

The effects of hyperventilation on postural control mechanisms

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Summary

The effect of hyperventilation on postural balance was investigated. Voluntary hyperventilation increased body sway in normal subjects, particularly in the sagittal plane. The possibility that this hyperventilation-induced unsteadiness is due to interference with lower limb somatosensory input, vestibular reflexes or cerebellar function was assessed. (i) The effect of hyperventilation on peripheral compound sensory action potentials (SAPs) and somatosensory evoked potentials (SEPs) (recorded centrally, from the scalp) elicited by electrical stimulation of the sural nerve was measured in six normal adults. A reduction in the scalp SEP amplitude and an increase in the peripheral SAP amplitude were observed during hyperventilation, which reversed during the recovery period. These changes indicate increased peripheral neural excitability which could lead to a higher level of ectopic activity; the latter would interfere with central reception of peripheral input. (ii) The click-evoked vestibulo-collic reflex was recorded to study the effect of hyperventilation on vestibulo-spinal activity. EMG recordings from both sternocleidomastoid muscles of six healthy subjects were

made in response to loud clicks presented to either ear. Neither the amplitude nor the latency of the response were altered significantly by hyperventilation. (iii) Eye-movement recordings were obtained in the six normal subjects to assess the effect of hyperventilation on the vestibulo-ocular reflex and its visual suppression, the latter being a function largely mediated by the cerebellum; no changes were detected. (iv) Three-dimensional eye-movement recordings and body-sway measurements were obtained in six patients with long-standing unilateral vestibular loss in order to evaluate if hyperventilation disrupts vestibular compensation. In all patients, a horizontal nystagmus either appeared or was significantly enhanced for ≥ 60 s after voluntary hyperventilation. Sway was also enhanced by hyperventilation in these patients, particularly in the frontal plane. This study suggests that hyperventilation disrupts mechanisms mediating vestibular compensation. The increase in sway may be, at least partly, mediated by deranged peripheral and central somatosensory signals from the lower limbs. Hyperventilation seems to spare vestibular reflex activity and cerebellar-mediated eye movements.

Keywords: posture; dizziness; hyperventilation; vestibular; somatosensory

Abbreviations: ANOVA = analysis of variance; SAP = sensory action potential; SEP = somatosensory evoked potential; VOR = vestibulo-ocular reflex

Introduction

Hyperventilation is ventilation in excess of metabolic needs. It can occur when subjects face stressful situations but it is often encountered as part of panic or anxiety syndromes (Lum, 1976). In the neurological context, clinicians suspect hyperventilation when patients report balance symptoms, dizziness, and distal and perioral paraesthesias, in the absence of organic findings (Evans, 1995). In some studies,

hyperventilation is listed as one of the most frequent diagnoses in 'dizzy' patients (Drachman and Hart, 1972; Hanson, 1989; Colledge *et al.*, 1996).

Recently, we investigated whether hyperventilation induces objective postural changes and found that forced, voluntary hyperventilation increases body sway in normal subjects (Sakellari and Bronstein, 1997). Furthermore, a group of

patients with bilateral absence of vestibular function showed a comparable enhancement of sway after hyperventilation. Since such patients do not have functioning vestibulo-spinal pathways, the findings suggested that the mechanism mediating this sway increase is extra-vestibular.

However, the mechanisms responsible for the appearance of hyperventilation-induced symptoms are not clear. That hyperventilation influences CNS activity has been known for decades, e.g. hyperventilation is one of the most widely used methods for EEG activation (Gotoh *et al.*, 1965; Patel and Mulsby, 1987). The presence of paraesthesiae and clinically visible muscular spasms suggests that neuro-muscular hyperexcitability is involved, and some evidence for this has been found in peripheral nerve-EMG studies of the upper limb (Macefield and Burke, 1991). The relevance of these findings to the question of hyperventilation-induced unsteadiness is not immediately apparent and we therefore decided to look at several mechanisms involved in balance control to see if they were impaired by voluntary hyperventilation.

First we report on the effects of hyperventilation on postural stability in a larger sample of normal subjects than that described in our first study. In subsequent sections we address the question of which neurological mechanisms could mediate the effects of hyperventilation on postural control. We attempted to determine whether hyperventilation interferes with somatosensory information from the lower limbs by investigating peripheral sensory action potentials (SAPs) and somatosensory evoked potentials (SEPs) recorded from the scalp. The effects of hyperventilation on vestibular function was investigated with measurements of the vestibulo-ocular reflex (VOR) and click-evoked, vestibulo-colic responses. Ocular-motor performance, particularly VOR suppression and smooth pursuit, are heavily dependent on the cerebellar flocculus; accordingly we quantified these eye movements before and after hyperventilation. Finally, as a way of assessing the effects of hyperventilation on the process of recovery from a vestibular lesion, patients with unilateral peripheral vestibular lesions were investigated with oculography and posturography.

Material and methods

Subjects

All the patients and normal volunteer subjects tested in the following experiments gave informed consent to participate. The study was approved by the Ethical Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology, London.

Carbon dioxide measurements

The transcutaneous partial pressure of carbon dioxide ($p\text{CO}_2$) was used as a measure of hyperventilation in sway and somatosensory evoked-potential experiments, as it correlates

closely with CO_2 measurements in capillary blood samples (Severinghaus *et al.*, 1978; Wimberley *et al.*, 1985). A self-adhesive, heated (44°C) membrane electrode (Radiometer Copenhagen, type TCM3) was attached to the skin on the inner side of the forearm ~3 cm below the elbow. The membrane was allowed to stabilize for ≥ 15 min before recordings were obtained. The electrode was calibrated before each experiment, using a Corning Calibration Cylinder (Radiometer Copenhagen, type TCC3).

Experimental strategy

In order to overcome artefacts produced by movement during hyperventilation, all neurophysiological recordings were obtained immediately after subjects hyperventilated for periods of specified duration. The respiration rate was self-paced, emphasis being placed on depth rather than on frequency in order to produce effective hyperventilation. With the above instructions an average of ~40 breaths per minute was obtained. Attempts to use a sound-paced breathing rate proved distracting and difficult to maintain during the whole hyperventilation period. At specified time intervals (*see below*), the experimenter asked subjects to stop hyperventilation and breathe normally. Recordings would then start at this point; the subjects were instructed to remain as still as possible. The results from this and pilot studies show that hyperventilation has effects for up to 2–5 min after the end of hyperventilation.

Postural sway

The subjects stood bare-foot on the platform. The feet were placed on marks symmetrically drawn at an angle of $\sim 30^\circ$, with heels 2.5 cm apart. They were instructed to hyperventilate whilst on the platform. Immediately after the hyperventilation had stopped, recordings of 30-s duration each were taken. The subjects kept their eyes open whilst hyperventilating but were asked to close them during the recording. Baseline recordings without hyperventilation were also obtained. Inter-recording intervals were 5–6 min.

Sway was measured indirectly by recording the movement of the centre of foot pressure with a force measuring platform [model OR6–3; AMTI, Watertown, Mass., USA], linked to a PC (sampling rate 20 Hz). The following sway parameters were used: X_m and Y_m = mean sway deviation (cm) from the mean position in the lateral (X , frontal) and anterior–posterior (Y , sagittal) directions; Vel = the combined (X , Y) distance travelled by the centre of foot pressure during the recording time, divided by the recording time (cm/s); A_o = area within the projected trajectories of centre of pressure (cm^2).

Data were collected for 17 normal subjects (10 female), mean age 37 years, range 21–67 years, after 30 s of hyperventilation.

Recording peripheral SAPs and scalp SEPs evoked by sural nerve stimulation

Scalp SEPs and peripheral compound SAPs were recorded using an electro-diagnostic recording system (Nihon Kohden Neuropack 4 Mini, Model MEB-5304K). The test stimuli were delivered to the right sural nerve; the subsequent changes in peripheral SAPs and scalp SEPs were recorded simultaneously. Recordings were performed during runs of 50 stimuli, one every minute. The duration of each run was ~20 s, and for the first six runs the subjects were allowed to relax for the rest of the minute (baseline condition). The subjects then hyperventilated for 1 min and a further six runs were recorded during which, after each recording period of ~20 s (without hyperventilation), the subjects hyperventilated for the remaining 40 s of the minute. This procedure, for measuring the effect of hyperventilation, was adopted on the grounds that 50 sweeps is about the minimum number necessary to record an average scalp SEP without undue noise contamination (also noise would have been excessive if the SEPs had been recorded during hyperventilation). In this second set of recording sessions, the subjects would not have recovered fully from hyperventilation at the end of each 20 s pause, so the effects of further hyperventilation would have been cumulative. Finally, 18 further recordings at 1-min intervals were made at the end of the hyperventilation to monitor the recovery of any changes induced by hyperventilation on these evoked potentials.

