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The human horizontal vestibulo-ocular reflex in response to high-acceleration stimulation before and after unilateral vestibular neurectomy

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Summary. The normal horizontal vestibulo-ocular reflex (HVOR) is largely generated by simultaneous stimulation of the two horizontal semicircular canals (HSCCs). To determine the dynamics of the HVOR when it is generated by only one HSCC, compensatory eye movements in response to a novel vestibular stimulus were measured using magnetic search coils. The vestibular stimulus consisted of low-amplitude, high-acceleration, passive, unpredictable, horizontal rotations of the head with respect to the trunk. While these so called head "impulses" had amplitudes of only 15–20 degrees with peak velocities up to 250 deg/s, they had peak accelerations up to 3000 deg/s/s. Fourteen humans were studied in this way before and after therapeutic unilateral vestibular neurectomy; 10 were studied 1 week or 1 year afterwards; 4 were studied 1 week and 1 year afterwards. The results from these 14 patients were compared with the results from 30 normal control subjects and with the results from one subject with absent vestibular function following bilateral vestibular neurectomy. Compensatory eye rotation in normal subjects closely mirrored head rotation. In contrast there was no compensatory eye rotation in the first 170 ms after the onset of head rotation in the subject without vestibular function. Before unilateral vestibular neurectomy all the patients' eye movement responses were within the normal control range. One week after unilateral vestibular neurectomy however there was a asymmetrical bilateral HVOR deficit. The asymmetry was much more profound than has been shown in any previous studies. The HVOR generated in response to head impulses directed away from the intact side largely by ampullofugal disfacilitation from the single intact HSCC (ignoring for the moment the small contribution to the HVOR from stimulation of the vertical SCCs), was severely deficient with an average gain (eye velocity/head velocity) of 0.25 at 122.5 deg/sec head velocity (normal gain = 0.94 +/− 0.08). In contrast the HVOR generated in response to head impulses directed toward the intact side, largely by ampullopetal excitation from the single intact HSCC, was only mildly (but nonetheless significantly) deficient, with an average gain of 0.80 at 122.5 deg/sec head velocity. At these accelerations there was no significant improvement in the average HVOR velocity gain in either direction over the following year. These results indicate that ampullopetal excitation from one HSCC can, even in the absence of ampullofugal disfacilitation from the opposite HSCC, generate a near normal HVOR in response to high-acceleration stimulation. Furthermore, since ampullofugal disfacilitation on its own, can only generate an inadequate HVOR in response to high-acceleration stimulation, it may under some normal circumstances make little contribution to the bilaterally generated HVOR.

Key words: Vestibulo-ocular reflex – Unilateral vestibular neurectomy – Vestibular compensation – Labyrinth – Semicircular canal – Human

Introduction

The horizontal vestibulo-ocular reflex (HVOR) normally originates from simultaneous stimulation of the 2 horizontal semicircular canals. For example a rightward head acceleration not only produces ampullopetal endolymph flow in the right horizontal semicircular canal (HSCC) which excites neurons in the right vestibular nerve, but also produces ampullofugal endolymph flow in the left HSCC which disfacilitates neurons in the left vestibular nerve. Type 1 secondary vestibular neurons in the right vestibular nucleus are therefore not only excited by excitation from the right HSCC, but are also disinhibited by disfacilitation from the left HSCC (Shimazu and Precht 1966; Precht and Shimazu 1965, Shimazu 1983). The resulting compensatory eye movements are therefore an outcome of stimulation of both HSCCs.

The question we wished to answer here was a simple one. "What difference does it make to the dynamics of the

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HVOR if it is produced by only one HSCC instead of two?". This is not a new question. Nearly a century ago Ewald (1982) showed that a symmetrical impulsive vestibular stimulus would produce an asymmetrical ocular motor response from a single SCC. He found a lesser nystagmic response to ampullofugal stimulation than to ampullopetal stimulation of a single HSCC in the pigeon. Although there have been many subsequent attempts to demonstrate Ewald's ampullopetal-ampullofugal HVOR asymmetry in humans with only a single intact labyrinth, it has proved difficult to do so. Most previous studies have shown only a slight asymmetry (Baloh et al. 1977; Honrubia et al. 1982; Istl et al. 1983; Jenkins 1985; Allum et al. 1988; Segal and Katsarkas 1988; Paige 1989) or have only shown the asymmetry indirectly (Hain et al. 1987).

To investigate the extent of ampullopetal-ampullofugal HVOR asymmetry in humans, we measured the HVOR response to impulsive vestibular stimulation, i.e. high-acceleration head rotation, in 14 patients before unilateral vestibular neurectomy and then 1 week, and in some patients also 1 year after vestibular neurectomy. Compensatory horizontal eye movements in response to rapid, passive, unpredictable, unidirectional horizontal head rotations were measured with magnetic search coils. These rapid head rotations (which for convenience we have called head "impulses") had peak accelerations up to 3000 deg/s/s, considerably higher than the head accelerations used in previous studies.

Our results showed that immediately after unilateral vestibular neurectomy there was a profound HVOR asymmetry with a severe HVOR deficit in response to ampullofugal disfacilitation from the single intact HSCC, and a mild HVOR deficit in response to ampullopetal excitation from the single intact HSCC. Neither of these deficits recovered significantly in the following year. We relate these findings to the known behaviour of primary and secondary vestibular neurons and compare them with the results of previous studies of the human HVOR after unilateral vestibular deafferentation. A preliminary report on part of this work has previously appeared (Cremer et al. 1988).

Material and methods

The recording system

General description. Horizontal displacement of the head and eye were recorded using search coils, within a $2 \times 2 \times 2$m cube magnetic field (CNC Engineering, Seattle). Eye displacement was recorded with a scleral contact lens search coil (Skalar, Delft) worn on the left eye. Head displacement was recorded with a similar search coil orientated in the fronto-parallel plane and rigidly fixed to the nosepiece of a lightweight spectacle frame.

Linearity and resolution. Before each test session a gain and linearity check was carried out on both the head and the eye coil using a specially built 25 cm diameter 3-axis plexiglas calibration jig. The jig was positioned at the centre of the magnetic field with the eye coil located at the point corresponding to a subject's left eye and the head coil located at the point corresponding to the bridge of the subject's nose. Horizontal rotations of the jig through a range of $+/-$ 30 deg produced an output voltage range of $+/-10$ V. There was a linear relation between angular position and output voltage: a polynomial trend analysis of angular position at 5 deg intervals (between +30 deg and −30 deg) and A-D converter counts, showed that a straight line accounted for 99.9% of the variance. The system could accurately resolve rotations of 0.1 deg.

Possible errors and artifacts. The effect of translation on the measurement of horizontal rotation was assessed by a method similar to the one used by Grossman et al. (1989) in a recent study of the human VOR during locomotion. The entire calibration jig was translated to a position 100 mm to the left or right of centre and the above calibration procedure was repeated. The value of 100 mm was chosen as the maximum translation of the head that could occur during passive rotation of the head. The offset error produced by translating the search coil 100 mm was 0.6 deg. In all 3 positions (centre, left and right) there was a linear relation between angular position and voltage output (A–D converter counts) – in each case 99.9% of the variance was accounted for by the linear component of a polynomial trend analysis. For the eccentric positions there was a small change in the slope of the line relating angular position to voltage output amounting to a total of 0.64 deg change over a 30 deg angular range when the calibration jig was 100 mm to the left of centre. In other words a 30 deg rotation produced a voltage indicating 30.64 deg of head rotation had occurred. This amounts to about a 2% position error introduced by the maximal possible head translation. We concluded that translation artifacts did not alter the linearity of the system or contribute in a substantial way to the results we have obtained.

