Short latency disconjugate vestibulo-ocular responses to transient stimuli in the audio frequency range

P Jombik, V Bahyl

Objective: To determine whether unilateral activation of the vestibular labyrinth by brief air conducted tones can elicit disconjugate reflex eye movements in healthy subjects.

Methods: 40 normal volunteers, one patient with bilateral congenital sensorineural deafness, and four patients with an acoustic neuromas were subjected to monoaural air conducted tones (125 to 6000 Hz; 132 dB SPL; 3–4 ms). Eye movements were recorded by averaged EOG.

Results: The stimuli elicited bi- or triphasic transient EOG responses with a duration of about 10 ms and a 7–8 ms latency in 16 of 40 tested volunteers and in the patient with congenital deafness. In patients with acoustic neuromas the responses were induced only by stimuli to the healthy ear. The responses in the vertical EOG were recorded predominantly from the eye contralateral to the stimulated ear and were negligible ipsilaterally. These responses were similar to those found in patients with only one functioning labyrinth reported in a previous study. In the remaining subjects the responses were absent or barely discernible.

Conclusions: (1) Disconjugate eye movements in response to brief mechanical stimuli in this audio frequency range always indicated the side of the activated vestibular labyrinth. (2) In contrast to longer stimuli used by conventional vestibular activation methods, brief stimuli may activate only the direct monocular vestibulo-ocular pathway. This may be because the responses elicited by brief stimuli cease well before the slower indirect vestibulo-ocular subsystem can align the eyes.
previous study with reflex eye movements elicited by short air conducted sound stimuli in normal subjects.

**METHODS**

**Subjects**

We studied 40 normal volunteers aged between 19 and 69 years (mean (SD), 42.3 (14.9)) without a history or clinical signs of vestibular or oculomotor disorder, one subject with congenital sensorineural deafness, and four patients with acoustic neuroma. Two of the latter four had undergone neuroma resection, and hearing was preserved in one of them. All control subjects, as well as the volunteer with congenital deafness, had normal responses in the head thrust test and normal vestibulo-collic responses in the sternocleidomastoid muscles. The patients with neuromas had consistent ipsilateral absence of these responses. The study was carried out in accordance with the 1964 Declaration of Helsinki protocol and with approval of the institutional ethics committee.

**Test procedures**

Subjects were seated upright in a dimly lit room and viewed a small illuminated target straight ahead from a 3.5 m distance. Several subjects were also studied with eccentric horizontal gaze positions. Care was taken to obtain relaxation of the jaw muscles. The ACS were 125 to 6000 Hz logons*, spaced approximately in half octave or octave steps (see fig 4), with a duration of 3–4 ms and intensity of 132 dB sound pressure level (SPL). They were delivered monoaurally through headphones with a repetition rate of 3.1 per second. Reflex thresholds were determined in four subjects with well formed responses using 10 dB decrements in sound intensity. Responses were recorded by means of bilateral monocular vertical, and binocular horizontal EOG. Eye movements were calibrated with 10° up, down, left, and right saccades. The signal was amplified and bandpass filtered at 5–2000 Hz. Thirty responses were averaged twice, using a sampling rate of 10 000 Hz for each channel, 5 ms before and 45 ms after each stimulus. The upward deflection of the recorded eye position signal in vertical and horizontal EOG channels corresponded to upward and rightward eye movement, respectively. With the exception of stimulation method—that is, air conducted sound stimuli instead of head taps and

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* The logon is a particular type of tone burst with a raised cosine, instead of trapezoidal enveloping function.
bone conducted tones—the recording conditions were identical to those used in our previous study.15

