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VESTIBOLOGY

Hyperventilation-induced nystagmus in a large series of vestibular patients

Nistagmo evocato dall'iperventilazione in un'ampia popolazione di pazienti vestibolari

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SUMMARY

The Hyperventilation Test is widely used in the "bed-side examination" of vestibular patients. It can either activate a latent nystagmus in central or peripheral vestibular diseases or it can interact with a spontaneous nystagmus, by reducing it or increasing it. Aims of this study were to determine the incidence, patterns and temporal characteristics of Hyperventilation-induced nystagmus in patients suffering from vestibular diseases, as well as its contribution to the differential diagnosis between vestibular neuritis and neuroma of the 8th cranial nerve, and its behaviour in some central vestibular diseases. The present study includes 1202 patients featuring, at vestibular examination, at least one sign of vestibular system disorders or patients diagnosed with a "Migraine-related vertigo" or "Chronic subjective dizziness". The overall incidence of Hyperventilation-induced nystagmus was 21.9%. It was detected more frequently in retrocochlear vestibular diseases rather than in end-organ vestibular diseases: 5.3% in Paroxysmal Positional Vertigo, 37.1% in Menière's disease, 37.6% in compensated vestibular neuritis, 77.2% in acute vestibular neuritis and 91.7% in neuroma of the 8th cranial nerve. In acute vestibular neuritis, three HVIN patterns were observed: Paretic pattern: temporary enhancement of the spontaneous nystagmus; Excitatory pattern: temporary inhibition of the spontaneous nystagmus; Strong excitatory pattern: temporary inversion of the spontaneous nystagmus. Excitatory patterns proved to be time-dependent in that they disappeared and were replaced by the paretic pattern over a period of maximum 18 days since the beginning of the disorder. In acoustic neuroma, Hyperventilation-induced nystagmus was frequently observed (91.7%), either in the form of an excitatory pattern (fast phases towards the affected site) or in the form of a paretic pattern (fast phases towards the healthy side). The direction of the nystagmus is only partially related to tumour size, whereas other mechanisms, such as demyelination or a break in nerve fibres, might have an important role in triggering the situation. Hyperventilation-induced nystagmus has frequently been detected in cases of demyelinating diseases and in cerebellar diseases: in multiple sclerosis, hyperventilation inhibits a central type of spontaneous nystagmus or evokes nystagmus in 75% of patients; in cerebellar diseases, hyperventilation evokes or enhances a central spontaneous nystagmus in 72.7% of patients. In conclusion the Hyperventilation Test can provide patterns of oculomotor responses that indicate a diagnostic investigation through cerebral magnetic resonance imaging enhanced by gadolinium, upon suspicion of neuroma of the 8th cranial nerve or of a central disease. In our opinion, however, Hyperventilation-induced nystagmus always needs to be viewed within the more general context of a complete examination of the vestibular and acoustic system.

KEY WORDS: Vestibular neuritis • Acoustic neuroma • Multiple sclerosis • Cerebellar diseases • Hyperventilation • Hyperventilation-induced nystagmus

RIASSUNTO

Il Test di Iperventilazione è spesso usato nell'ambito della "bed-side examination" del paziente vestibolare. Esso può attivare un nistagmo latente in caso di patologie vestibolari periferiche o centrali, o può interagire con un nistagmo spontaneo, rinforzandolo od inibendolo. Gli scopi del nostro studio sono stati di determinare frequenza, caratteristiche, durata del Nistagmo Evocato dall'Iperventilazione in pazienti affetti da patologie vestibolari, il suo ruolo nella diagnosi differenziale clinica tra neurite vestibolare acuta o compensata e neurinoma dell'VIII, nonché il suo comportamento in alcune patologie centrali che determinassero sintomi e segni vestibolari. Lo studio include 1202 pazienti in cui sia stato riscontrato, durante l'esame vestibolare, almeno un segno oculomotorio di sofferenza del sistema vestibolare o in cui sia stata posta diagnosi di Vertigine emicranica o di "Instabilità cronica soggettiva". Nella popolazione di studio, l'incidenza complessiva del Nistagmo Evocato da Iperventilazione è stata del 21.9%. Tale nistagmo è stato riscontrato più frequentemente nella patologia retrolabirintica che in quella labirintica, con frequenza del 5,3% nella Vertigine Parossitica Posizionale, del 37,1% nella Malattia di Menière, del 37,6% negli esiti di Neurite vestibolare, del 77,2% nella Neurite vestibolare in fase acuta e del 91,7% nel Neurinoma dell'VIII. Nella Neurite vestibolare acuta, abbiamo osservato tre pattern di Nistagmo Evocato dall'Iperventilazione:
1. Pattern deficitario: Rinforzo temporaneo del nistagmo spontaneo;
2. Pattern eccitatorio: Inibizione temporanea del nistagmo spontaneo;
3. Pattern fortemente eccitatorio: Inversione temporanea del nistagmo spontaneo.
I pattern eccitatori si sono dimostrati essere tempo-dipendenti, nel senso che essi sono sempre scomparsi, sostituiti dal pattern paretico, in un tempo massimo di 18 giorni dall'esordio della sintomatologia vertiginosa. Nel Neurinoma dell'VIII, il Nistagmo Evocato dall'Iperventilazione è stato osservato in 11/12 casi (91,7%), tanto come pattern eccitatorio (fasi rapide dirette verso il lato malato), che come pattern inibitorio (fasi rapide dirette verso il lato sano). La direzione del nistagmo è apparsa solo parzialmente relazionabile alla grandezza del neurinoma, in quanto entrambi i pattern sono stati osservati in tumori di diversa grandezza, per cui è sembrato verosimile che altri meccanismi, quali la presenza di aree di demielinizzazione o l'interruzione delle fibre nervose, possano avere un ruolo nel determinarla. Il