Six healthy volunteers, three male and three female (mean age 26 years, range 22–32 years) participated in the study. The subjects were seated in a comfortable armchair in a normally heated room and encouraged to remain relaxed. After cleaning the skin around the foot and ankle with alcohol the negative recording electrode was placed 3 cm distal to the lateral malleolus and the positive 3 cm distal to the negative one, parallel to the sole of the foot. The ground electrode was ~10 cm proximal to the lateral malleolus. The cathode of the stimulating electrode was on the belly of gastrocnemius muscle ~5 cm proximal to the ground electrode, adjusted to be close to the sural nerve, as identified by its typical electrically-evoked paraesthesia and action potential. This montage allowed the antidromically-conducted peripheral SAP to be recorded.

Cortical SEP waveforms were obtained simultaneously from the scalp. The recording electrodes were placed as follows: one 2 cm posterior to the vertex and the other two 7 cm lateral from each side of the vertex, 2 cm posterior to the line connecting the vertex and external auditory meatus foramen. The reference electrode for the three scalp sites was located 12 cm above the nasion, over the frontal cortex. Silver disc electrodes were attached with 'Elefix', after skin impedance had been reduced to <5 k Ω by mild scarification with 'Skinpure'.

The sural nerve was stimulated with square wave, constant current impulses of 0.2-ms duration, frequency 3 Hz. Stimulus intensity was adjusted to three times the subjective sensory

threshold. The mean intensity used was 12 mA; for the six individual subjects the intensities were 16.4, 9, 9.6, 9.6, 14.4 and 13 mA. The average sampling rate for the scalp SEPs was 5.12 points/ms and the peripheral SAPs 51.2 points/ms. Bandpass filters were set between 1 Hz and 3 kHz for the scalp SEP signals and between 20 Hz and 3 kHz for peripheral SAPs.

Analysis

The amplitude of the peripheral SAP was measured from the peak of the initial positivity to the peak of the negative phase. The positive peak latency of the peripheral SAP was measured from stimulus onset, and the rise-time of the negative peak was measured from the initial positivity. The amplitude and latency of the cortical SEP were measured at the midline electrode 2 cm posterior to the vertex. Latencies were measured from the stimulus to the peak of the initial positivity (P40) and also to the following negative peak (N50). P40 amplitude was measured between the onset and the peak of the positivity. The amplitude of the N50 component was measured from the peak of P40.

The peripheral SAP and scalp SEP for each subject obtained during each block of 50 stimuli were measured and then averaged across the six subjects. Within each section of the experiment (i.e. baseline, hyperventilation and recovery phases 1–3) this grouping of the data provides five sets of across-subjects averages (see Fig. 2). A two-way analysis of variance (ANOVA; parameter by subject and hyperventilation period) followed by multiple comparisons where significant differences were observed was carried out; $P < 0.01$ was considered significant.

Click-evoked vestibulocollic reflex

Six normal subjects (three female), mean age 27 years, range 24–30 years, participated in the experiment. During the experiment the subjects were lying comfortably in an armchair (backrest–seat angle 170°) in a quiet room. Two surface silver/silver chloride EMG electrodes were placed in symmetrical sites over the middle and two over the lower part of each sternocleidomastoid muscles. The reference electrode was placed over the upper sternum. EMG signals were bandpass filtered between 30 Hz to 3 kHz.

Two blocks of 125 clicks each, were presented at a rate of 3 Hz to one ear via headphones, and responses averaged for each condition (i.e. for the baseline and then under the influence of hyperventilation). For the latter condition, the two blocks were presented one immediately after 60 s of hyperventilation and the other after an additional 30 s of hyperventilation. For the baseline condition the second block was also presented 30 s after the first one. The clicks were rarefactive square waves of 0.1-ms duration, generated by an ST10 stimulator. A stimulus intensity 95 dB HL was always used, as cross-indicated by a sound level meter (type D-1422C, RS).

Since the background muscle activity exerts a strong influence on reflex amplitudes (Bloem *et al.*, 1993) the subjects were asked to hold their heads slightly raised to achieve a standard level of background contraction. Feedback of the rectified EMG activity was displayed to the subjects on an oscilloscope screen. The target level of EMG activity set for the duration of each average was $\sim 100 \mu\text{V}$. The amplified and bandpass filtered EMG recordings were averaged using a sampling rate of 5 kHz from 20 ms before the clicks to 80 ms afterwards. Further technical details can be found in Colebatch *et al.* (1994).

VOR, visual suppression of the VOR and ocular smooth pursuit

A pilot study on three normal subjects (one female), ages 25–37 years, involving repeated calibrations before and after hyperventilation, ensured that the linearity of the EOG (electro-oculogram) and the size of the EOG signal was not affected by hyperventilation (e.g. through changes in the corneo-retinal potential).

For the main study, six healthy subjects were examined (mean age 27 years, range 22–30 years). They were seated in a computer controlled rotating chair, fitted with a chin rest, in a dark room. Technical difficulties (chair motion and darkness) did not allow for simultaneous transcutaneous pCO_2 recording. Horizontal eye movements were digitally recorded at 250 Hz by both EOG (bitemporal recordings) and infra-red oculography ('IRIS', Skalar, Delft) and were later edited to exclude saccades and artifacts. Calibrations were made before and after each experimental condition. Eye velocity was measured by digital differentiation using interactive software and results expressed as gain (peak slow-phase eye velocity/peak stimulus velocity).

Since both pursuit performance and VOR suppression decay as a function of stimulus frequency, a frequency of 0.6 Hz was used in order to increase the difficulty of the task and to allow a possible effect of hyperventilation to be detected. Six testing conditions were employed. (i) VOR baseline-responses to sinusoidal rotation of the experimental chair in the dark at a frequency of 0.6 Hz and peak velocity of $80^\circ/\text{s}$. (ii) Repetition of the VOR recording immediately after 60 s of hyperventilation. (iii) Baseline recording of VOR suppression. The subjects were instructed to maintain fixation on a red light dot attached to the chair, 70 cm in front of the their eyes (chair-fixed target). Chair movement was exactly the same as in VOR testing. (iv) Recording VOR suppression after 60 s of hyperventilation [as in (iii)]. (v) Smooth-pursuit baseline recording. The subjects were instructed to track a computer-controlled red-laser dot, moving sinusoidally at 0.6 Hz, peak velocity $74^\circ/\text{s}$, as accurately as possible. (vi) Smooth pursuit recording after 60 s of hyperventilation.

Body sway and spontaneous nystagmus in patients with unilateral vestibular lesions

Six patients with unilateral peripheral lesions (four female), mean age 57 years, range 49–68 years were tested. Three of them had undergone vestibular neurectomies for treatment of refractory vertigo (2.5, 3 and 12 months before testing), three had long-standing unilateral absence of nystagmic response (canal paresis) to irrigation at 30 and 44°C (one from presumed viral labyrinthitis, one from unilateral Meniere's disease and one a probable Herpes zoster cochleo-vestibular neuritis). Two groups of normal subjects were used as controls for the video-oculography (eye-movement) recordings, a group of six subjects (four females and two males; mean age 28 years, range 22–42 years) and a group of six older subjects (two females, four males; mean age 54 years, range 47–59 years).

Postural sway and eye-movement recordings were obtained independently. Body-sway recordings (two repetitions each) were performed before and after 30 and 60 s of hyperventilation, always with eyes closed, as described above for normal subjects. Binocular eye movements were recorded using computerized, three dimensional video-oculography (SMI, Berlin). The subjects were seated on the edge of a couch, with the head placed on a chin-rest. They wore a diving mask which had an infra-red video camera mounted over one eye. The video images were processed at a sampling rate of 50 Hz for horizontal and vertical, and 25 Hz for torsional, components of the eye movement. Recordings were obtained with the subjects looking straight ahead in the light and dark before hyperventilation, and in the dark after 60 s of hyperventilation. Calibration of eye movement was performed using targets placed at 5° up-down-left-right. Average slow phase eye velocity of nystagmus was calculated every 10 s by digitally differentiating eye position. Direct observation of the high quality video images, visual inspection of the eye recording traces as well as slow phase velocity measurements of representative beats of nystagmus was undertaken to ascertain that computer processing was reliable.

