ELSEVIER

Journal of Vestibular Research, Vol. 7, No. 5, pp. 369–380, 1997

0957-4271/97 $17.00 + .00

PII S0957-4271(96)00162-0

Original Contribution

VESTIBULO-OCULAR REFLEX DEFICITS TO RAPID HEAD TURNS FOLLOWING INTRATYMPANIC GENTAMICIN INSTILLATION

R. S. Allison,*¶ M. Eizenman,*†¶ R. D. Tomlinson,§ J. Nedzelski§ and J. A. Sharpe‡¶

Institute of Biomedical Engineering, Departments of *Electrical and Computer Engineering, †Ophthalmology, ‡Neurology, and §Otolaryngology, University of Toronto, Toronto, Canada;
¶Eye Research Institute of Canada, Toronto, Canada
Reprint address: Robert S. Allison, Centre for Vision Research, York University, 103 Farquharson, North York, ON M3J 1P3 Canada.
Tel: (416) 736-5659; E-mail: allison@hpl.ists.ca

□ **Abstract — The response of the vestibulo-ocular reflex following unilateral vestibular deafferentation by gentamicin ablation was studied using transient stimuli. The response to these rapid passive head turns showed a strong asymmetry with permanent, reduced gains toward the side of lesion. These gain reductions have large variation (gains of 0.26 to 0.83), which may result from preferential sparing of regularly firing afferent fibers following gentamicin ablation. Based on the size and nature of the nonlinearity, an explanation based on Ewald's second law was discounted. © 1997 Elsevier Science Inc.**

□ **Keywords — vestibular; vestibulo-ocular reflex; ototoxic; Ménière's; gentamicin.**

Introduction

Acute unilateral loss of vestibular function results in signs and symptoms of vertigo, ataxia, oscillopsia, nystagmus, and postural imbalance. Static symptoms of unilateral loss occur when the patient does not move his head. These symptoms are due to an imbalance in tonic vestibular input resulting from the loss of the resting discharge from afferents in one ear. Dynamic vestibulo-ocular symptoms that occur during head movements, such as oscillopsia, are due to deficits in the VOR gain. Acutely, the VOR gain is lower in both horizontal directions of rotation and asymmetric with significantly lower gain for rotation towards the side of lesion (1,2). In experimental animals, VOR gain drops from 1 to approximately 0.5 following a unilateral labyrinthectomy or mechanical plugging of the canal (2,3).

Compensation to static symptoms is rapid and nearly complete within a short period of time (several days), so that little spontaneous nystagmus remains after this period (2). Recovery to dynamic imbalance is less rapid and not as complete (1,2,4), but over time the VOR gain for midband frequencies (that is, 0.1 to 4 Hz) gradually recovers. In monkeys, considerable recovery of VOR gain occurs within several days, and by 3 months, gain has recovered to near normal levels following unilateral labyrinthectomy (2). In these animals, the response to caloric testing of the intact ear is enhanced, indicating that an increase in the sensitivity of the remaining ear is responsible for the recovery of VOR gain.

The adaptive capabilities of the VOR make detection of a unilateral lesion with rotational testing difficult. Laboratory testing of the VOR is normally performed at low frequencies (for example, 0.1 Hz) and velocities (for example, 20°/s) of rotation in a horizontal plane. For unilateral lesions, however, too little asymmetry exists in the response to conventional low frequency rotation to be a reliable indicator for localizing the side of a vestibular lesion (1).

Clinical studies using passive rotation have indicated that the VOR asymmetries resulting from unilateral deafferentation are more pro-

RECEIVED 22 May 1996; ACCEPTED 24 September 1996.

nounced at higher frequencies (5). The high velocity and frequency necessary to bring out asymmetries due to lesions are difficult to achieve in a vestibular chair, but can be achieved by active head shaking. Voluntary head shaking has the disadvantage of being predictable, and the influence of neck muscle proprioception and of motor efferent programs is a concern (6).

Halmagyi and Curthoys (7) described a clinical test for canal paresis whereby the patient's head is grasped firmly and rapidly turned to one side. The head turns are of modest amplitude and velocity (10°–20°, 150+°/s), but acceleration is high (1500+°/s^2). If the VOR gain is adequate, the eyes will rotate opposite to the head an amount equal to the size of the head turn and will maintain stable gaze. If inadequate, the compensatory smooth eye movement will be insufficient, and slip of the retinal image will occur. The inadequate VOR gain can be detected by observing the eyes while performing the maneuver. If the VOR gain is too low, one or more visible compensatory saccades (quick refixation movements) in the direction opposite to the head movement are required to maintain gaze. Halmagyi and colleagues (8) recorded eye movements and measured the VOR gain for this type of rapid passive head turn in patients with unilateral paresis as a result of vestibular neurectomy. They found that gain recovers for rotation away from the lesion, but remains significantly and permanently depressed for rotation towards the side of lesion.

Vestibular neurectomy is sometimes performed to treat severe, intractable vertigo resulting from Ménière's disease. An alternative procedure that has been used in several institutions is ablation of the vestibular sensory epithelia by means of intratympanic gentamicin instillation (9). Gentamicin is known to be selectively ototoxic, with vestibular effects preceding cochlear damage. In this procedure, gentamicin is instilled through the tympanic membrane of one ear in order to selectively destroy vestibular function in the ear. This procedure can result in total paresis of vestibular function as evaluated by the ice water caloric test (9). We investigated the VOR response in patients following gentamicin ablation under rapid passive head turns.