Nistagmo Evocato dall'Iperventilazione è stato anche frequentemente riscontrato in caso di malattie demielinizzanti con impegno tronco-cerebellare, ed in caso di patologie cerebellari: nella Sclerosi multipla l'Iperventilazione ha evocato nistagmo o ha inibito un nistagmo spontaneo di tipo centrale nel 75% dei pazienti osservati; nelle patologie cerebellari essa ha evocato nistagmo o rinforzato un nistagmo spontaneo preesistente nel 72,7% dei casi. In conclusione il Test di Iperventilazione fornisce dati utili alla diagnostica differenziale tra patologia infiammatoria e tumorale dell'VIII nervo cranico e può evocare risposte nistagmiche tali da giustificare un approfondimento diagnostico mediante RMN cerebrale con gadolinio non solo nel sospetto di un neurinoma dell'VIII ma anche di patologie neurologiche centrali. In ogni caso, comunque, riteniamo che i risultati di tale test vadano sempre inseriti nel più ampio contesto di una completa analisi del sistema audiovestibolare.

PAROLE CHIAVE: *Neurite vestibolare • Neurinoma dell'acustico • Sclerosi multipla • Patologie cerebellari • Iperventilazione • Nistagmo evocato dall'Iperventilazione*

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Introduction

Hyperventilation is "ventilation that exceeds metabolic needs" [1]. It increases serum pH and lowers the concentration of ionized calcium; it reduces both the cerebral and inner ear circulation and reduces the tissue oxygenation through a left shift of the haemoglobin-oxygen dissociation curve; it lowers both the middle ear pressure, according to CO_2 partial pressure between middle ear and blood, and the intra-cranial pressure [2-4].

It can provoke the "hyperventilation syndrome": unsteadiness, paraesthesia, anxiety and seldom, muscular convulsions or epileptic seizures.

Hyperventilation is a widely used test in the bed-side examination of vertiginous patients, since it induces neuro-physiological modifications able to reveal latent cerebellar or vestibular diseases, while the incidence of Hyperventilation Induced Nystagmus (HVIN) in normal subjects is low [5-8].

The Hyperventilation Test (HVT) can evoke a paretic nystagmus (fast phases beating toward the healthy side) by disrupting central compensation mechanisms in cases of vestibular neuritis and acoustic neuroma, but, in these pathological conditions, it can also evoke an excitatory-type of nystagmus, the fast phases of which beat, on the contrary, towards the affected side, by improving the neural conduction in demyelinated nerve fibres or increasing the peripheral neural excitability [1 6 8-11].

By means of a three-dimensional eye movement analysis, using the search-coil technique, Minor et al. related the planar characteristics of HVIN, in acoustic neuroma, to the intra-neural localization of the tumour [8].

In Perilymphatic fistula (PF) and in the Superior Canal Dehiscence Syndrome (SCDS), HVT, by means of changes in intra-cranial and peri-lymphatic pressures, can evoke either a horizontal nystagmus, in the case of larger defects in the bony wall of the semicircular canal with associated hypofunction, or torsional nystagmus, in the case of smaller defects causing a third mobile window into the inner ear [12 13].

In cerebellar diseases [6], HVT can increase or evoke a downbeat nystagmus through metabolic effects both on Ca^{2+} voltage-dependent channels, that are present in the cerebellum and are very sensitive to pH changes of cerebrospinal fluid, and on the activation threshold of other ionic channels. This latter action is more frequent in sensory fibres than in motor fibres, where the effects of hyperventilation on Na^+ and K^+ channels are less important [14 15].

In Multiple sclerosis, HVT can evoke nystagmus, but it can also temporarily inhibit a spontaneous nystagmus, improving the conduction in demyelinated nervous fibres [2].

In brainstem injuries of various origin, HVT increases the rate of visualization of vestibular abnormalities, uncovering a latent nystagmus [16].

HVT can also cause an increase in body sway, while there seems to be no effect on the Vestibulo-Ocular-Reflex, on its visual suppression or on the Vestibulo-Collic Reflex [1].

Since, in peripheral vestibular diseases, HVIN is inhibited by the visual fixation, the test sensitivity is increased by the three-dimensional scleral search coil technique and Infrared videonystagmography, and decreased by Frenzel's glasses [5], with direct observation, and by electronystagmography, in the latter case due to the low frequency DC drift [17].

Aims of the present study were: to determine HVIN frequency in a large series of unselected vestibular patients; revealing HVIN patterns in several peripheral and central vestibular diseases; detecting whether HVIN can add relevant elements in the bed-side differential diagnosis between vestibular neuritis and acoustic neuroma.

The study is based on clinical data, in unselected vestibular patients: some doubts, some imperfect diagnoses and some errors are possible, but, in our opinion, this is not unusual and is, perhaps, unavoidable in every clinical context.

Material and methods

HVT was performed on 50 healthy volunteers (age range 15-72 years) (control group), with no sign of cochleo-vestibular disease (hearing loss, tinnitus, fullness, unsteadiness, vertigo, headache) and in 1505 vestibular patients observed from January to December, 2008.