Results

Body sway after hyperventilation

The values of transcutaneous CO_2 in this experiment dropped from (mean \pm SD) 4.8 ± 0.6 to 3.8 ± 0.6 kPa after 30 s of hyperventilation (a mean decrease of 21%) and from 4.8 ± 0.6 to 3.3 ± 0.6 kPa after 60 s of hyperventilation (mean reduction of 31%).

Figure 1 shows the sway data with eyes closed for the 17 normal subjects tested after 30 s of hyperventilation. The shaded area shows the increase in sway after hyperventilation. It can be seen that the main increase in sway is reflected in parameters Y_m (mean sagittal sway deviation; ANOVA, $F = 11.91$, $P < 0.01$) and A_o (sway area; ANOVA, $F = 9.28$, $P < 0.01$). Sway parameters

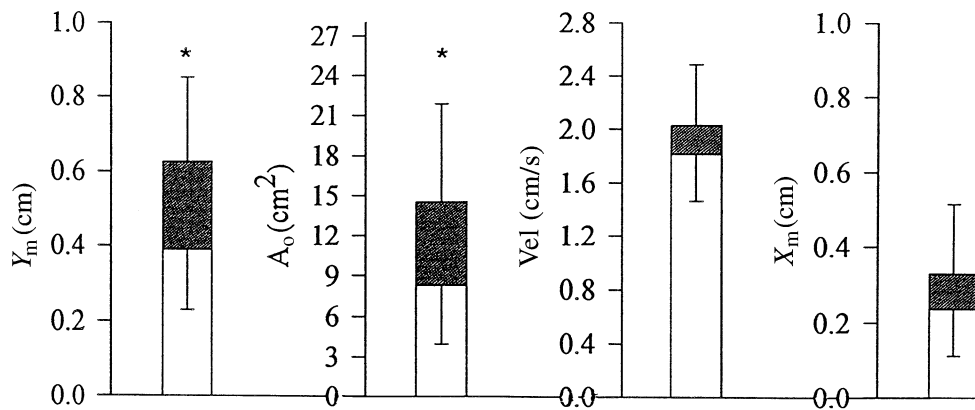


Fig. 1 Postural sway with eyes closed in 17 normal subjects before and after forced, voluntary hyperventilation for 30 s. The shaded area indicates the increase after hyperventilation. Means and SDs are shown; asterisks indicate statistically significant differences ($P < 0.01$).

X_m (mean lateral deviation) and Vel [mean (X , Y) combined velocity] increased by a smaller amount and the difference did not quite reach statistical significance.

Evoked potentials (peripheral SAP and scalp SEP) and hyperventilation

In the somatosensory experiments, after the hyperventilation, pCO_2 decreased from a mean (\pm SD) of 4.7 ± 0.6 to 2.3 ± 0.4 kPa, i.e. an average drop of 51% (Fig. 2).

Figure 3 (top) shows the peripheral SAP amplitude data for the baseline, hyperventilation and recovery periods. It can be seen that, even from the first minute of hyperventilation, the amplitude of the potential was increased above the baseline level, remaining at similar levels for the rest of the hyperventilation period. The peripheral SAP increased on average 7% during the hyperventilation phase; this increase dropped to 4% during the initial recovery phase ('Rec 1', Fig. 3). The effect of hyperventilation on the amplitude of the peripheral SAP was statistically significant (ANOVA, $F = 26.46$, $P < 0.0001$); *post hoc* comparisons between the period of hyperventilation and baseline ($t = 6.46$, $P < 0.0001$), and between baseline and the initial period of recovery post-hyperventilation ($t = 3.35$, $P < 0.01$) were also significant.

The data from the scalp recordings are presented in Fig. 3 (bottom), which shows the P40 amplitude changes throughout the experiment. During hyperventilation it was depressed by ~20% compared with the baseline, and during the first recovery period by a mean of 22%. These effects were statistically significant (ANOVA, $F = 4.63$, $P < 0.001$). *Post hoc* comparisons indicated that there was a significant difference in P40 amplitude between hyperventilation and baseline periods ($t = 3.44$, $P < 0.001$) and between 'Recovery 1' and baseline ($t = 3.84$, $P < 0.001$).

The onset and the peak P40 mean latencies (\pm SD) were 32.8 ± 2.6 and 39.8 ± 2.8 ms, respectively, showing no significant change throughout. The latency of N50 (mean 50.3 ± 2.6 ms) and the peak-to-peak amplitude (mean $4 \pm$

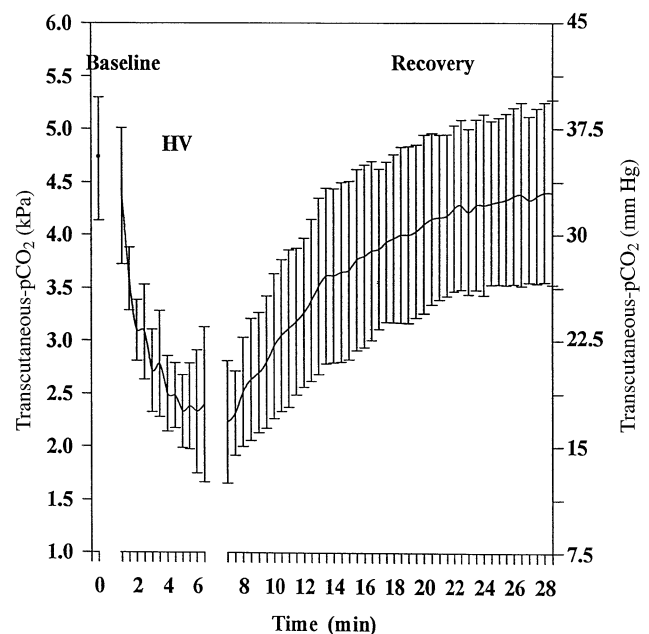


Fig. 2 Transcutaneous CO_2 changes (mean and SD) in six normal subjects during hyperventilation (HV) and during the recovery from hyperventilation, in kPa (left) and mmHg (right). The corresponding changes in peripheral SAPs and scalp SEPs in these subjects are shown in Fig. 3.

$2 \mu V$) were also not altered significantly at any time. For the compound action potentials the positive peak latency and the negative peak rise time for the peripheral SAP were, respectively, 4.5 ± 0.6 and 3.7 ± 0.58 ms; these were also not altered significantly. Latencies of the peripheral SAP were slightly but gradually increased as the testing session progressed, including the recovery period, presumably as a result of progressive cooling of the lower limb.

Vestibulo-colic responses and hyperventilation

Figure 4 shows a typical result from a normal subject during recordings of click-evoked cervical EMG potentials.

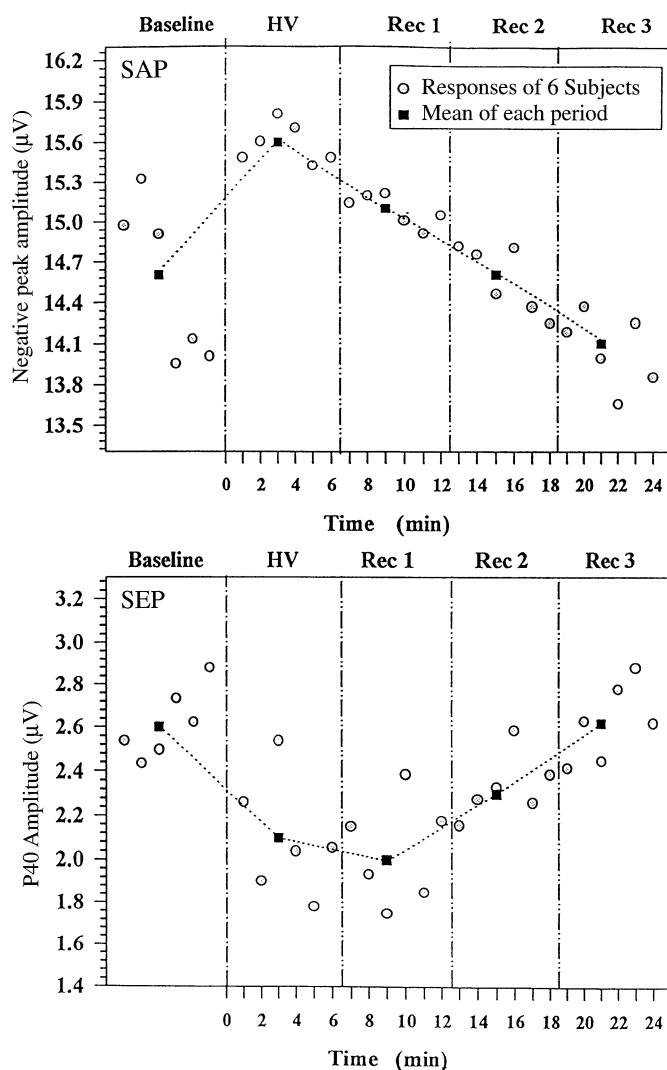


Fig. 3 Amplitude of the peripheral compound SAP (*upper panel*) and scalp SEP (*lower panel*) in six normal subjects before (baseline), during and after hyperventilation. See corresponding changes in CO_2 in Fig. 2.