Methods

Subjects

The response to rapid, passive head turns was studied in 9 patients (4 men, 5 women, ages 31 to 71, mean 49) following unilateral intratympanic gentamicin ablation as treatment for Ménière's disease. Treatments had been completed between 8 months and 5 years prior to the experiment. The treatment protocol was as follows (9). Gentamicin in dosage of 17 mg was delivered into the middle ear via a catheter 3 times daily. Treatment continued for 4 days or until onset of spontaneous nystagmus. An electronystagmographic examination was performed on the day of the experiment to verify ablation of the treated ear and subsequent compensation. Loss of vestibular function in the treated ear was verified by lack of response to ice water caloric testing, which is the most sensitive clinical test for residual vestibular function. The patients were considered clinically compensated to their lesion and had no spontaneous nystagmus when measured in the dark with or without mental alerting (slow phase of nystagmus less than 5°/s in the dark is considered in the normal range for our laboratory). The subjects had no indications of involvement of the opposite ear in vestibular and auditory tests (that is, the Ménière's disease had not become bilateral). The patients had all recovered from their treatment and resumed normal active lifestyles.

Normal subjects (N = 6, 4 male, 2 female, ages 25 to 51, mean 35) were used as controls. Subjects had no signs of vestibular, oculomotor, or central nervous system dysfunction.

Procedure

A binocular head and eye tracking device was used to monitor the position of the head and eyes. The system is based upon an infrared video eye tracking system (VTS, Series 2000, EL-MAR Inc., Downsview, ON, Canada) and a magnetic head tracking system. The VTS provides real time (120 Hz) estimates of vertical and horizontal positions of both eyes as well as pupil size. The VTS is based upon estimation of

the distance of multiple corneal reflections to the center of the pupil (10) and has system noise with standard deviation of less than 0.05° and a linear range of ±40° horizontally and ±30° vertically. To track head movements, a small receiver mounted on the VTS goggle frame sensed a pulsed magnetic field transmitted from a larger, earth-fixed unit (Flock of Birds, Ascension Technology Corp., Burlington, VT). The head tracker transduces head position (x, y, z) and orientation (azimuth, elevation, roll) and has an RMS noise of 0.1° RMS and a linear range of 180°. Six channels of head movement (x, y, z, azimuth, elevation, and roll) and 4 channels of eye movement (2 channels for each eye: horizontal and vertical rotation) were recorded at 120 Hz. Raw digital estimates of head and eye position and orientation were recorded directly to disk for off-line analysis.

The subjects were seated while fixating a small bright target located centrally, approximately 1.2 m from the eye. Subjects were instructed to fixate on the target and to attempt to suppress blinks. Occasional reminders to fixate the target and to keep the eyes wide open were given throughout the experiment. While the subject fixated the target, the investigator grasped the head firmly from behind. At unpredictable intervals, rapid, passive, head turns were delivered manually. Attempts were made to randomize the timing and direction of the head turns in order to eliminate prediction. The head turns were of modest amplitude (10 to 25°) and velocity (150 to 300°/s), but of high acceleration (1500+/°s^2) and similar to those used to test patients following vestibular neurectomy (8).

Analysis

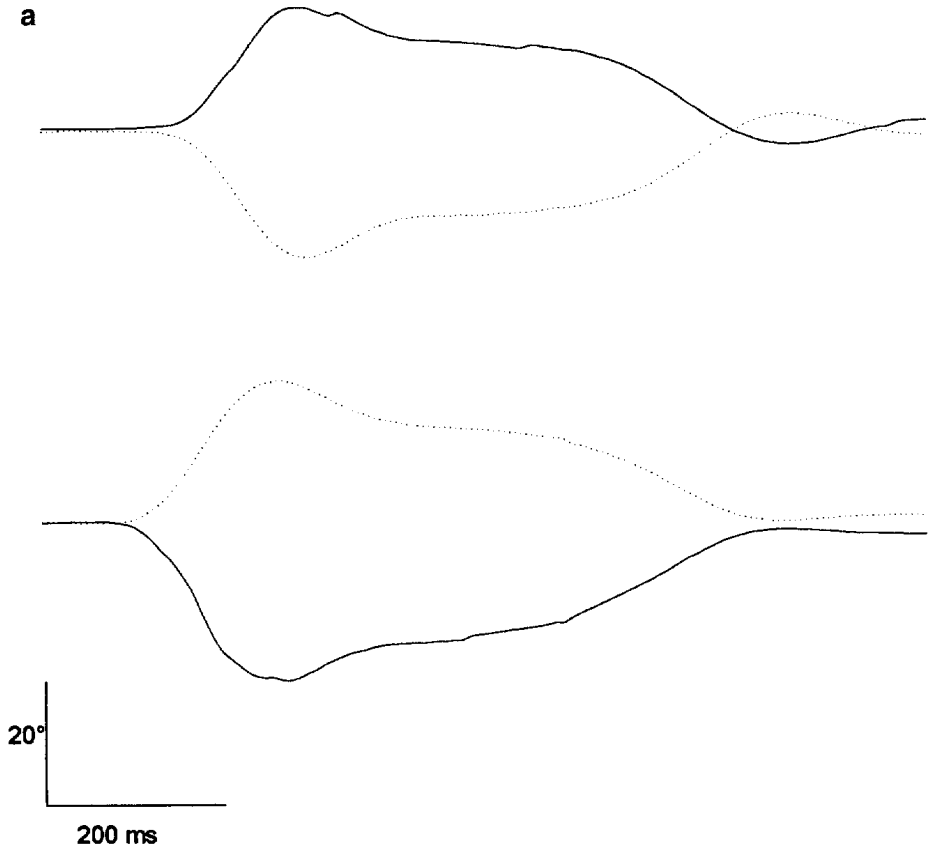
Head and eye velocity were obtained by differentiation with a 5-point FIR differentiator. The differentiator has a bandwidth exceeding 20 Hz. Analysis of the head pulse was restricted to the first 100 ms of the head turn response or to the peak of head velocity, whichever came first. Restricting the analysis to the first 100 ms of the response eliminates the contributions of visual following mechanisms (visual tracking has latency of greater than 100 ms (11)). Analyzing only the initial response and using unpredictable direction and timing for the head turns also precludes the use of preprogrammed compensatory saccades by the subject (6). Halmagyi and colleagues (8) have confirmed the vestibular origin of the response in that no eye movement response could be seen in a bilaterally deafferented subject during the first 100 ms of the head turn. Blinks, saccades, and artifact-contaminated records were identified by a combination of automated analysis and visual inspection of the unfiltered data and were removed from the analysis. At each sample interval during the initial portion of each head turn response, the instantaneous eye velocity and head velocity were sampled. These sample pairs were then pooled over all head turns for the session (for example, Figure 1b). To estimate the gain, the linear regression of instantaneous eye velocity versus head velocity was calculated for each direction of rotation. Because of the instrument delay in the head estimates relative to the eye estimates, the eye data was delayed by 8 ms prior to calculating the regressions. The slope of the regression line was used as a measure of the VOR gain. A measure of directional preponderance was used in order to quantify the asymmetry in response to left and right rotations. The directional preponderance was defined as:

