Adaptations and Deficits in the Vestibulo-Ocular Reflex after Sixth Nerve Palsy

Agnes M. F. Wong,[1,2] *Douglas Tweed,*[1,3] *and James A. Sharpe*[1,2]

Purpose. The effects of paralytic strabismus on the vestibulo-ocular reflex (VOR) have not been systematically investigated in humans. The purpose of this study was to analyze the VOR in patients with unilateral peripheral sixth nerve palsy.

Methods. Twenty-one patients with unilateral peripheral sixth nerve palsy (6 severe, 7 moderate, 8 mild) and 15 normal subjects were studied. Subjects made sinusoidal ±10° head-on-body rotations in yaw and pitch at approximately 0.5 and 2 Hz, and in roll at approximately 0.5, 1, and 2 Hz. Eye movement recordings were obtained using magnetic scleral search coils in each eye in darkness and during monocular viewing in light. Static torsional VOR gains, defined as change in torsional eye position divided by change in head position during sustained head roll, were also measured.

Results. In all patients, horizontal VOR gains in darkness were decreased in the paretic eye in both abduction and adduction, but remained normal in the nonparetic eye in both directions. In light, horizontal visually enhanced VOR (VVOR) gains were normal in both eyes in moderate and mild palsy. In severe palsy, horizontal VVOR gains remained low in the paretic eye during viewing with either eye, whereas those in the nonparetic eye were higher than normal when the paretic eye viewed. Vertical VOR and VVOR were normal, but dynamic and static torsional VOR and VVOR gains were reduced in both eyes in all patients.

Conclusions. In darkness, horizontal VOR gains were reduced during abduction of the paretic eye in all patients, as anticipated in sixth nerve palsy. Gains were also reduced during adduction of the paretic eye, suggesting that innervation to the medial rectus has changed. After severe palsy, vision did not increase abducting or adducting horizontal VVOR gains to normal in the paretic eye, but caused secondary increase in VVOR gains to values above unity in the nonparetic eye, when the paretic eye fixated. In mild and moderate palsy, vision enhanced the VOR in the paretic eye but caused no change in the nonparetic eye, suggesting a monocular readjustment of innervation selectively to the paretic eye. Vertical VOR and VVOR gains were normal, indicating that the lateral rectus did not have significant vertical actions through the excursions that we tested (±10°). Reduced torsional VOR gains in the paretic eye can be explained by the esotropia in sixth nerve palsy. Torsional VOR gain normally varies with vergence. We attribute the reduced torsional gains in the paretic eye to the mechanism that normally lowers it during convergence. The low torsional gains in the nonparetic eye may be an adaptation to reduce torsional disparity between the two eyes. (*Invest Ophthalmol Vis Sci.* 2002;43:99–111)

Sixth nerve palsy is the commonest ocular motor nerve palsy. Clinical testing of strabismus emphasizes static deviations. Little information is available about the effects of paralytic strabismus on eye movement dynamics such as during the vestibulo-ocular reflex (VOR).[1–4] Adaptive changes in the VOR occur in response to different visual stimuli.[5–9] Disconjugate VOR adaptation has been elicited in monkeys in response to anisometropic prisms[10] and experimental weakening of the horizontal recti muscles.[2,3] In the current study, we examined patients with unilateral peripheral sixth nerve palsy to assess their VOR and its adaptation, if any, to abduction palsy. As anticipated, horizontal VOR was weak in the paretic eye in the direction of palsy. Reduced horizontal VOR gains of the paretic eye in the direction opposite the palsy and reduced gains in the torsional dimension in both eyes were also identified. These findings provide evidence of monocular, neural adaptations in humans with peripheral neuromuscular deficits.

Methods

Clinical Assessment and Imaging Studies

Twenty-one patients with unilateral peripheral sixth nerve palsy were recruited from the Neuro-ophthalmology Unit at the University Health Network. A complete history was taken, and detailed ophthalmic and neurologic examinations were performed, recording the duration and age of onset of diplopia, the presence or absence of risk factors for ischemia (diabetes mellitus and hypertension), and associated neurologic symptoms and signs. The magnitude of strabismus was measured objectively using the prism and cover test and subjectively using the Maddox rod and prism test. When indicated, appropriate tests were performed to rule out myasthenia gravis, thyroid ophthalmopathy, other orbital diseases, or intracranial lesions.

Ranges of duction were estimated by either of two examiners (AMFW, JAS) who graded the abduction defect as the estimated percentage of the normal abduction in the other eye. Based on the abduction defect, patients were classified into three groups: mild (81%–95% of normal range of abduction), moderate (51%–80%), and severe (≤50%).

Serial axial and sagittal T_1- and T_2-weighted magnetic resonance (MR) images with gadolinium enhancement were obtained (slice thickness, 5 mm) for all patients under 50 years of age and those with other neurologic signs. In this investigation, computed tomographic (CT) images of the head with contrast were obtained in all patients with ischemic risk factors and in patients more than 50 years of age, although CT imaging is not our standard practice in such patients. If the CT scan was normal, patients were followed up at approximately 3 months. Those without improvement in the sixth nerve palsy at 3 months and those with an abnormal CT scan were further investigated with MR imaging.

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Fifteen normal persons served as control subjects (mean age, 52 ± 15 years; median, 58; range, 19–69; eight women).

Eye Movement Recordings

Experimental Protocol. With one eye occluded, subjects viewed a red laser spot of 0.25° in diameter, rear projected onto a uniformly gray vertical flat screen 1 m away from the nasion. Subjects made active sinusoidal ±10° head-on-body rotations in yaw to elicit the horizontal VOR and in pitch to elicit the vertical VOR, at approximately 0.5 and 2 Hz. Torsional VOR was elicited by head rotation in roll at approximately 0.5, 1, and 2 Hz. Head movements were paced by a periodic tone. The maintenance of desired amplitude and frequency of head movements was encouraged by placement of the examiner's hands on each parietal area of the subject's skull. The procedure was performed in light with one eye viewing to elicit visually enhanced VOR (VVOR) and repeated, with the other eye fixating and the fellow eye occluded. The VOR was then recorded in complete darkness while subjects were instructed to fixate on an imaginary earth-fixed target.

To measure the static torsional VOR, patients fixated on the center target with one eye occluded as we measured their ocular responses to static head rolls of approximately 30° toward each shoulder, as measured with a search coil. The procedure was then repeated with the other eye fixating and the fellow eye occluded and in total darkness.

Recordings of Eye Movement and Calibration. Positions of each eye were simultaneously measured by a three-dimensional magnetic search coil technique, using a 6-ft (183 cm) diameter coil field arranged in a cube (CNC Engineering, Seattle, WA). In each eye, the patient wore a dual-lead scleral coil annulus designed to detect horizontal, vertical, and torsional gaze positions (Skalar Instrumentation, Delft, The Netherlands). Phase detectors using amplitude modulation as described by Robinson[11] provided signals of torsional gaze position within the linear range. Head position was recorded by another coil taped to the subject's forehead. Each subject's head was centered in the field coils. Horizontal and vertical eye movements were calibrated with saccades to steps of the laser target. For the four patients with 10% or less abduction, horizontal eye movements were calibrated in the adducting orbital hemirange (where the coil system remained linear) and verified using a protractor to calibrate the eye coil. Head and torsional eye movements were calibrated by attaching the scleral coil to a rotating protractor. Torsional precision was approximately ±0.2°. There was minimal crosstalk. Large horizontal and vertical movements produced deflections in the torsional channel of less than 4% of the amplitude of the horizontal and vertical movement. Any coil slippage was assessed by monitoring offsets in torsional eye position signal during testing. Consistency of calibrated positions after each eye movement provided evidence that the coil did not slip on the eye. Eye position data were filtered with a bandwidth of 0 to 90 Hz, digitized at 200 Hz, and recorded on disc for off-line analysis. Analog recordings were also displayed in real time by a rectilinear thermal array recorder (Model TA 2000, Gould Inc., Cleveland, OH).

