Latency and Initiation of the Human Vestibuloocular Reflex to Pulsed Galvanic Stimulation

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Aw, Swee T., Michael J. Todd, and G. Michael Halmagyi. Latency and initiation of the human vestibuloocular reflex to pulsed galvanic stimulation. J Neurophysiol 96: 925–930, 2006; doi:10.1152/jn.01250.2005. Cathodal galvanic currents activate primary vestibular afferents, whereas anodal currents inhibit them. Pulsed galvanic vestibular stimulation (GVS) was used to determine the latency and initiation of the human vestibuloocular reflex. Three-dimensional galvanic vestibuloocular reflex (g-VOR) was recorded with binocular dual-search coils in response to a bilateral bipolar 100-ms rectangular pulse of current at 0.9 (near-threshold), 2.5, 5.0, 7.5, and 10.0 mA in 11 normal subjects. The g-VOR consisted of three components: conjugate torsional eye rotation away from cathode toward anode; vertical divergence (skew deviation) with hypertropia of the eye on the cathodal and hypotropia of the eye on the anodal sides; and conjugate horizontal eye rotation away from cathode toward anode. The g-VOR was repeatable across all subjects, its magnitude a linear function of the current intensity, its latency about 9.0 ms with GVS of ≥2.5 mA, and was not suppressed by visual fixation. At 10-mA stimulation, the g-VOR [x, y, z] on the cathodal side was [0.77 ± 0.10, −0.05 ± 0.05, −0.18 ± 0.06°] (mean ± 95% confidence intervals) and on the anodal side was [0.79 ± 0.10, 0.16 ± 0.05, −0.19 ± 0.06°], with a vertical divergence of 0.2°. Although the horizontal g-VOR could have arisen from activation of the horizontal semicircular canal afferents, the vertical–torsional g-VOR resembled the vestibuloocular reflex in response to roll-plane head rotation about an Earth-horizontal axis and might be a result of both vertical semicircular canal and otolith afferent activations. Pulsed GVS is a promising technique to investigate latency and initiation of the human vestibuloocular reflex because it does not require a large mechanical apparatus nor does it pose problems of head inertia or slippage.

METHODS

Subjects

Eleven normal subjects (range: 23–65 yr; 38.7 ± 4.9 yr, mean ± 1 SE) were tested with GVS after giving informed consent. The protocol was approved by Royal Prince Alfred Hospital Ethics Committee in accordance with the Helsinki II Declaration (BMJ 1991; 302: 1194).

Recording system

Binocular three-dimensional (3D) eye positions in response to pulsed GVS were recorded using the search coil technique. Each subject was supine during the recording with head secured to a head-holder to prevent any motion artifact and in darkness viewing a 2-mm-fixation LED located 600 mm away. Binocular eye positions in three axes—horizontal, vertical, and torsional—were recorded with dual-search coils (Skalar, Delft, The Netherlands), precalibrated to determine the search coil gains and offsets. During recording, the search coil signals obtained after preamplification and phase detection (CNC Engineering, Cleveland, OH) and the computer-controlled current switch voltage were sampled with 24-bit resolution at 5 kHz using LabVIEW (National Instruments, Austin, TX) on a Win2000-based PC (Microsoft, Redmond, WA). Resolution of the eye movement recording system was <0.1 min of arc. Maximum errors and cross-coupling were <2% (Aw et al. 2003).

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TABLE 1. Latencies and peak eye positions of the gVOR

<table>
<thead>
<tr>
<th>Current Intensity, mA</th>
<th>Cathodal Side</th>
<th>Anodal Side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Latency, ms</td>
<td>Peak Eye Position,°</td>
</tr>
<tr>
<td></td>
<td>Torsional</td>
<td>Vertical</td>
</tr>
<tr>
<td>0.9</td>
<td>31.2 ± 1.8</td>
<td>0.05 ± 0.01</td>
</tr>
<tr>
<td>2.5</td>
<td>9.3 ± 0.7</td>
<td>0.16 ± 0.02</td>
</tr>
<tr>
<td>5.0</td>
<td>9.0 ± 0.3</td>
<td>0.36 ± 0.05</td>
</tr>
<tr>
<td>7.5</td>
<td>9.0 ± 0.4</td>
<td>0.58 ± 0.08</td>
</tr>
<tr>
<td>10.0</td>
<td>9.0 ± 0.7</td>
<td>0.77 ± 0.10</td>
</tr>
</tbody>
</table>

Values are group means ± 95% confidence intervals (95%CI) of the latencies and peak eye position from pooled g-VOR responses (torsional, vertical, and horizontal) for left-cathode/right-anode and right-cathode/left-anode configurations from pulsed GVSs of 0.9, 2.5, 5.0, 7.5, and 10.0 mA.