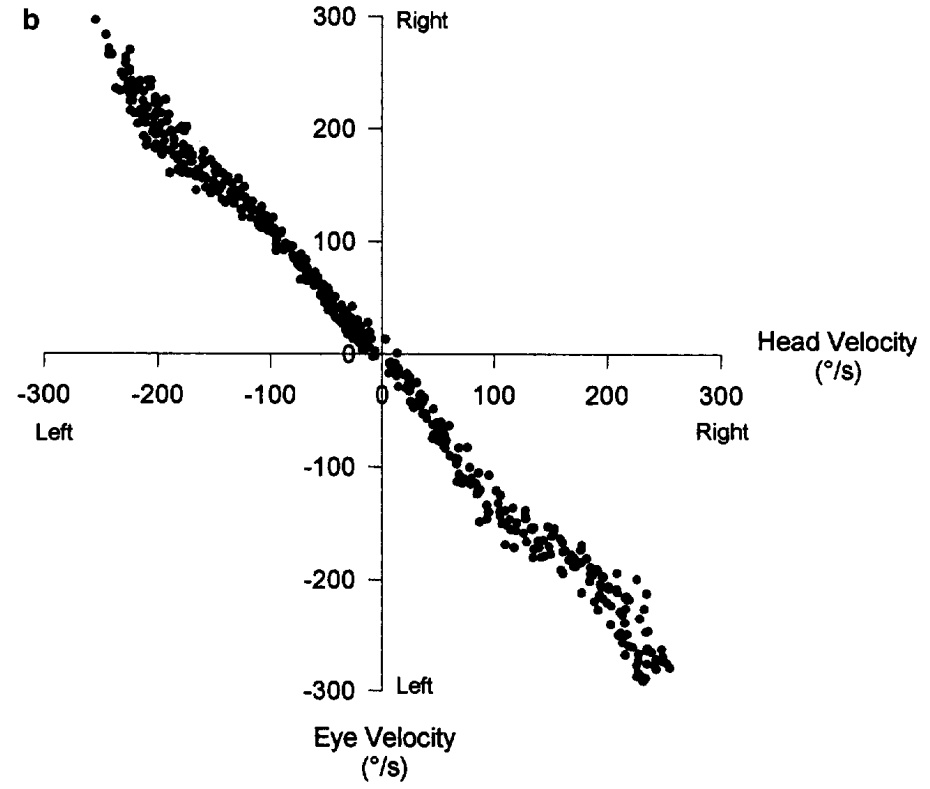
$$DP = \frac{Gain_{RIGHT} - Gain_{LEFT}}{Gain_{RIGHT} + Gain_{LEFT}}$$

Positive directional preponderance indicates that the response to rightward rotation is greater than the response to leftward rotation.

Results

In normal subjects the eye velocity was highly correlated with head velocity during the first 100 ms of head movement (see Table 1 for a summary of the results in normal subjects). Figure 1b shows an x–y plot of instantaneous eye velocity versus head velocity during the initial 100 ms of the head turn in subject N4. The mean correlation (Pearson's r value) between head and eye velocity during the first 100 ms is −0.98. In normal subjects, the average gain for rightward


a
20°
200 ms


b
300
Right
200
100
0
-100
-200
-300
Left
-300
-200
-100
0
100
200
300
Left
Right
Head Velocity
(°/s)
Eye Velocity
(°/s)

head rotation is 1.04 ± 0.06 and for leftward rotation is 1.04 ± 0.05. Ideal VOR gain for a target at a distance of 1.2 m is 1.1 (12). The difference between the response for rightward and the response for leftward head rotation was not statistically significant ($P > 0.1$). Directional preponderance was 0.001 ± 0.046, which is not statistically significantly different from zero ($P > 0.1$). Eye movement response tended to be approximately equal and opposite to the head movement (Figure 1a). Quick phases or catch-up saccades were rarely seen before 200 ms and tended to be small corrections to the gaze position.