Data Analyses. In one dimension, the input (head velocity) and output (eye velocity) of the VOR are regarded as scalar quantities (i.e., real number), and the reflex is characterized by its gain, which is the ratio of eye velocity to head velocity. In most natural head rotation, however, the input and output of the VOR are not scalar but three-component vectors (the angular velocity vectors of the head and eye), having not only magnitudes but also directions. Thus, a more complete characterization of the VOR requires a description, not only of the relative sizes of eye and head velocities, but also of their relative directions—that is, the axes around which the eye and the head rotate.

The VOR, however, can be treated as one dimensional if head rotation occurs around only one axis. For example, during pure horizontal head rotation (that is, around the earth-vertical axis), the vertical and torsional components of the three-component rotation vector become zero. In this situation, the velocity of rotation can be derived by differentiation of position data. In this study, whereas horizontal, vertical and torsional head positions were measured simultaneously, gaze position data were measured in one dimension. That is, horizontal gaze positions were recorded during horizontal head motion, vertical gaze positions during vertical head motion, and torsional gaze positions during head roll. Pure head rotation around one axis was approximated by analyzing only data in which the other two axes showed less than 1° variation from baseline (Fig. 1A).

Eye position was derived by subtracting head position from gaze position signals. Fast phases of vestibular nystagmus were identified by a computer program using velocity and acceleration criteria.[12] Results of fast-phase identification were edited on a video monitor, allowing the operator to verify cursor placement for fast-phase removal. Eye positions between 80 msec before and after the identified fast-phases were removed, and the gaps were replaced with quadratic fits. Their average slopes were used to calculate the contribution of the ongoing slow phase during the fast phase. The offset due to the fast phase was then removed, and the ongoing slow phase was interpolated to yield a cumulative trace of eye position.

Using position data, each cycle of rotation was identified by marking adjacent peaks with opposite direction, and the frequency was computed. Using a least-squares sinusoidal fit,[13] eye and head positions were fitted with one cycle, and the phase and amplitude were computed. The ratio of the amplitude of the eye and the amplitude of the head was the gain, and the difference between the phase of the eye and the phase of the head was the phase shift.

To calculate the gain in each direction, eye and head position data from each half cycle were used and reflected to form a full cycle. Each cycle was then fitted using a least-squares sinusoidal fit,[13] and the gain was computed for each direction. In addition, we plotted head velocity against eye velocity, and performed a linear regression for each direction. The slopes of the fitted lines were the gains, and the results were comparable to those computed by the least-squares sinusoidal fit technique (Fig. 1B).

To account for the prismatic effect or rotational magnification induced by spectacle adaptation,[9,14] horizontal and vertical VOR gains were adjusted in subjects who habitually wore corrective spectacles, by using the formula[9,14]: $M_{pred} = 40/(40 - D)$, where D is the lens power in diopters and M_{pred} is the predicted magnification. For example, a hyperope who habitually wears +10 diopters spherical lenses has an $M_{pred} = 40/(40 - 10) = 1.3$. This means that while wearing +10 D lenses, a VOR gain of 1.3, instead of 1.0, is required to prevent the visual scene from moving on the retina during head rotations.

Mean peak velocities of nystagmus quick-phase during horizontal head rotation were quantified. Asymptotic velocities were derived by computer analysis of velocity-amplitude scatterplots using an exponential best-fit curve[15–17]: $P = V(1 - e^{-A/C})$, where P is peak velocity at any point on the curve, V is asymptotic velocity, A is saccade amplitude, and C is a constant.

For the measurement of static torsional VOR, head and gaze position signals were sampled for 6 seconds for 30° lateral head tilt in each of 20 positions, 10 toward the right shoulder and 10 toward the left shoulder. The position of the eye in the head was derived from the difference between head and gaze position signals. Head and eye positions were computed off-line over each 6-second period after the eye had come to a torsional resting position (defined as having angular velocity of ≤1 deg/sec). Responses containing blinks or rapid drifts were not analyzed. Change of torsional eye position was plotted as a function of static change of head position after roll, and a linear regression was performed. Static torsional VOR gain, defined as change in torsional eye position divided by change in head position in static roll, was calculated from the slope of the regression line.

Oculography was performed at one point in each patient's course (Table 1). Thus, changes from normal, rather than serial intrasubject changes, were available for analyses. Statistical analyses of horizontal, vertical, and torsional VOR and VVOR gains and phase were performed using two-tailed Student's *t*-tests with unequal variance. Differences from normal were defined as significant when $P < 0.05$.

