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Temporal dynamics of semicircular canal and otolith function following acute unilateral vestibular deafferentation in humans

Jun-ru Tian, Akira Ishiyama, and Joseph L. Demer

J.-r. Tian, J. L. Demer, Department of Ophthalmology, University of California, Los Angeles, CA 90095-7002, USA. J. L. Demer, Department of Neurology, University of California, Los Angeles, CA 90095-7002, USA. A. Ishiyama, Department of Head and Neck Surgery, University of California, Los Angeles, CA 90095-7002, USA. J.-r. Tian, J. L. Demer, Jules Stein Eye Institute, University of California, 100 Stein Plaza, Los Angeles, CA 90095-7002, USA. J. L. Demer, Neuroscience Interdepartmental Program, University of California, Los Angeles, CA 90095-7002, USA. J. L. Demer, Bioengineering Interdepartmental Program, University of California, Los Angeles, CA 90095-7002, USA

Abstract

Dynamic changes of deficits in canal and otolith vestibulo-ocular reflexes (VORs) to high acceleration, eccentric yaw rotations were investigated in five subjects aged 25–65 years before and at frequent intervals 3–451 days following unilateral vestibular deafferentation (UVD) due to labyrinthectomy or vestibular neurectomy. Eye and head movements were recorded using magnetic search coils during transients of directionally random, whole-body rotation in darkness at peak acceleration $2,800^\circ/\text{s}^2$. Canal VORs were characterized during rotation about a mid-otolith axis, viewing a target 500 cm distant until rotation onset in darkness. Otolith VOR responses were characterized by the increase in VOR gain during identical rotation about an axis 13 cm posterior to the otoliths, initially viewing a target 15 cm distant. Pre-UVD canal gain was directionally symmetrical, averaging 0.87 ± 0.02 ($\pm\text{SEM}$). Contralesional canal gain declined from pre-UVD by an average of 22% in the first 3–5 days post-UVD, before recovering to an asymptote of close 90% of pre-UVD level at 1–3 months. This recovery corresponded to resolution of spontaneous nystagmus. Ipsilesional gain declined to 59%, and showed no consistent recovery afterwards. Pre-UVD otolith gain was directionally symmetrical, averaging 0.56 ± 0.02 . Immediately after UVD, the contralesional otolith gain declined to 0.30 ± 0.02 , and did not recover. Ipsilesional otolith gain declined profoundly to 0.08 ± 0.03 ($P < 0.01$), and never recovered. In contrast to the modest and directionally symmetrical effect of UVD on the human otolith VOR during pure translational acceleration, otolith gain during eccentric yaw rotation exhibited a profound and lasting deficit that might be diagnostically useful in lateralizing otolith pathology. Most recovery of the human canal gain to high acceleration transients following UVD is for contralesional head rotation, occurring within 3 months as spontaneous nystagmus resolves.

Keywords

Eye movements; Otolith; Semicircular canal; Vestibulo-ocular reflex; Saccades

Introduction

The vestibulo-ocular reflex (VOR) normally rotates the eyes to maintain stable images on the retina during head perturbations. The VOR is composed of two components: the angular VOR derived from semicircular canals input, and the linear VOR derived from otolith input. After unilateral vestibular deafferentation (UVD), the canal VOR is known to be deficient during sudden high acceleration rotations toward the side of the lesion (Aw et al. 1996; Crane and Demer 1998; Foster et al. 1997; Halmagyi et al. 1993; Lasker et al. 1999, 2000; Tabak and Collewyn 1995; Tian et al. 2001b, 2002).

Transient rotational testing at high acceleration more reliably discloses chronic unilateral vestibular deficits than does steady state rotation (Halmagyi et al. 1990, 1991, 1993; Tian et al. 2001b), avoids confounding effects of quick phases, permits measurement of latency and permits comfortable delivery of accelerations intolerable to subjects in the steady-state. Transient rotation at high acceleration has been employed in combination with eccentric rotation axes and different target distances in monkey (Snyder and King 1992) and in younger (Anastasopoulos et al. 1996; Crane et al. 1997; Crane and Demer 1998) and older humans (Tian et al. 2001a). Rotation about eccentric axes can deliver significant otolith stimulation that is either synergistic or antagonistic with canal stimulation, and produces an effect on the VOR that varies systematically with target distance (Viirre et al. 1986; Snyder and King 1992; Crane et al. 1997; Crane and Demer 1998; Tian et al. 2001a). As geometrically appropriate to gaze stabilization, VOR gain for rotation about an axis posterior to head is greater for near than for distant targets (Viirre et al. 1986; Crane and Demer 1998; Tian et al. 2001a), but is reduced for a near target for rotation about an axis anterior to head (Sargent and Paige 1991; Crane and Demer 1998; Tian et al. 2001a). The earliest component of the transient VOR of younger normal subjects is attributable to the semicircular canals and has a latency of 7–10 ms; it is independent of rotational axis and target distance (Crane and Demer 1998). After a slightly longer latency, canal mediated VOR gain is increased with target proximity regardless of the rotational axis, even when this increase is visually inappropriate. About 40 ms following onset of eccentric head rotation, an effect of otolith stimulation is observed, approximately scaled by the inverse of target distance (Crane and Demer 1998), but the otolith effect is reduced in longstanding UVD (Crane and Demer 1998).