In the patients, after compensation following gentamicin ablation, subjects had reduced gains for head rotation towards the side of the lesion (see Table 2). Figure 2b shows an x–y plot of eye velocity versus head velocity in one patient (G5). It can be seen that the eye velocity does not match the head velocity toward the side of lesion, and the slope is significantly less than 1. Toward the intact side, the slope is considerably greater and is similar to that seen in normal subjects. This asymmetry is reflected in the directional preponderance measure, which indicates a preponderance towards the intact side in all patients. The mean value of the absolute value of directional preponderance was 0.31 across the gentamicin patient group, significantly greater than that of the normal population ($P < 0.01$). The absolute value of directional preponderance was used in order to eliminate the effect of side of lesion. In some subjects, however, the asymmetry was relatively small. For example, subject G9 had reduction in gain for both directions of rotation, but exhibited little asymmetry as evidenced by a directional preponderance of only 0.03 (Table 2). Figure 3 shows the eye movement response for rapid passive head turns in patient G6. Much less asymmetry is apparent than in Figure 2. Gain is reduced toward both the intact and the lesion side, and several small compensatory saccades can be noted. The range of directional preponderances found in the gentamicin population was quite broad, from 0.03 to 0.57.

Table 1. Measured VOR Gains and Directional Preponderance for Rapid Passive Head Rotation in Normal Subjects. Also shown is the unsigned or absolute value of directional preponderance. (Group means, standard deviation (SD), and 95% confidence intervals (CI) are shown for gains in both directions and for absolute value of directional preponderance).

Subject	Gain to right	Gain to left	DP	Unsigned DP
N1	1.08	0.98	0.05	0.05
N2	0.97	1.05	−0.04	0.04
N3	1.03	1.10	−0.04	0.04
N4	1.05	1.02	0.01	0.01
N5	1.00	1.08	−0.04	0.04
N6	1.13	1.00	0.06	0.06
Mean	1.04	1.04	0.00	0.04
SD	0.06	0.05	0.05	0.02
95% CI	0.046	0.038	0.037	0.013

For rotation towards the side of lesion, the patients typically had lower amplitude compensatory smooth eye movements, and foveating saccades were typically required (Figure 2a). These saccades tended to occur more than 150 ms after the start of the head turn and rarely occurred in the first 100 ms. Blinks and saccades were quite frequent, and large catch-up saccades were often observed. Patients often reported more difficulty fixating on the target or apparent motion of the target for rotation towards the side of lesion. Compensatory quick phase movements or catch-up saccades were typical in the response for rotation toward the side of lesion and reduced the error in the gaze angle resulting from the inadequate VOR gain.

Discussion

Following intratympanic gentamicin ablation, a deficit exists in the response to rapid

Figure 1. (a) In this normal subject (N4), the eye movement response to rapid, passive head turns is of approximately equal size and in the opposite, compensatory direction. The traces show head position (dotted) and eye movement response (solid) for leftward and rightward head rotation. Upward deflection of the eye and head position traces correspond to rightward movement. (b) Eye velocity in the first 100 ms of the head turn is nearly equal to head velocity, and no asymmetry can be seen.

Table 2. Measured VOR Gains and Directional Preponderance for Rapid Passive Head Rotation in Subjects following Compensation to Therapeutic Unilateral Gentamicin Ablation (side of treatment shown). (Also shown are the individual values for gain specified towards the intact and lesioned side and the absolute value or unsigned directional preponderance. Group means, standard deviation (SD), and 95% confidence intervals (CI) are shown for gain towards and away from lesion and the absolute value of directional preponderance.)

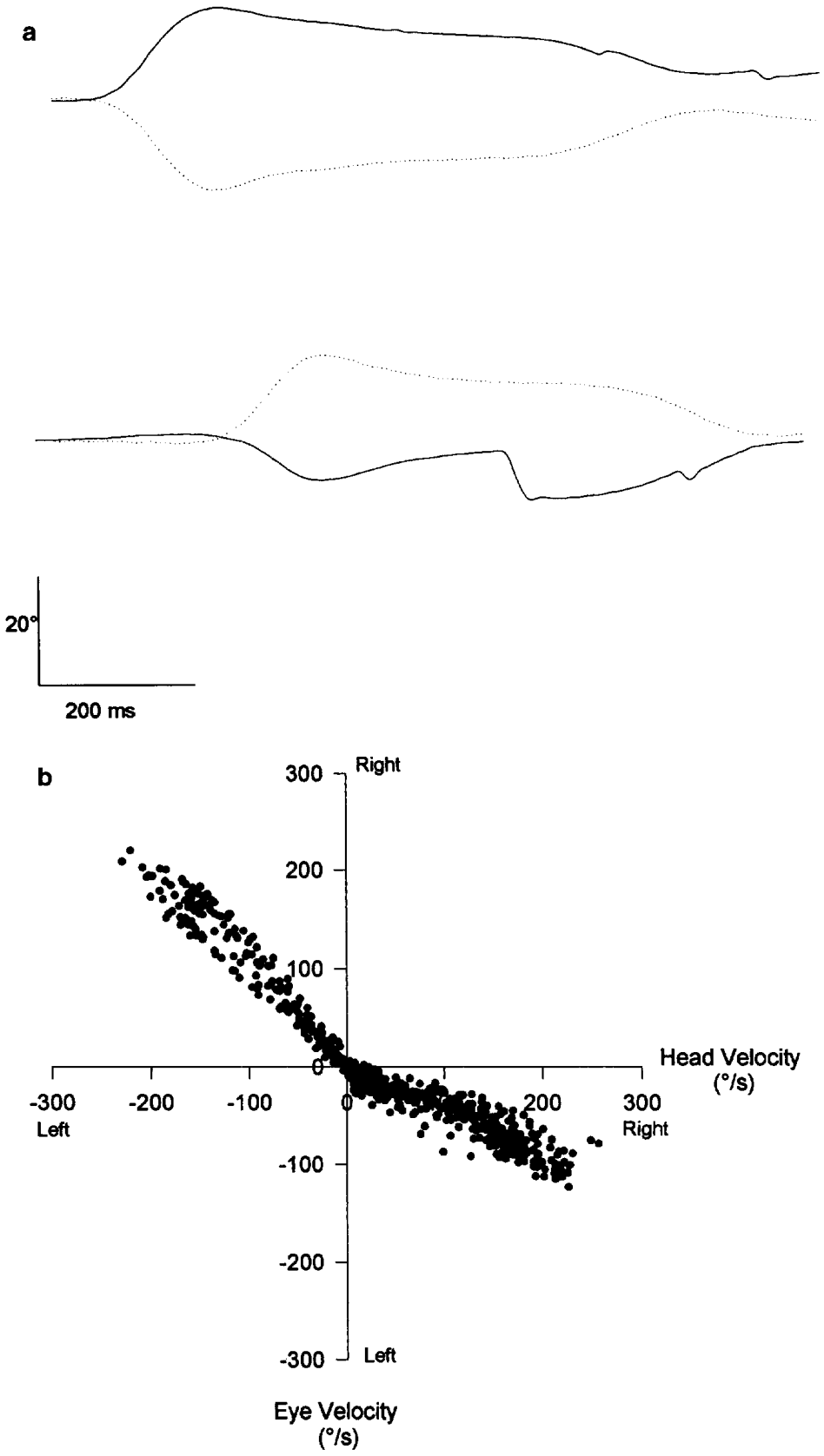
Subject	Side of lesion	Gain to right	Gain to left	DP	Gain to intact side	Gain to lesion side	Unsigned DP
G1	LEFT	0.93	0.26	0.57	0.93	0.26	0.57
G2	RIGHT	0.51	0.75	−0.19	0.75	0.51	0.19
G3	LEFT	0.84	0.40	0.36	0.84	0.40	0.36
G4	LEFT	1.02	0.46	0.38	1.02	0.46	0.38
G5	RIGHT	0.35	1.02	−0.49	1.02	0.35	0.49
G6	LEFT	0.76	0.61	0.11	0.76	0.61	0.11
G7	LEFT	0.85	0.33	0.44	0.85	0.33	0.44
G8	LEFT	1.17	0.75	0.22	1.17	0.75	0.22
G9	LEFT	0.89	0.83	0.03	0.89	0.83	0.03
Mean					0.92	0.50	0.31
SD					0.13	0.20	0.18
95% CI					0.088	0.128	0.118

