The Laryngoscope

Investigating Hyperventilation Syndrome in Patients Suffering From Empty Nose Syndrome

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Objectives/Hypothesis: Patients with empty nose syndrome (ENS) following turbinate surgery often complain about breathing difficulties. We set out to determine if dyspnea in patients with ENS was associated with hyperventilation syndrome (HVS). We hypothesized that lower airway symptoms in ENS could be explained by HVS.

Study Design: Observational prospective study.

Methods: All consecutive patients referred to our center for ENS over 1 year were invited to participate. Patients completed the Nijmegen score and underwent a hyperventilation provocation test (HVPT) and arterial blood gas and cardiopulmonary tests. HVS was defined by a delayed return of the end-tidal partial pressure of carbon dioxide in the expired gas to baseline during HVPT. Patients with HVS were asked to complete the Sinonasal Outcome Test (SNOT)-16 questionnaire before and after a specific eight-session respiratory rehabilitation program.

Results: Twenty-two of the 29 patients referred for ENS during the study period were eligible for inclusion and underwent a complete workup. HVS was diagnosed in 17 of these patients (77.3%). In the five patients who completed the SNOT-16, the score was significantly lower after rehabilitation.

Conclusions: This study suggests that HVS is frequent in patients with ENS, and that symptoms can be improved by respiratory rehabilitation. Pathophysiological links between ENS and HVS deserve to be further explored.

Key Words: Empty nose syndrome, hyperventilation syndrome, nasal obstruction, dyspnea, hyperventilation test.

Level of Evidence: 2b

***Laryngoscope*, 127:1983–1988, 2017**

INTRODUCTION

Empty nose syndrome (ENS) is a rare clinical entity occurring after surgical procedure on the nasal respiratory mucosa of the inferior or middle turbinates or, more rarely, on the nasal septum.[1–4] It was first reported by Eugene Kern in the 1990s, and symptoms may be as varied as paradoxical nasal obstruction, nasal or pharyngeal dryness, sleep disorders, and nasal pain.[2,3,5] The physical examination of patients with ENS is poor, as nasal endoscopy is usually normal other than the consequences of the turbinate surgery. Imaging (besides the thickness of turbinal mucosa particularly in the central and posterior nasal region[6]) and functional tests are also normal.[7–9] ENS is associated with psychological symptoms such as frustration, irritability, anger, anxiety, and depression, as well as chronic fatigue, which all lead to poor tolerance of the symptoms.[7–10] Local treatment, nasal hygiene, and psychological support can help the patient better tolerate the symptoms.[1,11] Surgical reconstruction of the inferior turbinate gives varied results.[1,11–13] However, there is an overall lack of effective therapies, and patients often suffer from poor quality of life. Hence, it is important to understand the pathophysiology to improve management of these patients.

In addition to nasal discomfort, patients with ENS often complain of similar lower airway symptoms to those

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Editor's Note: This Manuscript was accepted for publication March 7, 2017.

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This study was presented at the 26th Congress of European Rhinologic Society, Stockholm, Sweden, July 3–7, 2016.

D.M., B.L, J.F.P., and S.A. participated in the study design and writing of the article. E.B., L.B., and M.D.D. participated in the study design, supervision, data analysis, and writing of the article. F.Z.-L. and A.C. participated in the study design, data analysis, and writing of the article. D.I. participated in the study design and data analysis.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.26599

found in patients with hyperventilation syndrome (HVS), such as chronic or exertion dyspnea and shortness of breath. HVS is characterized by a variety of respiratory, cardiac, or neurological symptoms induced by physiologically inappropriate and reproducible hyperventilation.[14–18] The Nijmegen questionnaire, comprising 16 items corresponding to the most frequent symptoms of HVS, can be used as a screening tool.[19–21] Each item of the questionnaire is scored from 0 to 4, giving a maximum score of 64, and a score of >23 is commonly used as a cutoff.[18] Other suggestive parameters for HVS are hypocapnia and respiratory alkalosis. However, a low Nijmegen score and normal arterial blood gas values do not rule out a diagnosis of HVS. The more specific hyperventilation provocation test (HPVT) can diagnose HVS in up to 79% of the cases.[20] A positive HPVT is defined as an end-tidal pressure of CO_2 in the expired gas ($EpCO_2$) lower than 30 mm Hg or 90% of the $EpCO_2$ at baseline after a 5-minute recovery period following 3 minutes[22] of voluntary hyperventilation.[19] It has been shown that specific respiratory physiotherapy is an effective treatment of HVS, enabling the patient to recover adapted ventilation.[19,22,23]