FIG. 1. Time series recording of the binocular three-dimensional (3D) eye positions and derivative of the initial torsional eye positions from a normal subject in response to bilateral, bipolar 5-mA, 100-ms rectangular pulse of galvanic vestibular stimulation (GVS) in the left-cathode/right-anode configuration. Galvanic vestibulococular reflex (g-VOR) latency was determined by an automated software algorithm as the interval between the GVS onset and the point when the initial torsional eye velocity exceeded 1 SD of its baseline noise. Horizontal, Hor; vertical, Ver; torsional, Tor.

Statistical analysis

Means ± 1 SE of the binocular g-VOR for each current intensity were determined from >30 GVS repetitions in each subject. At each current intensity (0.9, 2.5, 5.0, 7.5, and 10 mA) group means ± 95% confidence intervals (95%CI) were determined from eight subjects. Student’s t-test for differences between two means of dependent observations was used to test for differences between the eye positions on cathodal and anodal sides. A significance level of $P = 0.05$ was used in the statistical analysis.

RESULTS

Latency

The latency of the g-VOR was about 9 ms with a GVS of $\geq 2.5$ mA (Fig. 1). Group means ± 95% CIs of the pooled g-VOR latency (for left-cathode/right-anode and right-cathode/left-anode configurations) are displayed in Table 1. However, when the GVS was near-threshold at 0.9 mA, the g-VOR latency was prolonged to about 32 ms. Latency of the g-VOR for the eye on the cathodal side was not significantly different ($P > 0.05$) from the eye on the anodal side.

Directions

The binocular g-VOR evoked by bilateral, bipolar GVS consisted of three components: conjugate torsional eye rotations approximately equal in amplitude and rotated away from the cathode toward the anode; vertical divergence (skew deviation) with the intorting eye hypertropic on the cathodal side and the extorting eye hypotropic on the anodal side; and torsional rotations from the subject’s view were positive for horizontal ($\zeta$), vertical ($\gamma$), and torsional ($\phi$) eye rotations, respectively. Rotation of the upper pole of the eye toward the subject’s right was CW and toward the subject’s left was counterclockwise (CCW). The torsional and horizontal data obtained for the right-cathode/left-anode configuration were inverted before pooling with data from the left-cathode/right-anode configuration. Magnitude of the g-VOR ($\sqrt{x^2 + y^2 + z^2}$) was determined from horizontal ($\zeta$), vertical ($\gamma$), and torsional ($\phi$) eye velocities derived in 3D at peak eye positions (Haslwanter 1995).

Latency of the g-VOR was determined using an automated software algorithm. It was defined as the interval between the GVS onset (i.e., onset of the computer-controlled current switch) and the point where the derivative of the torsional eye position (i.e., eye velocity) first exceeded 1 SD of its baseline noise (Aw et al. 2003). Because the torsional, vertical, and horizontal onsets were the same, the largest of the three components—the torsional component—was used to determine the latency (Fig. 1).

Galvanic vestibular stimulation

The galvanic stimulus was a bilateral, bipolar 100-ms rectangular pulse of current at preset intensities (0.9–10 mA) delivered by 4-cm$^2$ transmastoid surface electrodes (Neutralect, MSB Limited, London, UK). It was generated by a battery device and delivered through an isolated computer-controlled switch at a repetition rate of one/s for 60 repetitions. Eleven subjects were tested with 5-mA current intensity in isolated computer-controlled switch at a repetition rate of one/s for 60 transmastoid surface electrodes (Neutralect, MSB Limited, London, pulse of current at preset intensities (0.9 –10 mA) delivered by 4-cm$^2$
conjugate horizontal eye rotations also approximately equal in amplitude and rotated away from the cathode toward the anode (Fig. 2, A and B). Figure 2A shows a typical binocular 3D eye position time series recording from a normal subject illustrating these patterns of eye movements in response to two 5-mA pulsed GVSs of left-cathode/right-anode and two of right-cathode/left-anode configurations. When the current intensity was increased from 0.9 (near-threshold) to 2.5, 5.0, 7.5, and 10.0 mA, the patterns of 3D eye movement responses of the g-VOR remained consistent, as shown by the means ± 1 SE of eye positions from eight subjects in Fig. 2B.

**Amplitude, magnitude, and slope**

The amplitudes of the torsional, vertical, and horizontal components of the g-VOR increased with current intensity from 0.9 to 10 mA (Fig. 2B). The peak g-VOR eye positions \([x, y, z]\) pooled from left-cathode/right-anode and right-cathode/left-anode configurations are displayed in Table 1. The magnitude of the g-VOR scaled linearly with the current intensity (Fig. 3), showing that the total g-VOR output, and not just its individual components, increased linearly with current intensity from 0.9 to 10 mA. The slope of g-VOR magnitude versus
the current intensity on the cathodal side was $0.94^\circ \cdot s^{-1} \cdot mA^{-1}$ and on the anodal side was $0.92^\circ \cdot s^{-1} \cdot mA^{-1}$ (mean square error = 0.02).