It is possible that some errors may have occurred through slippage of the spectacle frame-worn head coil. We tested for this by fixing an eye coil to a lightweight bitebar and simultaneously recording from both coils, i.e. the coil on the spectacle frame and the coil on the bitebar, during high-acceleration head rotations in 3 normal subjects. The maximum difference between head angular velocity recorded at these two locations was 10%. The velocity recorded from the spectacle frame was always lower than the velocity recorded from the bitebar. For example when a peak velocity of 200 deg/s was recorded from the bitebar, the value from the spectacle frame could be as low as 180 deg/s. These results suggests that the error in HVOR gain due to slippage of the spectacle frame could be of the order of 0.1 at the high head accelerations used in this study. However it should be noted that this error would be an *over*estimate of HVOR gain and not an *under*estimate. This implies that a post-operative HVOR gain measured at say 0.25, could have been even lower, perhaps as low as 0.15. On the other hand since the HVOR gain from normal subjects on this paradigm was in fact 0.93–0.95, it appears that in practice the error from slippage of the head coil was less than the maximum error measured above. Moreover any residual artifacts in the recording system would have been cancelled out by testing two groups of controls, firstly normal subjects and secondly the patients themselves *before* as well as after operation. In particular the patients were tested in exactly the same way before and after vestibular neurectomy, so systematic artifacts in the recording system could not have produced the differences that have been demonstrated between the HVOR before and the HVOR after unilateral vestibular neurectomy.

Protocols

Each patient sat with his left eye at the centre of the magnetic field, fixating a solitary light emitting diode 1m from his eyes in an otherwise totally darkened room. Without warning the light would be extinguished for about 3 s. This was the cue for one of the investigators, standing behind the patient, holding the patient's head, to deliver a rapid, passive, unpredictable, step displacement of head angular position (called here a head "impulse") by quickly rotating the patient's head around its longitudinal (Z) axis, through an angle of 10–20 degrees either to the left or to the right. The patient's instructions were to keep fixating the remembered position of the light and to refixate it as soon as it was re-illuminated. For each

patient, ten to fifteen head impulses were generated in each direction. The experimenter attempted to randomize the direction of head rotation as well as the delay between the extinction of the fixation light and the onset of the head rotation.

The peak velocity of head movements varied from 100 to 250 deg/s and the peak acceleration from 1500 to 3000 deg/s/s. Head and gaze velocity were derived by analog differentiation of position signals. Eye position was derived by subtracting head position from gaze position. Eye velocity derived either by differentiating eye position or by subtracting head velocity from gaze velocity. These two different methods of calculating eye velocity did not affect the results. The seven pole analog differentiators used to derive head and eye velocity were matched and had a bandwidth of 100 Hz (roll-off = −18 dB/decade).

Data processing

Signals were captured on-line mostly at 500 Hz with 12-bit resolution using either a MINC 11/03 or an IBM-PC; in some cases the signals were also displayed on-line on an ink-jet recorder, and stored on FM-tape. More recently signals were captured on-line at 1 kHz with 16-bit resolution using a PDP 11/73 minicomputer. The data were analysed off-line using either an IBM-PC or a PDP 11/73. The results from these different machines do not differ, except in that the signal resolution was superior with 16-bit sampling on the PDP 11/73.

To minimize possible contributions to compensatory eye movements from extra-vestibular sources such as the cervico-ocular reflex, which is reported to have a latency greater than 100 msec (Barlow and Freedman 1980; Bronstein and Hood 1986; Halmagyi and Curthoys 1987), eye movement responses were only analysed up to the peak of head velocity, since this always occurred within 150 ms of the onset of head rotation. Saccades and eye-blinks which were identified visually on the eye velocity records by their very high accelerations (in the case of blinks by their multiple phases as well), were edited out using a cursor-driven interactive computer program. Saccades and blinks usually did not occur until 100–150 ms after the onset of head movement, but in some records, particularly those taken 1 year after unilateral vestibular neurectomy, saccades tended to appear earlier. Because of these blinks and saccades it was in some cases difficult to obtain complete results particularly at high head velocities. Early in the study, peak eye and head acceleration was measured manually from the velocity records; later it was derived by digital differentiation of the velocity data using 20 passes through a 3-point moving average filter.

Subsequently most of the data were analysed in the following way. Instantaneous eye velocity was plotted as a function of instantaneous head velocity for individual patients. For each impulsive stimulus, head velocity was divided into bins 5 deg/s wide and the average eye velocity response during each 5 deg/s bin was determined and depicted on an X–Y plot of eye velocity, as a function of head velocity. For each patient and subject the eye velocity data for each head velocity bin was averaged for all impulses in one direction thus producing a vector (a matrix consisting of a single column of values) of average eye velocity for each 5 deg/s head velocity bin for the two directions of head rotation. The vectors across individuals were averaged to show the mean +/− 1 standard deviation at each head velocity bin. In Figures 2, 4 and 6 data from head velocities below 5 deg/s were excluded because at these low velocities the error due to system noise and 12-bit A–D conversion was unacceptable. In later data, acquired on a lower noise 16-bit system, valid results were obtained even at these low head velocities (Figs. 8, 9). The results were just as obvious on the relatively noisy and lower resolution 12-bit system as they were on the less noisy, higher resolution 16-bit system.

However it should be emphasized that there is such a profound asymmetry of the compensatory eye movement response to equivalent stimuli directed to the two sides after unilateral vestibular neurectomy, that the results of this study are largely independent of the precise quality of the measurement and analysis system.

Although we made no systematic attempt to measure the latency of eye velocity with respect to head velocity, it was evident from a visual inspection of the velocity records that any delay in eye velocity, either at onset or at peak was less than 15 msec (Maas et al. 1989).

All patients had spontaneous nystagmus in darkness 1 week after vestibular neurectomy. However we elected to ignore it in our calculations since the nystagmus slow-phase velocity was never greater than 8 deg/s in the primary position and could therefore, even in the worst case, only be a small source of error with head movements up to 150 deg/s. The spontaneous nystagmus was even a smaller possible source of error at 1 year since the slow-phase velocity was by then always less than 3 deg/s.

Statistical testing. Unpaired t-tests for groups of unequal size were used to compare the measures of entire groups at each epoch (Winer 1962). For each unpaired t-test homogeneity of the two group variances was tested, and with one exception the variances in each tests were homogeneous. Thus a variance estimate based on the pooled weighted variance of the two groups was used in the t-test. In the single inhomogeneous case, the Welch approximation of the t′ statistic was used. For specific comparisons of measures of the same 4 patients tested at every epoch, paired t-tests were used.

For presentation and analysis the operated side was arbitrarily assigned as being on the left. This meant that for patients with left neurectomies all the signs and conventions were untouched whereas for patients with right neurectomies the data were appropriately reflected so that the neurectomized side was designated as the left.

Subjects and patients

We studied a total of 50 patients who had only one functioning HSCC. Each patient had undergone unilateral vestibular neurectomy either as treatment for intractable vertigo (Silverstein et al. 1987) or in the course of removal of an acoustic neurilemmoma. All the acoustic neurilemmomas were small, with less than 2.5 cm of tumor extending from of the porus acousticus on CT or MR scan, and none of the patients had symptoms or signs of brainstem dysfunction.

The patients were studied, in most cases serially, from 1 week up to 3 years after operation. However here we only wish to report the results from a special subgroup of 14 patients each of whom was tested before operation and whose preoperative results on this impulsive test of HVOR function fell within the normal control range. This subgroup was chosen to ensure a degree of homogeneity which would allow a straight-forward interpretation of the results. Ten of these patients were then tested 1 week or 1 year after operation and 4 of these patients were tested 1 week and 1 year after operation. Their results form the bulk of this report. Before operation all but 1 of these 14 patients had reduced nystagmic response to bithermal caloric stimulation of the affected ear, but all had brisk, normal caloric responses from the intact ear.

It should be noted that since it was not possible to acquire data from every patient on every occasion the numbers in the statistical comparisons are unequal. For example only 6 of the 14 patients provided data 1 year after operation and only 4 of the 14 provided data at all 3 epochs.