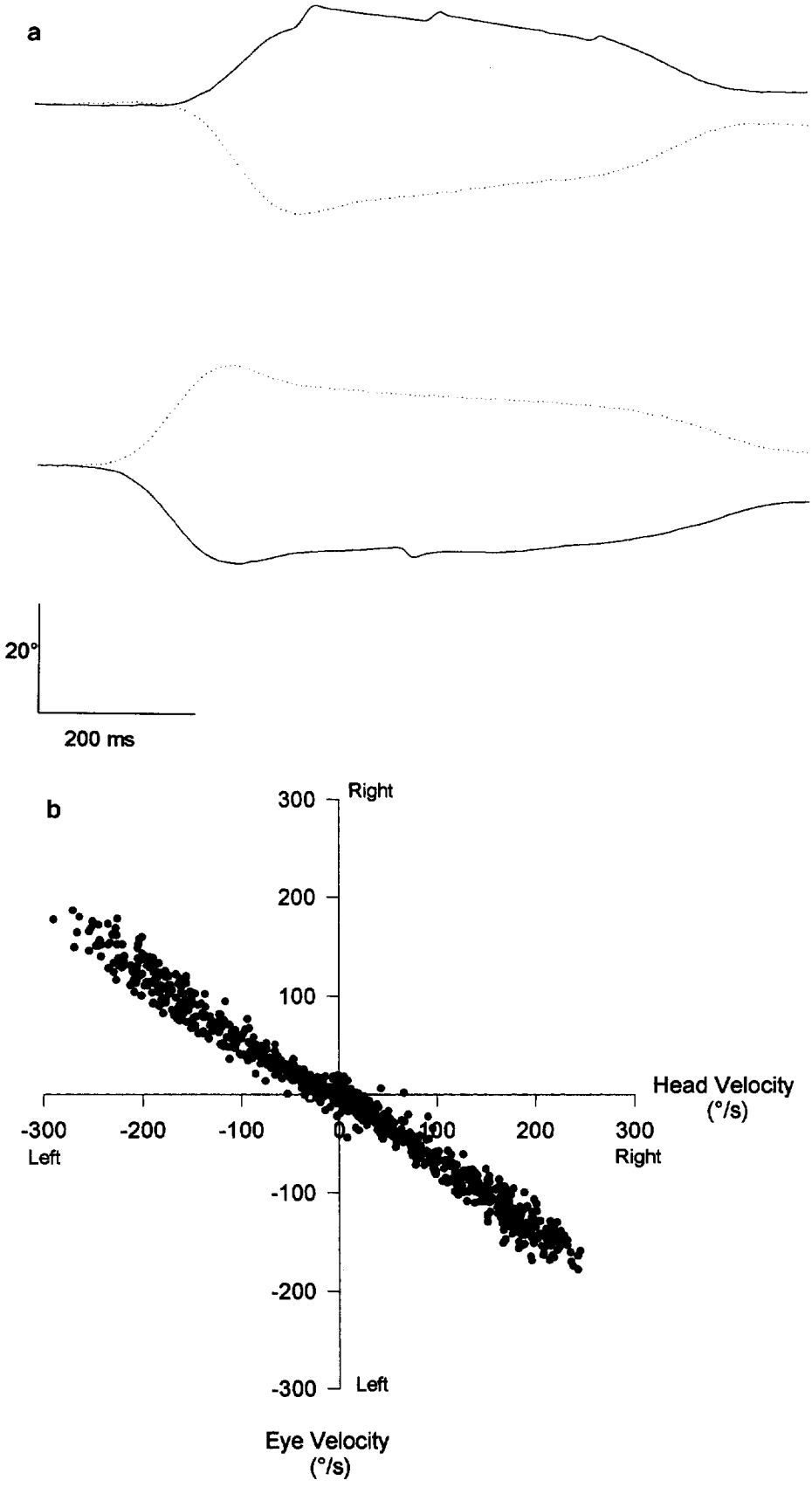
head turns toward the side of lesion. This persistent deficit occurs despite nearly complete recovery from static symptoms and signs such as spontaneous nystagmus, vertigo, and recovery of low frequency VOR gain symmetry and after a return to an active lifestyle.

