Otology & Neurotology
36:303–306 © 2015, Otology & Neurotology, Inc.

Hyperventilation-Induced Nystagmus in Patients With Vestibular Schwannoma

Luigi Califano, Giuseppina Iorio, Francesca Salafia, Salvatore Mazzone, and Maria Califano

Department of Audiology and Phoniatrics, ''G. Rummo'' Hospital, Benevento, Italy

Main Objective: To determine the utility of the hyperventilation test (HVT) in the diagnosis of vestibular schwannoma (VS).
Study design: A retrospective analysis of hyperventilation-induced nystagmus (HVIN) in 45 patients with unilateral VS.
Setting: A tertiary referral center.
Patients: Forty-five patients with VS; 30 patients with chronic vestibular neuritis; 20 healthy subjects with normal hearing and without symptoms or a history of vertigo, migraine, or neurological diseases (control group).
Interventions: Audiological and vestibular examination; ''side-stream'' measurement of end-tidal CO_2 pressure (P_{EtCO2}) to standardize the procedure; magnetic resonance imaging (MRI) centered on the cerebellopontine angle.
Main outcome measures: An analysis of HVIN, its patterns, and its appearance threshold via the measurement of P_{EtCO2} correlations with the tumor size.
Results: HVIN was observed in 40 of 45 cases (88.9%) in the schwannoma group and in 12 of 30 cases (40%) in the chronic vestibular neuritis group; HVIN was not observed in the control group (0/20 cases) ($p < 0.001$). In the schwannoma group, HVIN was evoked at a mean P_{EtCO2} value of 16.5 ± 1.15 mm Hg. The hypofunctional labyrinth was identified with high sensibility and specificity through caloric test, head shaking test, and head thrust test. The excitatory pattern, which included HVIN with slow phases that beat toward the hypofunctional side, and the paretic pattern, which included HVIN with slow phases that beat toward the hypofunctional side, were not significantly associated with VS size (19.04 ± 10.56 mm for the excitatory pattern and 19.06 ± 11.01 mm for the paretic pattern). The difference in the VS size in HVIN+ (19.05 ± 10.60 mm) and HVIN− (8.40 ± 2.19 mm) cases was significant ($p = 0.009$).
Conclusions: A 60-second hyperventilation event causes metabolic changes in the vestibular system and reveals a latent vestibular asymmetry. The presence of an excitatory pattern is the major criterion that suggests VS in patients with signs of unilateral vestibular deficit. **Key Words:** Acoustic neuroma—Hyperventilation-induced nystagmus—Hyperventilation test—Vestibular bed-side examination—Vestibular schwannoma.

Otol Neurotol **36:**303–306, 2015.

The hyperventilation test (HVT) can reliably evoke nystagmus in various pathological conditions of the central and peripheral vestibular systems in cases in which a latent vestibular asymmetry exists (1–8). The HVT does not rely on the properties of the vestibulo-ocular reflex, and the percentage of false positives in subjects not affected by vestibular diseases is very low (1).

A high incidence of hyperventilation-induced nystagmus (HVIN) has been reported in vestibular neuritis and vestibular schwannomas (VS) (1,3–8). The most typical pattern of vestibular deficits in VS exhibits caloric hypofunction of the affected side, head shaking–induced nystagmus (HSIN) and vibration-induced nystagmus (VIN) that beat toward the affected side, paretic HVIN (p-HVIN) or excitatory HVIN (e-HVIN), and a positive head thrust test (HTT) when the affected side is tested (Fig. 1) (4–8).

Objectives

This study is focused on HVIN in vestibular schwannoma (VS):

1. to standardize HVT procedure using the measurement of end-tidal CO_2 pressure (P_{EtCO2}) through a ''side-stream'' capnographic method (9);
2. to determine the frequency and patterns of HVIN in VS;
3. to determine the correlations between HVIN patterns and VS size;
4. to determine the correlations between HVIN and other signs of vestibular asymmetry: HSIN, VIN, unilateral caloric hyporeflexia, and head thrust–induced saccades (HTIS); and
5. to compare HVIN in VS and unilateral chronic vestibular neuritis (CVN).

Address correspondence and reprint requests to Luigi Califano, Department of Audiology and Phoniatrics, ''G. Rummo'' Hospital, Via A. Lepore, A4 bis, 82100 Benevento, Italy; E-mail: luigi.califano@tin.it

The authors disclose no conflicts of interest.

Supplemental digital content is available in the text.