Data analysis
In addition to slow baseline drift, EOG has a rather high baseline noise level which limits resolution to 0.5–1˚ at best. However, for a high frequency signal with a short latency that is time locked to the stimulus, an averaging technique can increase the resolution by about one order. The vertical EOG always reflects an interaction of eye and lid movements. The eyelid acts as a sliding electrode, increasingly shunting the positive corneal pole to the upper EOG electrode while covering the larger surface of the cornea. Measured potentials associated with vertical eye movements are further distorted because the upper lid does not maintain a constant position with respect to the cornea. Moreover, the negative pole of the corneoretinal dipole does not lie exactly at the fovea, but instead it is displaced nasally by about 15˚. This means that the electrical field is not precisely aligned with the optic axis, and so torsional movements of the globe may give rise to potential changes which are misinterpreted as horizontal or vertical movements.24 25 The signal in the horizontal binocular EOG is an approximate arithmetical sum of the signals from the left and the right eye. Conjugate eye movements, and even those that are disconjugate in amplitude of movement, but not in direction of movement—that is, disassociated eye movements—cause an increase in the signal amplitude in the binocular EOG channel. Conversely, those that are disjunctive (oppositely directed) will be cancelled. Owing to the complexity of the recorded signals and the limited reliability of our recording technique, we displayed and analysed the EOG signal in microvolts and our analysis was focused on vertical eye movements. Statistical analyses were done using the Student t test and common analysis of variance. Results were considered significant at p<0.05.

RESULTS
ACS did not elicit any response, or the responses were ambiguous, in 24 subjects. In 16 subjects, stimuli in the frequency range of 750–1000 Hz to either ear elicited transient disconjugate biphasic or triphasic responses with duration of about 10 ms, predominantly in the vertical EOG of the contralateral eye (fig 1A, fig 2, fig 3). Vertical EOG responses were initially directed upward and then downward. Latency of onset, defined as the first sharp decline from baseline, was about 7–8 ms, and amplitudes measured from peak to peak were in the range of 5–37 µV. The responses of the ipsilateral eye were in general negligible (table 1). Horizontal EOG responses were initially directed toward and then away from the stimulated ear. Above and below the range of 500–1000 Hz the responses tended to diminish or were absent; thus the frequency tuning was in the range already shown for vestibular activation by ear conducted sound, with thresholds between 102 and 122 dB SPL (fig 4).1 6 10 The responses seemed to be vestibular dependent, because they were also obtained in a subject with bilateral congenital sensorineural deafness but normal vestibular function (fig 1A). However, the responses in the patients with acoustic neuroma were elicited only when the stimuli were applied to the healthy ear, but were absent with stimulation on the lesioned side. Horizontal gaze slightly increased the response amplitude on the side of the abducting eye and decreased it on the side of the adducting eye, but without a reversal of the asymmetry.

DISCUSSION
In the present study, reflex eye movements were obtained in 38 of 90 ears in response to ACS. The absence of response to stimulation of the lesioned ear in the four patients with acoustic neuroma was obvious. The stimulation intensity at 132 dB SPL was equivalent to 92 dB of normal hearing level; thus it was about the threshold for vestibular activation by ear conducted sound.1 6 16 Hence, subthreshold stimulation might be one of the reasons for the absence of the responses in the remaining 48 ears.

Brain stem reflexes and auditory evoked potentials
The early R1 component of the blink reflex can generally be elicited only by stimulating the first division of the trigeminal nerve. It occurs only ipsilaterally on the side of stimulation, and possesses a latency that is somewhat longer than was associated with vertical eye movements are further distorted because they were also obtained in a subject with bilateral congenital sensorineural deafness but normal vestibular function (fig 1A). However, the responses in the patients with acoustic neuroma were elicited only when the stimuli were applied to the healthy ear, but were absent with stimulation on the lesioned side. Horizontal gaze slightly increased the response amplitude on the side of the adducting eye and decreased it on the side of the adducting eye, but without a reversal of the asymmetry.