In comparison to the results with patients following unilateral vestibular neurectomy (8), the persistent asymmetry following intratympanic gentamicin ablation is smaller. One year after unilateral neurectomy, the VOR gain was 0.92 for rotation towards the intact side (versus 0.94 in normals) and only 0.25 for rotation towards the lesion (8). After gentamicin treatment, the gain towards the lesion side was 0.50 (range 0.26 to 0.83) and towards the intact side was 0.92 (range 0.75 to 1.17). It is interesting to note that patient G9, for example, had almost normal response for rotation towards the side of lesion and very little asymmetry. It appears that at least some gentamicin patients retain some vestibular function in the higher frequency range. We noted a small but significant reduction in VOR gain for rapid passive head turns towards the intact side following compensation versus the normal response (0.92 versus 1.04 in normals). Although Halmagyi and colleagues (8) found no such reduction, gain reductions towards the intact side following compensation to unilateral lesions have been reported in several other studies (2,3,5) and presumably reflect intersubject variability in the degree of compensation.

The ototoxic effects of gentamicin have been well studied. Gentamicin has a known affinity for type I hair cells in the vestibular epithelia and for the endolymph-regulating dark cells of the vestibular system (13,14). Thus, any hair cells likely to be spared following the gentamicin treatment were likely to be type II hair cells, which are correlated with regularly firing primary afferents (15). Angelaki and Perachio (16) demonstrated that selective ablation of the ir-

Figure 2. (a) The response to rapid passive head turns is shown for patient G5 following compensation to a right side lesion. Following unilateral gentamicin ablation, initial response for rotation towards the side of lesion is typically weak (bottom traces). Compensatory saccades are often noted later in the eye movement response in order to correct for the deficit. Toward the intact side (upper traces), response is nearly normal. Response strength towards the lesioned side varies between subjects. Upward deflection of the eye (solid) and head (dotted) position traces correspond to rightward movement. (b) Eye velocity in the first 100 ms of the head turn is nearly equal to head velocity for rotation toward the intact side. Toward the lesioned side, gain is reduced even at low velocities of head rotation.


a
20°
200 ms
b
300
200
100
0
-100
-200
-300
Right
Left
-300
-200
-100
0
200
300
Left
Right
Head Velocity
(°/s)
Eye Velocity
(°/s)


a
20°
200 ms
b
Right
300
200
100
-100
-200
-300
Left
Head Velocity
(°/s)
-300
Left
-200
-100
100
200
300
Right
Eye Velocity
(°/s)

regularly firing afferents (while sparing the regularly firing afferents) did not affect high frequency gain, but did reduce the gain of the VOR during constant velocity rotation. Since the irregularly firing afferents are correlated with type I hair cells, they would be affected by gentamicin before the regularly firing afferents. Thus, Angelaki and Perachio's results (16) are consistent with our finding that caloric response is affected earlier and more severely than high frequency response in our patients. The variability seen in the response to rapid passive head turns following gentamicin treatment presumably reflects intersubject variability in the degree of damage to the regularly firing afferent population.

The marked asymmetry seen in the response to rotations towards and away from the lesion in many patients following gentamicin ablation or vestibular neurectomy indicates that significant nonlinearity is present in the response to high frequency, high acceleration head rotation. In contrast, after compensation from unilateral ablation, the low frequency VOR shows mild VOR gain deficits and shows significant asymmetry only at high head velocities (1). The symmetry at low frequencies and the large asymmetry with high-frequency transient stimuli indicates that the nonlinearity in the VOR response after unilateral loss is frequency selective. Other studies have noted a frequency or acceleration sensitivity in response to transient vestibular stimuli in unilaterally deafferented patients (for example, 17). These studies provide additional evidence that the compensation mechanisms to unilateral loss of vestibular function are frequency dependent.

The basic neural substrate for the horizontal VOR is a 3-neuron reflex arc (18). Primary afferents from the lateral canals excite ipsilateral central interneurons in medial and ventrolateral vestibular nuclei (18). These secondary neurons, in turn, excite contralateral lateral rectus motoneurons and ipsilateral medial rectus motoneurons in order to drive the eyes opposite to head rotation. The permanent VOR gain deficit to transient stimuli following vestibular nerve ablation can arise from frequency sensitive asymmetry in either the *peripheral vestibular response* or in the organization and response of the *central vestibular system.*

Two possible peripheral mechanisms could contribute to the frequency-dependent asymmetry: a) primary afferent disfacilitatory saturation as suggested by Halmagyi and colleagues (8), and b) the acceleration sensitivity of primary vestibular afferents (4). Ewald's second law for the horizontal canals states that excitation of the canal afferents by rotation towards the side of the canal is more effective than disfacilitation by rotation away from the canal and is believed to be a result of disfacilitatory saturation of afferent firing (4). The average primary afferent has a resting discharge of approximately 90 spikes/s and a sensitivity to head velocity of 0.5 (spikes/s)/(°/s) for midband frequencies (19). Since the firing rate cannot be reduced below zero, the average primary response will saturate during head velocity in the disfacilitatory direction at velocities greater than 180°/s. Since the afferent firing can reach more than 350 spikes/s (19), excitatory saturation does not occur until much higher velocities. Thus, for low velocities, the response of a single canal is approximately linear and symmetric, whereas high velocity rotation results in an asymmetric response due to disfacilitatory saturation. With only one labyrinth functioning, this suggests that the VOR would saturate at approximately 180°/s for rotation towards the side of lesion (3). Since the gain reduction in our data (see Figure 2b) can be noted at velocities much lower than 180°/s, Ewald's second law cannot provide an adequate explanation for the asymmetry observed in this experiment.