Deficits in the transient otolith VOR to pure linear acceleration following chronic UVD are usually modest (Aw et al. 2003; Bronstein et al. 1991; Crane et al. 2005; Lempert et al. 1998; Tian et al. 2006) and directionally symmetrical (Aw et al. 2003; Bronstein et al. 1991; Crane et al. 2005; Lempert et al. 1998). It has been supposed that otolith VOR deficits revealed during eccentric yaw rotation with near target viewing might better lateralize otolith pathology than would the modest and directionally symmetrical effect during pure translational acceleration (Paige 2002; Seidman et al. 2002; Takeda et al. 1991).

Methods

Subjects

Five unilaterally vestibulopathic subjects of mean age 42 ± 12 [standard deviation (SD), range 25–64] years were studied after giving written informed consent to participate in this study according to a protocol approved by the UCLA Human Subject Protection Committee (Table 1). All unilaterally vestibulopathic subjects had undergone either neurectomy or labyrinthectomy 3–25 days prior to the experiment. Both types of surgeries led to functionally similar UVD either by destruction of the sensory end organ or by interruption of their central projections. All subjects underwent ophthalmological examination to verify that they were free of ocular disease and underwent manifest refraction to attain best-corrected visual acuity at 20/20 or better in each eye. Subjects were instructed to omit medication on the day of the

experiment. Subjects with UVD had undergone measurements of initial VOR gain in response to transient, whole-body yaw rotations according to a previously-published protocol (Crane et al. 1997; Crane and Demer 1998; Tian et al. 2001a) before the surgery and they were included only if pre-surgery VOR gain was bilaterally symmetrical. The pre-surgery results confirmed that all subjects who later developed UVD had bilaterally symmetrical VOR gain in an interval of 55–75 ms, similar to normal subjects. All subjects were tested with the same protocol prior to and after surgical UVD at recovery times starting 3 days and continuing up to 451 days.

Magnetic search coil measurements

Angular eye and head positions were measured with magnetic search coils, as employed by other investigators (Grossman et al. 1989; Grossman and Leigh 1990) and in the current laboratory (Crane and Demer 1998; Tian et al. 2001a). Reference magnetic fields were generated by three pairs of solenoid coils, each 2 m in diameter, and arranged to form the sides of a cube (C-N-C Engineering, Seattle, WA). This configuration placed the center of the cube near eye level. The two vertically oriented coil pairs were driven by 60 KHz sinusoidal currents in phase quadrature (Collewijn et al. 1975). The horizontally oriented coil pair was driven by a 120 KHz sinusoidal current (Robinson 1963). Angular head position was measured with a search coil mounted on a bitebar, custom molded to the upper teeth of each subject. A dual-winding scleral magnetic search coil embedded in an annular suction contact lens (Skalar Medical, Delft, The Netherlands) (Collewijn et al. 1975) was placed on one eye to measure angular eye position in space. The right eye was selected for most of subjects. Search coils were connected to external detectors (C-N-C Engineering, Seattle, WA), and were calibrated goniometrically before experiments. Horizontal angular positions were demodulated by a phase angle method that is linear over a range of $\pm 80^\circ$.

The region within and around the reference field coils was maintained free of all significant metal objects. Homogeneity of the reference magnetic field was directly verified to assure that angular measurements were not contaminated by translation of the search coils. Coil sensitivity calibration curves were constant at $\pm 5\%$ within a central cube 58 cm on each side, and $\pm 1.6\%$ within a central cube measuring 11 cm on each side. Measured peak-to-peak position noise level of the search coil system at a bandwidth of 0–100 Hz was 2 minarc/s. The root-mean-square (RMS) horizontal velocity noise of the system over a bandwidth of 0–43 Hz was 30 minarc/s.

Topical proparacaine 0.5% was applied to the eye before inserting the search coil, which was removed within 30 min and were connected to external phase detectors as described elsewhere (Crane and Demer 1998; Tian et al. 2001a). Horizontal, vertical and torsional components of eye and head positions were displayed on a digital polygraph, passed through precision-matched, programmable low-pass filters with bandwidth set to 300 Hz, and digitally sampled at a rate of 1,200 Hz at 16 bit resolution by a Macintosh compatible computer running the MacEyeball software package (© Regents of the University of California) under LabView (National Instruments, Austin, TX).

Stimuli

Whole body yaw rotation was delivered by a powerful stepper motor (500 Nm) configured as a position servo (Crane and Demer 1998; Tian et al. 2001a, b). Since the motor step resolution was 0.5 min/arc, the steps were indistinguishable from continuous rotations. The presence of the motor did not have a detectable effect on search coil measurements. Subjects were secured via multiple belts in a cushioned, nonmetallic chair mounted on the servomotor (Crane and Demer 1998a). The special foot holder and knee protector were developed later to secure the stability during rotation. In order to faithfully couple rotator motion to the head, the forehead, temples, malar regions and chin of each subject were firmly secured to a chair-mounted head

holder by pads and adjustable clamps cushioned with stiff conforming foam (Conforfoam, Aearo Speciality, Indianapolis, IN).