The research protocol was approved by the University Health

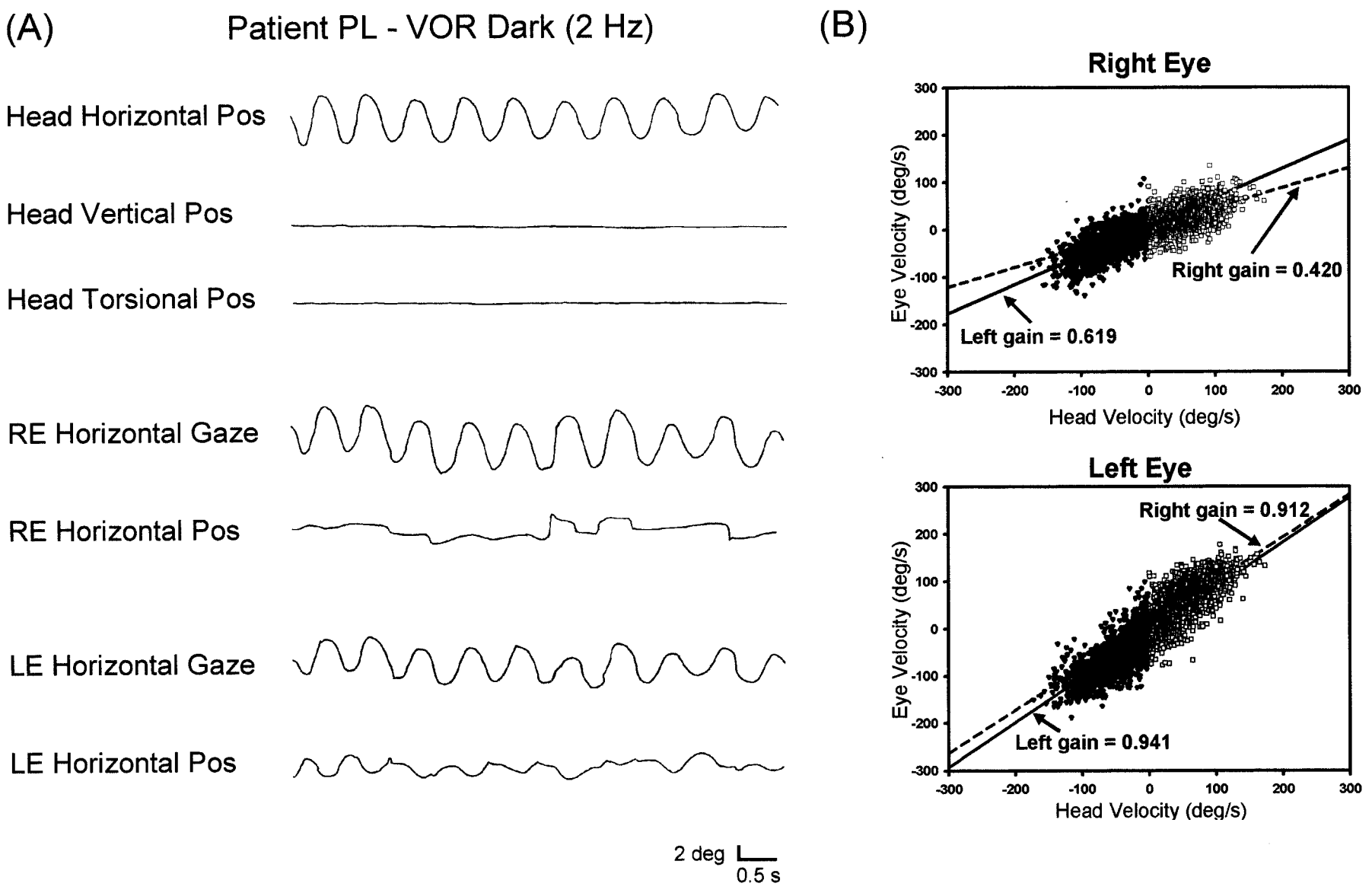

FIGURE 1. (A) Recordings of a patient (PL) with severe right sixth nerve palsy during horizontal head rotation about an earth-vertical axis at 2 Hz in darkness. (B) Plots of head velocity versus eye velocity of the paretic right eye (*top graph*) and the nonparetic left eye (*bottom graph*) of the same patient. VOR gains, defined as the slopes of the lines of best fit, were reduced in the paretic right eye in both directions (*top graph*), whereas gains were normal in the nonparetic left eye in both directions (*bottom graph*). RE, right eye; LE, left eye; *open squares*, data during rightward movements; *dashed line*, line of best fit for data during rightward movements; *filled circles*, data during leftward movements; *solid line*, line of best fit for data during leftward movements.

TABLE 1. Characteristics of Patients with Sixth Nerve Palsy

Patient	Age/Sex	Side of Lesion	Duration	Abduction Deficit (% Normal)	Imaging Findings	Comments
1 (PL)	21/M	Right	2 wk	0 (Severe)	Normal MRI	Improved after 4 months
2 (JM)	46/M	Right	2 wk	0 (Severe)	Normal MRI	Resolved after 3 months
3 (KE)	75/F	Right	2 mo	10 (Severe)	Normal CT	Resolved after 4 months (HTN, DM)
4 (AM)	75/F	Right	2 mo	50 (Severe)	Normal CT	Resolved after 6 months (HTN)
5 (VI)	65/F	Left	36 mo	50 (Severe)	Normal MRI	Idiopathic
6 (MB)	19/F	Left	3 wk	0 (Severe)	MRI: left cavernous sinus hemangioma	Botulin injection at 3 months
7 (SC)	66/M	Right	3 wk	80 (Moderate)	Normal CT	Resolved after 4 months (DM)
8 (JC)	49/M	Right	9 mo	80 (Moderate)	MRI: Sphenoid wing meningioma with invasion of right cavernous sinus	Diplopia, right facial paraesthesia
9 (TH)	77/M	Right	30 mo	60 (Moderate)	Normal MRI	Idiopathic
10 (DW)	65/M	Left	96 mo	70 (Moderate)	Normal MRI	Idiopathic
11 (SCH)	50/F	Left	24 mo	80 (Moderate)	Normal MRI	Idiopathic
12 (JM2)	46/M	Left	3 wk	80 (Moderate)	Normal MRI	Resolved after 6 months (HTN)
13 (EM)	64/M	Left	3 wk	80 (Moderate)	Normal CT	Resolved after 5 months (HTN)
14 (NR)	75/F	Right	4 mo	90 (Mild)	Normal MRI	Idiopathic
15 (RL)	77/F	Right	10 mo	95 (Mild)	Normal MRI	Idiopathic
16 (EF)	52/M	Right	3 wk	95 (Mild)	Normal MRI	Idiopathic
17 (GD)	64/M	Right	15 mo	90 (Mild)	Normal CT	Claustrophobia
18 (THA)	57/M	Right	2 mo	90 (Mild)	Normal CT	Resolved after 4 months (HTN, DM)
19 (GC)	57/M	Left	34 mo	90 (Mild)	Normal MRI	Idiopathic
20 (IW)	75/F	Left	12 mo	90 (Mild)	Normal MRI	Idiopathic
21 (LC)	54/F	Left	60 mo	80 (Mild)	Normal MRI	Idiopathic

HTN, hypertension; DM, diabetes mellitus.

Network Ethics Committee and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

RESULTS

General Characteristics of Patients

The characteristics of the 21 patients are shown in Table 1. The mean age was 59 ± 17 years (median age, 64 years; range, 19–77 years). There were 12 men. The duration of symptoms ranged from 2 weeks to 96 months, with a mean duration of 16 months. Mean follow-up duration was 16 months (range, 9–26). Six patients had severe, seven had moderate, and eight had mild peripheral sixth nerve palsy. Nineteen patients had idiopathic, presumed ischemic, peripheral lesions and two had cavernous sinus lesions on MR imaging. Of the 19 patients with idiopathic peripheral palsy, 13 had normal MR images and 6 had normal CT scans of the brain (Table 1). Five of the six patients with normal CT scan had ischemic factors, such as hypertension and diabetes, and had a complete resolution of the palsy within 4 to 6 months. All patients had an incomitant esodeviation, which increased in the field of action of the paretic muscle. No other eye movement abnormalities or neurologic signs were present in any patient.

Horizontal VOR Gain and Phase

Severe Sixth Nerve Palsy. In darkness, horizontal VOR gains of the paretic eye were reduced symmetrically during both abduction and adduction in each (Fig. 1) of the six patients ($P < 0.01$), whereas gains of the nonparetic eye remained normal in both directions (Fig. 2A, top graph and Table 2). During paretic eye viewing (Fig. 2A, middle graph), horizontal VVOR gains of the paretic eye were low in both directions ($P < 0.01$), whereas VVOR gains of the nonparetic occluded eye were higher than in normal control eyes ($P < 0.01$; Table 2). During nonparetic eye viewing (Fig. 2A, bottom graph), horizontal VVOR gains of the occluded paretic eye were reduced ($P < 0.01$), whereas those of the viewing nonparetic eye remained normal (Table 2). In light and in darkness, the mean phase differences between the eye and head positions approximated 180°, designated as zero phase shift.

Moderate and Mild Palsy. In darkness (Figs. 2B, 2C, top graphs), horizontal VOR gains of the paretic eye during abduction and adduction were lower than in normal control eyes ($P < 0.05$), whereas gains in the nonparetic eye were within normal in both directions (Table 2). During viewing with either eye (Figs. 2B, 2C, middle and bottom graphs), horizontal VVOR gains were normal for both the paretic and nonparetic eyes in both directions (Table 2). Neither eye showed any significant phase shift from zero in light or in darkness.

Mean peak velocities of horizontal nystagmus quick phase were asymmetric in the paretic eye in each of 21 patients, being reduced for abduction and normal for adduction. For a 5° horizontal quick phase, mean peak velocity of the paretic eye during abduction was 114.3 ± 22.8 deg/sec, compared with 188.4 ± 24.5 deg/sec during adduction ($P < 0.05$), and 199.5 ± 41.5 deg/sec in normal control eyes ($P < 0.05$). Mean peak velocities of horizontal quick phase were normal and symmetric in the nonparetic eye.