We hypothesized that lower airway symptoms in ENS could be explained by HVS. The aim of this study was therefore to identify HVS in patients suffering from ENS.

MATERIALS AND METHODS

Patients and Study Design

In this prospective single-center study, all consecutive patients who were referred to our center for ENS between October 2013 and November 2014 were invited to participate. Criteria for inclusion were: 1) a history of endonasal surgery of the inferior or middle turbinate; 2) at least two symptoms of ENS such as paradoxical nasal obstruction, nasal pain, rhinopharyngeal dryness, lack of nasal airflow sensation, hypersensitivity to cold air, sleep disorder, and dyspnea; 3) a normal nasal endoscopy other than the consequences of the turbinate surgery, with healthy turbinates (no scabs or enanthem); 4) absence of abnormalities on sinus computed tomography scan other than the consequences of the prior surgery and nasal mucosal thickening[6,9]; and 5) a binasal resistance lower than 3 Pa/L/s, measured with posterior rhinomanometry (BIOPAC MP30B; BIOPAC Systems Inc., Goleta, CA).[2,3] Patients under 18 years old or those with a contraindication to the HVPT or cardiac stress test were excluded.

All the patients filled in the Nijmegen questionnaire, including questions about breathlessness, and underwent an HVPT. Patient characteristics such as age, gender, body mass index, and medical history of allergy were recorded. Turbinate surgery was classified as inferior turbinate resection, middle turbinate resection, inferior and middle turbinate resection, or inferior turbinoplasty. Tobacco use and any history of anxiety or depressive disorders were also reported. All the patients gave their informed consent for the use of their data for research purposes. The study was approved by the Committee for the Evaluation of Observational Research Protocols of the Society of Pneumology of French Language (CEPRO 026).

Functional Tests

Each participant underwent spirometry, plethysmography, and diffusing capacity of the lung for carbon monoxide (DLCO) measurement according to the American Thoracic Society/European Respiratory Society consensus guidelines.[24] The HVPT was conducted by a capnography via a mouthpiece and a nose clip (Vmax; SensorMedics, Yorba Linda, CA). It was considered positive if the $EpCO_2$ was <30 mm Hg or <90% of the initial $EpCO_2$ after a 5-minute recovery period following 3 minutes of voluntary hyperventilation.

If the HVPT was positive, the patients underwent a cardiopulmonary cycle-ergometer stress test (SensorMedics) to measure oxygen consumption (VO_2 max), and a chest x-ray to exclude differential diagnosis.[25] Lung function tests were considered normal if the forced expiratory volume (FEV_1)/forced vital capacity (FVC) ratio was >0.8 of total lung capacity and the DLCO >80% of the predictive value.

VO_2 max was considered normal if the maximum heart rate was >85% of the theoretical maximum rate, VO_2 >84% of the predicted value, and respiratory frequency at VO_2 peak <60 breaths per minute.

If the HVPT was negative, the patients were considered free of HVS.