Another peripheral mechanism that can be postulated to explain the frequency-dependent asymmetry of the VOR response in patients is the frequency-dependent sensitivity of primary afferents (20). Peripheral vestibular afferents can be

Figure 3. (a) In patient G6, following left side gentamicin ablation, the response toward the intact (bottom) and lesion (top) side exhibits less asymmetry than seen in Figure 2. Toward both the intact side and the lesion side, initial response is less effective than normal. Eye and head traces are denoted as in Figure 1 and 2. (b) Eye velocity in the first 100 ms of the head turn is reduced in both directions and shows less asymmetry than in Figure 2a.

grouped according to their response regularity. When grouped in this manner, regularly discharging afferents have a weak phasic characteristic and show only slight sensitivity to acceleration. On the other hand, irregularly discharging fibers exhibit a strong acceleration sensitivity.

Using a bilateral VOR model based upon Hain and colleagues (21), we could simulate the observed magnitude of acceleration and frequency-dependent behavior after unilateral lesion only if the input to the model was strictly from irregular afferents (22). However, evidence suggests that the VOR is predominantly driven by regular, not irregular, afferents. Minor and Goldberg (23) could find no change in the VOR response after functionally ablating the irregular afferents. In their study, the sensitivity of the irregular afferents to galvanic current was exploited by using bilateral inhibitory galvanic current to bias the irregular afferents off while only inhibiting the regulars slightly. The minimal effect on VOR gain that resulted suggests that the VOR is driven mainly by regular afferents. In summary, the frequency-dependent asymmetries seen in this experiment cannot be explained by peripheral nonlinearity due to saturation of the afferent firing rate at zero, even when the frequency-dependent behavior of peripheral afferent neurons is considered.

Possible central mechanisms for a frequency-selective, nonlinear VOR response may involve a) frequency channels, b) selective commissural transfer, c) asymmetries in motor neuron activation, or d) the nonlinear behavior of floccular target neurons (FTNs). Miles and colleagues (24) have provided evidence from adaptation experiments that the VOR is composed of a series of bandpass, overlapping frequency channels. The frequency selectivity in compensation seen in this study suggests that the adaptive capabilities may differ in channels for high and low frequency information. For example, the high frequency channel may be served by a subset of interneurons with a strong rectification leading to a strong frequency-selective asymmetry. Besides parallel frequency channels, recent evidence suggests that the commissure may selectively pass low frequency information (D. Broussard, personal communication). Injections of ketamine in cats cause no changes at 10 Hz, but result in reduced gain below 5 Hz. Ketamine selectively blocks the NMDA receptors believed to mediate the synaptic connections in the commissure. If the ketamine blocks the commissural connections and no other important VOR connections, then this implies that commissure selectively passes low frequency information. After a complete unilateral lesion, the ipsilateral vestibular nucleus gets only indirect commissural input, while the contralateral side receives direct primary afferent input. Differences in the commissural and direct pathways would result in differential, frequency-selective activity in the two vestibular nuclei during head rotation. Another potential substrate for a central asymmetry has been identified in the recent study of Scudder and Fuchs (25). These investigators have found evidence for a strong asymmetry in the push–pull projections of vestibular nucleus to abducens motoneurons. The predominant projections from horizontal position-vestibular-pause neurons (believed to be the main VOR interneuron class) in the vestibular nucleus have an approximately 6:1 ratio of contralateral excitation to ipsilateral inhibition. This evidence suggests that the vestibular nuclei may not drive the motoneurons in a perfectly push–pull arrangement. Alternatively, the central nonlinearity may be found in the characteristics of the FTNs, believed to mediate adaptive changes in VOR gain. These cells exhibit a nonlinear eye position gain: for example, no modulation of firing rate for ipsilateral (to primary position) eye positions and a strong modulation for contralateral rotation (26). A strong nonlinearity in the adaptive pathways mediated by the FTNs may provide the central nonlinearities.

The VOR is physiologically relevant during activities such as locomotion, in which the predominant head perturbations are between 0.5 and 15 Hz (27). Thus, patients who have shown recovery to low frequency testing may complain of poor vision and oscillopsia during locomotion or of unsteadiness during rapid head turns (27). During locomotion, high frequency, moderate velocity (200°/s) vibrations can be transmitted to the head during heel strike (27). These events are similar to the types of perturbations used in

our experiment. The response to rapid, unpredictable head perturbations such as those in this study may prove to be a useful functional indicator of VOR performance and an adjunct to low frequency caloric testing.

Loss of caloric response following intratympanic gentamicin instillation is regarded as functional ablation and considered to be as effective as vestibular neurectomy. However, following successful gentamicin treatment of Ménière's disease (no vertiginous symptoms), there is sometimes a conservation of high frequency response in the treated ear. The ability to provide relief from vertigo while maintaining some vestibular function in a physiologically relevant frequency range may be an advantage of gentamicin ablation.