Inclusion criteria in the "study group" were:
1. age ≥ 10 years;
2. the presence of at least one oculo-motor sign of vestibular disease; and/or:
3. diagnosis of Migraine-related vertigo; or:
4. diagnosis of "Chronic subjective dizziness".

1202 patients (683 female, 519 male) were included in the study; mean age 54.3 years (range 10-88 years).

All underwent:

A) Audiological evaluation: Pure tone audiometry, Timpanometry, Acoustic reflex threshold test, Reflex decay test. When necessary: Speech audiometry, Auditory Brainstem Responses (ABR), Cervical Vestibular-Evoked Myogenic Potentials (c-VEMP), Otoacoustic emissions.

B) Vestibular evaluation: "Bed-side examination": observation of the spontaneous nystagmus, Head Shaking Test (HST), Head Thrust Test, Gaze Test, HVT, Positional tests: Dix-Hallpike and Pagnini-McClure diagnostic manoeuvres for posterior and lateral canalolithiasis; Bithermal caloric test, following the Fitzgerald-Hallpike technique; Pendular test from 0.05 to 0.5 Hz; Saccadic and smooth pursuit tests.

In the bithermal caloric test, Jongkees formulation for vestibular paresis was used to normalize the difference between total left and right caloric responses to the sum of response:

$$[(44°\text{Right (R)} + 30°\text{R})-(44°\text{Left (L)} + 30°\text{L})] / (44°\text{R} + 30°\text{R} + 44°\text{L} + 30°\text{L}) \times 100.$$

A vestibular paresis > 25%. was considered significant.

Ocular movements were observed and measured with video-nystagmoscopy and infra-red video-nystagmography (Ulmer VNG, Marseille, France) in total darkness; the direction of nystagmus was indicated by the direction of the fast phases.

HVT was performed in a sitting position through quick and deep respiratory cycles for 70 seconds: this duration might be enough to cause the metabolic and neurophysiological effects of the hyperventilation. HVIN was present if its slow-phase velocity (SPV) was of at least 5°/sec. within one minute after the end of hyperventilation, with a duration of at least 5 seconds.

If spontaneous nystagmus was already present, HVIN was present if it increased or decreased SPV of the spontaneous nystagmus of at least 5°/sec., for at least 5 seconds.

Normative data were obtained following an analysis of the oculo-motor responses evoked by HVT in the Control group (outlined below).

Serum variations induced by HVT ($PaCO_2$, concentrations of Ca^{2+}, pH, etc.) were not evaluated, while, for the purposes of our study, cerebral Magnetic Resonance Imaging (MRI) with gadolinium was prescribed when HVIN was evoked, with the exception of patients diagnosed with Benign Paroxysmal Positional Vertigo (BPPV).

Menière's disease was diagnosed according to the criteria of A.A.O. [18]; BPPV was diagnosed evaluating the presence of torsional paroxysmal nystagmus evoked by the Dix-Hallpike diagnostic manoeuvre for posterior canalolithiasis [19] or the presence of horizontal paroxysmal geotropic or apogeotropic nystagmus evoked by the Pagnini-McClure diagnostic manoeuvre for lateral canalolithiasis [20 21]; acute vestibular neuritis was diagnosed when spontaneous horizontal nystagmus was present in patients with sudden onset of an acute peripheral vertiginous syndrome (vertigo, ataxia, neuro-vegetative symptoms, no other neurological sign or symptom); compensated vestibular neuritis was diagnosed when the previous acute neuritis was clearly confirmed by our archives or by the patient's documentation; the diagnosis of Migraine-related vertigo was based on a history of recurrent vertigo and/or recurrent unsteadiness, with or without the presence of oculomotor signs during the vestibular examination, without hearing loss, in patients who met the International Classification of Headache Disorders II criteria for migraine [22]. Neuromas of the 8th cranial nerve, multiple sclerosis and cerebellar diseases, suspected on the basis of the clinical examination, were diagnosed by MRI; SSCD, suspected through the clinical examination and the results of c-VEMP, was diagnosed by inner ear Computed Tomography (CT) scans.

Diagnostic criteria for the following diseases are more controversial.

We included in the "Neurovascular compression group" patients with the typical symptom of this still controversial disease [23 24], i.e. brief paroxysms of vertigo, often induced by changes in the position of the head, or patients with Menière-like symptoms (unilateral hearing loss and recurrent attacks of vertigo lasting for minutes or even hours) when ABR showed an increase in the I-III conduction as a sign of neural sufferance of the VIII cranial nerve, not usually present in Menière's disease, and MRI assessed a contact and a possible compression of a vessel on the VIII cranial nerve on the same side as the cochleovestibular deficit.

The "Vascular vertigo" group is non-homogeneous and is quite difficult to evaluate since it includes diseases sometimes very different in their clinical severity.

Our inclusion criteria were: medical history of relevant cardiovascular diseases, especially previous episodes of vertebro-basilar TIA; ultrasound (US) diagnosis of obstruction of the supra-aortic arterial trunks, which is usually a sign of vascular sufferance in the anterior arterial district, but we can also consider it as an indirect sign of possible vascular sufferance in the vertebrobasilar district; imaging (MRI and/or CT scans) featuring acute or compensated cerebro-vascular diseases; no other possible explanation for either the vertiginous medical history and the vestibular symptoms and signs.