Treatment of HVS

Each patient with HVS was invited to undergo respiratory rehabilitation. This was performed by a single experienced physiotherapist, specialized in breathing correction, once a week for 2 months in sessions lasting 40 minutes. The doctor was not present at these sessions. The rehabilitation was based on reproduction of the symptoms by voluntary hyperventilation and on educating the patient about the symptoms. The physiotherapist also provided supportive psychotherapy at the same time to diminish the psychological impact. Corrective treatment included learning diaphragmatic breathing and hypoventilation techniques (apnea of 4 seconds after each inspiration) and identifying and eliminating parasitic respiratory movements. Before the eight respiratory rehabilitation sessions, and 6 months later, the patients were contacted by phone or by mail and asked to fill in a quality-of-life questionnaire to assess the impact of the rehabilitation on their quality of life. For this we used the Sinonasal Outcome Test (SNOT-16).[26] This questionnaire, for which a French translation has been validated, is correlated with the score of the generic study Short Form 36 and has been validated in chronic rhinosinusitis with nasal polyps.[27] It is the only questionnaire evaluating quality of life associated with rhinologic symptoms as opposed to the SNOT 20-25 questionnaires, which evaluate the severity of the symptoms but not their repercussions. No midterm evaluation of the program was performed by the ear, nose, and throat or lung specialist.

Statistical Analysis

The patients were classified into two groups according to the results of the HVPT: patients with HVS (HVS group) and patients without (non-HVS group). We then compared the age, gender, body mass index (BMI), history of allergy, tobacco use, binasal resistance, Nijmegen score, and dyspnea criteria between the two groups. We compared the results of functional lung tests between the two groups: FEV_1, FVC, FEV_1/FVC ratio, total lung capacity, and DLCO. We also compared the results of HVPT (baseline $EpCO_2$, $EpCO_2$ immediately after voluntary hyperventilation, $EpCO_2$ after a 5-minute recovery period). All analyses were performed using a statistical software package (Statview 4; SAS Institute, Inc., Cary, NC). Data are expressed as mean ± standard deviation.

To compare the two groups, we used the Mann-Whitney test for continuous variables and the χ^2 test for categorical variables. The χ^2 with Yates correction was used for tables with very small expected frequencies. Correlations between variables were evaluated using the least-squares linear regression technique. We calculated the sensitivity, specificity, and positive predictive value of the Nijmegen score and dyspnea symptom for the diagnosis of HVS. For all comparisons, P values $<.05$ were considered significant.

RESULTS

Study Population

During the study period, 29 patients were referred to our center for ENS. Seven patients were not included, six who refused to participate and one due to heart failure. Our study population thus comprised 22 patients who underwent a complete workup to detect HVS. There were 14 men (63.7%) and eight women (36.3%). The mean age was 42.5 ± 12.1 years and mean BMI was 23.9 ± 4.2 kg/m^2. Four patients (18.2%) were active tobacco users, and two patients (9.1%) presented allergic manifestations. The type of nasal surgery and symptoms are listed in Table I. Nineteen patients (86.5%) had undergone a turbinate resection and three (13.5%) a turbinoplasty. A submucosal resection had been performed in one case, and two patients had undergone a radiofrequency volumetric tissue reduction of inferior turbinates but with a short-term postoperative complication—damage of the overlying mucosa observed for 8 weeks after surgery. Five of the patients (23%) had an anxiodepressive disorder, and 12 (54.5%) complained of sleep disturbance.

Prevalence of HVS

Seventeen of the 22 patients (77.3%) were diagnosed with HVS (positive HVPT and negative functional tests). There was no difference in patients from the HVS and non-HVS groups in terms of age, BMI, type of turbinate surgery, symptoms, tobacco use, medical history of allergy, or binasal resistance. The clinical characteristics of the patients with and without HVS are compared in Table II. There was no significant difference between the two groups concerning the functional lung tests, as shown in Table III. None of the patients who were current smokers or had a medical history of allergy had chronic obstructive pulmonary disease. All patients had normal FEV%, FVC%, DLCO% values (data not shown). Baseline $EpCO_2$ was significantly lower in the patients from the HVS group (32.9 ± 3.6 mm Hg vs. 36.6 ± 2.7 mm Hg; $P = .0231$). $EpCO_2$ after 5 minutes of recovery was also significantly lower in the patients from the HVS group (23.8 ± 4.4 mm Hg vs. 35.0 ± 1.22 mm Hg; $P < .01$). Dyspnea was reported by 15 patients (88.2%) in the HVS group versus two (40%) in the non-HVS group ($P = .03$). Ten of the 17 patients (58.8%) in the HVS group had a positive Nijmegen score compared to two of the five patients (40%) in the non-HVS group. The Nijmegen score had a sensitivity of 59%, a specificity of 60%, and a positive predictive value of 83% for the diagnosis of HVS. Patient-reported dyspnea had a sensitivity of 88%, specificity of 80%, and a positive predictive value of 93% for the diagnosis of HVS.