Trials for each condition lasted 50 s during which 20 sudden rotations (10 in each direction) were administered in random order. Rotations lasting 200–1,000 ms were approximately evenly distributed throughout the trial, with onset varying randomly by up to 250 ms. Subjects were rotated at a high peak stimulus acceleration of $2,800^\circ/\text{s}^2$, attaining a maximum velocity of $190^\circ/\text{s}$ as it rotated the head 40° in 250 ms, and at a low peak stimulus acceleration of $1,000^\circ/\text{s}^2$, attaining a maximum velocity of $70^\circ/\text{s}$ as it rotated the head 14° in 250 ms. Earth-fixed targets were centered directly in front of the right eye at distances of 15 or 500 cm. The target 15 cm distant consisted of a 4 cm black cross surrounded by radiating lines at the center of a white background 50 by 43 cm. The target located at 500 cm was a 14 cm cross on a 102 by 81 cm background. Appropriate individual corrective lenses, including presbyopic correction, were provided as necessary for clear viewing of each target distance. The laboratory was illuminated between rotations to enable subjects to maintain an accurate memory of the target for fixation, a procedure that did not result in perceptible after-images. The earth-fixed target was thus visible except during rotation period beginning at a random time 50–70 ms before the onset of each head rotation and ending immediately after the chair had returned center ~400 ms later. Subjects were continuously reminded to maintain single vision of the target through a loudspeaker as it was visible throughout most of the experiment except during the brief rotational transients.

Contributions of the semicircular canals and otoliths were distinguished by varying the eccentricity of the head relative to the rotational axis to alter the relative linear acceleration delivered to the otoliths. Repositioning the head holder relative to the chair, and the chair relative to the motor hub varied eccentricity of the head relative to the rotational axis. Eccentricity was defined from the midpoint between the eyes with more posterior positions taken as positive. To isolate the VOR response to semicircular canal stimulation only with minimal net otolith contribution, subjects were rotated at an eccentricity of 7 cm posterior to the interocular midpoint of eyes, corresponding to the midpoint between the otoliths (Crane et al. 1997; Crane and Demer 1998). This otolith-centered rotational axis was simplified and defined as canal rotational axis since it induced a pure canal (AVOR) response especially at remote target distance of 500 cm. To evaluate otolith enhancement of VOR, subjects were rotated at eccentricities of 20 cm posterior to the interocular midpoint of eyes or 13 cm posterior to otoliths, while viewing a near target at a distance of 15 cm. This posterior rotational axis was used to measure the otolith contribution (LVOR). This eccentricity of rotational axis results in a change in peak linear acceleration of 0.6 G at the maximum angular acceleration employed here. Subjects were also rotated about this axis while viewing the remote target at 500 cm in effort.

Data analysis

Data were analyzed using custom software written using the LabView package (National Instruments, Austin, TX) as described in detail elsewhere (Crane and Demer 1998; Tian et al. 2001a). Processing of all data channels was identical to avoid introduction of temporal artifacts. Trials where eye position varied by more than 20 min/arc in the 80 ms preceding head rotation were automatically removed as failures of fixation and not considered for further analysis. After differentiation, data was filtered using a third order low pass Butterworth filter with a cutoff frequency of 50 Hz. Gain was determined by dividing compensatory eye velocity by head velocity. This approach normalized the effect of small variation in the head stimulus. Gain computation requires division by head velocity, which is near zero during the first 20 ms of motion onset; this noisy and unreliable interval was therefore omitted from the gain analysis and plots.

During rotation about a posterior eccentric axis, slow phase VOR eye velocity was greater for near than for remote targets (Fig. 1b). Gain of the VOR was taken to be eye velocity divided by head velocity. Initial otolith gain was defined, during rotation about an axis 13 cm posterior to the otoliths, as the increase in VOR gain for a near target at 15 cm, relative to a remote target at 500 cm. Given the fact that otolith VOR latency is at about 40 ms, considerably longer than canal VOR latency of 10 ms (Crane and Demer 1998), gain was computed as an average over the time interval 55–75 ms from rotation onset. The foregoing method of computation of otolith gain was considered to be more conservative than the alternative method of subtracting gain with a remote target during otolith-centered rotation. Initial canal (AVOR) gain was averaged during the same interval for rotation about the otolith-centered axis 7 cm posterior to the eyes with a target 500 cm distant, a situation that minimized both net otolith acceleration and vergence.

Results

All experiments were conducted using both 1,000 and 2,800°/s² peak head accelerations under all conditions. Results were similar for both peak accelerations, but we emphasize results for the higher peak acceleration because the signal to noise ratio was higher, and because this condition most clearly distinguishes ipsi- and contralesional responses.

Transient VOR prior to UVD

Shortly after onset of transient whole body yaw rotation, all subjects exhibited a compensatory VOR slow phase response in the opposite direction to head rotation. Representative head and eye velocities are illustrated in a typical subject with left Meniere's disease in Fig. 1. The VOR slow phase eye velocity was similar during contra- and ipsilesional rotation. This generally normal performance was required for all subjects who later underwent UVD. Representative instantaneous VOR gain during transient rotation is plotted for the same subject in Fig. 2. Traces average 5–10 rotations under identical conditions. During the early response 40–55 ms from rotation onset, ipsilesional canal gain was about 0.73, significantly less than the contralesional gain of 0.82. Ipsilesional gain became identical to the contralesional gain thereafter. This directional symmetry was typical for most subjects who later underwent UVD. Mean initial canal gain was quantified during the period 55–75 ms. In the representative subject of Fig. 2a, there was no significant difference between mean contralesional gain at 0.91 ± 0.004 (mean $\pm$ SEM) and ipsilesional gain at 0.90 ± 0.008 during this interval ($P > 0.05$). The group mean from all subjects was 0.87 ± 0.01 contralesionally, identical to 0.87 ± 0.02 ipsilesionally.