"Chronic subjective dizziness" was defined according to the criteria of Staab and Ruckensein [25]: persistent unstead-

iness (< 3 months), light-headedness or heavy-headedness that is often present; hypersensitivity to one's own movements (towards an unspecific direction), and to movements of objects around; "visual vertigo": increase in symptoms with complex visual stimulations or when precision visual tasks are carried out; absence of active neuro-otological diseases, medical conditions, or use of medications causing dizziness; the medical history can highlight an episode of acute vertigo; negative imaging for neurologic diseases and neuro-otological clinical and instrumental examinations with no relevant data, except for those derived from a possible previous vestibular disease.

A statistical analysis was performed using the SPSS© (SPSS Inc., Chicago, IL, USA) statistical package (version 11.5) according to criteria proposed by Jeckel et al. [26]

Results are expressed as mean ± standard deviation (SD) for continue variables and absolute (percentage) values for discrete variables. Contingency chi square tests and analysis of variance with Bonferroni correction for multiple comparisons were used to test the between-group differences in non-parametric and parametric variables, respectively. Logistic regression analysis was used to evaluate the association of a given variable with occurrence of HVIN, accounting for confounders.

Results

A. Control group (50 healthy volunteers): In 6 subjects, HVT induced few oculomotor shakes of nystagmus, with average SPV of 2°/sec ± 1.7°, lasting less than 3 seconds.
From an analysis of these data, we obtained normative data: the lowest SPV considered relevant for HVIN is 5°/sec, representing the superior 95° percentile of normal subjects, with a Gaussian distribution; following the same criteria, the shortest significant duration is 5 sec.

B. Study group (1202 patients): The HVIN incidence is reported in Table I.

Table I. HVIN in vestibular disorders sorted by incidence.

Diagnosis	HVIN+
Pre-surgery acoustic neuroma	11/12 (91.7%)
Post-surgery acoustic neuroma	7/9 (77.8%)
Multiple sclerosis	9/12 (75%)
Cerebellar diseases	8 /11 (72.7%)
Acute vestibular neuritis	39/54 (72.2%)
Neurovascular compression	3/5 (60%)
Labyrinthine Fistulas and Superior canal dehiscence Syndrome	11/20 (55%)
Unilateral Menière's disease	35/93 (37.6%)
Compensated vestibular neuritis	33/89 (37.1%)
Bilateral vestibular loss of function	1/5 (20%)
Migraine-related vertigo	36/188 (19.1%)
Vascular vertigo	27/152 (17.8%)
BPPV	24/455 (5.3%)
Chronic subjective dizziness	0/23
Undiagnosed vertigo	19/74 (25.7%)
Overall	263/1202 (21.9%)

Vestibular neuroma

a. *Pre-surgery evaluation*. We observed HVIN in 11/12 cases (91.7%), in 4 cases paretic HVIN (p-HVIN), in 7 cases excitatory HVIN (e-HVIN). The affected side was clinically identified by the presence of a significant vestibular paresis, on caloric tests, and by the direction of the slow phases of the nystagmus evoked by HST; it was then confirmed by visualizing the tumour on the suspected side by means of MRI.
In tumours > 10 mm, e-HVIN was present in 5/6 cases (83.3%), p-HVIN in 1/6 cases (16.7%); in neuromas ≤ 10 mm, p-HVIN was present in 3/6 cases (50%), e-HVIN in 2/6 cases (33.3%), HVIN was absent in 1/6 cases (16.7%) (Table II).
SPV ranged from 6.1 to 13°/sec (mean ± S.D. = 7.2 ± 6.8°/sec). Only one 23-year-old patient did not present HVIN: she had normal hearing, no other bed-side vestibular sign and featured unilateral loss of the vestibular function on caloric tests and pathological A.B.R. (I-III interpeak = 2.65 msec) on the right side. The patient had already undergone MRI before our observation and a 10 mm neuroma of the right 8th cranial nerve had been discovered.

b. *Post-surgery evaluation*. Overall 9 subjects were evaluated who had undergone surgery in a period ranging from 15 days to 5 years before the present investigation; 4 of these subjects are included also in the "pre-surgery group".
Paretic spontaneous nystagmus was present in 3 cases, p-HVIN was evoked in 7/9 cases (77.8%), with SPV ranging from 5.3 to 13.8°/sec (mean ± S.D. = 7.1 ± 6.8°/sec). HVIN was absent in two patients who had undergone surgery 20 and 24 months, respectively, before our observation, but it was also present in a patient who had undergone surgery 60 months before.

Multiple Sclerosis

In all cases, the structures of the posterior cranial fossa were involved (brainstem and/or cerebellum).
In 3/12 cases, acute vertigo was the first symptom of a still unidentified disease; in the other cases, the disease had already been diagnosed.
HVT affected oculomotor responses in 9/12 cases (75%): it inhibited a spontaneous downbeat nystagmus in 3 cases, a spontaneous upbeat nystagmus in one case and a spontaneous rotatory nystagmus in one case, which were present during an acute poussée of the disease.
HVT, on the other hand, evoked *ex-novo* a horizontal nys-

Table II. HVIN in pre-surgical vestibular neuromas.

	Neuromas > 10 mm	Neuromas ≤ 10 mm	Overall
Excitatory HVIN	5/6 (83.3%)	2/6 (33.3%)	7/12 (58.3%)
Paretic HVIN	1/6 (16.7%)	3/6 (50%)	4/12 (33.3%)
HVIN	0/6	1/6 (16.7%)	1/12 (8.4%)
	6	6	12

Differences of HVIN patterns based on the size of neuromas are not significant.

tagmus in 2 cases and a downbeat nystagmus in 2 other cases.