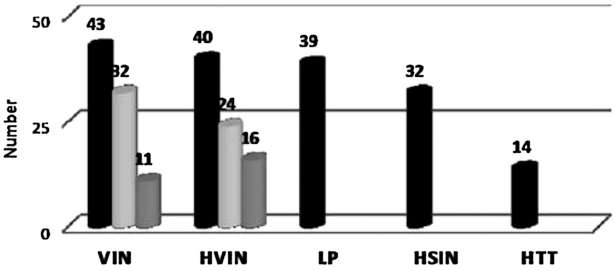

FIG. 1. Vestibular signs in VS. VIN indicates vibration-induced nystagmus; HVIN, hyperventilation-induced nystagmus; LP, labyrinthine prevalence; HSIN, head shaking–induced nystagmus; HTT, head thrust test positive cases. *Black columns* indicate overall cases; *light gray columns*, inhibitory VIN or HVIN; *gray columns*, excitatory VIN or HVIN.

Patients and Interventions (see also Supplemental Digital Content 1, http://links.lww.com/MAO/A271)

- 45 patients with VS
- 30 patients with CVN
- 20 healthy subjects, necessary to exclude the possibility that the metabolic modifications induced by HVT evoke nystagmus in normal subjects too.

Main Outcome Measures

- the absence or presence of HVIN;
- the pattern of HVIN: p-HVIN, if the slow phases beat toward the tumor; e-HVIN, if the slow phases beat toward the healthy side; i.e., the slow phases that beat towards the tumor indicate a correspondence between HVIN and a hypofunctional labyrinth;
- HVIN SPV;
- the correlation between the HVIN patterns and tumor size;
- P_{EtCO2} values at 0, 30, 60, 90, and 120 seconds after the beginning of the HVT and at the appearance and disappearance of HVIN.

RESULTS

Statistical Analysis (see Supplemental Digital Content 2, http://links.lww.com/MAO/A272)

Hyperventilation Test

Differences in the P_{EtCO2} values and in the lowest P_{EtCO2} value observed between 50 and 75 seconds from the beginning of the HVT among the three groups were not significant at any control point (Table 1).

HVIN was not observed in the control group.

In VS, a horizontal spontaneous nystagmus with slow phases that beat toward the affected side was observed in five patients with VSs of 20, 28, 28, 30, and 42 mm. HVIN was observed in 40 of 45 cases (88.9%), with onset at a mean P_{EtCO2} value of 16.5 ± 1.15 mm Hg and disappearance at a mean value of 21.3 ± 4.01 mm Hg. HVIN was excitatory in 24 cases, in three cases reversing a spontaneous nystagmus, and paretic in 16 cases, in two cases strengthening a spontaneous nystagmus. A biphasic HVIN was observed in a 20-mm schwannoma. p-HVIN was evoked at a mean P_{EtCO2} value of 16.47 ± 1.19 mm Hg and e-HVIN at a mean P_{EtCO2} value of 16.62 ± 1.06 mm Hg ($p = 1$). The mean value of HVIN SPV was 7.1 ± 6.7 degrees/sec with a range of 6.2 to 13 degrees/sec, and no significant difference was observed between the excitatory and paretic patterns. The mean sizes of VS in the excitatory and paretic patterns of HVIN were 19.04 ± 10.56 mm for the e-HVIN and 19.06 ± 11.01 mm for the p-HVIN ($p = 1$). The difference in the VS size in the HVIN+ (19.05 ± 10.60 mm) and HVIN− (8.40 ± 2.19 mm) cases was significant ($p = 0.009$). The difference in the lowest P_{EtCO2} values in the HVIN+ and HVIN− cases (12.08 ± 1.81 and 12.03 ± 0.55 mm Hg, respectively) was not significant. The HVIN distribution in relation to the size of the tumor according to Sanna's classification is presented in Table 2; the differences in the distributions of the HVIN patterns between the various classes were not significant ($p = 0.48$).

In CVN, horizontal spontaneous nystagmus with slow phases beating toward the affected side was observed in 6 of 30 cases (20%). HVIN was observed in 12 of 30 cases (40%), 11 p-HVIN and 1 e-HVIN; HVIN appeared at a P_{EtCO2} mean value of 16.1 ± 1.46 mm Hg and disappeared at a P_{EtCO2} mean value of 21.0 ± 3.76 mm Hg. The mean HVIN SPV was 6.1 ± 6.7 degrees/sec, with a range of 5.7 to 9.3 degrees/sec.

HVIN was significantly more frequent in VS than in both the control ($p < 0.0001$) and CVN ($p < 0.0001$) groups. Comparing VS group and CNV group, e-HVIN was significantly more frequent in VS group ($p < 0.001$), whereas no significant difference was observed between the incidence of the p-HVIN in the two groups ($p = 0.9$).