To determine if the compensatory eye movements measured and analysed here were truly of vestibular origin one subject without any vestibular function at all was also studied. He had undergone bilateral vestibular neurectomy 6 years previously during removal of bilateral acoustic neurilemmomas. His results on other tests of vestibular function have been previously reported (Halmagyi and Curthoys 1987; Dai et al. 1989). To illustrate the permanent nature of the HVOR changes after unilateral vestibular deafferentation, data from one patient who was tested 3 years after operation is also reported in some detail.

Thirty volunteers without clinical evidence of eye, ear or brain disease served as normal controls. All patients and subjects gave

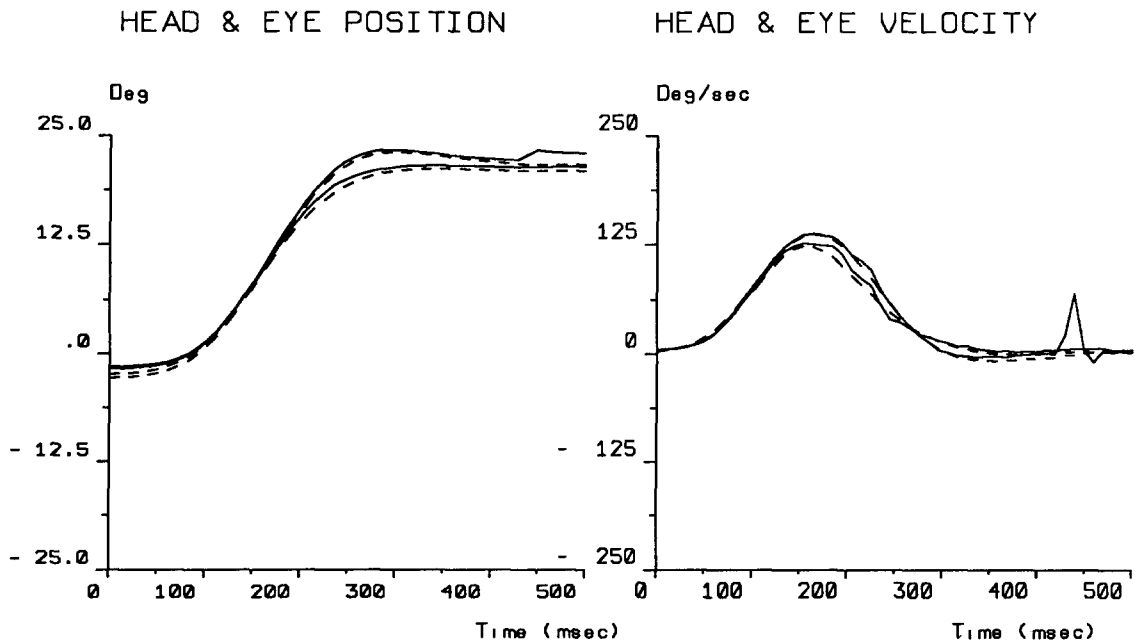
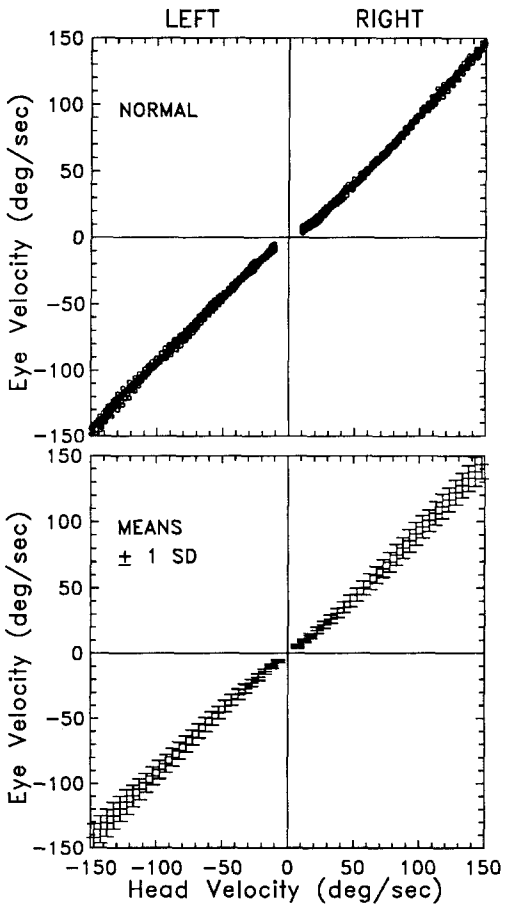


Fig. 1. Two superimposed head impulses from a normal subject. Head position and head velocity are shown in dashed lines; eye position and eye velocity in continuous lines. For convenience the eye signals have been inverted and superimposed on each other as well as on the head signals. During the head impulse eye position and eye velocity closely mirror head position and velocity respectively. There is a small saccade in the direction of head rotation after one of the head impulses. Peak head acceleration is about 2000 deg/s/s



informed consent and all protocols were approved by the RPA Hospital Human Ethics Committee.

Results

Normal subjects

In normal subjects the compensatory eye movement response closely matched the impulsive head movement stimulus as shown in Fig. 1. From data of this type instantaneous eye velocity can be depicted as a function of head velocity for a series of head impulses. Figure 2 (upper panel) shows 30 head impulses from one normal subject, as well as the averaged data (mean +/−1 s.d.) from 30 normal subjects (lower panel). At an arbitrary high head velocity of 122.5 deg/s, compensatory eye velocity in the group of normal subjects was 114.2+/−9.8 deg/s for rotations to the left and 116.7+/−9.3 deg/s for rotations to the right. These values correspond to velocity gains of 0.93+/−0.08 and 0.95+/−0.08 respectively. (The "+/−" values refer to +/−1 standard deviation here and throughout the report). These velocity gains are not significantly different ($t=0.95$; $p>0.05$).

Fig. 2. Compensatory eye velocity from one normal subject (top panel – all data points shown), and from a control group of 30 normal subjects (bottom panel – data in 5 deg/sec bins, vertical bars being +/−1 sd in this figure and in Fig. 6), depicted as a function of head velocity for 30 head impulses of the type shown in Fig. 1. Eye velocity is close to head velocity, particularly at the higher head velocities, indicating that HVOR gain is close to 1.0

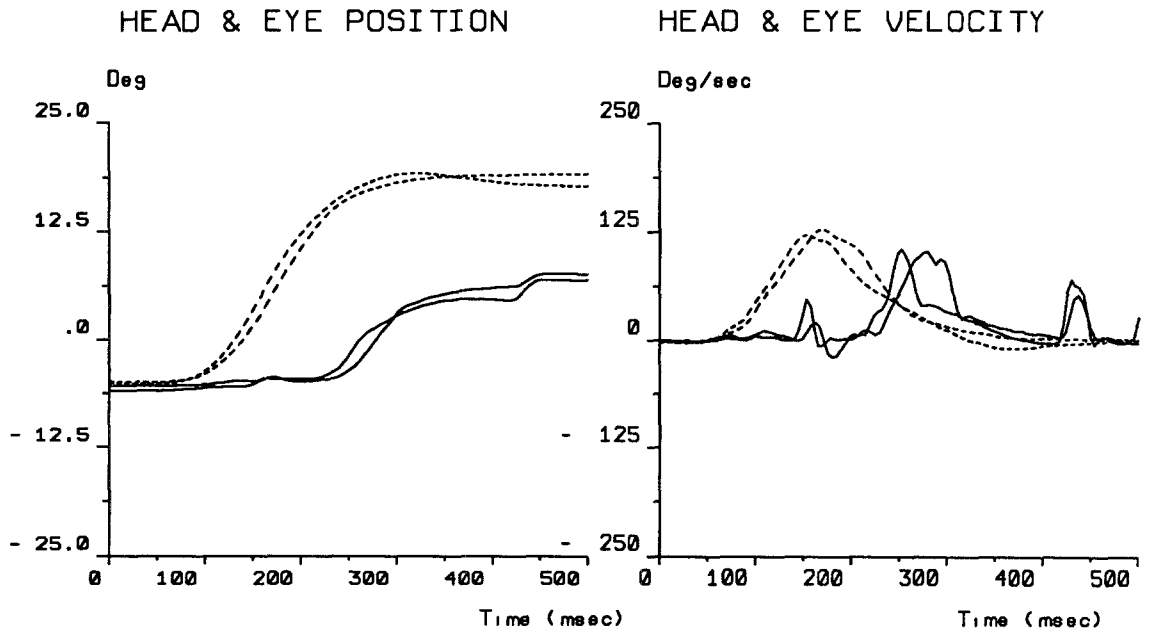


Fig. 3. Two superimposed head impulses from a subject without vestibular function, 6 years after bilateral vestibular neurectomy. Head position and head velocity are shown in dashed lines; eye position and eye velocity in continuous lines. Note that the major compensatory eye movement response, with a peak velocity approaching the peak velocity of head movement (125 deg/s), does not begin for almost 170 ms after the onset of head rotation. The source of this compensatory eye response is uncertain. It could represent the cervico-ocular reflex or it could be a modified saccade. Two other small compensatory saccades occur before and after this major response