In the present experiment, it was possible to compute otolith gain by two reasonable but different methods. Otolith gain was alternatively calculated by subtraction at each time point of gain measured during far target viewing during rotations about an axis 7 cm posterior to the eyes from that measured during near viewing with a rotational axis 13 cm posterior to the labyrinths. The results were very similar to those obtained with rotation about the axis 13 cm posterior to the labyrinths, subtracting gain for the far from that obtained with the near viewing distance. The present report has emphasized the latter data as more conservative, since it is immune to potential artifacts from inhomogeneity of the magnetic field in the eye movement recording system. Importantly, the same conclusions are supported regardless of which method was selected to compute otolith gain.

Instantaneous otolith gain in representative subject 1 is demonstrated in the bottom panel of Fig. 2b, and was determined by subtraction at each time point of gain measured during near minus far target viewing during identical rotations about an axis 13 cm posterior to the otoliths. Ipsilesional otolith gain was 0.28, significantly greater than the contralesional gain of 0.21 during the early response 40–55 ms from rotation onset. Ipsilesional gain became identical to contralesional gain as both increased thereafter. Mean initial otolith gain was quantified during

the interval of 55–75 ms from rotation onset. Both contralesional gain and ipsilesional gain were identical in this interval and thereafter. There was no significant difference between contralesional otolith gain of 0.48 ± 0.01 and ipsilesional otolith gain of 0.50 ± 0.02 during this interval of the response ($P > 0.05$). Symmetrical otolith gain was typical for all subjects. The group mean from all subjects was 0.53 ± 0.03 contralesionally, not significantly different from 0.60 ± 0.01 ipsilesionally ($P > 0.05$).

Transient VOR within 1 week after UVD

Spontaneous nystagmus developed immediately after UVD with the slow phase toward the lesioned side. Intensity of spontaneous nystagmus in darkness varied, with average slow phase velocity varying among subjects from 3 to 13°/s. Spontaneous nystagmus velocity was much lower than slow phase eye velocity evoked by the high acceleration rotation. Initial canal and otolith VOR responses were markedly altered immediately after UVD. The earliest possible post-UVD testing in any subject was 3 days following lesion. Representative slow phase eye velocity in response to a peak head acceleration of $2,800^\circ/\text{s}^2$ is illustrated in Fig. 3. Note that regardless of rotational axis location, slow phase velocity during ipsilesional rotation was markedly reduced compared with contralesional rotation (Fig. 3). During posterior eccentric axis rotation, VOR slow phase velocity was not increased by near target viewing, although during contralesional rotation near target viewing was associated with increased VOR velocity in comparison with remote target viewing (Fig. 3). Instantaneous canal and otolith gains for subject 1 are illustrated in Fig. 4, and are typical of all subjects with UVD. During high acceleration rotation, contralesional canal gain decreased from the pre-UVD value of 0.82–0.61 during the early interval 40–55 ms, and then increased to 0.68 during the period 55–75 ms from rotation onset. Ipsilesional canal gain significantly declined from the pre-UVD value of 0.73–0.24 in the early interval 40–55 ms from rotation onset ($P < 0.01$), and remained low at around 0.26 during the period 55–75 ms from rotation onset. This reduction was significant compared with gain before lesion ($P < 0.01$), representing a 71% mean reduction for ipsilesional rotation. Averaged over all subjects, mean canal gain during the interval 55–75 ms from high acceleration onset in the first week post-UVD was reduced to 0.68 ± 0.03 contralesionally and 0.30 ± 0.03 ipsilesionally. Although variability was greater, the pattern was similar in response to lower acceleration rotation.

Otolith gain is demonstrated for a subject in Fig. 3b. In the early post-UVD period, in response to high acceleration eccentric rotation, contralesional otolith gain of this subject in the interval 55–75 ms from rotation onset declined significantly to 0.30, while ipsilesional gain declined to 0.02 ($P < 0.01$). These gain reductions persisted throughout the interval recorded. Averaged over all subjects, mean otolith gain during the interval 55–75 ms from high acceleration onset in the first week post-UVD was reduced to 0.30 ± 0.02 for contralesional and 0.08 ± 0.03 for ipsilesional rotation. Although variability was greater, the pattern was similar in response to lower acceleration rotation.