TABLE I.
Baseline Characteristics of the 22 Patients With Empty Nose Syndrome.

Characteristics	No.	%	Mean ± SD
Age, yr			42.5 ± 12.1
Body mass index, kg/m^2			23.89 ± 4.25
Gender			
Male	14	63.7	
Female	8	36.3	
Endonasal surgery			
Inferior turbinate resection	18	81.8	
Middle turbinate resection	0	0	
Inferior and middle turbinate resection	1	4.5	
Turbinoplasty	3	13.7	
Symptoms			
Nasopharyngeal dryness	14	63.7	
Nasal pain	13	59.1	
Sleep disorder	11	50	
Nasal obstruction	18	81.8	
Nasal crusting	10	45.4	
Active smoking			
Yes	4	18.2	
No	18	81.8	
Medical history of allergy			
Yes	2	9.1	
No	20	90.9	

SD = standard deviation.

Results of the SNOT-16 Before and After Respiratory Rehabilitation

The respiratory rehabilitation program was performed in five patients with HVS (30%) and all of them answered the SNOT-16 questionnaire before and after the eight respiratory rehabilitation sessions. The mean score was significantly lower after rehabilitation (27.6 ± 4.1 vs. 20.4 ± 2.3; $P = .02$). The results of the SNOT-16 scores obtained before and after rehabilitation are shown in Figure 1.

DISCUSSION

Our results show that ENS was associated with HVS in 77.3% of the patients in our study population. This is the first time that such an association has been identified.

ENS is a rare clinical entity most often occurring after turbinate surgery. In a recent study, ENS with a smaller inferior turbinate volume is significantly associated with specific items from the SNOT-25 questionnaire such as excessive dryness and facial pain.[28] However, in our series, we also describe three cases of ENS after surgery only affecting the mucosal surface of the turbinates (one case of submucosal resection and two of radiofrequency volumetric tissue reduction of inferior turbinates). Our findings are in accordance with those of Coste et al.[3] and Sozansky et al.[29] who defined an ENS subtype with sufficient-appearing turbinate tissue.

TABLE II.
Comparison of Clinical Characteristics Between HVS and Non-HVS Groups.

Characteristics	HVS Patients, n = 17	Non-HVS Patients, n = 5	*P*
Age, yr, mean ± SD	41.2 ± 11.9	46.8 ± 12.9	.34
Body mass index, kg/m^2, mean ± SD	24.2 ± 4.4	22.6 ± 3.6	.38
Endonasal surgery, n (%)			
Inferior turbinate resection	15 (88.2)	3 (60)	.29
Middle turbinate resection	0 (0)	0 (0)	NC
Inferior and middle turbinate resection	0 (0)	1 (20)	.08
Turbinoplasty	2 (11.7)	1 (20)	.69
Symptoms, n (%)			
Nasopharyngeal dryness	10 (58.8)	4 (75)	.31
Nasal pain	10 (58.8)	3 (50)	.42
Sleep disorder	10 (58.8)	2 (33.3)	.09
Nasal obstruction	15 (88.2)	3 (50)	.17
Nasal crusting	8 (47)	2 (33.3)	.42
Active smoking, n (%)			
Yes	3 (17.6)	1 (20)	.95
No	14 (82.4)	4 (80)	
Medical history of allergy, n (%)			
Yes	2 (11.7)	0 (0)	.5
No	15 (88.3)	5 (100)	
Binasal resistance, cm H_2O/L/s, mean ± SD	1.37 ± 0.18	1.36 ± 0.84	.68

HVS = hyperventilation syndrome; NC = not calculated; SD = standard deviation.