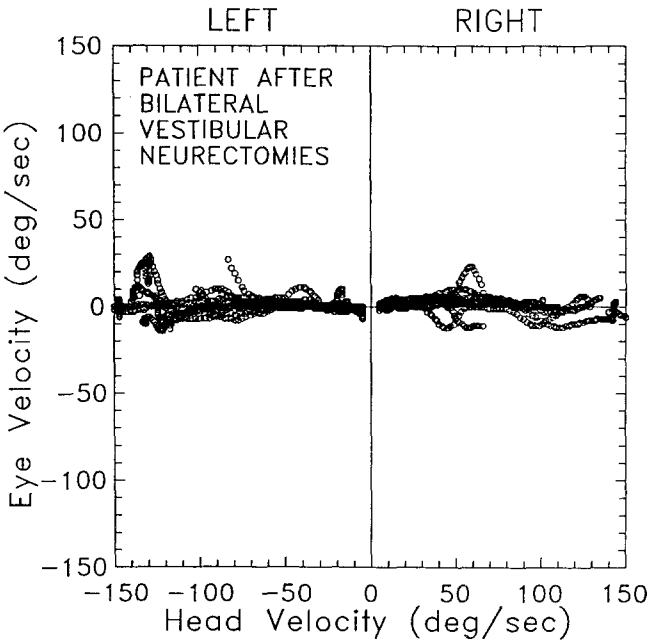


Fig. 4. Compensatory eye velocity depicted as a function of head velocity from the subject without vestibular function for 30 head impulses of the type shown in Fig. 3. Saccades and eye blinks have been edited out. Note that there is no consistent compensatory eye response up to 150 deg/s head velocity. (Data in 5 deg/s bins)

Bilateral vestibular neurectomy subject

The results from this subject showed no consistent compensatory eye movement responses for the first 170 msec after the onset of the impulsive stimulus (Fig. 3). A high-gain compensatory eye movement response did occur on some trials, but the onset of this was always more than 150 msec after the onset of head movement. These findings were confirmed when this subject's instantaneous eye velocity was plotted as a function of his instantaneous head velocity (Fig. 4) and his results are compared to those from normal subjects (Fig. 2).

Unilateral vestibular neurectomy patients
Preoperative results

These 14 patients were selected from a larger group of 50 patients on the criterion that their pre-operative HVOR gain was, at all measured head velocities, within 2.0 standard deviations of the mean of the normal control group. Therefore the patients' preoperative results were by definition not significantly different from that of the normal controls. Figure 5 (left panel) shows a single normal rightward head impulse from patient GG, 1 day before his right vestibular neurectomy for intractable vertigo. In Figure 6 (top left panel) the velocity of his compensatory eye movements is depicted as a function of the velocity of his impulsive head movements for 30 such head impulses, 15 in each direction. There is a slight but not statistically significant HVOR deficit for head impulses toward his affected right side. The preoperative results for the entire group of 14 patients (Fig. 6, bottom left panel) show a slight but again not statistically significant HVOR deficit for head impulses toward the affected side. (For presentation and analysis the affected side is always designated as the left side).

Postoperative results

General observations. On the day after operation all 14 patients were examined at the bedside and had, in varying degrees, the classic symptoms and signs of acute unilateral vestibular deafferentation (UVD). All complained of vertigo, all had vegetative symptoms such as pallor and nausea and some vomited. All had a 3rd degree horizontal nystagmus beating toward the intact side; the nystagmus was augmented when visual fixation was removed with Frenzel glasses. All past-pointed toward the operated side. One week later when the first post-operative measurements were made, all the patients had, as expected, improved symptomatically. None had primary position nystagmus in the presence of visual fixation but a low velocity (always less than 8 deg/s) horizontal nystagmus beating toward the intact side, could be recorded in darkness in all cases. One year after operation all 6 of the original 14 patients who were available for examination had made a satisfactory clinical recovery and only 1 complained of oscillopsia, gait ataxia, or other symptoms suggesting chronic vestibular insufficiency. Some patients were also tested at various other times after operation but these results are not reported in detail.

HVOR measurements. In one typical patient (GG) 1 week after unilateral vestibular neurectomy, the ampullopetal-HVOR, i.e. the compensatory eye movement response generated by ampullopetal excitation from the single functioning HSCC (Fig. 5, right panel), still resembles the patient's own, essentially normal, preoperative response (Fig. 5, left panel). In contrast the ampullofugal-HVOR, i.e. the compensatory eye movement response generated by ampullofugal disfacilitation from the single functioning HSCC (Fig. 5, centre panel), obviously does not. The ampullofugal-HVOR generates a compensatory eye movement response that has a much lower velocity than the head movement stimulus so that eye position lags head position and compensatory saccades are required to keep fixing the imagined target light (Halmagyi and Curthoys 1988). This patient's compensatory eye velocity is depicted in the top row of Fig. 6 as a function of head velocity 1 day before (top left), 1 week after (top centre) and 1 year after (top right) right vestibular neurectomy.

The bottom row of Fig. 6 shows the average of these results across the entire group of 14 patients. These show that after UVD there is a profound and permanent deficit in compensatory eye movements produced by the ampullofugal-HVOR. The mean velocity gain 1 week after UVD, at 122.5 deg/sec head velocity (a value selected to minimize errors due to rounding or noise inherent in using lower values of head velocity), was 0.25 ± 0.21, $n = 11$. This value is significantly different from the mean velocity gain of these patients before UVD (0.92 ± 0.06, $n = 12$). The variances of these two groups of values were not homogeneous and accordingly the Welch approximation to the t′ statistic for unequal groups with unequal variances (Winer 1962) was used. This showed that the difference between the HVOR gains of the two groups was statistically significant ($t' = 10.21$, $df = 11$, $p < 0.001$). The mean velocity gain 1 year after UVD (0.27 ± 0.14, $n = 6$) was not significantly different from the velocity gain at 1 week after UVD ($t = 0.21$; $p > 0.05$).

