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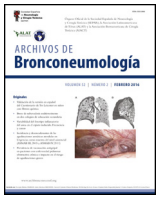

Original article

Hypercapnia Response in Patients With Obesity-Hypoventilation Syndrome Treated With Non-Invasive Ventilation at Home☆

Ramón Fernández Álvarez,* Gemma Rubinos Cuadrado, Ines Ruiz Alvarez, Tamara Hermida Valverde, Marta Iscar Urrutia, María José Vázquez Lopez, Pere Casan Clara

Servicio de Neumología, Área de Pulmón, Hospital Universitario Central de Asturias, Oviedo, Spain

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ABSTRACT

Introduction: Respiratory center (RC) dysfunction has been implicated in the pathogenesis of obesity-hypoventilation syndrome (OHS), and often requires treatment with home non-invasive ventilation (NIV). Our objective was to measure the effect of NIV on RC function in patients with OHS, and the factors that determine such an effect.
Methods: We performed a prospective, repeated measures study to evaluate hypercapnia response (HR) by determining the $p01/pEtCO_2$ ratio slope at baseline and after 6 months of treatment with NIV in a group of OHS patients. A threshold of 0.22 $cmH_2O/mmHg$ had previously been established in a control group, in order to differentiate optimal RC response from suboptimal RC response.
Results: A total of 36 cases were included, 19 men (52%) aged 65 (SD 9) years, 63% of whom had $p01/pEtCO_2$ below the reference value. Baseline $p01/pEtCO_2$ was 0.17 (SD: 0.14) $cmH_2O/mmHg$ and, after 6 months of NIV, 0.30 (SD: 0.22) cm $H_2O/mmHg$ (P=0.011). After 6 months of treatment with NIV, depressed RC function persisted in 12 cases (33%).
Conclusion: In total, 63% of OHS patients had RC dysfunction. The application of NIV improves RC function but not in all cases.

Respuesta a la hipercapnia en pacientes con síndrome obesidad-hipoventilación en tratamiento con ventilación no invasiva en domicilio

Palabras clave:
Obesidad-hipoventilación
Ventilación no invasiva
Respuesta a la hipercapnia
Apnea del sueño
Centro respiratorio

RESUMEN

Introducción: En la patogenia del síndrome de obesidad-hipoventilación (SOH) se ha postulado una disfunción del centro respiratorio, que muchas veces precisa la utilización de ventilación no invasiva (VNI) en domicilio para el tratamiento. Nuestro objetivo fue medir el efecto de la VNI en la función del CR en pacientes con SOH y los factores que lo determinan.
Métodos: Con un diseño prospectivo de mediciones repetidas se estudió la respuesta a la hipercapnia (RHC) midiendo la pendiente de la relación $p01/pEtCO_2$ en situación basal y tras 6 meses de tratamiento con VNI en un grupo de pacientes con SOH. Previamente en un grupo control se estableció un umbral en 0,22 $cmH_2O/mmHg$ para diferenciar la respuesta óptima (RO) de la respuesta subóptima (RSO) del CR.
Resultados: Se incluyeron 36 casos, 19 varones (52%), de 65 (DE: 9) años de edad; un 63% de ellos tenían un $p01/pEtCO_2$ por debajo del valor de referencia. El valor basal de $p01/pEtCO_2$ fue de 0,17 (DE: 0,14) $cmH_2O/mmHg$ y tras 6 meses de VNI fue de 0,30 (DE: 0,22) $cmH_2O/mmHg$ (p=0,011). Tras 6 meses de tratamiento con VNI, 12 casos (33%) mantienen una función deprimida de su CR.
Conclusión: Un 63% de los pacientes con SOH mostraron disfunción de su CR. La aplicación de VNI mejora la función del CR, aunque no en todos los casos.

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* Corresponding author.
E-mail address: enelllano@gmail.com (R. Fernández Álvarez).

Introduction

Obesity-hypoventilation syndrome (OHS) is defined as the combination of obesity, daytime hypercapnia, and night-time ventilatory disorder not explained by other causes.[1,2] It is a disease that is increasing in frequency in our setting, and home treatment with non-invasive ventilation (NIV) is often required. Indeed, OHS is currently one of the entities that most frequently requires the use of this type of treatment.[3,4]

The pathogenesis of OHS is multifactorial, and many mechanical and humoral factors are involved, along with changes in the control of breathing and the inability of the respiratory center (RC) to respond appropriately to increases in $PaCO_2$.[1,2,5,6] However, the role of each of these factors in the development of this entity has not been clarified.

The impulse generated by the RC is determined by measuring mouth pressure during the first 100 ms of inspiration (p01). In normal subjects, p01 increases with the increase of $paCO_2$, while in subjects with OHS, the p01 response is reduced.[6]

Data on the clinical usefulness of this test and the course of RC response in patients treated with NIV are still scant. Our hypothesis is that the study of the RC in patients with OHS will help detect dysfunction and measure the impact of NIV on RC function. Our objectives were to determine RC dysfunction in patients with OHS, to measure the effect of NIV on RC function, and to analyze possible determinant factors.