A response is recorded from the left sternocleidomastoid muscle 8.6 ms after presenting the click stimulus to the left ear; the response consisted of a positive potential peak at 13.1 ms followed by a negative peak at 20 ms, and the peak-to-peak amplitude was 167 μV . The second wave, also seen on the right, is an acoustic response to the click (n34–p44) and the rest is unlikely to be of labyrinthine origin (Colebatch *et al.*, 1994). The response obtained under the influence of hyperventilation was very similar (Fig. 4, dotted line).

The average latency (\pm SD) of the vestibular response in the ipsilateral muscle before and after hyperventilation was 7.6 ± 1.1 and 7.5 ± 1.0 ms, respectively. The p13–n23 wave was always present. As expected (Colebatch *et al.*, 1994) no vestibular response was recorded in the contralateral sternocleidomastoid muscle.

The average level (\pm SD) of background muscle activity before and after hyperventilation was 100 ± 10 and $107 \pm$

15 μV , respectively. To confirm that this range of activity was not wide enough to influence the amplitude of the response, a regression analysis between the peak-to-peak amplitude of the p13–n23 response and the tonic muscle activity was made. No correlation was found. This enabled application of a Wilcoxon test to assess the significance of the difference in mean p13–n23 amplitude (\pm SD) before ($188 \pm 52 \mu\text{V}$) and after ($174 \pm 48.5 \mu\text{V}$) hyperventilation. Figure 5 shows the data for the individual subjects; there was no statistically significant change after hyperventilation ($P > 0.05$).

VOR, visual VOR suppression and pursuit

Reliable data were obtained from all six subjects tested. Five had good quality infra-red recordings and five good quality EOGs. Examples of raw data records of the eye movements elicited before and after hyperventilation by sinusoidal rotation in the dark with fixation on a target (VOR suppression), and without fixation (VOR), are shown in Fig. 6.

Figure 7 shows velocity gains before and after hyperventilation in five subjects (EOG acquisition). The mean VOR, VOR suppression and smooth pursuit gain (right and left combined) were not altered significantly after the 60 s of hyperventilation. Statistical analysis (Wilcoxon matched-pairs) did not reveal significant differences ($P > 0.05$).

Nystagmus and postural sway in patients with unilateral vestibular lesions

In these patients, the transcutaneous pCO_2 (mean \pm SD) decreased from 5.2 ± 0.6 to 4.2 ± 0.5 kPa (a mean reduction of 19%) after 30 s and to 4 ± 0.6 kPa after 60 s of hyperventilation (a mean reduction of 23%).

Eye-movement recordings

Figure 8 shows raw horizontal video-oculographic recordings from a patient with right vestibular neurectomy. A spontaneous nystagmus in the dark was just observable before hyperventilation (top recordings). After hyperventilation the nystagmus increased in amplitude, slow phase velocity and regularity.

Before hyperventilation, none of the patients had consistent nystagmus in the light. In the dark, horizontal beats of nystagmus of 0.5 – $2^\circ/\text{s}$ were present in three patients. A weak downbeat component was observed in the video-images in two patients. Torsional nystagmus was not clearly observed in any of the patients. Hyperventilation triggered the onset of nystagmus in three patients in whom it was not initially present and established regularly beating nystagmus in the three with spontaneous beats. In order to check if the effects of hyperventilation could have been due to increased alertness, two patients were asked to shake the head for 1–5 s before hyperventilating but in contrast to hyperventilation this

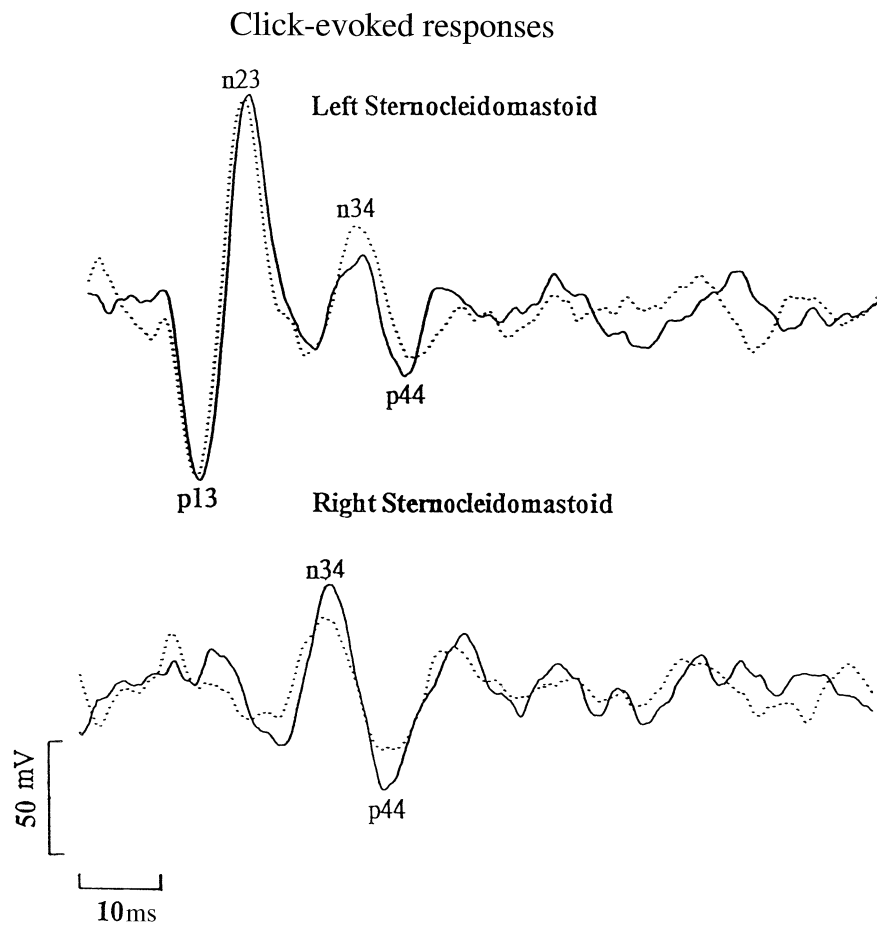


Fig. 4 Vestibulo-collic EMG potentials in response to clicks presented to the left ear in a normal subject before (continuous line, baseline response) and after (dotted line) hyperventilation. The vestibular waveforms (p13 and n23) are almost identical in the two conditions.

elicited no consistent nystagmus. Although the recordings obtained during the hyperventilation were not always of good quality (some patients were unable to maintain stable gaze or keep their eyes open) the increase in nystagmus was frequently observed before the end of the hyperventilation (Fig. 8).

The direction of beat of the spontaneous nystagmus (fast phase) was towards the healthy side in three patients. In two patients the direction of the nystagmus was reversed (towards the lesion side) and remained so after the hyperventilation. The latter two patients had neither vestibular nerve section nor severe hearing loss. Finally, in one of the patients with vestibular nerve section, the direction of the nystagmus reversed from beating towards the affected side (before hyperventilation in the dark) to beating towards the healthy side (after hyperventilation in the dark).

Figure 9 shows a 10-s average of the slow phase velocity of the vertical and horizontal components of the nystagmus in the dark of each individual patient before, and immediately after, the 60 s of hyperventilation.