Since not every patient was available to be tested at each epoch after UVD, individual velocity gain data are presented separately for all of the 14 patients and for those 4 patients who provided data at every epoch (Fig. 7). Separate statistical analyses from the 4 patients tested at every major epoch confirmed the pattern shown by the larger group data. Specifically the results using paired t-tests showed:

(1) a significant reduction in ampullofugal HVOR gain from before to 1 week after UVD (mean gain decrease $= 0.66 \pm 0.25$, $t = 5.28$, $p < 0.05$)

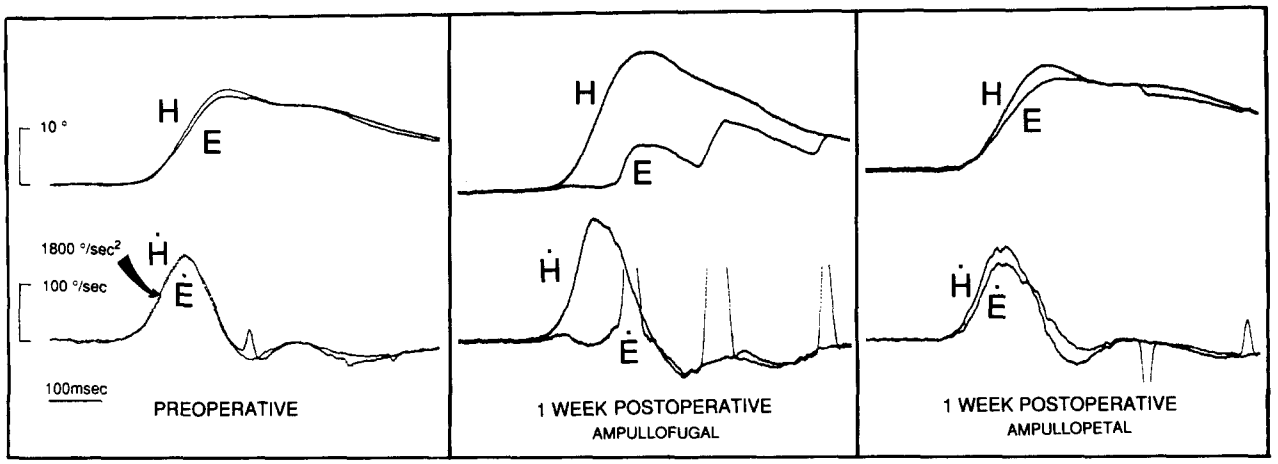


Fig. 5. Raw ink-jet records of single head impulses from patient GG, before (left panel) and 1 week after right vestibular neurectomy (centre and right panels). Before operation the HVOR is normal and symmetrical to each side to that even during a rightward head impulse with a peak acceleration of 1800 deg/s/s, eye position (E) and eye velocity (Ė) closely follow head position (H) and head velocity (Ḣ) respectively. After operation ampullofugal disfacilitation of the single functioning left HSCC by a rightward head impulse elicits 3 compensatory saccades but virtually no HVOR. In contrast ampullopetal excitation of the single functioning left HSCC by a leftward head impulse elicits a slightly deficient but near-normal HVOR

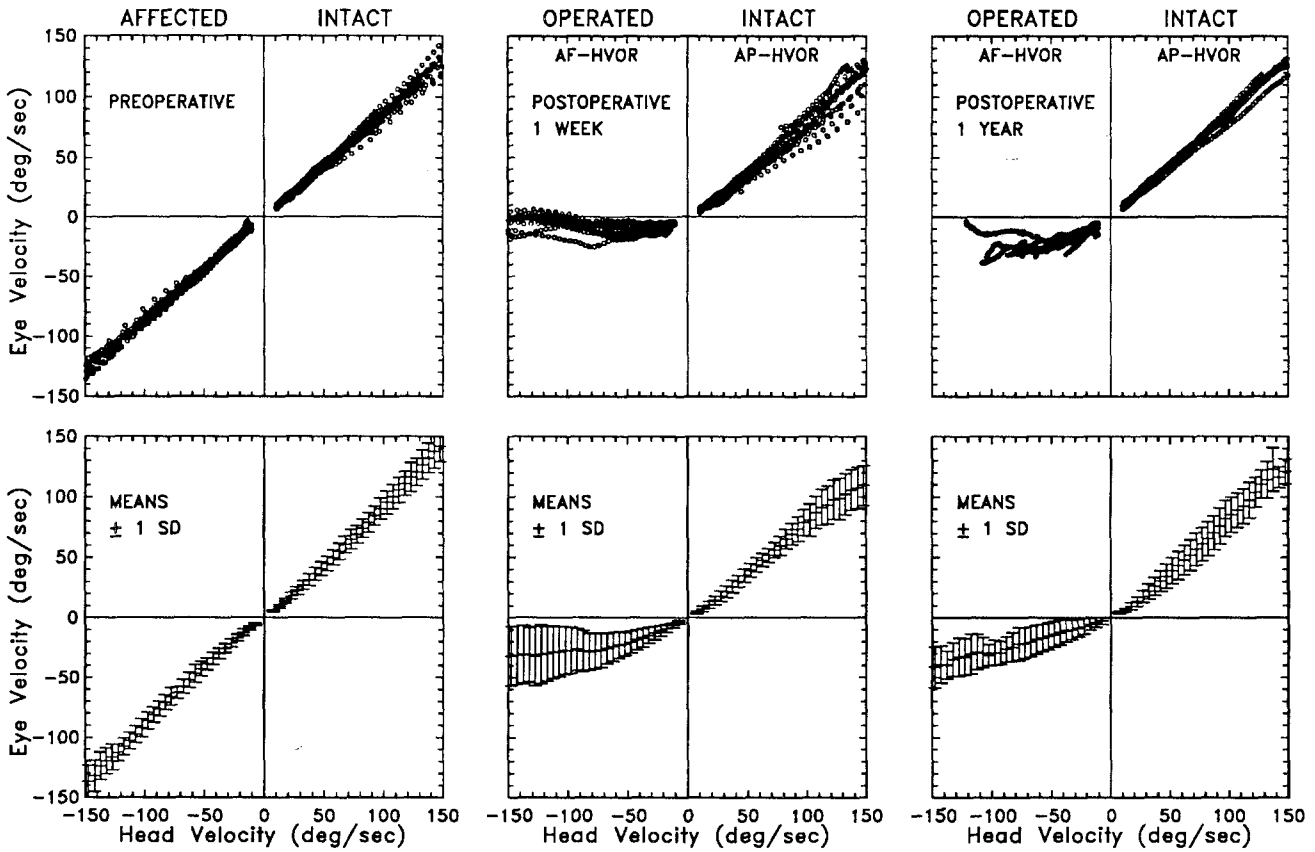


Fig. 6. Data from patient GG (top row) and from the entire group of 14 patients (bottom row), before (left column), 1 week after (centre column) and 1 year after (right column) unilateral vestibular neurectomy. Note that before operation there is only a slight, and statistically insignificant HVOR deficit for head impulses toward the affected side. After operation there is a severe HVOR deficit for head impulses toward the operated side; the HVOR that remains represents the ampullofugal HVOR (AF-HVOR) generated by normal ampullofugal disfacilitation from the remaining left HSCC. There is also a mild but nonetheless significant HVOR deficit for head impulses toward the intact side and the HVOR that remains represents the ampullopetal HVOR (AP-HVOR) generated by normal ampullopetal excitation from the remaining left HSCC. There is no quantitative evidence of vestibular compensation with this paradigm; neither the ampullofugal HVOR nor the ampullopetal HVOR improves significantly in 1 year