TABLE 1. *Mean P_{EtCO2} values (mm Hg) in the control, schwannoma, and chronic vestibular neuritis groups during the HVT*

	Baseline	30 s	60 s	120 s	180 s	Minimum value
Control group	34.1 ±1.28	20.4 ±1.28	12.6 ±1.17	27.7 ±1.86	30.8 ±1.73	12.0 ±1.99
Schwannoma group	33.9 ±1.53	20.2 ±1.37	12.1 ±1.66	28.9 ±1.58	31.7 ±1.38	12.1 ±1.74
Chronic vestibular neuritis group	34.6 ±1.34	20.5 ±1.19	12.5 ±1.21	26.9 ±1.24	30.7 ±1.67	12.2 ±1.71

The P_{EtCO2} differences between the healthy controls and the patients affected by an VIIIth cranial nerve schwannoma or chronic vestibular neuritis were not significant at any time point. The lowest P_{EtCO2} values were registered between 50 and 75 seconds from the beginning of the HVT.

TABLE 2. *Distribution of paretic and excitatory HVIN according to Sanna's classification of vestibular schwannomas*

	Grades 0–1 (≤10 mm)	Grade 2 (11–20 mm)	Grade 3 (21–30 mm)	Grade 4 (31–40 mm)	Grade 5 (>40 mm)	Overall
Paretic HVIN	5	6	3	1	1	16
Excitatory HVIN	4	14	2	3	1	24
	9	20	5	4	2	40

Differences are not significant ($p = 0.55$)

Other Vestibular Tests (see Supplemental Digital Content 3, http://links.lww.com/MAO/A273).

CONCLUSIONS

To our knowledge, for the first time a capnographic measurement of the P_{EtCO2} has been proposed to standardize HVT.

In VS group, HVT presented high sensitivity in the detection of vestibular asymmetry with a positivity rate of 88.9%; this finding was significant when compared with the control group, in which HVIN was never present, and the CNV group, in which HVIN was present in 12 of 30 cases with a high prevalence of the paretic pattern (11 of 12 cases). In the VS group, the HVIN specificity in the detection of the hypofunctional side (p-HVIN: 35.6%) was lower. The most relevant difference between HVIN in VS group and CNV group was the highest incidence of the e-HVIN in VSs ($p < 0.001$).

In the VS and CVN groups, the P_{EtCO2} value that triggered HVIN was homogeneous, at approximately 16 mm Hg. To standardize the test, we suggest that the HVT should be interrupted at this P_{EtCO2} value if a capnographic measurement is performed; otherwise, more generally, if a capnographic measurement is not performed, a 60-second hyperventilation is sufficient to lower the P_{EtCO2} to levels that act on the vestibular system, if a vestibular disease is present.

The average size of VS was 19.4 mm in the e-HVIN and 19.6 mm in the p-HVIN ($p = 1$). No significant correlation was noted between HVIN patterns and VS distribution according to Sanna's classification (10) (Table 2). The HVIN− cases exhibited a smaller mean size than the HVIN+ cases (8.4 vs. 19.05 m, respectively, $p = 0.009$), even if the small number of HVIN− cases was not sufficient to draw a definite conclusion.

We accept the hypothesis that the presence of demyelinated fibers causes the e-HVIN (2), whereas the p-HVIN is observed in the absence of demyelination or if discontinuity of neural fibers is present. Decreased $PaCO_2$, decreased Ca^{2+}, alkalosis, and hypocapnia induced through the HVT cause a transient improvement of conduction along partially demyelinated fibers because demyelination locally reduces the blood-cerebrospinal fluid barrier, which causes metabolic alterations at the CSF level too. It is possible that rupture and demyelination may be absent in the smallest VSs; in the largest tumors, it is most likely that demyelination and rupture occur more frequently. The lack of demyelination areas and nerve rupture could justify the absence of HVIN in the smallest tumors; in these cases, the caloric test, HST, the vibration test (VT), and the head thrust test (HTT) might reveal vestibular asymmetry or a unilateral abnormal vestibulo-ocular reflex (Table 3).