Vertical and Torsional VOR Gain and Phase

In all three groups of patients, vertical VOR and VVOR gains were normal in both eyes (Fig. 3). In contrast, torsional VOR and VVOR gains were significantly reduced in both the paretic and nonparetic eyes when compared with normal control eyes ($P < 0.05$; Fig. 4, Table 3). Neither eye showed any significant phase shift from zero during vertical or torsional rotation.

Static Torsional VOR Gain

Static torsional VOR and VVOR gains of each eye were conjugate between the two eyes in all patients and did not differ during right or left eye viewing, irrespective of the severity of palsy. Static torsional VOR gains are, therefore, reported as the pooled mean of both eyes under both viewing conditions in light and in darkness. Mean gains in patients were 0.14 ± 0.08 in light and 0.13 ± 0.09 in dark, compared with 0.21 ± 0.10 in light and 0.20 ± 0.11 in dark in normal subjects ($P < 0.01$).

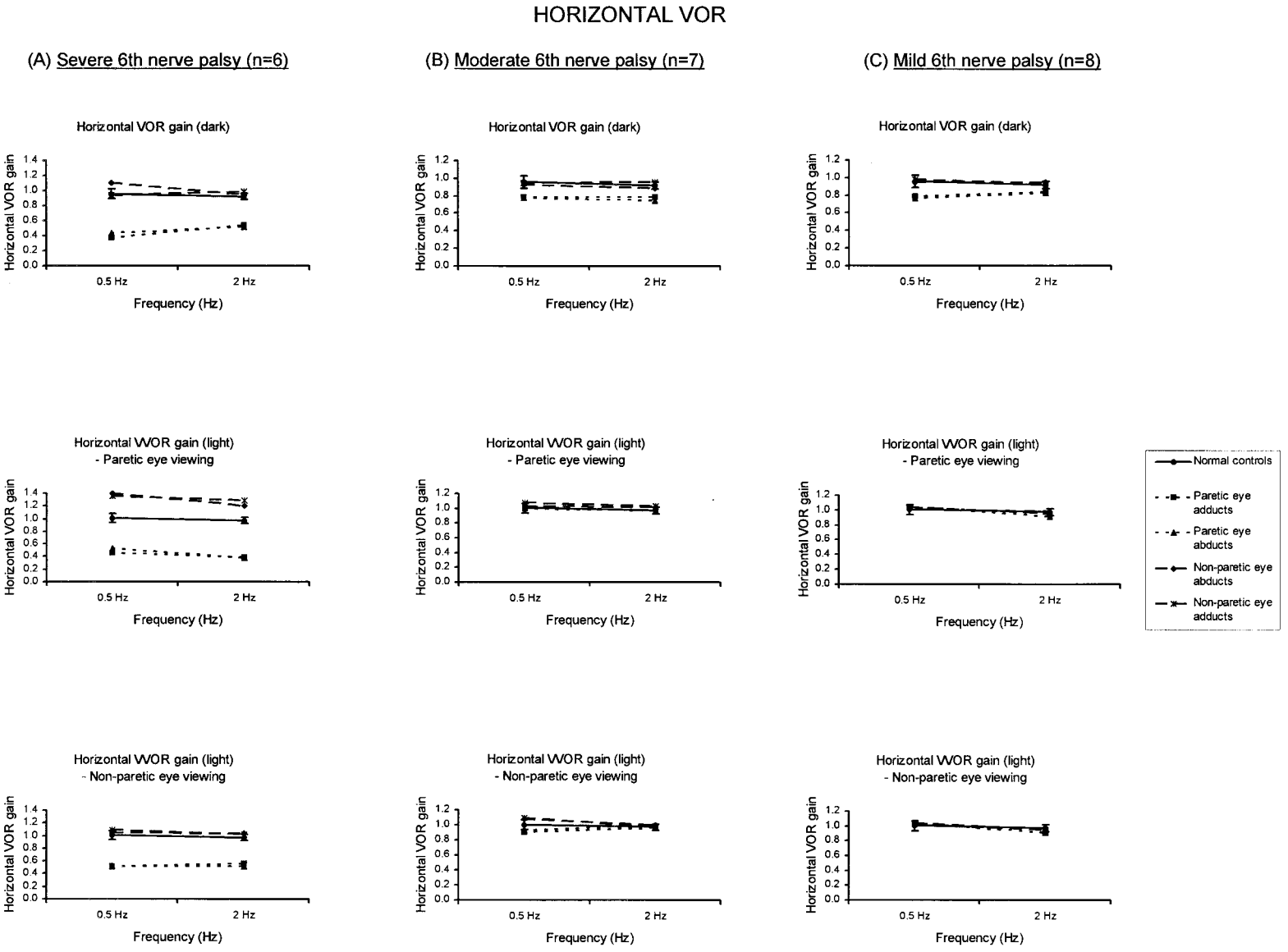

FIGURE 2. Mean horizontal VOR gains in patients with (**A**) severe, (**B**) moderate, and (**C**) mild peripheral sixth nerve palsy.

TABLE 2. Horizontal VOR and VVOR Gains in Patients with Sixth Nerve Palsy

	Dark		Paretic Eye Viewing		Nonparetic Eye Viewing	
	0.5 Hz	2 Hz	0.5 Hz	2 Hz	0.5 Hz	2 Hz
Normal control eyes (n = 15)	0.96 ± 0.07	0.92 ± 0.04	—	—	1.01 ± 0.04	0.97 ± 0.05
Severe (n = 6)						
Paretic eye abducts	0.43 ± 0.12*	0.51 ± 0.19*	0.54 ± 0.07*	0.37 ± 0.16*	0.52 ± 0.09*	0.51 ± 0.07*
Paretic eye adducts	0.37 ± 0.18*	0.54 ± 0.11*	0.46 ± 0.08*	0.40 ± 0.12*	0.52 ± 0.08*	0.56 ± 0.06*
Nonparetic eye abducts	1.10 ± 0.12	0.94 ± 0.16	1.40 ± 0.08*	1.21 ± 0.04*	1.05 ± 0.12	1.10 ± 0.09
Nonparetic eye adducts	0.94 ± 0.27	0.98 ± 0.22	1.36 ± 0.09*	1.30 ± 0.07*	1.04 ± 0.11	1.02 ± 0.13
Moderate (n = 7)						
Paretic eye abducts	0.78 ± 0.13†	0.74 ± 0.07†	1.02 ± 0.10	0.97 ± 0.06	0.93 ± 0.14	1.00 ± 0.20
Paretic eye adducts	0.79 ± 0.14†	0.79 ± 0.12†	0.99 ± 0.08	0.97 ± 0.09	0.91 ± 0.16	0.97 ± 0.18
Nonparetic eye abducts	0.93 ± 0.18	0.89 ± 0.17	1.04 ± 0.07	1.02 ± 0.11	1.08 ± 0.11	1.00 ± 0.11
Nonparetic eye adducts	0.95 ± 0.16	0.96 ± 0.14	1.08 ± 0.09	1.03 ± 0.06	1.10 ± 0.18	0.97 ± 0.12
Mild (n = 8)						
Paretic eye abducts	0.77 ± 0.19†	0.83 ± 0.11†	1.04 ± 0.09	0.91 ± 0.19	1.03 ± 0.12	0.91 ± 0.13
Paretic eye adducts	0.78 ± 0.11†	0.84 ± 0.09†	1.05 ± 0.10	0.95 ± 0.10	1.04 ± 0.11	0.91 ± 0.10
Nonparetic eye abducts	0.95 ± 0.18	0.95 ± 0.23	1.01 ± 0.07	0.98 ± 0.06	1.02 ± 0.05	0.95 ± 0.09
Nonparetic eye adducts	0.98 ± 0.18	0.94 ± 0.21	1.05 ± 0.13	0.95 ± 0.11	1.04 ± 0.08	0.95 ± 0.09

Data are mean VOR ± SD.
* $P < 0.01$.
† $P < 0.05$.