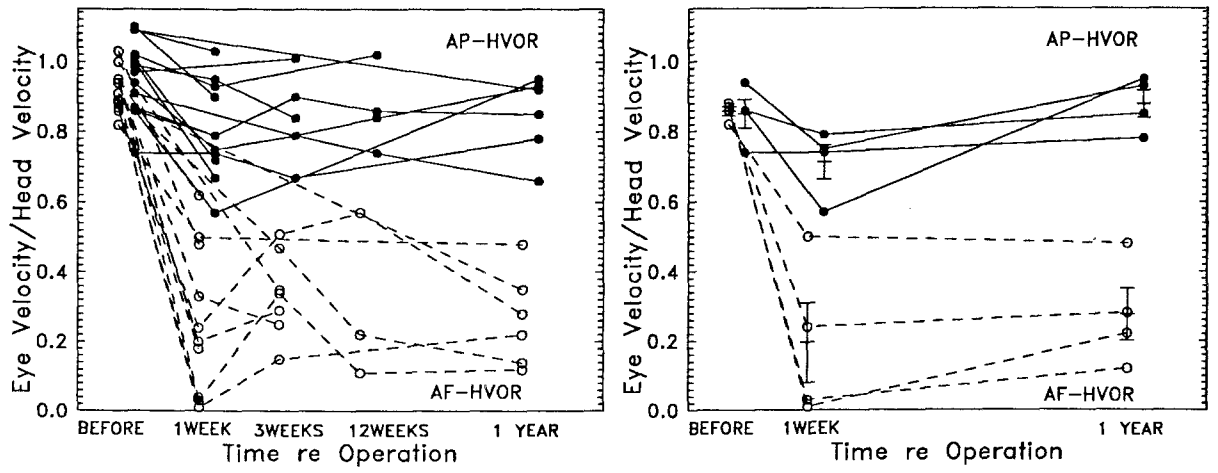


Fig. 7. Velocity gain of the horizontal vestibulo-ocular reflex (HVOR) at 122.5 deg/s head velocity, before and after unilateral vestibular neurectomy. Individual results are shown from all 14 patients tested (left panel) and from only the 4 patients who were able to be tested both at 1 week and at 1 year after operation (right panel). Ampullopetal velocity gain is shown in solid lines, ampullofugal velocity gain in dashed lines. The error bars show +/−1 standard error of the mean. All patients were within 2 standard deviations of the mean of normal subjects before operation. There is a profound and permanent decrease in the gain of the HVOR produced by ampullofugal disfacilitation and a slight but significant and also permanent decrease in the gain of the HVOR produced by ampullopetal excitation

(2) no significant recovery in ampullofugal HVOR gain from 1 week to 1 year after UVD (mean gain increase $=0.08+/-0.10$, $t=1.60$, $p>0.05$).

From this data it is clear that whereas all these patients were, by definition, within the normal range before UVD, after UVD they show a large and apparently permanent decrease in ampullofugal-HVOR gain.

One week after UVD there also appeared to be an absolute saturation in the average ampullofugal-HVOR at an eye velocity of only about 30 deg/sec (Fig. 6). Although the results show that there is no significant quantitative change in the ampullofugal-HVOR in the 1 year after UVD, it no longer appears as it did 1 week after UVD that there is an eye velocity saturation, but rather that there is now a linear increase in eye velocity with a constant velocity gain of about 0.25.

The deficit in compensatory eye movements generated by the ampullopetal-HVOR is less clear. The mean velocity gain 1 week after UVD, at 122.5 deg/s head velocity, was $0.80+/-0.14$, $n=9$. This value is significantly different from the velocity gain of this group of patients before UVD ($0.95+/-0.10$, $n=13$, $t=2.94$, $p<0.01$). This value is not significantly different from their velocity gain 1 year after UVD, ($0.85+/-0.11$, $n=6$, $t=0.73$, $p>0.05$).

Considering only the 4 patients who were measured at every major epoch, all 4 showed a reduction in ampullopetal HVOR gain from before to one week after UVD, but this reduction was not statistically significant using paired t-tests (mean gain decrease $=0.14+/-0.13$, $t=2.15$, $p>0.05$). Furthermore although all 4 patients showed an increase in ampullopetal HVOR gain from 1 week to 1 year after UVD, this increase was also not statistically significant (mean gain increase $=0.17+/-0.16$, $t=2.13$, $p>0.05$). From this we conclude that while there may have been some reduction followed by some recovery of ampullopetal HVOR gain, more data and more powerful statistical analyses are needed to resolve the question of the ampullopetal HVOR deficit.

To emphasize the permanent nature of the HVOR deficit after UVD and to analyze the role of eye velocity and of eye acceleration in origins of this deficit, recent data from a single patient, free of all vestibular symptoms 3 years after unilateral vestibular neurectomy for Menière's disease are also presented. The recordings of head and eye velocity, and of head and eye acceleration as a function of time, show that there is still a profound deficit in the HVOR produced by ampullofugal disfacilitation of the single intact HSCC (Fig. 8). Furthermore when eye velocity is depicted as a function of head velocity (Fig. 9), it is clear that the ampullofugal-HVOR eye velocity increases linearly as a function of head velocity with a low constant gain of about 0.2. On the other hand when eye acceleration is depicted as a function of head acceleration (Fig. 9) it appears that eye acceleration may have reached a saturation value of about 400 deg/s/s.

In contrast the HVOR produced by ampullopetal excitation from the single intact HSCC appears to be almost normal (Figs. 8, 9), with eye velocity increasing linearly as a function of head velocity (Fig. 9) with a near normal gain of about 0.92. Further data will be required to validate these suggestions.

Although the postoperative results from the other 35 unilateral vestibular neurectomy patients tested so far were essentially the same as the results from this group of 14, their results have not been included here as some of them were only tested after operation and others had abnormal results before operation. However even in this larger group there was no evidence of any substantial recovery of the HVOR after 1 year in response to high-acceleration, impulsive vestibular stimulation.

Discussion

The origin of compensatory eye movement responses to head impulses

Several lines of evidence indicate that the compensatory eye movements which occur in response to head impulses are largely of vestibular origin.

1. Since they are present in total darkness, they could not be of visual origin.

2. Since they were absent in a subject with intact cervical proprioceptors and stretch receptors, but with absent vestibular function, they could not be of cervical origin.

3. Since they were absent in a subject with absent vestibular function, it is reasonable to conclude that they must be of vestibular origin. On the other hand it is not certain that these compensatory eye movements originate entirely from stimulation of the HSCCs. The vertical SCCs must also have been stimulated by these head impulses and could have made a significant contribution to the HVOR (Fetter et al. 1986), particularly since the plane of the head impulses was not rigorously limited to the plane of the HSCCs.

The ampullofugal HVOR

The most notable result of this study is the finding of a severe, permanent HVOR deficit in response to head impulses toward the deafferented HSCC. This deficit must largely be due to loss of the ampullopetal excitation that would normally arise from stimulation of the now deafferented HSCC. Furthermore not only is the HVOR deficit permanent – it is still present 3 years after deafferentation – but it also appears to be fixed, since it does not decrease significantly between 1 week and 1 year after deafferentiation.

The residual HVOR, i.e. the HVOR that does remain in response to head impulses toward the deafferented HSCC, arises mainly by ampullofugal disfacilitation from the single intact HSCC and as such can be said to represent the ampullofugal-HVOR. It is clear from this data that in response to high-acceleration vestibular stimulation the ampullofugal-HVOR alone can only generate an inadequate compensatory eye movement, with a maximum gain of only about 0.25.

The ampullopetal HVOR

The slight HVOR deficit which we have shown occurs in response to head impulses toward the intact HSCC is most likely due to loss of the ampullofugal disfacilitation that normally arises from the now deafferented HSCC. The