The average horizontal slow phase velocity rose from 0.7 to 2.4°/s (Fig. 9). Unlike the horizontal nystagmus, vertical nystagmus was not consistently increased by hyperventilation

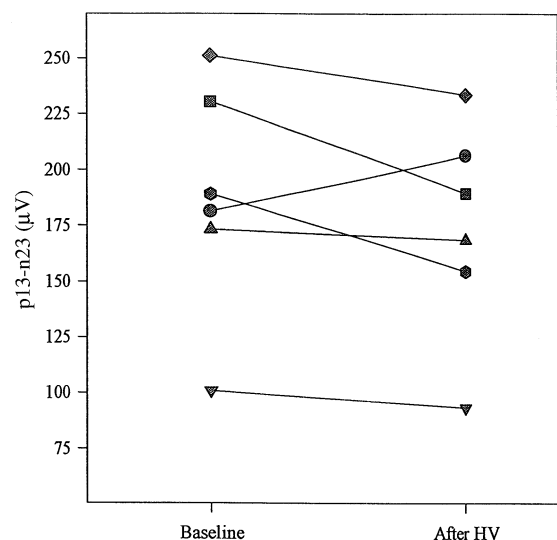


Fig. 5 Amplitude of click-evoked vestibulo-collic responses in six normal subjects before and after hyperventilation (HV). There were no statistically significant differences.

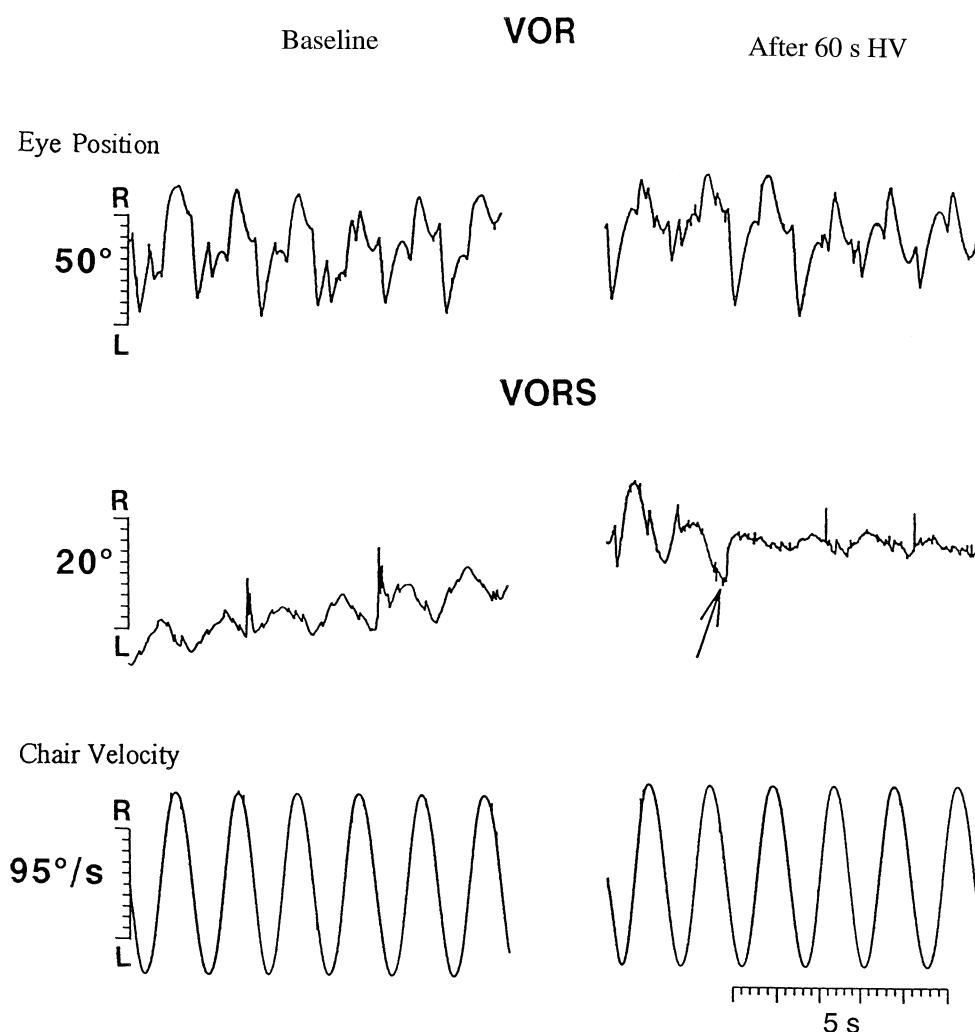


Fig. 6 Raw electro-oculogram (EOG) of the vestibulo-ocular reflex (VOR) and its visual suppression (VORS) in a normal subject, before and after 60 s of hyperventilation (HV). The arrow indicates the point at which the subject actually started suppressing the VOR by fixating the chair-fixed target.

(mean slow phase velocities 0.7 and 0.5°/s before and after hyperventilation, respectively). Torsional velocities were never consistently detected. A Wilcoxon test confirmed that while horizontal slow phase velocity increased significantly ($Z = 2.20$, $P = 0.02$), vertical velocities remained similar before and after hyperventilation ($Z = 0.40$, $P = 0.68$).

Figure 10 shows the average absolute increase in the slow phase velocity of the nystagmus immediately after hyperventilation (plotted against time after hyperventilation). It can be seen that, even 60 s after hyperventilation had stopped, nystagmus had retained 60% of its original increase in the patients. Figure 10 also incorporates similar measurements undertaken in the two groups of normal subjects. In the younger normal control group, the spontaneous eye velocity and the absolute increase induced by hyperventilation was smaller than in patients, and smaller than in the older control group. Inspection of video-images and raw eye recordings showed that hyperventilation could also induce, or enhance, nystagmus in normal subjects but that this

nystagmus was always short-lived. This is reflected in Fig. 10 by a rapid decline in slow phase velocity, so that at 30 s baseline values in both control groups were within 1 SD of the hyperventilation-induced nystagmus.

Postural-sway recordings

Figure 11 shows raw sway data before and after 60 s of hyperventilation showing increased sway, particularly in the lateral direction, after hyperventilation. Figure 12 shows the changes, in the individual patients, of the main sway parameters examined; the most consistent increase was in mean lateral sway.

Two-way ANOVA (sway parameter by subject and hyperventilation time) was used to analyse body sway. Hyperventilation was found to increase the lateral deviation significantly (X_m ; $F = 5.925$, $P = 0.011$), and the mean sway velocity only marginally (Vel; $F = 3.689$, $P = 0.045$) while it did not change the anterior-posterior deviation nor the

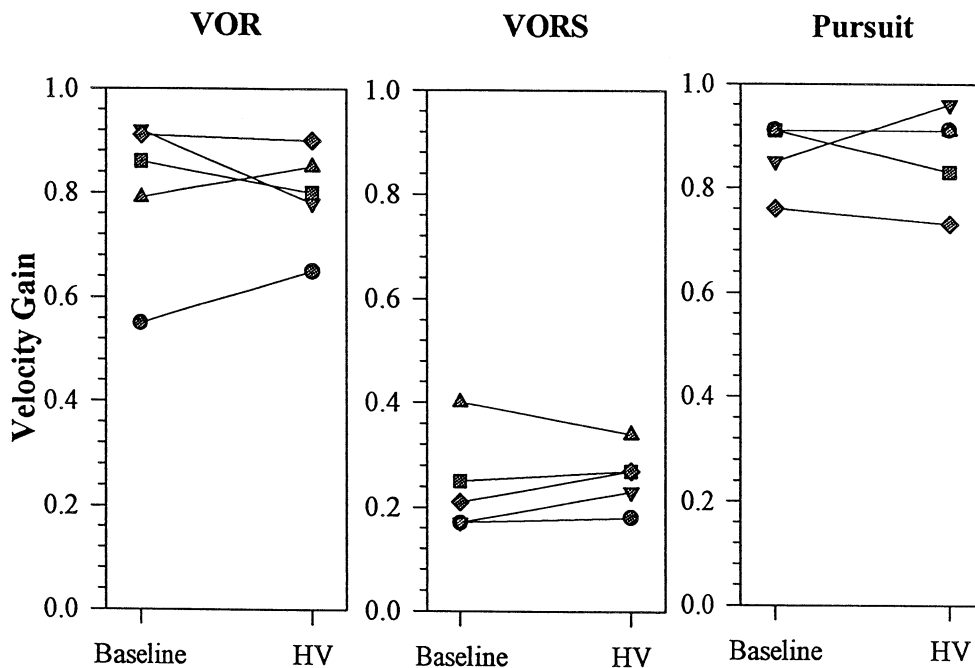


Fig. 7 EOG data [VOR, its suppression (VORS) and pursuit data], expressed as velocity gain, in five subjects before and after 60 s of hyperventilation (HV). No statistically significant differences were present.

sway area covered (Y_m and A_0 ; $F < 2.589$, $P > 0.1$). *Post hoc* multiple comparisons of the means showed that the increase in X_m reached significant levels only after 60 s of hyperventilation ($t = 2.24$, $P < 0.05$) and not after 30 s of hyperventilation ($t = 0.22$, $P > 0.1$). Thus, the mean X_m (\pm SD) before (0.22 ± 0.14 cm) and after (0.23 ± 0.11 cm) 30 s of hyperventilation remained at similar values, while after 60 s of hyperventilation it increased by ~45% (0.32 ± 0.21 cm). In spite of the finding that, in normal subjects, sway increased more in the sagittal than in the frontal plane, whereas the opposite was the case in unilateral vestibular patients, the overall effects of hyperventilation on body sway were not dissimilar in unilateral vestibular patients and in normal subjects (at 60 s of hyperventilation there were no statistically significant differences in any of the sway parameters: ANOVA, $F < 0.343$, $P > 0.1$).