Cerebellar diseases

This group includes: 3 patients with Chiari malformations; 3 with Vermian hypogenesis; 2 with familial cerebellar degenerations; 2 with chronic sporadic cerebellar degenerations; 1 with cerebellar paraneoplastic degeneration linked to a large temporo-parietal melanoma metastasis.

HVIN was evoked in 8/11 cases (72.7%): it increased spontaneous downbeat nystagmus in 3 cases of cerebellar degenerations, it evoked downbeat nystagmus in 2 cases of Vermian hypogenesis and in 2 with Chiari malformations, and evoked horizontal nystagmus in 1 case with Vermian hypogenesis.

Acute Vestibular Neuritis

Overall, 54 cases of acute vestibular neuritis were observed between 3 hours and 2 days after the onset of the pathological condition.

All patients presented paretic horizontal spontaneous nystagmus, with fast phases towards the healthy side, in addition to other typical symptoms of sudden unilateral loss of the vestibular function (vertigo, severe unsteadiness, nausea, vomiting, etc.); moreover, severe unilateral vestibular paresis, on caloric tests, was present in each case.

Cerebral RMI was carried out within a few days of the clinical diagnosis and did not show either neuroma of the 8th cranial nerve or central neurological diseases.

In 15/54 cases (37.8%), HVT did not modify the spontaneous nystagmus, while HVIN was present in 39/54 cases (72.2%).

We identified three HVIN patterns (Table III):

1. Paretic pattern: HVIN is added to spontaneous nystagmus and increases it by at least 5°/sec for at least 5 seconds (32 cases);
2. Excitatory pattern: HVIN, beating in the opposite direction to the spontaneous nystagmus, is algebraic added to it and partially or totally inhibits it (3 cases);
3. "Strongly excitatory" pattern: the algebric sum of the spontaneous nystagmus and HVIN causes a nystagmus that beats toward the affected side, with consequent inversion of the spontaneous nystagmus (4 cases).

Table III. HVIN in Acute Vestibular Neuritis.

HVIN	15/54 (27.8%)
Paretic HVIN	32/54 (59.2%)
Excitatory HVIN	3/54 (5.6%)
Strongly excitatory HVIN	4/54 (7.4%)

HVIN duration was always temporary: therefore, within one minute, the spontaneous nystagmus assumed its initial characteristics again, in all cases.

"Excitatory" and "strongly excitatory" patterns disappeared between 6 and 8 days after the beginning of the disease in 6 cases; in 1 case, the "strongly excitatory" pattern disappeared after 18 days. In all cases, these were replaced by the paretic pattern.

The SPV of p-HVIN (correct for the spontaneous nystagmus) ranged from 10 and 16°/sec (mean ± S.D. = 12.2 ± 11.3°/sec), whereas SPV of the "strong excitatory" pattern reached 28°/sec (average ± S.D. = 19.1 ± 9.8°/sec).

Neurovascular compression

Five patients were included in this group. Four of them presented symptoms of a Menière-like disease, whereas the other patient had only vertiginous symptoms (brief paroxysms of vertigo), without hearing loss. e-HVIN was observed in 3/5 cases (60%), always in Menière-like patients.

ABR alterations (delay of I-III conduction) were always present in Menière-like patients and were considered important in the clinical diagnosis as a sign of neural sufferance (induced by the contact/compression?).

In each case, MRI showed that the 8th cranial nerve, ipsilateral to the clinical signs, was in contact with AICA and, in 2 cases, megadolichobasilar anomaly was also present.

Labyrinth Fistula (LF) and Superior Canal Dehiscence Syndrome (SCDS)

A total of 15 LF were observed, 12 of them appeared after middle ear surgery, and 5 SCDS, revealed by inner ear CT scans. HVIN was detected in 2/15 LF (13.3%) and in 3/5 SCDS (60%). In the LF, HVIN was horizontal, paretic, beating toward the healthy side; in SCDS, HVIN was vertical and torsional.

Unilateral Menière's Disease

We observed patients with unilateral Menière's disease under three conditions:

1. *During an acute vestibular crisis (30 patients).* Of these, 25 patients had paretic spontaneous nystagmus, and the remaining 5 had irritative spontaneous nystagmus (fast phases toward the affected ear). In 20 patients (66.7%), spontaneous nystagmus was influenced by HVT that evoked 18 p-HVIN and 2 e-HVIN.
2. *During an inter-critical period ranging from 1 to 52 months since the last acute vestibular crisis (53 patients).* In 28 cases, we observed horizontal apogeotropic spontaneous nystagmus beating towards the healthy side, when patients layed on their affected side. HVIN was detected in 10 patients (18.9%): p-HVIN in 8 patients, e-HVIN in 2 patients. In these cases, the last acute crisis was in a period ranging from 1 to 3 months before our observation.
3. *After intra-tympanic gentamycin therapy (10 patients).* This therapy has been practiced on the affected ear in a period ranging from 3 to 42 months before our observation. Of these, 5/10 patients (50%) showed p-HVIN; in the cases lasting more than 36 months, p-HVIN was present in 2/5 patients (40%).

Compensated Vestibular Neuritis

A total of 89 patients were observed who suffered a sudden unilateral vestibular deficit, from 3 months to 3 years before our actual observation. Upon caloric stimulations, a significant vestibular asymmetry was detected in 41 cases.