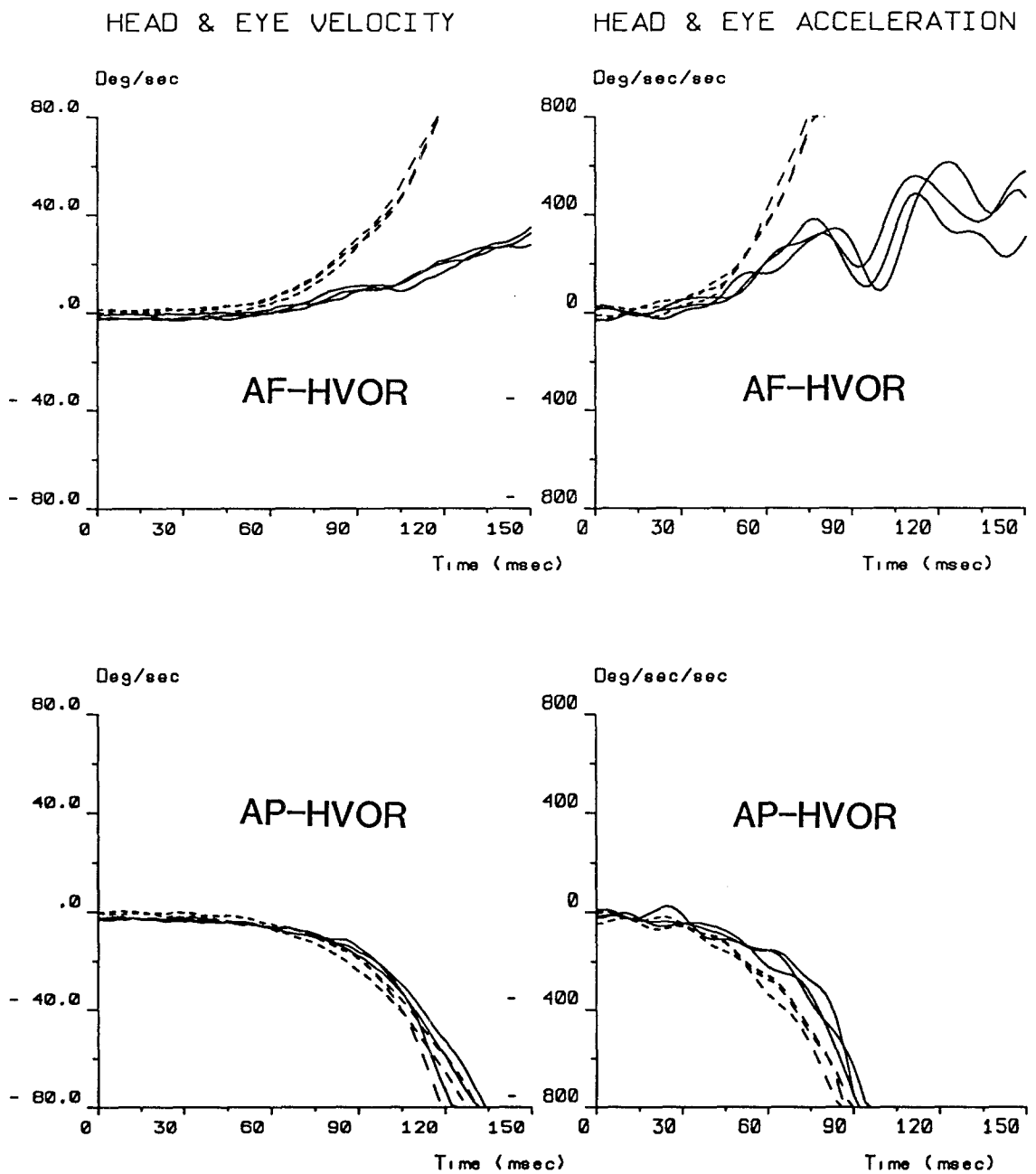


Fig. 8. Three superimposed head impulses from a patient 3 years after unilateral vestibular neurectomy. Head velocity and head acceleration are shown in dashed lines; eye velocity and eye acceleration in continuous lines. Only the early responses are shown. Eye velocity and eye acceleration more or less mirror head velocity and head acceleration respectively, in response to the ampullopetal excitation produced by head rotation toward the intact side (bottom row). In contrast both eye velocity and eye acceleration lag head velocity and head acceleration from the onset of head rotation in response to ampullofugal disfacilitation produced by head rotation toward the deafferented side (top row)

residual HVOR, i.e. the HVOR that does remain in response to this stimulus, most likely arises by ampullopetal excitation from the single intact HSCC and as such can be said to represent the ampullopetal-HVOR. Although the HVOR deficit is only slight, it does appear to be permanent and fixed since it does not decrease significantly in the year after UVD.

Possible mechanisms of the ampullofugal HVOR

Two simple mechanisms suggest themselves to explain the severe HVOR deficit which occurs in response to high-acceleration ampullofugal disfacilitation of the single intact HSCC:

(1) saturation of neural activity and

(2) low sensitivity.

The long term (1 year+) post-UVD data are more suggestive of low sensitivity to ampullofugal stimulation than of velocity saturation. Eye velocity does not saturate but increases linearly as a function of head velocity with a velocity gain which is constant at about 0.2, even at the lowest head velocities (Fig. 6 bottom right; Fig. 9 top). Eye acceleration in contrast may be approaching a saturation value at about 400 deg/s/s. Further data will need to

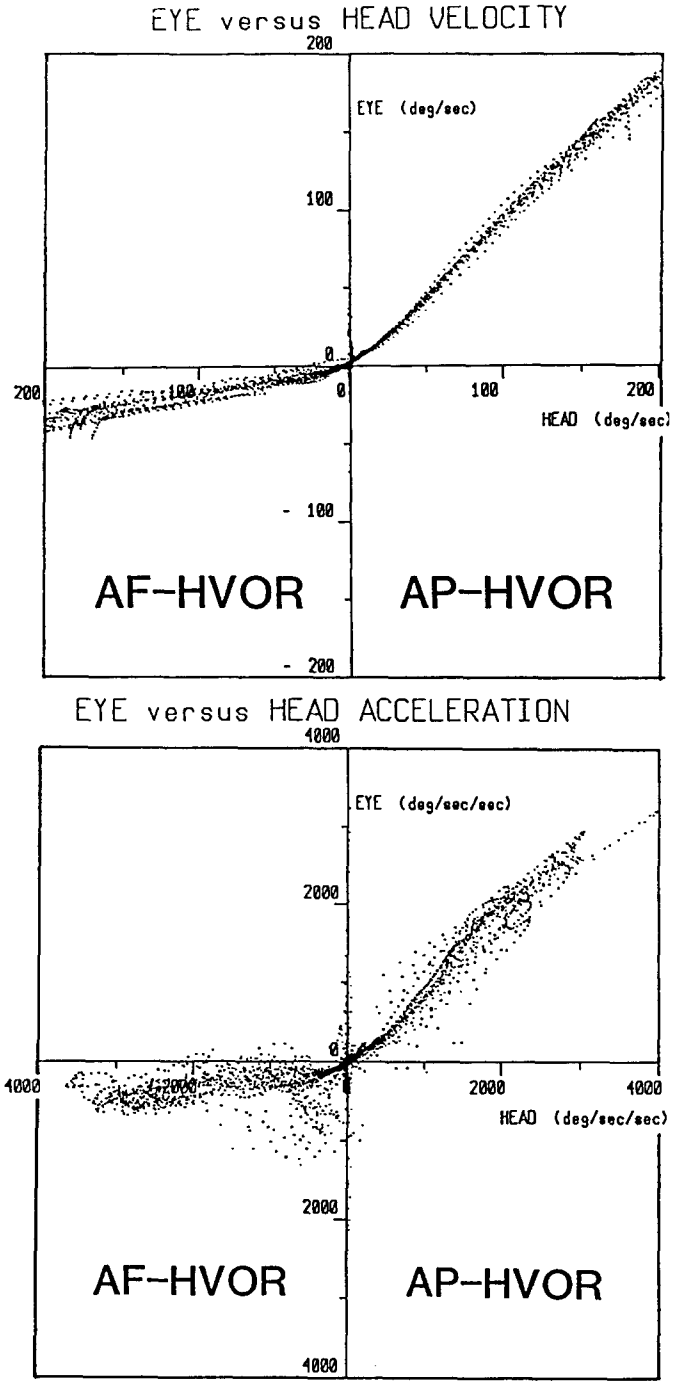


Fig. 9. Compensatory eye velocity and eye acceleration from a patient 3 years after unilateral vestibular neurectomy depicted as a function of head velocity and acceleration for 40 head impulses of the type shown in Fig. 8. Note that eye acceleration appears to be saturating at a value of about 400 deg/s/s so that eye velocity increases constantly with a gain of only about 0.2

be gathered to clarify this point. The short term (1 week) post-UVD data are on the other hand, consistent with the concept of an eye velocity saturation at about 30 deg/s.