Nineteen (90%) of the 21 patients had significantly reduced gains in light and in dark (z-tests, $P < 0.05$). The other two patients (one with mild and the other with moderate palsy) had lower than normal group mean gains, but they did not reach statistical significance.

DISCUSSION

In sixth nerve palsy, horizontal VOR gains in darkness were decreased in the paretic eye in both abduction and adduction, whereas those in the nonparetic eye remained normal in both directions. In light, horizontal VVOR gains became normal in both eyes in moderate and mild palsy. In severe palsy, horizontal VVOR gains remained low in the paretic eye during viewing with either eye, whereas VVOR gains rose to values above unity in the nonparetic eye during paretic eye viewing. Vertical VOR and VVOR were normal; however, dynamic and static torsional VOR and VVOR gains were reduced in both eyes.

Changes in the VOR in our patients, who were tested at one point in their courses, are expressed as changes from normal, rather than serial intrasubject changes. Recovery toward normal values was not determined. Abnormalities are interpreted as deficits or adaptation to those deficits.

Patients were tested during monocular viewing, with either the paretic or nonparetic eye viewing and the fellow eye occluded. The eye was patched immediately before each test, and the patch was removed after each test. The differences between VOR and VVOR responses due to constant patching were not assessed. In addition, the eye that patients habitually used for fixation was not controlled.

VOR Gains during Active Head Rotation in Normal Subjects

During passive whole-body rotation, horizontal VOR gains are less than unity, with typical gains ranging from 0.7 at 0.5 Hz to 0.95 at 1 Hz.[18,19] In agreement with previous studies,[20–23] higher VOR gains were observed during active head rotation. Horizontal VOR gains during active head rotation in darkness were close to unity, whereas vertical VOR gains in darkness were approximately 0.9 in our normal subjects.

Higher VOR gains during active head motion, as recorded in our normal subjects, could be explained by several influences. First, the cervico-ocular reflex may contribute. Vestibular and neck velocity signals are summed on neurons in the vestibular nuclei.[24,25] The response of ocular motor nerve fibers to vestibular stimulation is modulated by stimulation of neck proprioceptors.[26] However, the contribution of the cervico-ocular reflex in normal humans is negligible.[27,28] Second, during voluntary head motion, the rotational axis of the head is displaced backward to the vertebral column, as opposed to a more head-centered axis during passive whole-body rotation.[29] VOR gain increases with larger radii of rotation, because the angular VOR then receives an increasing contribution from the translational VOR.[30] Backward displacement of the rotational axis may contribute to the higher VOR gain recorded during active head rotation. Third, modulation by preprogrammed eye movements may also account for higher VOR gain during active head motion. When labyrinthine function is lost, gaze commands become important in generating compensating, stabilizing eye movements.[31] An efference copy of head motor commands during active head rotation could contribute to the higher gains of compensatory smooth eye movements.

Horizontal VOR in Unilateral Sixth-Nerve Palsy

Horizontal VOR in Darkness. During rotation in darkness, horizontal VOR gains were reduced during abduction of the paretic eye in all patients, as anticipated in abduction palsy. VOR gains during adduction of the paretic eye were also reduced. In contrast, in the nonparetic eye, VOR gains were normal during both abduction and adduction (Fig. 2). Apparently, the innervation to the medial rectus of the paretic eye is reduced without changing the innervation to the horizontal recti muscles of the nonparetic eye.

This adjustment is likely a functional adaptation to unilateral sixth nerve palsy. Without it, the VOR would be asymmetric in the paretic eye—weak in abduction but normal in adduction. The asymmetry would drive the paretic eye farther and farther into adduction with each cycle of head rotation, soon "pinning" it at its nasal limits, and aggravating the patient's diplopia. There are several strategies that might rectify this problem. The brain could increase its innervation to the paretic lateral rectus to increase VOR gain during abduction, but this strategy is limited by the palsy itself. Or, the brain may generate abducting saccades in the paretic eye to correct for low VOR

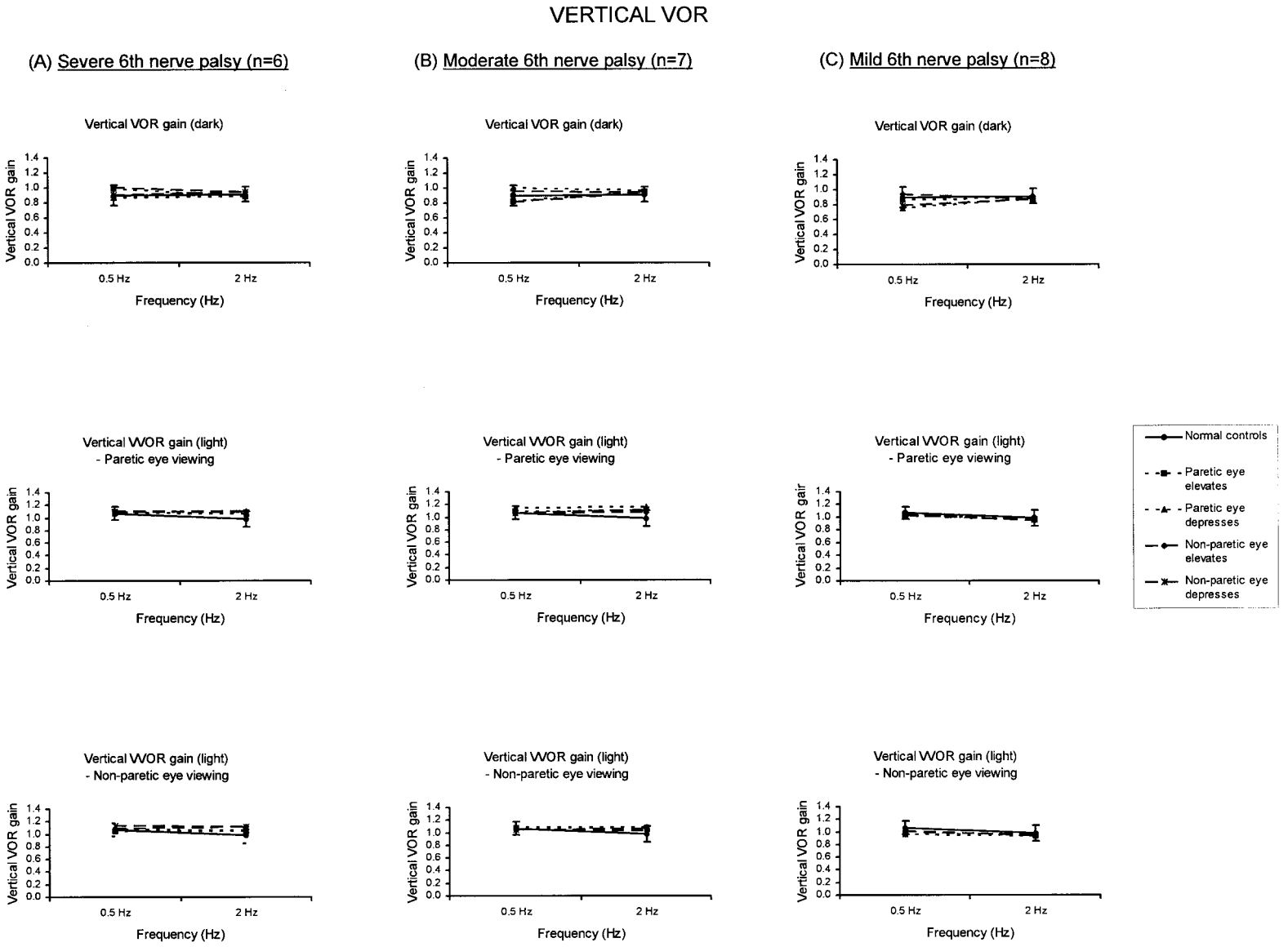

FIGURE 3. Mean vertical VOR gains in patients with (A) severe, (B) moderate, and (C) mild peripheral sixth nerve palsy.