The torsional component was about fourfold larger than either the vertical or the horizontal component. Binocular torsional eye rotations (away from cathode toward anode) were conjugate, approximately equal in amplitude and not significantly different ($P > 0.05$), and increased with current intensities between 0.9 and 10 mA. The peak torsional eye position at 10 mA was about $0.8^\circ$ (Table 1 and Fig. 2B). Vertical divergence (skew deviation) also increased with current intensity. The hypertropic eye on the cathodal side was significantly different ($P < 0.05$) from the hypotropic eye on the anodal side for all current intensities between 0.9 and 10 mA. At 10 mA, the vertical divergence was $0.20^\circ$. Horizontal eye rotations also increased with current intensity. Binocular horizontal eye rotations, away from the cathode toward the anode, were conjugate, approximately equal in amplitude, and were not significantly different ($P > 0.05$) from each other for all current intensities between 0.9 and 10 mA. The peak horizontal eye position at 10 mA was about $0.2^\circ$.

**DISCUSSION**

The initial g-VOR consisted of three components: conjugate torsional eye rotation away from cathode toward anode; significant vertical divergence (skew deviation) with hypertropia of the intorting eye on the cathodal side and hypotropia of the extorting eye on the anodal side; and conjugate horizontal eye rotation away from the cathode toward the anode. The torsional component was nearly fourfold larger than the horizontal or vertical components.

**FIG. 3.** Relationship between the peak binocular g-VOR magnitude and the current intensity. Magnitude of g-VOR scaled linearly with the pulsed GVS current intensity.
With a GVS of \( \geq 2.5 \text{ mA} \), the latency of the human g-VOR is about 9 ms. Because GVS activates the semicircular canals and otoliths together, this suggests that the angular and linear VOR may have a similar latency, about 9 ms, a value similar to the human (Aw et al. 1996; Collewijn and Sneeds 2000) and monkey (Minor et al. 1999) angular VOR latency, and monkey (Angelaki and McHenry 1999) linear VOR latency. Because GVS simultaneously activates semicircular canals and otoliths, both angular and linear VOR contribute to the torsional component of the g-VOR. Our data show a linear torsional position curve during the entire 100-ms rectangular pulse of GVS (Figs. 1 and 2); if the otoliths responded later than the semicircular canals, then the slope of the torsional position curve would change at the point the otolith response appeared. However, linear VOR latency was previously reported to be much longer in humans (>30 ms) (Aw et al. 2003; Bronstein and Gresty 1988; Crane and Demer 1998; Wiest et al. 2001) than in monkeys (8–12 ms) (Angelaki and McHenry 1999). This discrepancy might be explained by the difficulty of delivering transient linear high accelerations to humans as opposed to monkeys. Irregular vestibular afferents that are shown to be more sensitive to high-frequency stimuli (Hullar et al. 2005) are also much more sensitive to the galvanic currents (Goldberg et al. 1984). We suggest that g-VOR latency perhaps reflects the linear VOR latency when predominantly irregular afferents are activated and is similar to the angular VOR latency in response to the high-acceleration head rotations (Aw et al. 1996; Collewijn and Sneeds 2000; Minor et al. 1999). With near-threshold GVS (0.9 mA), the g-VOR latency was prolonged to about 32 ms, similar to the nearly 46 ms reported (Severac Cauquil et al. 2003). We suggest that this prolongation could be a result of a lower signal-to-noise ratio of the initial g-VOR when GVS is near-threshold.

The magnitude of the g-VOR (i.e., the total g-VOR output) was found to increase linearly with cathodal current intensity (Fig. 3). Cathodal galvanic current in the perilymphatic or endolymphatic space was shown to increase vestibular afferent firing (Goldberg et al. 1994), probably from increased trans-epithelial polarization by mechanotransduction channels in the hair cells (Norris et al. 1998). We speculate that the GVS range of 0.9–10 mA used in our study may have stimulated the hair cells within the linear range of transduction (Hudspeth and Corey 1977), thus resulting in a linear increase in g-VOR magnitude.

In contrast to the nystagmus evoked by maintained GVS, which shows large intersubject variability but within-subject reproducibility (MacDougall et al. 2002), the initial g-VOR evoked by pulsed GVS shows a high level of intersubject repeatability (Fig. 2B), probably because there is not enough time for the indirect vestibuloocular pathways in the brain stem and cerebellum, such as those responsible for velocity storage and adaptation, to become involved.

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GRANTS

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REFERENCES


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929