Materials and Methods

Using a prospective, repeated measurements design, patients diagnosed with OHS between March 2014 and March 2016 were included consecutively. OSH was defined as an association of obesity with a body mass index of at least 30 kg/m^2 and daytime pCO_2 greater than 45 mmHg, excluding cases with other causes of alveolar hypoventilation. The following variables were obtained from each patient: age, sex, body mass index (BMI), FEV1 (percentage predicted), apnea/hypopnea index (AHI), percentage of the night with SpO_2 <90% (T90), daytime PaO_2, $PaCO_2$ y HCO_3, ventilatory pattern: tidal volume (VC), inspiratory time (Ti), total time of each cycle (Ttot) and Ti/Ttot ratio. All patients were treated with NIV in ST mode using S9 VPAP ST equipment (ResMed), adapted to achieve comfort and normalization of PCO_2 and T90. NIV parameters (IPAP, EPAP, and respiratory rate) were collected, with the rate set at 2 breaths below the spontaneous respiratory rate measured during the adaptation period.

Patients receiving NIV were followed up at 6 months with determinations of arterial blood gases, night-time pulse oximetry (NPO) at home using NIV, and an analysis of the ventilator built-in software (BIS) focusing on treatment compliance (mean hours/day), residual AHI (events/hour), respiratory rate on NIV, percentage of spontaneous breaths, and air leaks (95th percentile in l/min). Patients who were non-compliant (less than 4 h/day average use), required supplemental oxygen, had exacerbations in the previous month, and those who, after 6 months of NIV therapy, had a daytime $PaCO_2$ greater than 46 mmHg and/or a T90 greater than 30% were excluded.

The ventilatory pattern was determined by measuring p01, inspiratory time (Ti), total time (Ttot), Ti/Ttot ratio, and tidal volume (TV) using the Hyp'Air compact+Muscle Study device (Medisoft). RC was studied with Read's modification of the hypercapnic rebreathing response method,[7] using Hyp'Air compact+Muscle Study, measuring the occlusion pressure in the first 100 ms of the inspiration (p01), while the patient was breathing a high oxygen mixture of 7% CO_2, with occlusions being performed up to a final $pEtCO_2$ of 70 mmHg. The results are shown as the slope of the least squares regression line resulting from $p01/pEtCO_2$ in cmH_2O/mmHg,

Ventilatory pattern and hypercapnic response were also studied in a group of 27 age-adjusted controls. The reference value for $p01/pEtCO_2$ was taken as the 25th percentile of the value obtained, which was 0.22 cm H_2O/mmHg. Using this value as the cut-off point, patients were divided into 2 groups: an RC response was considered optimal (oR) when the result was at least 0.22 cmH_2O/mmHg, otherwise it was suboptimal (sR).

Quantitative variables are expressed as mean (SD) and qualitative as percentages. Comparisons between quantitative variables were established between the oR and sR groups and between the initial and final values by comparison of means for independent and paired data (Student's *t*); Chi-squared was used for qualitative variables. The study was approved by the Research Ethics Committee of our center, and informed consent was obtained in writing from all patients included in the study.

Table 1
Baseline Values and After 6 Months of Treatment With NIV.

	Baseline	After NIV (6 months)	*P*
BMI	43.6 (8.5)	43.3 (8.6)	ns
Daytime pCO_2 (mmHg)	54 (3.8)	41.7 (2.2)	<0.0001
Baseline HCO_3 (mequiv/l)	27.4 (0.6)	24.4 (1.1)	0.012
p01 (cmH_2O)	2.7 (1.7)	2.7 (1.6)	ns
Tidal volume (ml)	745 (27)	753 (30)	ns
Ti (s)	1.2 (0.37)	1.19 (0.31)	ns
Ttot (s)	2.6 (1.1)	2.4 (0.9)	ns
Ti/Ttot	0.5 (0.3)	0.58 (0.18)	ns
AHI	40 (21)	4.3 (3.1)	0.0001
T90 (%)	84.3 (12)	13.3 (9)	0.0001
$p01/pEtCO_2$ (cmH_2O/mmHg)	0.17 (0.14)	0.30 (0.2)	0.011

AHI: apnea-hypopnea index; BMI, body mass index; T90: Night-time with SpO_2 <90%; Ti: inspiratory time; Ttot: total time of cycle.

Results

A total of 51 cases were evaluated, and 36 (70%) met the inclusion criteria, 19 men (52%), aged 65 (SD 9). Mean baseline $p01/pEtCO_2$ was 0.17 (SD 0.14) cmH_2O/mmHg and, after 6 months of NIV, 0.30 (SD 0.22) cmH_2O/mmHg (*P*=0.011). At baseline, 23 patients (63%) had $p01/pEtCO_2$ lower than the reference value: 0.11 (0.05) cmH_2O/mmHg, and 13 above: 0.33 (0.12) cmH_2O/mmHg (*P*=0.005). After treatment, 12 patients (33%) continued having suboptimal RC response. Table 1 shows the clinical and functional characteristics and therapeutic response of the complete series. Fig. 1 shows the course of the $p01/pEtCO_2$ values in each case.

If we compare the oR group with the sR group, we observe differences in only $p01/pEtCO_2$ and AHI, which are lower than in the sR group. After treatment, the oR group had a higher TV, lower programmed respiratory rate, and a significantly higher percentage of patient-initiated cycles. There were no significant differences in the ventilator parameters, hours of compliance, or air leak level (Table 2). None of the patients initially included in the oR group changed to the sR group in the second determination.

Discussion

In our series of OHS patients, we detected RC dysfunction compared to healthy individuals in 63% of cases. Treatment with NIV improved daytime pCO_2 and night-time oxygenation, and RC hypercapnic response. The most significant finding of our study is the identification of 3 different types of OHS patients, depending on their RC function. One group had RC function close to the reference value; another had significantly diminished function, and