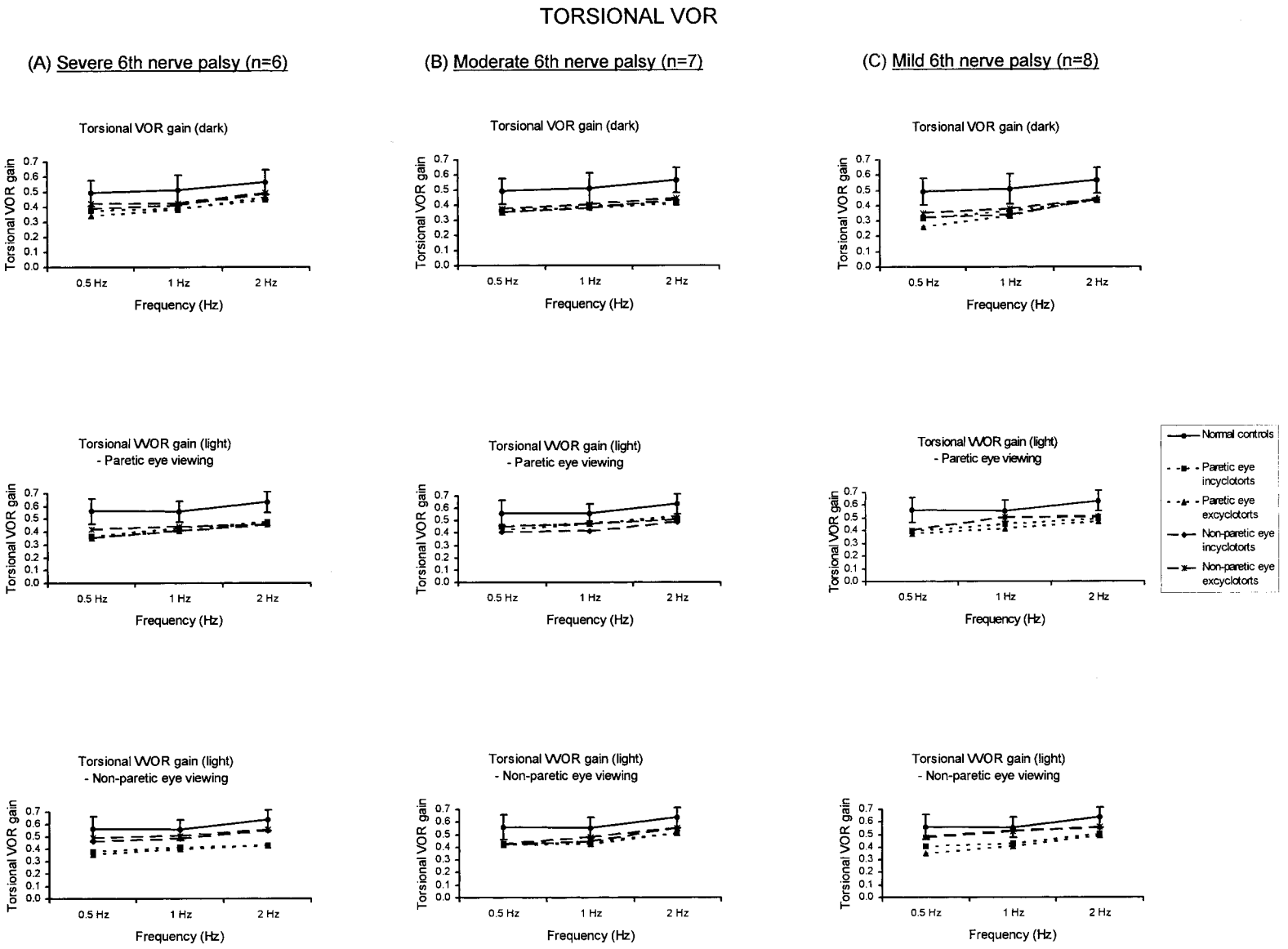

FIGURE 4. Mean dynamic torsional VOR gains in patients with (A) severe, (B) moderate, and (C) mild peripheral sixth nerve palsy.

TABLE 3. Torsional VOR and VVOR Gains in Patients with Sixth Nerve Palsy

	Dark			Paretic Eye Viewing			Nonparetic Eye Viewing		
	0.5 Hz	1 Hz	2 Hz	0.5 Hz	1 Hz	2 Hz	0.5 Hz	1 Hz	2 Hz
Normal control eyes (n = 15)	0.49 ± 0.09	0.51 ± 0.10	0.56 ± 0.08	—	—	—	0.56 ± 0.10	0.56 ± 0.08	0.63 ± 0.08
Severe (n = 6)									
Paretic eye incyclotorts	0.38 ± 0.11†	0.39 ± 0.09†	0.45 ± 0.04†	0.37 ± 0.14†	0.43 ± 0.08†	0.48 ± 0.18†	0.37 ± 0.13†	0.42 ± 0.12†	0.43 ± 0.14†
Paretic eye excyclotorts	0.34 ± 0.14†	0.38 ± 0.10†	0.46 ± 0.05†	0.35 ± 0.13*	0.41 ± 0.12†	0.47 ± 0.16†	0.36 ± 0.11*	0.40 ± 0.14†	0.43 ± 0.15†
Nonparetic eye incyclotorts	0.39 ± 0.10†	0.41 ± 0.07†	0.49 ± 0.12	0.35 ± 0.14*	0.41 ± 0.09†	0.46 ± 0.18†	0.46 ± 0.05†	0.49 ± 0.06†	0.55 ± 0.11
Nonparetic eye excyclotorts	0.43 ± 0.05†	0.42 ± 0.08†	0.49 ± 0.13	0.42 ± 0.14	0.44 ± 0.08†	0.46 ± 0.15†	0.49 ± 0.05†	0.51 ± 0.13	0.56 ± 0.13
Moderate (n = 7)									
Paretic eye incyclotorts	0.37 ± 0.13†	0.38 ± 0.12†	0.41 ± 0.15†	0.45 ± 0.10†	0.48 ± 0.06†	0.52 ± 0.10†	0.43 ± 0.11†	0.44 ± 0.11†	0.51 ± 0.11†
Paretic eye excyclotorts	0.35 ± 0.13†	0.39 ± 0.12†	0.42 ± 0.15†	0.43 ± 0.11†	0.48 ± 0.06†	0.54 ± 0.12	0.42 ± 0.10*	0.43 ± 0.12†	0.51 ± 0.11†
Nonparetic eye incyclotorts	0.35 ± 0.13†	0.38 ± 0.13†	0.43 ± 0.12†	0.41 ± 0.11†	0.42 ± 0.14†	0.49 ± 0.10†	0.42 ± 0.10*	0.45 ± 0.10†	0.55 ± 0.12
Nonparetic eye excyclotorts	0.38 ± 0.11†	0.40 ± 0.08†	0.45 ± 0.13†	0.45 ± 0.09†	0.47 ± 0.07†	0.51 ± 0.11†	0.43 ± 0.09*	0.48 ± 0.06†	0.55 ± 0.13
Mild (n = 8)									
Paretic eye incyclotorts	0.32 ± 0.13*	0.37 ± 0.11†	0.43 ± 0.14†	0.40 ± 0.17†	0.45 ± 0.07†	0.49 ± 0.16†	0.41 ± 0.16†	0.43 ± 0.15†	0.51 ± 0.13†
Paretic eye excyclotorts	0.26 ± 0.07*	0.34 ± 0.06*	0.45 ± 0.11†	0.38 ± 0.15*	0.42 ± 0.13†	0.47 ± 0.14†	0.35 ± 0.09*	0.40 ± 0.13†	0.49 ± 0.12†
Nonparetic eye incyclotorts	0.33 ± 0.10*	0.34 ± 0.13†	0.44 ± 0.14†	0.40 ± 0.15†	0.51 ± 0.13	0.51 ± 0.18	0.49 ± 0.05†	0.53 ± 0.10	0.56 ± 0.16
Nonparetic eye excyclotorts	0.35 ± 0.11*	0.38 ± 0.13†	0.44 ± 0.14†	0.40 ± 0.15†	0.51 ± 0.13	0.57 ± 0.17	0.48 ± 0.05†	0.53 ± 0.11	0.56 ± 0.15