Table 1

<table>
<thead>
<tr>
<th>Stimulated ear</th>
<th>Onset latency (ms)</th>
<th>Peak 1 latency (ms)</th>
<th>Peak 2 latency (ms)</th>
<th>Peak 1–2 amplitude (µV)</th>
<th>AR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contra</td>
<td>Ipsi</td>
<td>Contra</td>
<td>Ipsi</td>
<td>Contra</td>
</tr>
<tr>
<td>Left</td>
<td>7.20 (0.33)</td>
<td>7.49 (0.71)</td>
<td>9.57 (0.70)</td>
<td>9.85 (0.81)</td>
<td>14.67 (1.33)</td>
</tr>
<tr>
<td>Right</td>
<td>7.14 (0.46)</td>
<td>7.57 (0.61)</td>
<td>9.70 (0.87)</td>
<td>9.83 (0.79)</td>
<td>14.59 (1.01)</td>
</tr>
</tbody>
</table>

Values are mean (SD).
Contralateral and ipsilateral differences in peak 1 to peak 2 amplitudes are expressed as an asymmetry ratio (AR) calculated as AR% = 100×[(contra–ipsi)/(contra+ipsi)].
Statistical difference of the ipsilateral eye response to the corresponding value of the contralateral eye: *p<0.05; **p<0.01.
found for EOG responses in the present study. The bilateral R2 component of the blink reflex can be elicited by various sensory stimuli including loud sounds. The latency of the R2 component as well as the associated eye and lid movements generally exceeds 20 ms.26 27 Hence, any blink reflex could neither generate the short latency EOG responses nor interfere with them.

The ACS can elicit reflex responses in the ipsilateral sternocleidomastoid muscle and bilaterally in the dorsal neck muscles. However, the amplitudes of these responses are greatly dependent on the level of background muscle activity. Fairly strong tonic muscle contraction is necessary for recording the responses, even with electrodes located over the muscle belly.26 During the recording procedure these muscles were not unduly activated, so it is improbable that any significant volume conducted potential originating from them would interfere with the EOG signal. On the other hand, the sacciculo-reflex of the postauricular muscle and the early components of the middle latency auditory evoked potential could be picked up by EOG with similar latency as the responses in this study. However, this myogenic potential is bilateral and the middle latency auditory evoked potential also has widespread bilateral distribution in frontal areas; thus it would probably not appear mainly in the contralateral EOG channel.

**Transient ocular responses versus nystagmus**

Nystagmus in response to stimuli of longer duration has slow build up. It reflects an activation of the polysynaptic pathways including the quick phase generator and the velocity storage system. The transient ocular movements in our studies were immediate responses to individual transient stimuli. We suppose that, owing to the low intensity and short duration of the stimuli as well as their separation in time (that is, more than 300 ms), the velocity storage system could be not activated. However, the responses tended to disappear in the 30 to 60 ms following the stimulus. Though the studied subjects sometimes reported a mild degree of oscillopsia, eye movements were invisible to the naked eye.

**Disconjugate VOR responses**

In our previous study, disconjugate eye movements in the vertical EOG of patients with unilateral vestibular loss always indicated the side of the paretic labyrinth.13 The findings with ACS suggest that an active VOR generated the responses. Disconjugation of the eye movements might be a consequence of the spatial orientation of the unbalanced unilateral labyrinthine input.

The analysis in this report was focused on vertical eye movements, because the findings in the binocular horizontal EOG channel were hardly interpretable, for the reasons already mentioned. The latencies of the responses, about 7–8 ms, with very low intersubject variability, were compatible with the action of a simple reflex circuit that is working with machine-like precision. This finding suggests activation of the direct disynaptic VOR pathway. The present estimate of VOR latency is consistent with recent measurements reported in other studies.17 18 Nevertheless, the range of the estimated latencies was much narrower. The estimation of the VOR latency depends a great deal on the stimulus time profile. Owing to the exponential shape of the VOR response, estimation of the response onset is more difficult for stimuli of slower rise time used in other studies. The high frequency transients that were employed in the present study can elicit responses with a similar time profile and a rapid rise time, so they allow estimation of the response latency with higher precision. This was reflected in a narrower range of measured latencies in comparison with other studies.