Transient VOR 1–8 weeks post-UVD

There was little or no recovery in initial canal and otolith VOR gains from initial measurements post-UVD. By 1–8 weeks following UVD, the spontaneous nystagmus in darkness was markedly diminished, and was present in only some subjects at a slow phase velocity of 1–2°/s. Representative data of the same typical subject 46 days after left UVD are illustrated in Fig. 5. In this subject, contralesional canal gain in response to high acceleration rotation increased modestly but significantly to 0.77 in the early interval 40–55 ms ($P < 0.01$), and to 0.87 during the period 55–75 ms from rotation onset. These gains were significantly higher than 3 days after UVD, but still significantly lower than before UVD ($P < 0.01$). Ipsilesional canal gain exhibited no recovery, remaining 0.24 in the early interval 40–55 ms from rotation onset, and 0.26 during the period of 55–75 ms from rotation onset, representing 71% of reduction same

as 3 days post-UVD value ($P > 0.05$). Averaged over all subjects, mean canal gain during the interval 55–75 ms from rotation onset measured approximately 8 weeks post-UVD was 0.68 ± 0.06 contralesionally and 0.30 ± 0.04 ipsilesionally. These gain values were not significantly different from gains measured 1 week post-UVD. Similar trends were evident in responses to lower acceleration rotation; there was no evidence of canal gain recovery.

Otolith gain was more severely reduced than canal gain in both directions, and showed no consistent trend to recover over time. In contrast to initial canal gain during contralesional rotation at high acceleration, at approximately 7 weeks post-UVD, contralesional otolith gain of the representative subject was diminished by about 30% of pre-UVD during the interval 55–75 ms from rotation onset (Fig. 5b, $P < 0.01$). At 7 weeks post-UVD, ipsilesional otolith gain during high acceleration rotation was more profoundly reduced to 0.13 during the same interval ($P < 0.01$), although gain was greater than at 3 days post-surgery, and still reflecting a reduction of 75% compared to pre-UVD. Averaging over all subjects with UVD, otolith gain 7–8 weeks post-UVD averaged 0.24 ± 0.03 for contralesional and 0.02 ± 0.04 for ipsilesional rotation at high acceleration, both being similar to values measured within 1 week on UVD. Similar trends were evident in responses to lower acceleration rotation; there was no evidence of otolith gain recovery.

Longitudinal study of transient VOR following UVD

To examine possible evidence of VOR recovery over time following UVD, initial canal and otolith gains measured during the period 55–75 ms from rotation onset were averaged in all five subjects at corresponding times during recovery from 3 to 451 days. Initial canal gain is illustrated in Fig. 6a for high peak acceleration of $2,800^\circ/\text{s}^2$. Initial canal gain averaged 0.87 ± 0.01 ($\pm \text{SEM}$) for contralesional and 0.87 ± 0.02 for ipsilesional rotation before UVD. Within the first week post-UVD, mean initial canal gain for contralesional rotation decreased to 0.68 ± 0.03 (range from 0.60–0.75, 78% pre-UVD, $P < 0.05$), and did not exhibit any consistent change subsequently (Fig. 6A). In contrast, mean initial canal gain for ipsilesional rotation declined profoundly to 0.30 ± 0.03 (range 0.24–0.38, 35% pre-UVD, $P < 0.01$). The mean reduction in canal gain over the entire post-UVD period was $67 \pm 2\%$, significantly greater than the mean canal gain reduction during contralesional rotation of $18 \pm 2\%$ ($P < 0.01$). The symmetry ratio was defined as ratio of gains for ipsilesional to contralesional rotation. The symmetry ratio for the canal VOR was 1.0 before UVD and 0.4 after UVD ($P < 0.01$), indicating the ipsilesional canal gain was less than half of contralesional canal gain after surgery. Lack of recovery of initial canal gain in response to low acceleration rotation is also illustrated in Fig. 7a.

The time course of mean initial otolith gain is illustrated in Fig. 6b for the high peak acceleration of $2,800^\circ/\text{s}^2$. Initial otolith gain averaged 0.53 ± 0.03 during contralesional and 0.60 ± 0.1 during ipsilesional rotation ($P > 0.05$) before UVD. The ratio of otolith to canal gain averaged 0.6 contralesionally and 0.7 ipsilesionally before UVD ($P > 0.05$). Mean initial otolith gain declined to 0.30 ± 0.01 (range 0.25–0.34, 58% pre-UVD) during contralesional rotation within the first week following UVD, and thereafter did not change significantly (Fig. 6b). In contrast, during ipsilesional rotation the mean initial otolith gain was profoundly reduced to 0.08 ± 0.03 (range 0–0.1, 13% pre-UVD, Fig. 6b). The mean reduction in otolith gain over the entire post-UVD period was $91 \pm 2\%$ for ipsilesional rotation, significantly greater than the mean otolith gain reduction during contralesional rotation of $43 \pm 2\%$ ($P < 0.01$). The ratio of otolith to canal gain averaged 0.4 contralesionally and 0.2 ipsilesionally after UVD ($P < 0.01$). The initial asymmetry ratio for otolith gain was taken to be the ratio of gains for ipsilesional to contralesional rotation. The symmetry ratio was close to 1.0 before UVD and 0.2 after UVD ($P < 0.01$), only about half of the canal asymmetry ratio ($P < 0.01$). Absence of recovery of mean initial otolith gain is illustrated in Fig. 7b for the low peak acceleration of $1,000^\circ/\text{s}^2$.

Overall otolith gains were lower for the low peak head acceleration than for the higher acceleration, and there was a suggestion of gradual reduction in otolith gain for contralateral rotation late after UVD (Fig. 7b). Otolith gain for ipsilesional rotation remained nearly zero throughout the entire time interval following UVD.