Data are mean torsional VOR gain ± SD.
* $P < 0.01$.
† $P < 0.05$.

gains during abduction. However, abduction paresis would limit them. Moreover, if common premotor signals are sent to both the abducens motoneurons and internuclear neurons in the abducens nucleus (discussed later), the result may be unwanted adducting saccades in the nonparetic eye, taking it off its target. A better choice might be to reduce the innervation just to the medial rectus of the paretic eye, decreasing its adduction gain to make the VOR symmetrical in that eye, while leaving the VOR in the nonparetic eye intact. This is apparently the strategy that the brain uses to adapt to unilateral abduction palsy.

Orbital Mechanics and VOR Adaptation. Changes in normal orbital plant mechanics may contribute to the decreased VOR gains during adduction in the paretic eye. The relative contribution of agonist contraction and antagonist relaxation varies with orbital position,[32] and it may be altered when one muscle of an agonist–antagonist pair is palsied. In paralytic strabismus, "contracture" (shortening and increased stiffness) occurs in the nonparetic antagonist muscle,[33–36] whereas the paretic muscle lengthens in response to a change in orbital position of the globe. Anatomic and histologic study[37] show that shortening or contracture of the nonparetic antagonist is associated with a decrease in the number of sarcomeres, whereas lengthening of the paretic muscle is accompanied by an increase in sarcomeres.[37] In addition, denervation atrophy in the paretic muscle and changes in orbital tissues have been documented in paralytic strabismus.[38,39]

If the reduction in VOR gains in both directions were due to changes in extraocular muscle mechanics, one would predict that VOR gains would remain the same during rotation in darkness or in light and that the peak velocities of nystagmus quick phases would be reduced in each direction. However, our results indicate that although abducting and adducting VOR gains were decreased, they increased immediately to normal levels in light during the VVOR. In addition, although VOR gains were reduced in each direction and although abducting quick phase peak velocities in the paretic eye were reduced, adducting quick phase peak velocities in the paretic eye were normal. Our results provide evidence that the bidirectional decrease in VOR gains in sixth nerve palsy is not merely the result of changes in mechanical properties of the orbital plant, but is due to a functional adaptation to the palsy.

Proprioception and VOR Adaptation. Proprioceptive signals from extraocular muscles may contribute to VOR adaptation. When, during sinusoidal head rotation, the movement of one eye is limited by an opaque suction contact lens (the artificial vestibulo-ocular reflex technique), so that the imposed eye's velocity is slower than the head's velocity, VOR gains in the other eye increase immediately.[40–42] Sectioning of the ophthalmic branch of the trigeminal nerve, which carries proprioceptive signals to the trigeminal nucleus, abolishes this velocity-dependent effect on VOR gains from imposed eye movements.[43–45] In our patients, horizontal VOR gains of the paretic eye were reduced in both directions, whereas gains of the nonparetic eye remained normal. Why, then, did we not observe similar effects as in those observed in artificial VOR experiments? Proprioceptive signals may be defective after peripheral nerve palsy. Although proprioceptive signals are generally thought to project through the ophthalmic branch of the trigeminal nerve to the spinal trigeminal nucleus, a portion may also travel to the trigeminal nucleus through the ocular motor nerves.[46] In addition, effects of muscle palsy differ from the effects of imposed movement of one eye. The paretic muscle is slack, whereas the muscle of an eye with imposed movement is taut. Furthermore, artificial VOR elicited by passive eye motion confers no functional advantage. Diplopia and oscillopsia would result from motion of the fellow eye. Visual signals play a more dominant role than proprioceptive signals in the control of VOR, with or without peripheral nerve palsy.

Visually Enhanced Horizontal VOR. In darkness, the VOR functions poorly with a gain below one during passive head rotation at frequencies below 1 Hz. Vision enhances VOR gain to unity. VOR enhancement is a function of optokinetic system at very low frequencies.[47] At frequencies below 1 to 2 Hz, smooth pursuit appears to be responsible for gain enhancement. The fixation system may also contribute to visual enhancement of the VOR.[48–50]

We found that patients with mild and moderate palsy had normal horizontal VVOR gains in both eyes (Figs. 2B, 2C). This visual enhancement of VOR in the paretic eye could be the result of contributions from the smooth pursuit or fixation system at the frequencies tested. In addition, visual input enhances the response of the viewing paretic eye without inappropriately raising that of the occluded nonparetic eye, pro-

viding further evidence of monocular adjustment. However, like those of another patient,[4] VVOR gains in all our patients with severe palsy were below normal in the paretic eye, regardless of which eye was viewing, and above normal in the nonparetic eye when the paretic eye was viewing (Fig. 2A). In severe palsy, monocular adjustment is inadequate and the brain increases innervation conjugately to the two eyes. The increased innervation boosts the gain in the nonparetic eye to well above unity when the paretic eye is viewing, whereas gain of the paretic eye remains low in the face of severe weakness of the lateral rectus. To adopt a conventional term from strabismology, this constitutes a secondary deviation of the VOR.

Monocular Adaptation in Unilateral Sixth-Nerve Palsy. Hering[51] suggested that the brain circuitry controlling eye movements consists of two systems: one for conjugate movements and the other for vergence. Conjugate control typically operates the vestibulo-ocular, saccade, smooth pursuit, and optokinetic systems. Premotor neurons encode common signals to both abducens motoneurons and internuclear neurons in the abducens nucleus.[52–54] The abducens motoneurons innervate the ipsilateral lateral rectus, whereas axons of the internuclear neurons cross the midline and ascend within the medial longitudinal fasciculus to innervate the medial rectus motoneurons in the contralateral oculomotor nucleus.[55–57] Thus, conjugate commands are conveyed to both the ipsilateral lateral rectus and the contralateral medial rectus muscles.