Patients with ENS often complain of nasal breathing discomfort and a variety of other symptoms including frequent dyspnea. Diagnosing HVS is a matter of debate.[18] Although the Nijmegen score has a sensitivity of 91% and a specificity of 95% in the general population,[20] it has not been not formally established as a diagnostic test for HVS. The HVPT is fast, simple and noninvasive, and thus constitutes a good diagnostic tool for HVS.[30]

It has recently been suggested that HVS could be diagnosed based on two of the following criteria: a Nijmegen Score higher than 23, recurrence of two symptoms during the HVPT, and a delayed return of $EpCO_2$ to the baseline value during the HVPT, with other functional tests being negative.[30] We chose to diagnose HVS with a positive HVPT test and no evidence of obstructive, restrictive or interstitial lung disease on chest radiography or the functional lung tests, or of cardiac limitation on the cardiopulmonary stress test. In our study population, we showed that dyspnea had a higher positive predictive value for HVS than the Nijmegen score. This can be explained by the fact that a lot of the items of the Nijmegen questionnaire are also symptoms of ENS, leading to a lower performance of the Nijmegen score for diagnosing HVS in ENS patients. It therefore stands to reason that the Nijmegen score is not the ideal tool for investigating the prevalence of HVS in ENS patients.

TABLE III.
Comparison of Results of Functional Lung Test Between HVS and Non-HVS Groups.

Test, Mean ± SD	HVS Patients, n = 17	Non-HVS Patients, n = 5	*P*
FEV_1, % predicted	109.59 ± 12.59	112.60 ± 22.24	.33
FVC, % predicted	109.91 ± 16.61	121.8 ± 16.67	.16
FEV_1/FVC	82.97 ± 6.48	76.69 ± 10.74	.29
Total lung capacity, % predicted	102.59 ± 12.77	100.75 ± 12.04	.82
DLCO, % predicted	90.81 ± 9.93	89.75 ± 21.5	.67

DLCO = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume; FVC = forced vital capacity; SD = standard deviation.

Fortunately, ENS is a rare clinical entity, which explains our small study population. However, in spite of this small sample size, our study suggests that there could be an epidemiological link between ENS and HVS. The prevalence of HVS is estimated at around 6% in the general population,[14] whereas the prevalence of HVS in our ENS patients was 10-fold greater. This major difference in prevalence of HVS provides proof of evidence that there could be an epidemiological and physiopathological link between the two syndromes.

From a psychological point of view, ENS and HVS share common mechanisms. ENS is often associated with psychiatric disorders[3] including anxiodepressive and psychosomatic disorders that impact the quality of life of these patients. A recent study assessing psychological disorders in patients with ENS found that a majority of patients suffered from depression and anxiety (70% and 65%, respectively).[31] HVS is often triggered by psychological stress in an anxiodepressive context,[32] and is also associated with chronic fatigue syndrome.[33] Thus, turbinate surgery could constitute the initial psychological stress at the origin of the HVS in ENS patients. Stress may also

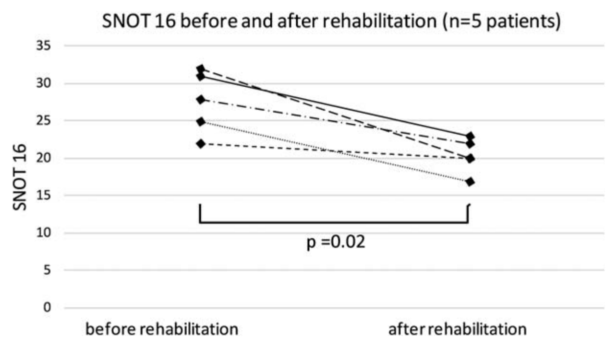

Fig. 1. Comparison of SNOT-16 scores before and after respiratory rehabilitation. SNOT = Sinonasal Outcome Test.

occur after the first episode of acute hyperventilation, which, in turn, could be worsened by the modification of nasal airflow dynamics and the modification of global airway resistance caused by turbinate surgery.