Individual transient VOR gains after UVD

Since there was no significant recovery of either the initial canal or otolith VOR over time, otolith and canal gains were averaged at all testing times post-UVD for each subject, and plotted individually for each subject (Fig. 8). This demonstrated consistent impairment in the initial canal (Fig. 8a) and otolith (Fig. 8b) gains in every subject. The symmetry ratio of ipsilesional to contralateral gains was 0.41 ± 0.05 (range 0.28–0.56) for the canal VOR, and was 0.20 ± 0.05 (range 0.09–0.34) for the otolith VOR.

Vestibular catch-up saccades

Vestibular catch-up saccades (VCUS) developed at varying times following UVD among individual subjects. No consistent VCUS occurred within the first 8 weeks after UVD in any subjects. After this, two subjects developed VCUS with latencies 150–250 ms from rotation onset, and amplitude 5° – 7° . By 6 months post-UVD, the VCUS of these two subjects became more stereotypic, with shorter latencies of 150–200 ms, and amplitudes increased to 6° – 9° . The remaining three subjects did not develop VCUS within 6 months of UVD.

Discussion

Transient canal and otolith VOR before UVD

We isolated the pure canal VOR using rotation about an axis midway between the otoliths to minimize net tangential acceleration on them, and through use of a remote target at 500 cm to minimize convergence (Snyder and King 1992; Anastasopoulos et al. 1996; Crane et al. 1997; Crane and Demer 1998; Tian et al. 2001a). Normally, the earliest component of the transient canal VOR of younger healthy humans has latency about 10 ms (Crane and Demer 1998). Since the average age of subjects with UVD was older and the study aimed to compare canal with otolith gain, transient canal gain was averaged during the interval 55–75 ms from head rotation onset. Mean transient canal gains were symmetrical before UVD.

We isolated the transient otolith VOR by eccentric rotation that delivered significant tangential acceleration to the otoliths, and by use of a near target 15 cm distant that evoked 23° convergence (Snyder and King 1992; Anastasopoulos et al. 1996; Crane et al. 1997; Crane and Demer 1998; Tian et al. 2001a). The approach assumed that the otolith contribution can be derived by subtraction of the time-aligned canal VOR response to the same rotation with a remote target, since the otolith VOR scales according to the inverse of target distance (Paige 1989, 1991, 2002). Otolith effects are not consistently detectable until about 40 ms following onset of eccentric head rotation (Crane and Demer 1998), so the transient otolith VOR was measured in the interval 55–75 ms from rotation onset. For comparability, the transient canal and otolith VORs were both measured during this interval. Mean transient otolith gains were symmetrical before UVD. We employed unpredictable, whole-body rotation at high acceleration, as this condition minimizes the opportunity for contributions by nonvestibular mechanisms.

Lack of recovery in transient canal VOR following UVD

After UVD, several processes have been proposed to contribute to recovery of AVOR gain during rotation at lower acceleration and frequency. These include recovery of afferent activity, learning and visual tracking (Gacek et al. 1992; Yamane et al. 1995; Gonshor and Melvill Jones

1973; Miles and Evarts 1979; Paige 1983; Fetter and Zee 1989). After chronic UVD, canal gain during unpredictable, ipsilesional rotations at high acceleration remain persistently low (Crane and Demer 1998; Halmagyi et al. 1993; Tian et al. 2001b). Nevertheless, studies of chronic UVD cannot assess possible short-term adaptive mechanisms and functional recovery. The present study had the unique ability to investigate the transient canal and otolith VORs prospectively before surgical UVD, acutely after UVD, and then longitudinally at intervals over a long period of time until the condition was indisputably chronic. The consistent finding for both the early canal and otolith VORs is the lack of any consistent recovery between 3 and 450 days post-surgical UVD. This finding strongly suggests that any other forms of vestibular compensation or adaptation after UVD occur downstream of peripheral vestibular afferents.

The main drive for the canal VOR is from the on-direction excitatory type I primary and secondary vestibular neurons driven by ipsilateral rotation; such neurons are silent during ipsilesional rotation in UVD. The remaining drive to the canal VOR during ipsilesional rotation is from disfacilitation of off-direction excitatory type I primary and secondary vestibular neurons, leading to type II maximal disinhibition of type I secondary vestibular neurons ipsilesionally (Halmagyi et al. 1993). The higher acceleration of $2,800^{\circ}/s^2$ employed here is more than sufficient to silence type II secondary vestibular neurons and vestibular afferents (Goldberg and Fernandez 1971), which have an inhibitory cutoff of $700^{\circ}/s^2$ (Fuchs and Kimm 1975). Even the lower acceleration of $1,000^{\circ}/s^2$ employed in the current study is more than adequate to reach this inhibitory cutoff. Therefore, the similar pattern of deficits between contra- and ipsilesional rotation was evident at the lower peak acceleration, although the decrease was much moderate and responses less consistent for the otolith VOR.