Because the neuronal connectivity appears to be conjugate, it had been assumed that only conjugate plasticity is possible. However, experiments in primates have shown that the ocular motor systems are capable of selective monocular adaptation.[2,3,58] For example, in monkeys, surgical weakening of the horizontal recti muscles of one eye causes an adaptation that selectively increases saccadic and VOR gains in the affected eye, whereas those of the unaffected eye remain normal.[2,3] Disconjugate ocular motor adaptation has also been demonstrated in normal humans[59,60] and monkeys[10] in response to optical devices, such as anisometropic spectacles and prisms. Disconjugate saccades and pursuit are generated to compensate for the disparate retinal errors produced by the optical device.[59,60]

To our knowledge, this study is the first to demonstrate monocular adaptation of the VOR to palsy in one direction in a series of patients with peripheral neuromuscular deficits. We found that horizontal VOR gains are selectively decreased during adduction of the paretic eye, and that VVOR gains are selectively increased in the paretic eye in mild and moderate palsy, without a conjugate increase in VVOR gains of the nonparetic eye. Retinal slip difference in the two eyes is the stimulus that drives the monocular adaptation that we have identified.

Monocular adaptation may occur at the level of motoneurons, although they receive only sparse direct projections from the cerebellum, which is thought to mediate such adaptive changes.[61] Another possibility is that supranuclear neural circuitry may not be purely conjugate. For example, for saccades, different populations of burst neurons mediate a pulse of innervation to each eye. In monkeys,[62] 79% of premotor excitatory burst neurons in the caudal pontine paramedian reticular formation that were thought to encode conjugate velocity commands for saccades,[52–54] actually encode monocular commands for either the ipsilateral or contralateral eye. Similarly, different populations of vestibular neurons provide innervation to the horizontal muscles of each eye. In addition to a major excitatory horizontal VOR pathway that mediates conjugate eye movements through the contralateral abducens nucleus and internuclear neurons, there is a second direct excitatory horizontal VOR pathway. This second pathway originates from the ventral lateral vestibular nucleus and ascends through the ascending tract of Deiters to the ipsilateral medial rectus subdivision of the oculomotor nucleus.[63,64] The selective change of innervation to the medial rectus muscle of the paretic eye in our patients during VOR may be through modulation of this second pathway.

The cerebellum plays important roles in adaptive control of saccades[65–68] and the VOR,[66,69–72] including disconjugate control.[73–75] Experimental inactivation of the deep cerebellar nuclei (including the fastigial nucleus) causes disconjugate saccadic dysmetria, so that both saccade magnitude and peak velocity differ in the two eyes.[73] Patients with cerebellar dysfunction also show disconjugate dysmetria during and immediately after saccades.[74] The flocculus regulates conjugate VOR responses, and unilateral lesions of the rabbit flocculus cause different VOR gain changes in the two eyes.[75] Thus the cerebellum exerts selective, monocular control and may participate in the adaptation that we have identified.

Vertical VOR

In the straight-ahead position, the lateral rectus acts as a pure abductor, with no vertical or torsional actions.[76,77] When the eye is in an elevated position, the lateral rectus may have a secondary component of elevation. Similarly, when the eye is depressed, it may have a secondary component of depression.[77–79] Whether the eye is in an adducted or abducted position, no additional vertical or torsional components of lateral rectus actions have been observed. Vertical VOR and VVOR mean gains in our patients were normal, upward, and downward, through a 20° range across the orbital midposition.

Torsional VOR

Dynamic and static torsional VOR and VVOR gains, by contrast, were reduced in all patients during rotation in light and in darkness. Other investigators have reported abnormal dynamic torsional VOR gain in patients with skew deviation (three patients having increased and one having decreased gain), spasmodic torticollis (one increased and two decreased) and eighth-nerve palsy (two decreased).[80] These patients also had abnormal static torsional VOR gain. One patient with skew deviation had increased gains and another had decreased gains, one with spasmodic torticollis had increased gain, and another with eighth nerve palsy had decreased gain.[80]

What is the mechanism of the reduced torsional gains in sixth nerve palsy? During dynamic head roll, compensatory eye movements are generated by torsional VOR, which is mediated predominantly by the vertical semicircular canals.[81–84] The dynamic torsional VOR has a lower gain than its horizontal or vertical counterparts, typically ranging from 0.4 to 0.7, depending on the frequency of head roll.[85–90] Static head roll evokes compensatory changes in torsional eye position, which are mediated by the otolith-ocular reflex from inputs of the utricles.[91] Static torsional VOR has a lower gain than its dynamic counterpart, ranging from 0.10 to 0.24, depending on target distance.[80,85,86]

Dynamic and static torsional VOR gains are lower when viewing a near target.[80,85,92,93] This behavior contrasts with that of the horizontal and vertical VOR gains, which increase when viewing a near object.[94] One study found a median dynamic torsional VOR gain of 0.82 during distance (7.2 m) viewing and 0.74 during near (20 cm) viewing.[80] Median static torsional VOR gain was 0.24 during distance viewing and 0.18 during near viewing.[80] In our study of normal subjects, we used a target at 1 m and observed a dynamic torsional VOR gain of 0.58 and static torsional VOR gain of 0.21, consistent with reported values.[80,85]

It makes functional sense to reduce torsional VOR gain during near viewing.[92,95] To see why, recall that torsional eye

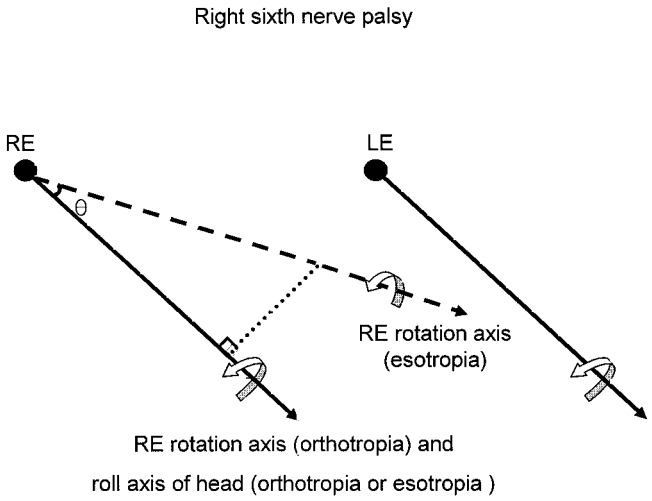

FIGURE 5. Changes in torsional VOR gain in orthotropia and esotropia. During roll of the head about its naso-occipital axis while the subject fixates a target at infinity, prevention of slippage of extrafoveal retinal images requires the eyes to rotate around their visual axes (*solid arrows*), which are parallel to the roll axis of the head. In sixth nerve palsy, the esotropic eye rotates around its visual axis (*dashed arrow*) subtending an angle θ with the roll axis of the head. The effective component of eye rotation around the roll axis of the head varies as a function of cos θ; as the eye deviates nasally (angle θ increases), cos θ decreases, so that the component of eye torsion around the roll axis of the head also decreases. Thus, both the dynamic and static torsional VOR gains decrease in esotropia. RE, right eye; LE, left eye.

rotation is defined to be rotation about the naso-occipital axis. When one looks into the distance, the lines of sight are roughly parallel with that axis, and the torsional VOR therefore does not affect the gaze direction; it merely turns the eyes around their own sight lines, reducing torsional image slip on the retinas. But when the lines of sight converge on a near target, they may no longer align with the naso-occipital axis, and now, therefore, the torsional VOR moves the sight lines, disrupting binocular convergence. The best solution is to reduce torsional VOR gain when the eyes converge.[92,95] In sixth nerve palsy, the esotropia of the paretic eye brings its line of sight out of alignment with the naso-occipital axis, just as normal vergence does (Fig. 5). The low torsional gains we found in the paretic eye may arise from the same mechanism that normally lowers torsional gain during convergence. The low torsional gains in the nonparetic eye may be an adaptation to equalize the gains in the two eyes to reduce torsional disparity of retinal images.

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