The purpose of the VOR is to provide clear vision when the head is moving. This reflex must be cancelled by visual fixation, when the stimuli are not accompanied by head movement, or when movement of the visual target is coupled with head movement. In this study the subjects were instructed to fixate a distant target in the absence of head movement. Nevertheless, the cancellation of the VOR and aVOR is very week up to 50 or 100 ms following the stimulus.28 29

If the responses were generated solely by horizontal or vertical eye rotation, the amplitude of eye movement would approach approximately 0.25–2°. The amplitudes were rather high, so lid artefacts could be implicated. Nevertheless, a high frequency gain enhancement might also operate. The increase in amplitude of the response in vertical EOG channel on the side of the adducting eye with horizontal gaze, and the decrease on the side of the abducting eye, could be compatible with subsequent activation of both inferior and superior oblique muscles.

Predominantly vertical transient eye movements similar to the responses that were recorded in the present study have been obtained by ACS in patients with superior canal dehiscence.4 In a study in monkeys, search coil recording of transient reflex eye movements in response to ACS revealed disconjugate horizontal movements that were similar in all four tested monkeys, but the vertical responses were highly variable and without contralateral predominance.2 We cannot say whether these discrepancies between the studies were caused by interspecies differences or by differences in experimental procedures. Nevertheless, the reproducible horizontal eye movements in monkeys suggest that the sacculo-ocular reflex was not the only one activated by the ACS. However, electrophysiological studies in cats have found only scanty polysynaptic connections from the utricle and the sacculae to the vertical and oblique muscles.21 22 These findings do not support the existence of a rapid VOR pathway from the otolithic organs to the muscles associated with vertical and torsional eye movements. Thus activation of the disynaptic pathway from the semicircular canals would be an explanation for the short latency responses in the vertical EOG that were found in our study and other, if an extrapolation of the data from cats to monkeys and humans is correct.

Eye movements generated by the VOR often have a roll component; thus the EOG has limited reliability for assessing these three dimensional eye movements.29 30 31 32 We do not know whether conjugate eye movements about an oblique axis might not lead to an apparently disconjugate EOG pattern owing to the torsional components and different eyelid interactions on either side. However, absence of reversal of the response asymmetry with eccentric horizontal gaze positions may suggest that this asymmetry was not caused by lid artefacts, and the responses might really be disconjugate.

The basically monocular organisation of the short latency transient VOR responses is the most important issue that can arise from the findings presented here. This notion was suggested more than a century ago by Helmholtz. On the other hand, Hering argued that both eyes are innervated by common command signals that yoke the eye movements (Hering’s law of equal innervation), and this view gained general acceptance up to recent times. However, several studies in the last decade showed evidence that Hering’s law is unlikely to be entirely correct. Studies in animals support the view that the general vertebrate bauplan is based on independent control units for each eye separately. The disconjugate nature of eye movements of monkeys during REM sleep suggests that there may be independent saccade generators for left and right eye movements.32
Electrophysiological studies in primates have shown that position-vestibular-pause neurones fire in relation to monocular eye position rather than to conjugate eye movements.\textsuperscript{13,14} Binocular coordination of saccadic eye movements and VOR depend on the state of alertness.\textsuperscript{32,34}

The vestibular nuclei can be subdivided in several functional areas. Those that provide direct VOR pathways might generate separate monocular command signals and activate the twitch motor units. The indirect system, with slower execution time, might participate in the neural integration of velocity to position, using non-twitch motor units and multiply innervated muscle fibres. The indirect system might carry signal command for the alignment and stabilisation of the eyes.\textsuperscript{15}

More conventional methods of vestibular activation use stimuli of rather longer duration, thus they provide enough time for the indirect VOR pathway to come into play. The audio frequency short duration vibrations that were used in our previous study and the sound stimuli presented here will elicit vestibular responses of similar short duration. These responses could depend on the more rapid direct VOR pathway that provides monocular command signals. Owing to the transient nature of the stimuli, the responses will cease well before the alignment of the eyes by the indirect pathway could begin. Thus these transient stimuli might provide a new non-invasive means for separate investigation of the direct rapid VOR pathway.

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