HVIN was observed in 33 cases (37.1%): p-HVIN in 32/89 cases (36%), e-HVIN in one case (1.1%). The SPV of HVIN ranged from 6.4 to 8.3°/sec (mean ± S.D. = 7.1 ± 4.3°/sec). There appears to be a correlation in the inverse proportion between the time of onset of the acute episode and the presence of HVIN: the longer the time elapsing, the lower the incidence of HVIN, In fact, HVIN was present in 21/44 patients (47.7%) when the acute neuritis had occurred less than one year earlier; in 8/30 patients (26.7%) when the acute neuritis had occurred between one and two years earlier; in 4/15 patients (16.7%) when the acute neuritis had occurred between 2 and 3 years earlier. HVIN and caloric tests had a weak correlation: both HVIN and significant vestibular asymmetry, on caloric tests, were present only in 20 cases, while 21 cases with significant vestibular asymmetry did not show HVIN and 13 cases with HVIN did not show significant canalar paresis.

Bilateral Vestibular Areflexia

In this series, 3 cases deriving from aminoglycoside ototoxicity were observed and 2 cases deriving from genetic cochleovestibular disorders. HVIN was detected in one case.

Migraine-related Vertigo

All 188 patients included in the group were observed in an intercritical period. Spontaneous nystagmus was observed in 35 cases: horizontal nystagmus in 8 cases, rotatory nystagmus in 21 cases; downbeat nystagmus in 4 cases and upbeat nystagmus in 2 cases.

HVIN was observed in 36 patients (19.1%): horizontal in 25 cases, downbeat in 11 cases; in 5 cases, HVIN was an enhancement of the horizontal spontaneous nystagmus and in 4 cases it was an enhancement of the downbeat spontaneous nystagmus. HVIN showed a weak correlation with other data related to the vestibular examination, such as HST results and caloric tests.

Central Vascular Vertigo

Included in this heterogeneous group were: 128 cases of chronic vertebrobasilar insufficiency, 8 cases of cerebellar stroke, 5 cases of cerebral vasculitis, 3 cases of thalamic stroke, 8 cases of brainstem stroke. The patients in this group are significantly older than those in the other groups, with an average age of 65 ± 12.2 years. Due to the extreme heterogeneity of the group, it is very difficult to rationalize the data, therefore only absolute data are reported: HVIN was horizontal in 19 cases, downbeat in 5 cases, upbeat in 2 cases, rotatory in one case of brainstem infarction, with an overall incidence of 27/152 cases (17.8%).

BPPV

A total of 394 cases of posterior canalolithiasis were observed and 61 cases of lateral canalolithiasis. In posterior BPPV, HVIN was detected in 17 cases (4.3%), it was torsional in 5 cases and horizontal in 12 cases, including 5 cases of Lindsay-Hemenway syndrome [27] characterized by an episode of acute vestibular deficit followed, after some time, by the onset of a paroxysmal positional vertigo: therefore, in these cases, the presence of HVIN is likely related to the primitive labyrinthine loss of function rather than to BPPV.

Chronic Subjective Dizziness

This was diagnosed in 23 cases. This group included patients with no oculomotor signs of vestibular diseases, while 5 patients who had suffered from acute vestibular neuritis and 7 patients with Menière's disease were respectively included in the "Compensated vestibular neuritis" and "Unilateral Menière's disease" groups, even if they clearly had psychological symptoms of phobic suffering.

Whereas HVIN was never evoked, 18 patients reported a sensation of unsteadiness, light-headedness, and one patient had sensations of rotation. Many of them defined such sensations as similar to their spontaneous symptoms.

Table IV. Logistic regression analysis evaluating the occurrence of HVIN in subjects with vestibular disorders compared to healthy controls, accounting for age and gender.

Variables	β	SE	p	Adjusted OR (95%CI)
Age	0.152	0.070	0.760	0.948 (0.680-1.325)
Sex	0.104	0.092	0.747	1.004 (0.714-1.454)
Vestibular disorders	0.691	0.137	< 0.001	13.724 (1.886-99.857)

SE: standard error; OR: Odds Ratio; 95%CI: 95% confidence intervals.

Undiagnosed Vertigo

Included in this group were 74 patients who were lost to follow-up or who had not undergone MRI or other examinations required. Within this group, HVIN was observed in 19 cases: 12 horizontal nystagmus, 5 downbeat nystagmus and 2 rotatory nystagmus.

Statistical analysis

Data reported are related to the HVIN statistical analysis, in healthy subjects as well as in pathological cases (Table IV), for every vestibular disease linked to the control group (Table V), in retro-labyrinthine and labyrinthine diseases according to age and sex (Table VI), in vestibular neuritis and neuroma of the 8th cranial nerve (Table VII).

HVIN prevalence is not remarkably related to sex and age, while its presence in the Study Group and in all the subgroups is significant if compared to the Control Group, except for BPPV, Chronic subjective dizziness, and Bilateral loss of vestibular function.

The prevalence of p-HVIN is significantly higher in acute vestibular neuritis compared to pre-surgery acoustic neuroma (Table VII), while e-HVIN and p-HVIN prevalence, in pre-surgery neuroma, is not significantly linked to the tumour size (Table II).

Discussion

The Hyperventilation test is usually part of the "vestibular bed-side examination" since it is easy to perform and well tolerated by patients.

Hyperventilation acts through non-vestibular mechanisms on several parts, whether central or peripheral, of the vestibular system, and it is able to highlight the neurophysiological effects in vestibular diseases, both central and peripheral, by interfering with the mechanisms of genesis and control of oculo-motor responses.