Subjective observations

All subjects in this study reported that hyperventilation made them 'feel lightheaded', 'dizzy', 'hot' or 'faint'. The vestibular patients gave similar reports but a rotational sensation, like their own acute vertigo, did not reappear. During the somatosensory experiments, which involved longer hyperventilation, the normal subjects also had tingling sensations in different parts of the body and three had incipient signs of tetany.

Discussion

The finding of increased sway after voluntary hyperventilation extends our recent findings (Sakellari and Bronstein, 1997)

to a larger sample of subjects. The increase occurs mainly in the sagittal plane, with a smaller increase in the frontal plane. It is to be noted that the sway increase is not due to respiratory movements because sway recordings were always obtained after hyperventilation. Whether part of the enhancement in sway is due to cardiovascular effects of hyperventilation (Alexopoulos *et al.*, 1995) is difficult to ascertain but experiments with variable workloads indicate that heart rate and body sway do not correlate (Seliga *et al.*, 1991).

One of the more frequent reports during voluntary hyperventilation is that of 'dizziness' or 'lightheadedness' and, indeed, some authors count hyperventilation as one of the most frequent causes of dizziness in the clinic (Drachman and Hart, 1972; Hanson, 1989; Colledge *et al.*, 1996). Our results showing objective increase in sway by hyperventilation could indicate that such subjective sensations could arise from correct perception of actual unsteadiness. This can only be partly so, however, since hyperventilation-induced lightheadedness can also be experienced whilst sitting or lying. In the following sections we will discuss possible causes for the increased sway induced by hyperventilation.

Somatosensory potentials during hyperventilation

Proprioceptive information from the lower limbs is probably the single most important sensory input for the control of postural balance in man (Bergin *et al.*, 1995). In this study, we attempted to see whether hyperventilation modifies the somatosensory potentials from the lower limb which, in turn,

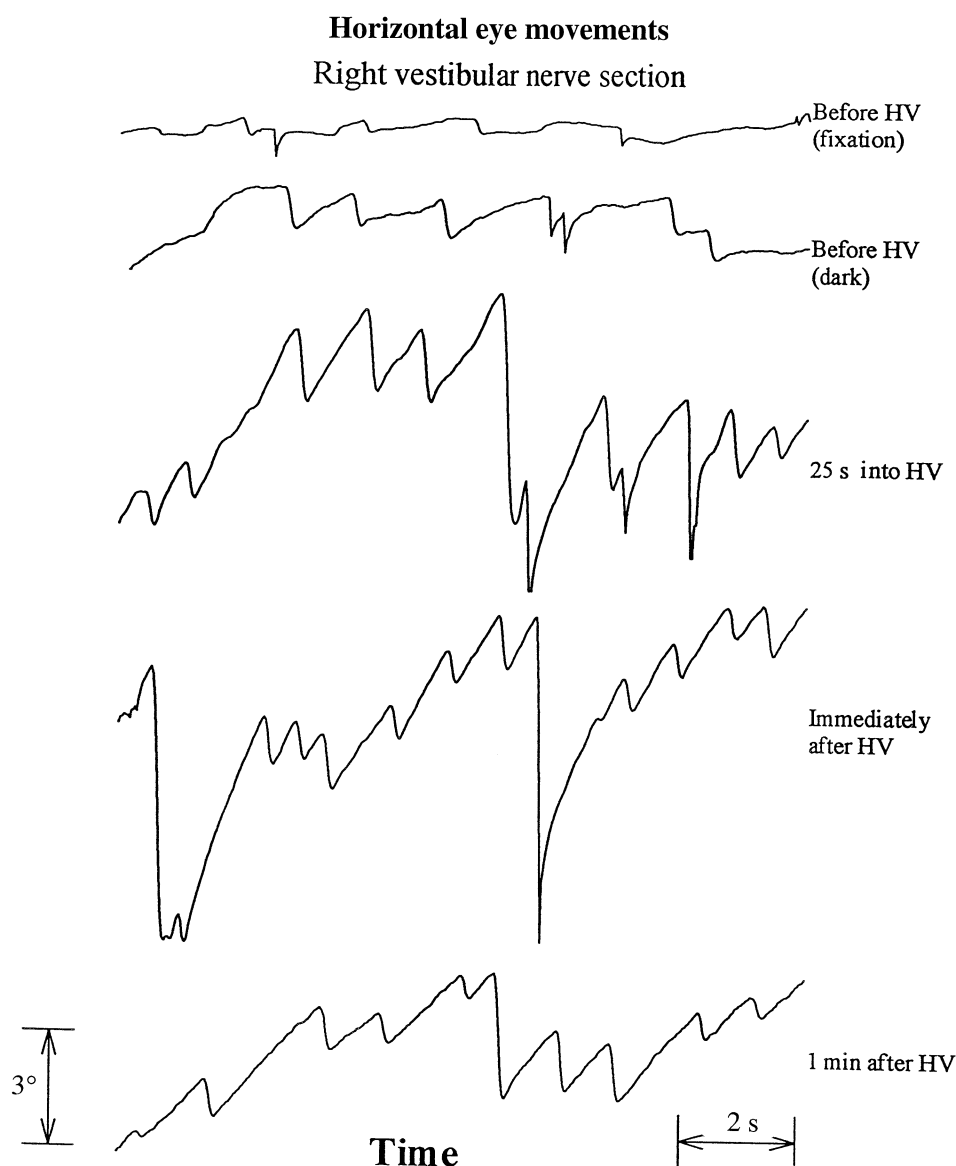


Fig. 8 Spontaneous horizontal eye movements during straight ahead gaze in a patient with right-sided vestibular nerve section, before, during and after hyperventilation (HV). Note the exacerbation of the nystagmus by hyperventilation. Upwards deflections indicate rightwards eye movements.

could underlie the unsteadiness observed after hyperventilation. The sural nerve is a cutaneous nerve but its behaviour in this study is likely to be representative of the changes brought about by hyperventilation in the whole of the distal somatosensory system, which conveys proprioceptive as well as tactile information from the ankle and foot. Also, it could be argued that cutaneous nerves carry afferents from underlying joint receptors ('Hilton's law') and that cutaneous input is also likely to be used for balance control. The scalp SEP is mediated via large-diameter peripheral sensory fibres and probably the dorsal column–lemniscal systems centrally (Eisen, 1982), which also convey proprioceptive inputs.

We found that hyperventilation induced changes, both peripherally (SAP) and centrally (SEP), in potentials evoked by sural nerve stimulation. The amplitudes of peripheral

SAPs increased whereas those of scalp SEPs decreased. No changes in latency due to hyperventilation were observed. The changes in the SAPs could reflect increased excitability of the peripheral nerve, resulting in a greater number of fibres being activated by a sub-maximal stimulus. Proprioceptive processes might thus be disturbed by a higher level of ectopic activity in hyperexcitable nerve fibres (Macefield and Burke, 1991; Burke, 1993).

