posterior portion.

Also here, the unique arrangement of hair cells and the size of the coefficients can give us a clue as to where in the sacculus the deficit is to be expected. Thus, a coefficient above 1.2 would indicate a deficit in the anterior portion of the macula sacculi, and a coefficient below 0.6 would indicate a deficit in the posterior portion of the sacculus.

We usually performed recordings over a period of 3–5 seconds while subjects swiftly tilted the head. We noted different results when subjects tilted the head for 10 seconds before recording. Thus, different clinical techniques will give different results, and adhering to a specific technique is necessary so as to obtain consistent results. That these two different techniques stimulate different hair cell units that have different characteristics appears possible. One technique might preferentially stimulate irregular discharging units, which are suspected to be

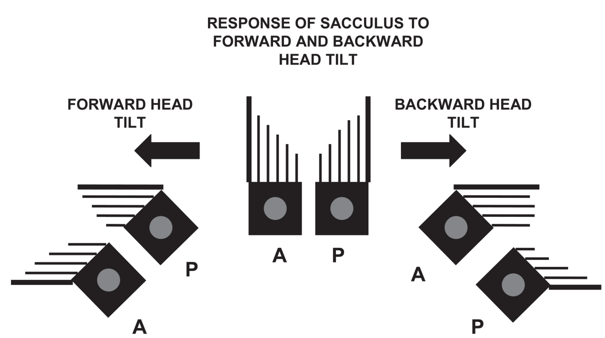

Figure 13. Hair cells of the macula sacculi are separated by the reversal line of the striola into a posterior and an anterior portion, and the kinocilia of hair cells have an orientation opposite to the utriculus. Forward head tilt will mainly stimulate the anterior portion of the sacculus, whereas backward head tilt will mainly stimulate the posterior portion. (P = posterior portion of macula sacculi; A = anterior portion of macula sacculi.)

located in the striola, whereas another technique might preferentially stimulate regular discharging units, which are suspected to be located in the extrastriolar region [6].

Our results compare well with those of experiments on squirrel monkeys by Fernandez et al. [7]. Those researchers found that the medial portion of the utriculus has a hair cell area comparatively larger than the lateral portion. In squirrel monkeys, the proportion is 60:40, and one can assume that it is similar in humans. However, more importantly, Fernandez et al. found that 70% of vestibular neurons were excited during ipsilateral tilt and 30% during contralateral tilt. Thus, one would expect a larger interquartile range when the medial portion is stimulated.

The situation is slightly different for the sacculus. The hair cell area of the anterior portion of the sacculus compares to the posterior portion, and responses in normal subjects are suspected to be fairly equal. In their experiments on squirrel monkeys, Fernandez et al. [7] found that forward head tilt and backward head tilt excited almost the same number of neurons. Those results compare well with our findings, in which the coefficient of the sacculus response hovers around 0.9 instead of around 1.

Though the quality of electrootolithography is dependent on the experience of the examiner and therefore is a far more subjective test, performing the amplitude range analysis test is easier, and it is more objective.

We do not believe that the movement of otoconia is responsible for the abnormal box-plot pattern in benign paroxysmal positioning vertigo. The recording is performed in a relatively short period during which movement of the otoconia hardly becomes effective. Clinical experience with benign vertigo demonstrates the existence of a delay of several seconds before a nystagmus is observed in the Dix-Hallpike maneuver or the patient experiences vertigo. Tilting the head in roll and in pitch also is not performed in the optimal plane of the semicircular canals, rendering movement of the otoconia more difficult. Above all, experience with electrootolithography shows that a successful repositioning can eliminate positioning attacks of vertigo but not necessarily a remaining instability during quick head movement. The remaining instability is due to a continuing measurable deficit in the otolithic organ [1]. Conversely, a positive Dix-Hallpike maneuver indicates only that otoconia have found their way into a semicircular canal. The maneuver does not indicate whether the otolithic organ has a deficit, and we might find a normal response of the otolithic organ.

We are routinely performing amplitude range analyses of the otolithic organ, although the results with this technique can be regarded as preliminary. We believe that contamination by muscle activity or responses from the semicircular canals can be ignored. It can also be avoided by using a tilt table.

Finally, this technique can be transferred to the caloric examination of the lateral semicircular canal. Pilot studies so far support this assumption, and the examination of the lateral semicircular canal already forms part of our test battery using this technique.

From examining directly all three units of the inner ear with a single electrode placed in the tympanic recess, our understanding of inner-ear disorders is gradually changing. Very rarely, we find a single unit of the inner ear responding independently. The rule is that the cochlea, the otolithic organ, and the semicircular canals are all part of a combined response to an insult inflicted on the inner ear, although individual responses and the combination therein may vary.

CONCLUSIONS

Benign paroxysmal positioning vertigo is a suitable clinical condition in which to examine the inner ear's response to head tilting in roll and in pitch using electrocochleography techniques. Amplitude range analysis is a more objective test than is electrootolithography, and a statistical summary can be displayed in box plots. Normal subjects show a different pattern as compared with those from patients with benign paroxysmal positioning vertigo.

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