Profound deficit and absence of recovery of transient otolith VOR after UVD

The deficits in the otolith VOR to pure interaural linear acceleration with near, central targets are modest following UVD (Aw et al. 2003; Bronstein et al. 1991; Crane et al. 2005; Lempert et al. 1998; Tian et al. 2006b) and directionally symmetrical (Aw et al. 2003; Bronstein et al. 1991; Crane et al. 2005; Lempert et al. 1998). The small and symmetric magnitude of the LVOR deficit in UVD has made it difficult to lateralize otolith pathology based on test findings. Exceptions have involved the anteroposterior otolith VOR with an eccentric visual target in monkey UVD (Angelaki et al. 2000) and human UVD (Tian et al. 2006). However, in contrast to the modest otolith VOR deficits during pure linear acceleration, the current study found that the otolith VOR evoked by eccentric yaw rotation with near target viewing was profoundly and asymmetrically ablated during ipsilesional rotation at high acceleration. Otolith gain was reduced by 91% for ipsilesional but only 43% during contralesional rotation, a difference that was highly significant ($P < 0.01$). Otolith gain never exhibited significant recovery for either rotational direction. Surprisingly, otolith gain during ipsilesional eccentric rotation was more profoundly impaired by UVD than was canal gain. This effect is quite the opposite of the finding for the otolith VOR in UVD, and suggests that otolith function is better tested during synergistic canal input than during an isolated linear acceleration stimulus. Canal and otolith inputs are likely to interact centrally in synergistic rather than linear ways. It has been proposed that the canals can influence the otolith VOR (Angelaki 2004; Glasauer and Merfeld 1997; Merfeld 1995; Merfeld and Zupan 2002), since afferent information from both canals and otoliths can be integrated to distinguish translation from tilt (Angelaki 2004; Angelaki et al. 1999; Glasauer and Merfeld 1997; Green and Angelaki 2003, 2004; Merfeld 1995; Merfeld and Zupan 2002; Merfeld et al. 1999; Mergner and Glasauer 1999; Zupan et al. 2002). The finding of the current study is in agreement with suggestions that the otolith VOR performs better when the canal VOR is simultaneously stimulated (Angelaki et al. 2002; Ramat and Zee 2003) and is thus calibrated to function synergistically (Crane et al. 1997; Demer and Crane 1998, 2001; Demer and Viirre 1996; Imai et al. 2001; Moore et al. 2001; Raphan et al. 2001).

Potential as clinical test for otolith pathology

Testing of the VOR during pure translation appears insufficiently robust to be a practical lateralizing test of otolith function (Tian et al. 2006). However, high acceleration eccentric yaw rotation with a near target in the current study disclosed a profound, immediate, enduring and lateralizing deficit in the otolith VOR in UVD. These robust features suggest possible utility as a clinical test of otolith function. Nevertheless, a caveat is that the present study could not assess otolith VOR function independent of a coexisting canal deficit. It might be the case that the robust otolith VOR deficit observed here in UVD would not manifest without a concurrent canal deficit. It would be worthwhile to investigate the current protocol of determining otolith gain in a model system in which otolith function is ablated despite normal canal function.

Vestibular catch-up saccades

Saccades, triggered by the vestibular system and calibrated to vestibular input, provide a compensatory mechanism to supplement the deficient VOR slow phase during the latter phase of ipsilesional rotation (Tian et al. 2000). These VCUS required months to develop the following acute UVD, and first became evident at times varying among subjects. Short latency, stereotype VCUS have been described to occur within 60–90 ms of onset of rotations ipsilesional to UVD that was chronic for many years (Tian et al. 2000). The current study permits the inference that such early and seemingly automatic VCUS require more than 18 months to develop.

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Fig. 1.

Representative horizontal slow phase eye and head velocities prior to UVD from subject 1 with left Meniere's disease who underwent transient rotation to the right and left at a peak head acceleration of $2,800^\circ/\text{s}^2$. Data sampled at 1,200 Hz from onset of head rotation at time zero, and averaged over ten trials. *Dotted lines* indicate ± 1 SEM. The contralesional eye velocity trace is inverted for easy comparison. **a** Labyrinth-centered rotational axis 7 cm posterior to the eyes, while viewing a target 500 cm away. VOR slow phase eye velocity was directionally symmetrical. **b** Posterior rotational axis 13 cm posterior to the labyrinths, viewing a near target 15 cm away, and a remote target 500 cm away. The difference due to target proximity reflects the otolith effect. VOR slow phase eye velocity was directionally symmetrical

Fig. 2.

Pre-UVD gain (eye velocity/head velocity) in subject 1 with left Meniere's disease who underwent transient rotation to the right and left at a peak head acceleration of $2,800^\circ/\text{s}^2$. Data sampled at 1,200 Hz from onset of head rotation at time zero, and averaged over ten trials.

Dotted lines indicate ± 1 SEM. **a** Instantaneous canal gain during rotation about mid-labyrinth axis 7 cm posterior to the eyes while viewing a remote target 500 cm away. Gains for contralesional and ipsilesional rotation were similar. There was no significant directional gain difference in the interval 55–75 ms ($P > 0.05$). **b** Instantaneous otolith gain derived as difference between responses while viewing a near target 15 cm away, and a remote target 500 cm away, in both cases rotating identically about an axis 13 cm posterior to the otoliths. Otolith gains

were similar for contralesional and ipsilesional rotations in the interval 55–75 ms from onset of head rotation, and remained identical afterwards ($P > 0.05$)

Fig. 3.