One possible explanation for the apparently contradictory finding of increased peripheral SAPs but reduced scalp SEPs after hyperventilation is that the excitability of peripheral nerve fibres and that of cortical neurons are affected in different ways. Hyperventilation is likely to induce changes in widespread neural circuits and the final effect on a particular function will depend on the balance of changes in

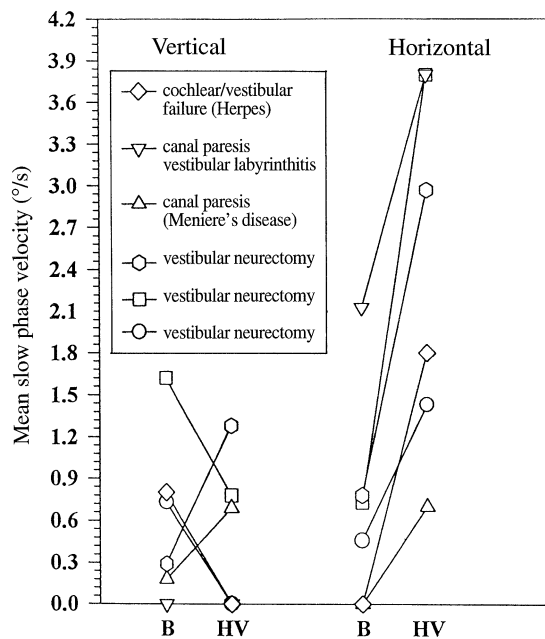


Fig. 9 Slow phase velocity of the spontaneous nystagmus in the vertical and horizontal planes in the dark, before (B) and after (HV) hyperventilation, in six patients with unilateral vestibular lesions.

excitatory as well as inhibitory neurons. In agreement with this, it has been shown that hyperventilation can decrease cortico-motor inhibition selectively (e.g. that evoked by transcranial magnetic stimulation) without modifying spinal inhibition (Priori *et al.*, 1995). However, the observations can alternatively be explained purely in terms of the peripheral effect. Kakigi and Jones (1986) showed that the scalp SEP is attenuated when the stimulus is given in the presence of continuous tactile stimulation of the skin innervated by the same nerve bundle. If, in addition to enlargement of the peripheral SAP, hyperventilation causes an increase in the spontaneous, ectopic firing of the sensory fibres (quite likely since normal subjects report paraesthesias), the volley due to the applied electrical stimulus will arrive at the cortex against a background of raised ongoing sensory input. This would have the effect of making the cortical sensory neurons partially refractory, reducing their response to the coherent volley. This mechanism might also contribute to the associated postural disturbances, by impairment of the cortical responses to proprioceptive input.

Vestibulo-colic responses during hyperventilation

Vestibulo-spinal reflexes contribute to postural control in man (Keshner *et al.*, 1987). The much studied vestibulo-colic reflexes are easier to elicit and have shorter latencies (Bronstein, 1988; Ito *et al.*, 1995). In this study, the technique of eliciting neck EMG responses by loud clicks was chosen (Colebatch *et al.*, 1994), but no changes were induced by hyperventilation; this finding would indicate that hyperventil-

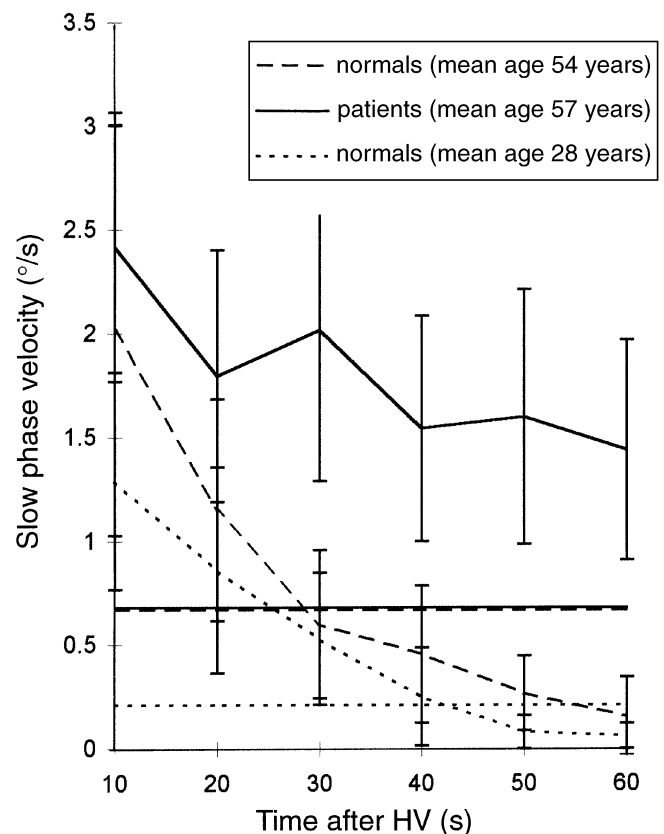


Fig. 10 Horizontal slow phase velocity (mean and SD) during the 60 s after subjects had hyperventilated for 60 s (time after HV). Data for six patients with unilateral vestibular lesions, six normal subjects of a comparable age and six young normal control subjects. Mean baseline (pre-hyperventilation) values are also shown (horizontal lines). These slow phase velocities have been normalized in the rightwards direction. Note the longer lasting effects of hyperventilation in the patients.

ation does not create unsteadiness by disrupting vestibulo-spinal activity. Since the click-evoked technique investigates oligosynaptic pathways, it would still be possible that longer latency pathways could be altered (Fukushima *et al.*, 1988). However, our previous finding that patients with total absence of vestibular function develop hyperventilation-induced unsteadiness to a similar degree to that observed in normal subjects (Sakellari and Bronstein, 1997), also indicates that the mechanism involved is extra-vestibular.

Ocular motor performance during hyperventilation

The purpose of measuring the VOR, visual suppression of the VOR and smooth pursuit movements was twofold. The VOR again gives us the opportunity to measure vestibular activity. In addition, VOR suppression and pursuit are visually-guided movements critically dependent on cerebellar function. The floccular nodule and, to a lesser extent, the dorsal vermis of the cerebellum (Leigh and Zee, 1991) are primarily responsible for these movements and, as known

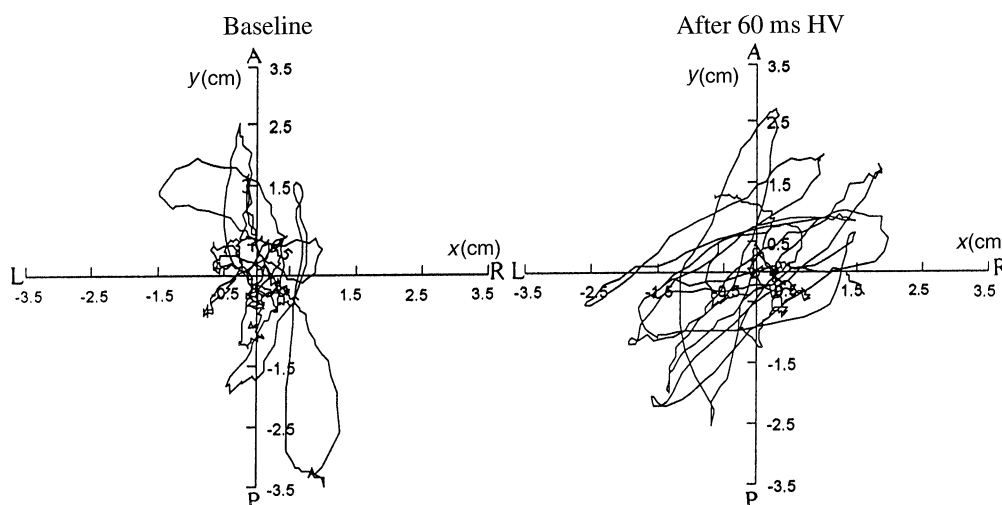


Fig. 11 X-Y sway plots in a patient with long standing complete left sided deafness and canal paresis. Note the increase in lateral sway after hyperventilation (HV), with a diagonal left-posterior to right-anterior trajectory. A = anterior; P = posterior; L = left; R = right.

from experimental and clinical work, lesions in those areas impair postural balance (Diener *et al.*, 1984). The result in this study was that hyperventilation of up to 60-s duration does not affect the VOR, its visual suppression or pursuit.

Theunissen *et al.* (1986) reported, in partial contrast with our study, some enhancement in VOR gain in normal subjects and patients with hyperventilation syndrome, using velocity steps for VOR assessment. Since we were particularly interested in assessing VOR, VOR suppression and pursuit with stimuli of similar dynamic characteristics, we used sinusoidal oscillation instead of velocity steps. This different stimulus profile could partly explain differences between the findings in the two studies, but it must be emphasized that hyperventilation-mediated effects in the study mentioned were slight and inconsistent. In summary, we could not demonstrate an important cerebellar or vestibular component mediating the hyperventilation effects on human postural balance.