Another potential mechanism of the e-HVIN could be the stimulation of partially damaged neural fibers caused by the reduction of the $PaCO_2$, H^+, and Ca^{2+} concentrations, which could provoke a transitory upregulation of the central vestibular compensation or the activation of threshold channels as demonstrated in the sensory fibers (11,12). e-HVIN and VIN were both present in eight cases, an excitatory VIN in three additional cases. Because VIN is caused by a mechanical and asymmetrical stimulation of the labyrinths and not by metabolic mechanisms, we hypothesize that in some cases e-HVIN could be evoked through a mechanism of peripheral denervation hypersensitivity.

p-HVIN could be induced by the inhibitory action of hyperventilation on compensatory cerebellar mechanisms (13). This interpretation could be indirectly confirmed by the post-therapeutic findings: after the surgical removal of VS, p-HVIN was exclusively observed (4,5,7), whereas the presence of e-HVIN was reported after stereotactic radiotherapy, which conversely induces demyelination of the neural fibers (14). The fact that HVT disrupts central vestibular compensation explains the increased frequency of p-HVIN compared with e-HVIN in the CVN, where

TABLE 3. *Vestibular signs in HVIN− schwannomas*

Size (mm)	HVIN	HSIN	VIN	HTT	Caloric test on the affected side
5	Absent	Absent	Excitatory	Negative	Normoreflexia
8	Absent	Paretic	Paretic	Negative	Hyporeflexia
9	Absent	Paretic	Excitatory	Negative	Hyporeflexia
9	Absent	Absent	Paretic	Negative	Hyporeflexia
11	Absent	Absent	Paretic	Negative	Hyporeflexia

HVIN indicates hyperventilation-induced nystagmus; HSIN, head shaking–induced nystagmus; VIN, vibration-induced nystagmus; HTT, head thrust test.

presumably demyelination or rupture of neural fibers is not present.

The caloric test (86.7%), HST (75.6%), VT (97.8%), and HVT (88.9%) exhibit high sensitivities in the identification of vestibular asymmetry in VS, whereas HTT is the least sensitive test (31.1%). The specificities of the tests in the identification of the affected side in VS markedly differ. The caloric test, HST, and HTT exhibit 100% specificity, VT demonstrates 71.1% specificity, whereas the HVT only exhibits 35.5% specificity, but the presence of an e-HVIN, i.e., the mismatch between the direction of e-HVIN and the side of the vestibular hyporeflexia, is really the most relevant element of suspicion for an expansive disease of the VIIIth cranial nerve.

HVT is not a magic test: its results have to be framed within the context of a more general audiological and vestibular diagnostic battery.

REFERENCES

1. Bance ML, O'Driscoll M, Patel N, Ramsden RT. Vestibular disease unmasked by hyperventilation. *Laryngoscope* 1998;108:610–14.
2. Davis FA, Becker FO, Michael JA, et al. Effects of intravenous sodium bicarbonate, disodium editate (Na2EDTA) and hyperventilation on visual and oculomotor signs in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1970;33:723–32.
3. Robichaud J, Des Roches H, Bance ML. Is Hyperventilation-induced nystagmus more common in retrocochlear vestibular disease than in end-organ vestibular disease? *J Otolaryngol* 2002;31:140–3.
4. Minor LB, Halswanter T, Strauman D, et al. Hyperventilation-induced nystagmus in patients with vestibular schwannoma. *Neurology* 1999;53:2158–67.
5. Choi KD, Cho HJ, Koo JW, et al. Hyperventilation-induced nystagmus in vestibular schwannoma. *Neurology* 2005;64:2062.
6. Choi KD, Kim JS, Kim HJ, et al. Hyperventilation-induced nystagmus in peripheral vestibulopathy and cerebellopontine angle tumor. *Neurology* 2007;69:1050–9.
7. Califano L, Melillo MG, Vassallo A, Mazzone S. Hyperventilation-induced nystagmus in a large series of vestibular patients. *Acta Otorhinolaringol Ital* 2011;31:17–26.
8. Mandalà M, Giannuzzi A, Trabalzini F, Nuti D. Hyperventilation-induced nystagmus in vestibular schwannoma and unilateral sensorineural hearing loss. *Eur Arch Otorhinolaryngol* 2013;270:2007–11.
9. Jaffe MB. Mainstream or sidestream capnography? http://www.oem.respironics.com/Downloads/Main%20vs%20Side.pdf.
10. Sanna M. Acoustic neurinoma and other CPA tumors. *Monduzzi editore Bologna* 1999:3–9.
11. Macefield G, Burke D. Paraesthesiae and tetany induced by voluntary hyperventilation. *Brain* 1991;114:527–40.
12. Mogyoros I, Kiernan MC, Burke D, et al. Excitability changes in human sensory and motor axons during hyperventilation and ischaemia. *Brain* 1997;120:317–25.
13. Walker MF, Zee DS. The effect of hyperventilation on down-beat nystagmus in cerebellar disorders. *Neurology* 1999;53:1576–9.
14. Bradley JP, Hullar TE, Neely JG, Goebel JA. Hyperventilation-induced nystagmus and vertigo after stereotactic radiotherapy for vestibular schwannoma. *Otol Neurotol* 2012;32:1336–8.