The neural basis of the profound HVOR deficit in response to ampullofugal disfacilitation is not entirely clear. It could be occurring at one or several possible levels in the ampullofugal-HVOR pathway. Following UVD, disfacilitation of primary HSCC neurons on the intact side by ampullofugal stimulation becomes the major source of drive for the HVOR in response to head accelerations toward the deafferented side. In this situation the dynamics of the ampullofugal-HVOR now becomes critically dependent on the levels of resting activity in primary and in secondary HSCC neurons, on both the intact and on the deafferented sides, as well as on their relative sensitivities to ampullofugal as opposed to ampullopetal stimulation. Three factors in particular could be important:

(1) The levels of resting activity, at the time of testing, of primary HSCC neurons in the intact vestibular nerve, and of secondary HSCC neurons in both the intact and the deafferented vestibular nuclei.

(2) The relative sensitivity to disfacilitation as opposed to excitation: of primary HSCC neurons on the intact side, of secondary, type I excitatory, HSCC neurons on the intact side and of secondary, type II inhibitory, HSCC neurons on the deafferented side.

(3) The relative sensitivity to disinhibition as opposed to excitation, of secondary, type I excitatory, HSCC neurons on the deafferented side.

The available data from single SCC neuron recordings do not distinguish between these possibilities, perhaps because none were gathered using high-acceleration stimulation of the type used here. A disfacilitatory velocity saturation has been clearly shown in regularly discharging, squirrel monkey primary HSCC neurons in response to accelerations one order of magnitude smaller than the accelerations we have used here (Goldberg and Fernandez 1971; Blanks et al. 1975; Curthoys 1982). This saturation could be the equivalent of the velocity saturation we have shown in the human ampullofugal-HVOR in the first week after UVD (Fig. 6, bottom centre). This however is unlikely to be the entire explanation since ampullofugal-HVOR velocity gain is low even at the lowest head velocities suggesting that low ampullofugal-HVOR velocity sensitivity is also contributing to the inadequacy of the response. Lower velocity sensitivity to ampullofugal than to ampullopetal stimulation may also largely explain the long-term results in which a fixed gain of about 0.2 approximates the ampullofugal-HVOR response. Furthermore it is possible that those primary HSCC neurons which signal head acceleration (i.e. cupular velocity) rather than head velocity at high stimulus frequencies (Goldberg and Fernandez 1971), may be the source of the apparent acceleration saturation in the long-term post-UVD patients. Finally it should be admitted that there may be mechano-electrical asymmetries at the level of cupular transduction which could account for some of the ampullofugal-ampulloeptal HVOR asymmetry shown by high-acceleration testing.

Low- vs high-acceleration vestibular stimulation

The question must arise: "Why has this study shown such a profound ampullofugal-HVOR deficit after UVD?". Previous studies have in contrast shown much less deficit (Baloh et al. 1977; Allum et al. 1988; Paige 1989) or none at

all particularly in long-term patients (e.g. Dohlman 1961; Hallpike 1961; Honrubia et al. 1982; Jenkins 1985.) The main reason for this apparent discrepancy may be that the stimulus accelerations used in this study were at least one order of magnitude higher than the highest accelerations used in any previous studies. The SCCs have been described as velocity transducers, mainly because primary SCC neurons in the vestibular nerve do, by and large, signal head angular velocity rather than head acceleration in the usual frequency ranges studied (Wilson and Melvill Jones 1979). Nonetheless since the adequate stimulus for the SCCs is angular acceleration, it should not be entirely surprising that the velocity of the eye response is in fact a function of the acceleration as well as of the velocity of the SCC stimulus. The data presented here do not clearly show whether high-acceleration SCC stimulation simply saturates the ampullofugal-HVOR or whether it decreases the velocity gain of the response. Further studies in which head velocity and head acceleration are varied independently may help to make this distinction.

One practical consequence of these observations is a warning against attempting to provide a comprehensive evaluation of HVOR dynamics after UVD, using only low-acceleration stimulation and linear analytic methods. These techniques may yield deceptively symmetrical results.

Caloric vs high-acceleration vestibular stimulation

The fact that before operation 13 of the 14 patients reported here had unilaterally diminished responses to caloric stimulation despite normal responses to high-acceleration stimulation, suggests that these two methods of stimulation measure different aspects of horizontal semicircular function. The caloric stimulus presumably measures low-frequency semicircular canal function, whereas the high-acceleration head rotation stimulus measure high-frequency semicircular canal function.

The HVOR and dynamic vestibular compensation

The main finding of this study and of previous studies (Fetter and Zee 1988; Smith and Curthoys 1988, 1988a) raises important questions about precisely what recovery does take place after UVD. Immediately after UVD there is, in all mammals, a vigorous spontaneous horizontal nystagmus which it is generally agreed disappears (at least in light) within 1 week. Since the nystagmus is present in the absence of any SCC stimulation, this aspect of vestibular compensation has been called "the recovery of static symptoms". (All the patients reported here experienced this stereotyped appearance-disappearance of static symptoms.) In contrast to the general agreement on the extent of static vestibular compensation, there is no such agreement on the extent of compensation of dynamic vestibular symptoms (see Smith and Curthoys 1989 for a review). Since the gain of the ampullofugal half-cycles of the HVOR response to low-frequency, low-acceleration sinusoidal stimulation is decreased immediately after UVD and then gradually returns to normal, it has been assumed that there is a corresponding recovery of HVOR gain across the entire dynamic range.

Although some previous studies on the extent of dynamic HVOR recovery in man have yielded contradictory results (see Precht and Dieringer 1985; Smith and Curthoys 1989 for reviews), our data which show no significant recovery in HVOR velocity gain between 1 week and 1 year after UVD, as well as recent results from monkey (Fetter and Zee 1988) and guinea pig (Smith and Curthoys 1988), raise serious doubts about the extent of the presumed recovery of dynamic symptoms. While we could not exclude some slight improvement in HVOR dynamics during the first post-operative week, before any measurements could be made, we found no quantitative evidence of significant recovery in the extremely low HVOR velocity gain (about 0.2) between 1 week and 1 year after UVD. There may have been some more subtle improvement in the pattern of the ampullofugal-HVOR from acceleration saturation at 1 week to velocity saturation at 1 year, but this result awaits confirmation by further studies.

There are several possible reasons for the apparent contradiction between the present results which do not, and previous results which do show dynamic vestibular compensation. These reasons include the use in previous studies of: (1) only low-acceleration, low-frequency vestibular stimulation (e.g. Olson and Wolfe 1984; Jenkins 1985); (2) protocols which allow contamination of data by eye movements of extra-vestibular origin (Takahashi et al. 1984); (3) patients without surgically verified complete unilateral vestibular deafferentation (Takahashi et al. 1984; Allum et al. 1988). In the present study we have tried to avoid these possible sources of error by using vestibular stimuli in the physiological velocity and acceleration range (Grossman et al. 1988), by taking care to avoid intrusions by eye movements of extra-vestibular origin and by using only patients with complete surgical section of the entire vestibular nerve. When high-acceleration SCC stimulation is used, it appears that there is little or no recovery of the HVOR deficit showing that UVD results in a permanently and profoundly asymmetrical HVOR.

This physiological result must be reconciled with the clinical observation, that 1 year after operation, despite the HVOR deficit, only one of these patients complained of symptoms indicating vestibular insufficiency such as oscillopsia or ataxia. Although this clinical observation seems at odds with the results we have obtained here, some of the patients' own comments may provide an explanation. They reported that they had learnt to blink during head movements toward the operated side. Our own data in fact shows an apparent increase, which needs to be formally confirmed, in the number of saccades and blinks during head movements toward the operated side (Segal and Katsarkas 1988; Berthoz 1988). It may be that patients avoid the visual blur that would inevitably accompany the retinal slip produced by head movements toward the operated side, by blinking and by making refixation saccades. And finally some patients have found perhaps the simplest strategy of all for dealing with the ampullofugal-HVOR deficit: they learn to restrict their

head movements toward the operated side. They learn to use only their eyes rather than their heads and eyes together to refixate objects of the interest within the orbital range on the operated side. The advantage of this simple strategy is that it does not put these patients' inadequate HVOR to the test.

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