Unilateral vestibular lesions and hyperventilation

It has been recommended that hyperventilation should be included as part of a battery of vestibular tests to elicit nystagmus (Drachman and Hart, 1972; Wilson and Kim, 1981; Kayan, 1987; Zee, 1996). Drachman and Hart (1972) reported the case of two patients with complaints of dizziness who manifested positional vertigo and nystagmus only after hyperventilation. Wilson and Kim (1981) reported that transitory direction-changing nystagmus was produced by hyperventilation in six of 18 patients with acoustic neurinoma. However the contribution of hyperventilation to spontaneous nystagmus is not very well defined. In fact, the presence of spontaneous nystagmus has been used as a criterion to exclude a diagnosis of hyperventilation syndrome in patients

presenting with symptoms suggestive of such a syndrome (Alvord and Herr, 1994).

Acute unilateral vestibular patients tend to sway more in the frontal plane and to veer to the side of their lesion on walking (Dichgans *et al.*, 1976), features which disappear as vestibular compensation develops. Since hyperventilation does not seem to affect the vestibular system directly, any changes observed in body sway may be attributed to either somatosensory or central mechanisms. The reappearance of the nystagmus and the development of predominantly lateral sway in our previously well compensated patients, strongly suggests that hyperventilation reverted the central mechanisms mediating recovery from vestibular lesions.

Therefore, it is likely that hyperventilation brought about a transient break down in the compensatory mechanisms restoring functional symmetry following unilateral vestibular lesions. These mechanisms are widespread in the CNS (Curthoys and Halmagyi, 1995) and might therefore be susceptible to ischaemia or metabolic changes brought about by hyperventilation (Gotoh *et al.*, 1965; Patel and Malsby, 1987). It is likely that the compensatory mechanisms disrupted by hyperventilation do not embrace VOR-suppression pathways, firstly because these patients' nystagmus was not strong in the dark before hyperventilation (indicative that the nystagmus was not merely visually suppressed) and, secondly, because of the lack of a significant effect of hyperventilation on VOR suppression as discussed in the preceding section.

The direction of the nystagmus after hyperventilation was in the expected direction (towards the healthy side) in four patients with either nerve section ($n = 3$) or with total unilateral deafness ($n = 1$; herpetic lesion). In the two patients with presumed subtotal labyrinthine damage (i.e. with neither nerve section nor deafness) the nystagmus was towards the side of the canal paresis. The number of patients is too small to draw firm conclusions on the matter, but it is

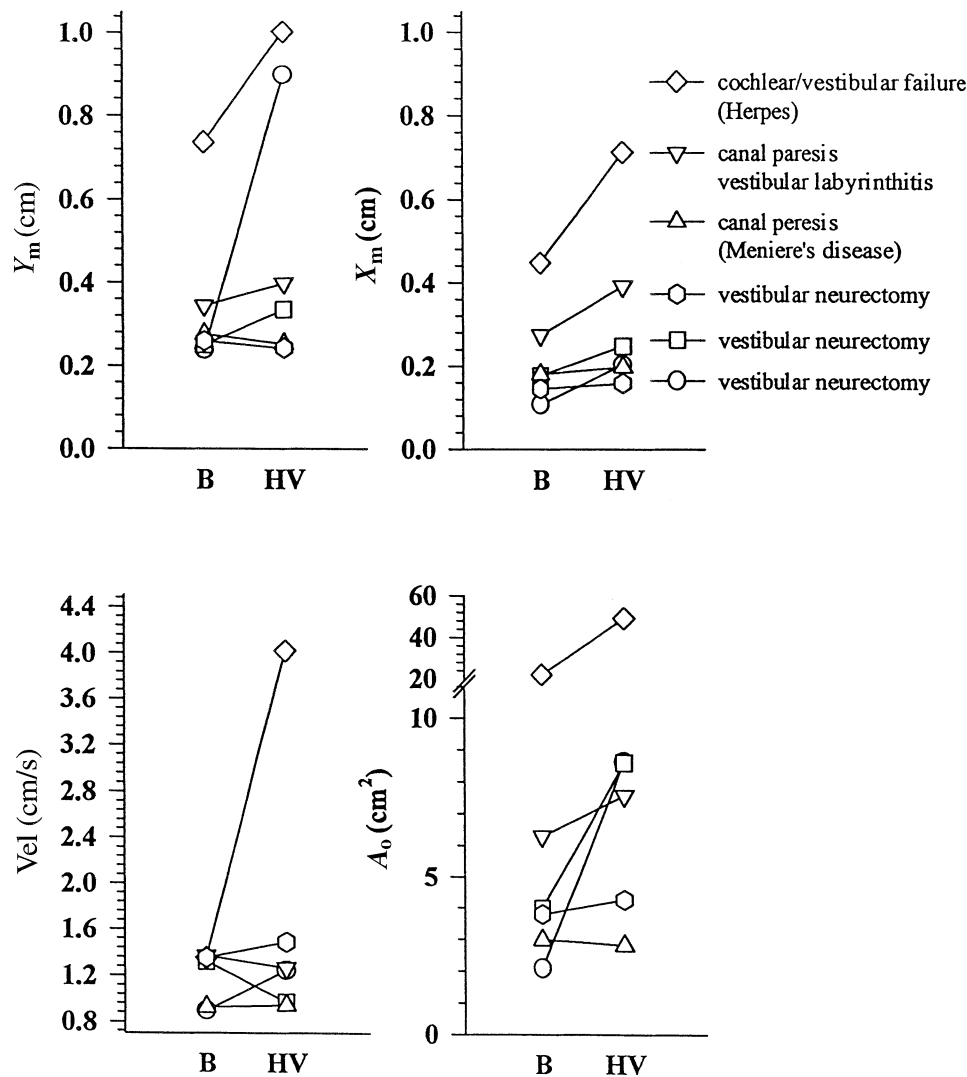


Fig. 12 Mean antero-posterior (Y_m) and lateral (X_m) deviations of the centre of foot pressure, mean sway velocity (Vel) and sway area (A_o) in six patients with unilateral vestibular lesions. Mean of two recordings before (B) and after (HV) 60 s of hyperventilation per patient are shown.

possible that hyperventilation may help to reveal differences in the way the CNS compensates for total or sub-total vestibular lesions. Alternatively, in the presence of subtotal labyrinthine lesions, the metabolic changes brought about by hyperventilation might stimulate partly damaged hair cells, or nerve endings, and provoke nystagmus by direct excitation of the abnormal side. This would be equivalent to the spike-generation by hyperventilation as seen in EEGs. This issue requires future investigation.

In spite of the finding that our patients develop lateral nystagmus and sway, they did not report clear-cut rotational vertigo. This dissociation may only suggest that the asymmetry which reappeared with hyperventilation is not large enough. Alternatively, it may be another example of the dissociation that can occur between vestibulo-ocular, postural and perceptual processes in patients with chronic balance disorders (Kanayama *et al.*, 1995; Bisdorff *et al.*, 1996).

Although the purpose of this work was not primarily to ascertain whether hyperventilation can or cannot be part of a battery of vestibular tests, a comment on the subject can be made, based on the provocation of nystagmus in unilateral vestibular patients and normal subjects. Although the results shown in Fig. 10 indicate clear differences between these groups, it must be acknowledged that these differences are quantitative rather than qualitative. Unfortunately, hyperventilation can provoke or exacerbate nystagmus in normal subjects. Finding a cut-off point between patients with less severe lesions and borderline normals may prove as difficult as it is with any other vestibular test. A small degree of asymmetry in vestibular function is a feature of many normal subjects, and hyperventilation might interfere with the mechanisms keeping such asymmetry in check, just as it does with patients. That hyperventilation can cause asymmetric phenomena, e.g. unilateral paraesthesia (Blau *et al.*, 1983; Perkin and Joseph, 1986) has been noted before,

and the possible mechanisms reviewed (Evans, 1995). Such mechanisms include anatomical differences in the peripheral nerves and their nutrient vessels, and asymmetrically decreased cerebral perfusion, alone or in combination with asymmetrical hemispheric processes.

In summary, this study confirms that hyperventilation causes an objective disturbance of postural control. The causes of this unsteadiness are likely to be multiple, in the light of the widespread metabolic changes induced by hyperventilation. However, in the main, the effects are not mediated by vestibular mechanisms but rather by interference with somatosensory and vestibular-compensation processes. The findings could have significance for the treatment of patients with balance disorders, since the rehabilitation specialist should be aware that hyperventilation, which could arise as part of anxiety, could aggravate patients' symptoms and signs. Similarly, in the light of our results showing that hyperventilation can decompensate an underlying vestibular disorder, symptoms of dizziness and unsteadiness should only be attributed solely to hyperventilation in the absence of findings in a careful neuro-otological examination.

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