Acknowledgments — We wish to thank Dr. D. Broussard for her scientific advice and valuable discussion. We would also like to thank Dr. J. Anderson, L. McIlmoyl, and A. Blakeman for their advice and help with the experiments. This study was supported by grant MT-11339 from the MRC (Canada) to M. Eizenman, R. Allison by a NSERC scholarship, and by MRC of Canada Grant MT5509 to J. Sharpe.

REFERENCES

1. Paige GD. Nonlinearity and asymmetry in the human vestibulo-ocular reflex. Acta Otolaryngol (Stockh) 1989;108:1–8.
2. Fetter M, Zee DS. Recovery from unilateral labyrinthectomy in rhesus monkey. J Neurophysiol 1988;59: 370–93.
3. Paige GD. Vestibuloocular reflex and its interactions with visual following mechanisms in the squirrel monkey; 2: Response characteristics and plasticity following unilateral inactivation of horizontal canal. J Neurophysiol 1983;49:152–68.
4. Baloh RW, Honrubia V, Konrad HR. Ewald's second law revisited. Acta Otolaryngol 1977;83:475–9.
5. Saito A, Takahashi M, Okada Y, Takei Y, Takeuchi I, Kanzaki J. Spatial gaze stability under active high frequency head oscillation after acoustic neuroma surgery. Acta Otolaryngol (Stockh) Supp 1991;487:106–13.
6. Kasai T, Zee DS. Eye–head coordination in labyrinthine defective human beings. Brain Res 1978;144: 123–41.
7. Halmagyi GM, Curthoys IS. A clinical sign of canal paresis. Arch Neurol 1988;45:737–39.
8. Halmagyi G, Curthoys I, Cremer P, Henderson C, Todd M, Staples M, Cruz D. The human horizontal vestibulo-ocular reflex in response to high acceleration stimulation before and after unilateral vestibular neurectomy. Exp Brain Res 1990;81:479–90.
9. Nedzelski JM, Chiong CM, Fradet G, Schessel DA, Bryce GE, Pfleiderer AG. Intratympanic gentamicin instillation as treatment of unilateral Ménière's disease: update of an ongoing study. Am J Otology 1993;14: 278–82.
10. DiScenna A, Das V, Zivotofsky A, Seidman S, Leigh RJ. Evaluation of a video tracking device for measurement of horizontal and vertical eye rotations during locomotion. J Neurosci Meth 1995;58:89–94.
11. Morrow MJ, Sharpe JA. Smooth pursuit initiation in young and elderly human subjects. Vision Res 1993; 33:203–10.
12. Viirre E, Tweed D, Milner K, Vilis T. A reexamination of the gain of the vestibuloocular reflex. J Neurophysiol 1986;56:439–50.
13. Watanuki K, Stupp HF, Meyer zum Gottesberge A. Toxic effects of gentamicin on the peripheral vestibular sense organs. Laryngoscope 1972;82:363–71.
14. Ge X, Shea JJ. Scanning electron microscopic observation of dark cells after streptomycin perfusion of the vestibule in guinea pigs. Scanning Microscopy 1995; 9:283–8.
15. Goldberg JM, Lysakowski A, Fernandez C. Structure and function of vestibular nerve fibres in the chinchilla and squirrel monkey. Ann N Y Acad Sci 1992; 656: 256–72.
16. Angelaki DE, Perachio AA. Contribution of irregular semicircular canal afferents to the horizontal vestibuloocular response during constant velocity rotation. J Neurophysiol 1993;69:996–99.
17. Johnston JL, Sharpe JA. The initial vestibulo-ocular reflex and its visual enhancement and cancellation in humans. Exp Brain Res 1994;92:302–8.
18. McCrea RA, Strassman A, May E, Highstein SM. Anatomical and physiological characteristics of vestibular neurons mediating the horizontal vestibulo-ocular reflex in the squirrel monkey. J Comp Neurol 1987; 264:571–94.
19. Goldberg JM, Fernandez C. Physiology of peripheral neurons innervating semicircular canal of the squirrel monkey; 2: Resting discharge and response to constant angular accelerations. J Neurophysiol 1971;34:675–84.
20. Goldberg JM, Fernandez C. Physiology of peripheral neurons innervating semicircular canal of the squirrel monkey; 3: Variations among units in their discharge properties. J Neurophysiol 1971;34:635–60.
21. Hain TC, Fetter M, Zee DS. Head shaking nystagmus in patients with unilateral peripheral vestibular lesions. Am J Otolaryngol 1987;8:36–47.
22. Allison RS. Combined head and eye tracking system for evaluation of the vestibulo-ocular reflex. M.A.Sc. Thesis, University of Toronto, 1994.
23. Minor L, Goldberg J. Vestibular nerve inputs to the vestibulo-ocular reflex: A functional nerve ablation study in the squirrel monkey. J Neurosci 1991;11: 1636–48.
24. Miles FA, Lisberger SG. Plasticity in the vestibulo-ocular reflex: A new hypothesis. Annu Rev Neurosci 1981;4:273–99.

25. Scudder CA, Fuchs AF. Physiological and behavioural identification of vestibular nucleus neurons mediating the horizontal vestibuloocular reflex in trained rhesus monkeys. J Neurophysiol 1992;68:244–64.
26. Lisberger SG, Palvelko TA, Broussard DM. Neural basis for motor learning in the vestibulo-ocular reflex of primates; 1: Changes in the responses of brainstem neurons. J Neurophysiol 1994;72:928–53.
27. Leigh RJ, Sawyer RN, Grant MP, Seidman SH. High-frequency vestibuloocular reflex as a diagnostic tool. Ann N Y Acad Sci 1992;656:305–14.
28. Angelaki DE, Perachio AA. Contribution of irregular semicircular canal afferents to the horizontal vestibuloocular response during constant velocity rotation. J Neurophysiol 1993;69:996–99.