Representative head and slow phase VOR eye velocity 3 days after UVD by left labyrinthectomy in subject 1, in response to peak acceleration at $2,800^\circ/\text{s}^2$. Data sampled at 1,200 Hz from onset of head rotation at time zero, and averaged over ten trials. The contralesional eye velocity trace (*gray line*) is inverted for comparison. Head velocity is illustrated in the opposite direction. **a** Rotation about mid-labyrinth axis 7 cm posterior to the eyes while viewing a remote target 500 cm away. VOR slow phase eye velocity was significantly reduced for ipsilesional (*black line*) compared with contralesional rotation (*gray line*). **b** Rotation about axis 13 cm posterior to the labyrinths while viewing a near target 15 cm away, and a remote target 500 cm away. The difference due to target proximity reflects the

otolith response. VOR slow phase eye velocity was significantly decreased for ipsilesional rotation (*black line*) compared with contralesional rotation (*gray line*)

Fig. 4.

Representative gains (eye velocity/head velocity) of subject 1, recorded 3 days after UVD by left labyrinthectomy, in response to rotation at a peak acceleration of $2,800^\circ/\text{s}^2$. Data sampled at 1,200 Hz from onset of head rotation at time zero, and averaged over ten trials. *Dotted lines* indicate ± 1 SEM. **a** Instantaneous canal gain derived from the response to rotation about a mid-labyrinth centered axis while viewing a remote target 500 cm away. Contralateral canal gain was decreased by 25% from pre-UVD ($P < 0.01$). Ipsilesional canal gain remained markedly decreased to 0.24 from the very early interval 40–55 ms from onset of head rotation, and subsequently ($P < 0.01$). **b** Instantaneous otolith gain derived as difference between responses while viewing a near target 15 cm away, and a remote target 500 cm away, in both

cases rotating identically about an axis 13 cm posterior to the otoliths. After UVD, contralesional otolith gain was reduced to 0.30, corresponding to a 38% reduction compared with pre-UVD ($P < 0.01$). Ipsilesional otolith gain was substantially decreased to around 0.02 indicating a severe reduction of 96% compared with pre-surgery value ($P < 0.01$). Contralesional and ipsilesional gains differed significantly in the interval 55–75 ms from rotation onset ($P < 0.01$)

Fig. 5.

Representative gains (eye velocity/head velocity) of subject 1, recorded 7 weeks after left UVD by labyrinthectomy. Rotations were contralesional (gray line) and ipsilesional (black line) at a peak acceleration of $2,800^\circ/\text{s}^2$. Dotted lines indicate ± 1 SEM. **a** Instantaneous canal gain for contralesional rotation gain increased slightly to 0.77 during the very early response 40–55 ms from onset of head rotation, further still to 0.87 in the interval 55–75 ms. A 71% reduction remained for ipsilesional gain ($P < 0.01$). Contralesional and ipsilesional gains significantly differed in the interval 55–75 ms from onset of head rotation ($P < 0.01$). **b** Instantaneous otolith gain during contralesional rotation was reduced to 0.34, corresponding to a 29% reduction compared with pre-UVD ($P < 0.01$). Gain for ipsilesional rotation was substantially decreased

to around 0.13, corresponding to a reduction of 75% compared with pre-UVD ($P < 0.01$). Contralesional and ipsilesional gains differed significantly in the interval 55–75 ms from head rotation ($P < 0.01$), and thereafter

Fig. 6.

Mean VOR gains of all five subjects with UVD measured in the period 55–75 ms following onset of head rotation at a peak acceleration of $2,800^{\circ}/s^2$, measured before and repeated at intervals up to 451 days following UVD. *Open circles* contralesional gain, *solid circles* ipsilesional gain. *Vertical lines* represent ± 1 SEM. **a** Canal gains declined immediately after UVD, and changed little thereafter. The decrease was greater for ipsi than contralesional rotation. **b** Otolith gains declined immediately after UVD, and changed little thereafter. Gain was modestly ablated during contralesional rotation, but severely ablated for ipsilesional rotation

Fig. 7.

Mean VOR gains of all five subjects with UVD measured in the period 55–75 ms following onset of head rotation at a peak acceleration of $1,000^{\circ}/s^2$, measured before and repeated at intervals up to 451 days following UVD. *Open circles* contralateral gain, *solid circles* ipsilateral gain. *Vertical lines* represent ± 1 SEM. **a** Canal gains declined immediately after UVD, similar to the pattern seen at high peak acceleration (Fig. 6). **b** Otolith gain for ipsilateral rotation declined immediately after UVD, and remained near zero thereafter

Fig. 8.

Gains of individual subjects before, and average of measurements at all studied times after UVD. Peak head acceleration $2,800^{\circ}/s^2$. **a** Average canal gain was significantly greater during contra than ipsilesional rotation ($P < 0.01$) for each individual. **b** Average otolith gain was significantly greater during contra than ipsilesional rotation ($P < 0.01$) for each individual

Table 1

Information for subjects with UVD

UVD subject	Sex	Age	Diagnosis	Surgery	Lesion side
1	M	25	MD	Labyrinthectomy	Left
2	F	49	AN	Labyrinthectomy	Left
3	M	39	AN	Neurectomy	Right
4	M	64	AN	Neurectomy	Left
5	F	32	MD	Labyrinthectomy	Left
6	M	65	AN	Labyrinthectomy	Left

M Male, *F* female