These two syndromes also share common respiratory symptoms in young patients.[33] The upper airways play an important role in lower airway function. Firstly, upper airway resistance represents 70% of the global airway resistance. This resistance is crucial for respiration both in the inspiratory and the expiratory phases. In the inspiratory phase, the respiratory muscles act against this resistance, and the extra effort serves to recruit the maximum number of pulmonary alveoli.[34,35] This results in the most effective gas exchange and an increased cardiac and lung venous return. On the expiration phase, the resistance brought about by the turbinates maintains these pulmonary alveoli open, thus improving the efficiency of the ventilation and the gas exchange.[34] When "excessive" nasal surgery disturbs the nasal resistance, a dysfunction of the respiratory system could occur at the alveolar level, leading to poor gas exchange that could induce HVS. Secondly, in normal individuals, cold neuroreceptors in the nasal mucosa induce protective bronchoconstrictor responses, which are inhibited by a local anesthesia of the nasal mucosa.[36] Turbinate surgery damages the nerve endings and receptors located in the nasal mucosa and impairs this bronchoconstrictor response.[29] Resection of the inferior turbinate can reduce the "air conditioning" capacity of the nose (i.e., to warm and humidify the air) by up to 16%.[35] It has been shown in an animal model that lung inhalation of cold and dry air activates stretch receptors in the lung that in turn initiates a reflex via the pterygoid and vagus nerves.[37] This leads to nasal turbinate mucosa vasodilation to reduce the nasal airflow and protect the lung from cold and dry air inhalation. Turbinate resection could modify this reflex and give rise to a ventilatory dysfunction in the form of HVS. HVS could occur after surgery because of an absence of this control of inspired air. Although we do not know if the HVS was already present at the time of turbinate surgery in our study or if it was a complication of the surgery, it could be a predisposing factor to develop ENS after turbinate surgery. Further data are required to determine the incidence of HVS in a larger cohort of patients who have undergone turbinate surgery.

In view of all of these potential links between ENS and HVS, we hypothesized that treating HVS could improve the quality of life of ENS patients. There is currently a lack of treatment guidelines for ENS, and results are often discouraging. The basic approach consists of local treatment and nasal hygiene. Reconstruction of the inferior turbinate by submucosal hyaluronic acid gel injection gives good results for the first 6 months, but the gel is absorbed after 1 year. Submucosal implants can be translocated or expelled; results vary from one patient to another and can sometimes worsen the symptoms of ENS. Our treatment approach was to alleviate symptoms by a respiratory rehabilitation program. One limitation of the study is the small number of patients who underwent respiratory rehabilitation, and this may have introduced bias in evaluating the effectiveness of treatment. This reluctance to undergo rehabilitation could be geographical; some patients who were referred to our center had to travel quite a distance from home. Attending the rehabilitation program was therefore impractical for them. We found that both HVS and nasal discomfort (SNOT-16) scores improved with rehabilitation, suggesting that the program was effective. Furthermore, these results would substantiate the numerous physiopathological links between ENS and HVS, which deserve to be confirmed in a larger population. Respiratory rehabilitation could constitute a useful treatment approach in patients with ENS whose symptoms are not relieved by other means.

CONCLUSION

The present study demonstrates for the first time a high prevalence of HVS in patients with ENS who suffer from chronic dyspnea. The link between the two syndromes could be explained by a common psychological context and nasal injury from turbinate resection altering the respiratory control system. This would suggest that a patient's psychological status should be investigated as part of the workup before nasal surgery to prevent iatrogenic ENS. Patients with ENS should also undergo testing for hyperventilation to diagnose HVS, which could impact their quality of life. Our results deserve to be confirmed by larger studies, but, if confirmed, could lead to improved treatment guidelines consisting of systematic and specific rehabilitation program to improve quality of life.

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