The standardization of HVT is difficult because measurements of metabolic variations, induced by hyperventilation on various parameters, such as CO_2 partial pressure, serum concentration of calcium, flow velocity in middle cerebral arteries and end-tidal CO_2 tension, are not routinely applied and, in fact, are only occasionally reported in the Literature [1 28].

Table V. Prevalence of HVIN in each vestibular disorder and logistic regression analysis evaluating the HVIN odds ratio in each of them compared to healthy controls and adjusted for age and sex.

Vestibular disorders	N	HVIN	%	β	SE	p	Adjusted OR (95%CI)
BPPV	455	24	5.3	0.147	0.077	0.496	2.729 (0.361-20.612)
Menière's disease	93	35	37.6	0.378	0.107	< 0.001	29.569 (3.908-223.753)
Acute vestibular neuritis	54	39	72.2	0.708	0.117	< 0.001	127.400 (16.117-1007.076)
Compensated vestibular neuritis	89	33	37.1	0.357	0.169	< 0.001	28.875 (3.807-218.989)
Labyrinthine fistulas	20	11	55	0.586	0.117	< 0.001	59.889 (6.858-522.955)
Pre-surgery acoustic neuroma	12	11	91.7	0.754	0.085	< 0.001	539.001 (31.244-9298.573)
Post-surgery acoustic neuroma	9	7	77.8	0.363	0.185	< 0.001	171.501 (13.693-2148.022)
Bilateral vestibular areflexia	5	1	20	0.207	0.107	0.175	12.250 (0.639-234.810)
Neurovascular compression	5	3	60	0.278	0.087	0.001	73.500 (5.098-1059.783)
Migraine-related vertigo	188	36	19.1	0.301	0.148	0.002	11.605 (1.550-86.867)
Multiple sclerosis	12	9	75	0.423	0.109	< 0.001	147.000 (13.712-1575.926)
Cerebellar diseases	11	8	72.7	0.486	0.111	< 0.001	130.667 (12.052-1416.28)
Vascular vertigo	152	27	17.8	0.358	0.107	0.004	10.584 (1.400-80.032)
Chronic subjective dizziness	23	0	0	-0.275	0.148	0.827	0.980 (0.942-1.020)
Undiagnosed vertigo	74	19	25.7	0.421	0.205	< 0.001	16.927 (2.185-131.149)

SE: standard error; OR: Odds Ratio; 95% CI: 95% confidence intervals; a p value < 0.003 was considered significant according to Bonferroni correction.

Table VI. Logistic regression analysis evaluating the occurrence of HVIN in subjects with retro-labyrinthine disorders compared to subjects with labyrinthine disorders accounting for age and gender.

Variables	β	SE	p	Adjusted OR (95%CI)
Age	0.147	0.077	0.749	0.952 (0.686-1.321)
Sex	0.107	0.078	0.734	1.006 (0.737-1.448)
Retro-labyrinthine disorders	0.417	0.137	0.019	1.405 (1.050-1.881)

SE: standard error; OR: Odds Ratio; 95%CI: 95% confidence intervals.

Table VII. Prevalence of p-HVIN and e-HVIN in vestibular neuritis and acoustic neuroma.

Vestibular disorders	p-HVIN	%	e-HVIN	%
Acute vestibular neuritis	32	82.05	7	17.95
Compensated vestibular neuritis	32	96.96	1	3.04
Pre-surgery acoustic neuroma	4	36.37	7	63.63
Post-surgery acoustic neuroma	7	100	0	0

p = 0.006; adjusted Odds Ratio 8.000; 95% confidence intervals (1.829-34.996).

There are, indeed, some studies regarding HVT effects in groups of selected patients affected by acoustic neuroma, cerebellar diseases, multiple sclerosis and peripheral vestibular diseases [5-11], but, to our knowledge, the present observation is the first to be focused on HVT effects on a broad range of unselected vestibular patients observed in a clinical context.

In the present survey, HVIN incidence was 21.9%, ranging from 0% of Chronic subjective dizziness to 91.7% of pre-surgery acoustic neuroma.

Several mechanisms have been proposed to explain the effects of HVT on the vestibular system [2 5-9 12 13 29-32]: the increase in neuronal excitability, in partially damaged fibres, caused by the reduction of pCO_2, of H^+ and Ca^{2+} concentration, which could cause a transitory up-regulation of the central compensation mechanisms of the vestibular deficit, or the activation of threshold channels, as shown in sensory fibres, might be involved in the excitatory patterns of acute neuritis; the mechanism of the temporary improvement of the conduction along demyelinated fibres might cause excitatory patterns in the early stages of acute neuritis and in acoustic neuroma and it might also cause the inhibition of a central-type nystagmus in Multiple sclerosis; the changes in intracranial and perilymphatic pressure might explain HVIN in Perilymphatic fistula and in Superior Canal Dehiscence Syndrome; the breakdown of central compensatory mechanisms might cause paretic HVIN in acute and compensated vestibular neuritis, in acoustic neuromas and in some phases of Menière's disease; metabolic effects on cerebellar Ca^{2+} channels might cause a central-type HVIN in cerebellar diseases.

In acute vestibular neuritis, three different HVIN patterns were observed, which were already described in one of our previous publications [33]: paretic pattern, excitatory pattern, strongly excitatory pattern.

The excitatory and strongly excitatory patterns were observed in a period ranging from 1 to 18 days since the beginning of the disease, and, during its course, they were always replaced by the paretic pattern, as also noted by Choi et al. [9] who reported a longer time for disappearance (up to 8 months).

The transition from excitatory patterns to the paretic pattern might be a sign of healing of the demyelinated fibres of the vestibular nerve; at this point, another mechanism of hyperventilation, such as the breakdown of central compensatory mechanisms of the vestibular imbalance, might cause the paretic pattern.

In pre-surgery acoustic neuroma, HVIN was detected in 11/12 cases (91.7%). The statistical analysis demonstrated that paretic and excitatory patterns are not significantly linked to the tumour size, even if the paretic pattern is more frequent in tumours ≤ 10 mm (3/6 HVIN+) and the excitatory pattern in neuromas > 10 mm (5/6 HVIN+) (Table II). The present data do not correspond to those by Bance et al. [5] and Choi et al. [9] who observed an opposite pattern of HVIN in relation to the tumour size, namely the prevalence of e-HVIN in smaller neuromas, but the dimension of the neuroma is not the exclusive parameter in determining the direction of nystagmus: in fact, the two smallest neuromas of our series (5 mm) both featured the excitatory pattern, whereas the largest neuroma (25 mm) featured the paretic pattern.

Other mechanisms must be taken into consideration to explain the different patterns of HVIN in acoustic neuroma: the p-HVIN might depend on neuronal damage that cannot be improved, not even temporarily, by hyperventilation, since it is either due, in the largest tumours to a total break of nervous fibres, or, in the smallest tumours, on the contrary, to the absence of demyelinated areas of the nerve. In these conditions, failure of the central vestibular compensation might act and cause the paretic HVIN. In favour of

this hypothesis, is the fact that, after surgical removal of the neuroma, e-HVIN always disappeared and was replaced by p-HVIN, as already reported by other Authors [8 9].

p-HVIN is more frequent in neuritis, while e-HVIN is more frequent in neuromas, but it is important to stress that p-HVIN does not specifically concern neuritis, just like e-HVIN does not specifically concern neuroma.

In our view, a key element is the clinical context where the sign is observed: in acute vestibular neuritis, e-HVIN, inhibits the spontaneous nystagmus or, even inverts it (strongly excitatory pattern), not excluding *a priori* the possibility that an acute vestibular neuritis could arise on a pre-existing neuroma. In neuromas, on the other hand, HVT can evoke *ex-novo* an excitatory nystagmus beating toward the affected side.

In Menière's disease, both in acute and inter-critical phases, HVT did not prove to be important in the clinical management of the patient. p-HVIN was the most frequently observed pattern, but it depends strongly on the time of observation and on the contra-lateral ear functional state, therefore on the compensation mechanisms activated during the disease.

In the Superior Canal Dehiscence Syndrome, "the evoked eye movements typically align with the plane of the dehiscent superior canal" [13]: the endo-cranial hypotension provokes an ampullofugal endolymphatic flow in the superior canal, that consequently causes a canal excitation with fast phases of downbeat and torsional nystagmus, as observed in the present study.

In cerebellar diseases, the most frequent response to HVT was a vertical downbeat HVIN, observed in vermian hypogenesis, in cerebellar degenerations, in one case of Paraneoplastic Cerebellar Degeneration and in Chiari malformations.

Under normal conditions, the mechanism proposed for the downbeat HVIN implies that the central nervous system features a prevalence of forces pushing eyes upward. Such asymmetry is usually controlled by cerebellar mechanisms that are compromised in some disorders of the nervous system, thus causing the onset of spontaneous downbeat nystagmus or of a downbeat nystagmus evoked by stimulations such as eye position in the orbit, HST or HVT, able to reveal the disorders of the system [6].

In chronic subjective dizziness, HVT responses are interesting: on the one hand, HVIN was never observed, but, on the other hand, many patients reported subjective symptoms that were similar to those which they spontaneously suffered from.

Perhaps, in these patients, metabolic modifications induced by hyperventilation were not sufficient to evoke nystagmus, even though they were sufficient to produce subjective symptoms.

Conclusions

HVT is a simple test.

Could it be useful in the bedside examination of a vestibular patient? We think so.

However, demonstrating how hyperventilation affects the vestibular system is a difficult task since several mechanisms can be hypothesized, which act either at a central level (cerebellum or other control sites for the compensation of a vestibular asymmetry) or on the vestibular nerve (transient improvement of the neural conduction), or on the labyrinthine periphery, acting by direct stimulation of hair-cells and/or by increasing neural excitability determined by hyperventilation-induced metabolic modifications.

Nonetheless, HVT is "the only test that unmasks unilateral vestibular disease without testing the dynamic properties of the vestibule-ocular reflex" [5].

HVT can provide patterns of oculo-motor responses that justify further evaluations through Gadolinium-enhanced MRI, in the search of an acoustic neuroma or of central neurological diseases: this is the case of the e-HVIN detected in unilateral acute or compensated vestibular loss of function (neuritis or neuroma) with an opposite oculomotor response to HST and caloric tests as well as the case of central-type HVIN (upbeat or downbeat nystagmus; rotatory nystagmus) and the case of inhibition of a central-type nystagmus, as in Multiple sclerosis.

HVT has proved to be accepted with excellent tolerability and to offer good clinical validity, although it is advisable to consider results of the investigation within the wider context of a general evaluation of auditory and vestibular functions.

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