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Effects of supplementary oxygen on obese patients with hypercapnia at 2 600 meters of altitude

Efectos del oxígeno suplementario en pacientes obesos con hipercapnia a 2 600 metros de altitud

Emily Rincón Álvarez[1], Francy Milena Cuervo[2], Viviana Parra Izquierdo[3], Natalia Agudelo[4], Daniel Botero[5], Daniel Arsanios Martin[6], Alirio Bastidas[7]

SUMMARY

Introduction: *Supplementary oxygen on a high flow in obese patients with elevated $PaCO_2$, carries the risk of worsening hypercapnia in patients at sea level. Nevertheless, at a altitude over 2 500 meters over sea level, is unknown the response to supplementary oxygen.* **Method:** *Randomized crossover clinical trial in subjects with BMI ≥ 30 kg/m² and initial arterial blood gases with a PCO_2 over 35 mmHg without supplementary oxygen, currently living for over a month at a height over 2 500 meters over sea level. Two tests were performed with supplementary oxygen of 28 % and 50 % to evaluate the $PaCO_2$ on arterial blood gases.* **Results:** *44 subjects were analyzed. The mean age, women and BMI was 57.36 ± 13.8 years, 59.1 %, 38.38 ± 6.31 kg/m², respectively. With supplemental oxygen at 28 % and 50 %, there was a -0.011 decrease in arterial pH (P = 0.003), an increase of 1 mmHg in $PaCO_2$ (P = 0.039), 16.6 mmHg in PaO_2 (P = 0.001) 0.007 mmHg at the HCO_3 (P = 0.795) and SO_2 levels of 1.62 % (P = 0.029).* **Conclusion:** *Supplementary oxygen at 28 and 50 % in obese patients with $PaCO_2$ greatest that 35 mmHg on heights over 2500 meters worsen hypercapnia on 1.00 mmHg.*

Keywords: *Obesity, altitude, hypercapnia, alveolar hypoventilation.*

RESUMEN

Introducción*: El oxígeno suplementario a alto flujo en pacientes obesos a nivel del mar con $PaCO_2$ elevada, se relaciona con mayor riesgo de empeoramiento de la hipercapnia. Sin embargo, a una altura superior a los 2 500 metros sobre el nivel del mar, se desconoce la respuesta al oxígeno suplementario.* **Métodos:** *Ensayo clínico cruzado aleatorizado en sujetos que viven a una altura superior a los 2 500 metros durante*

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ORCID: http://orcid.org/0000-0001-9972-9384[1]
ORCID: https://orcid.org/0000-0002-9754-765[2]
ORCID: https://orcid.org/0000-0003-2361-1018[3]
ORCID: https://orcid.org/0000-0002-8099-5495[4]
ORCID: https://orcid.org/0000-0002-2590-0756[5]
ORCID: https://orcid.org/0000-0003-1293-3759[6]
ORCID: https://orcid.org/0000-0002-8873-9779[7]

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[1]Pneumologist – Internal Medicine Universidad de la Sabana, Chía, Colombia. E-mail: emily.rincon.alvarez@gmail.com
[2]Reumatologist- Internal Medicine Universidad de la Sabana, Chía, Colombia. E-mail: francy.m.cuervo@gmail.com
[3]Internal Medicine Universidad de la Sabana, Chía, Colombia. E-mail: vivipaz16@hotmail.com
[4]Internal Medicine Universidad de la Sabana, Chía, Colombia. E-mail: nagudelov@gmail.com
[5]Medicine, Universidad de La Sabana. Chía. Colombia. E-mail: danybotero@hotmail.com,daniel.botero@unisabana.edu.co
[6]Internal Medicine Universidad de la Sabana, Chía, Colombia. E-mail: danielmaar@unisabana.edu.co
[7]MD, MSc. Pulmonologist and Clinical Epidemiologist, Universidad de la Sabana, Chía, Colombia.

más de 1 mes, con IMC ≥ 30 kg /m² y gasometría arterial inicial con PCO_2 superior a 35 mmHg sin oxígeno suplementario. Se realizaron dos pruebas con oxígeno suplementario al 28 % y al 50 % para evaluar la $PaCO_2$ en la gasometría arterial. **Resultados:** *Se analizaron 44 sujetos. La media de edad, mujeres e IMC fue de 57,36 ± 13,8 años, 59,1 %, 38,38 ± 6,31 Kg/m², respectivamente. Con oxígeno suplementario al 28 % y 50 %, se registró una disminución de -0,011 en el pH arterial (P = 0,003), aumento de 1 mmHg en $PaCO_2$ (P = 0,039), 16,6 mmHg en PaO_2 (P = 0,001), 0,007 mmHg en los niveles de HCO_3 (P = 0,795) y de SO_2 de 1,62 % (P = 0,029).* **Conclusión:** *El oxígeno suplementario al 28 y 50 % en pacientes obesos con $PaCO_2$ mayor de 35 mmHg en alturas superiores a 2 500 metros empeora la hipercapnia en 1,0 mmHg.*

Palabras clave: *Obesidad, altitud, hipercapnia, hipoventilación alveolar.*

INTRODUCTION

Supplementary oxygen is a common medical intervention, and it is administered in diverse scenarios. Supply oxygen to obese patients with $PaCO_2$ 45 mmHg in an acute setting worsens hypercapnia and with chronic use, increases mortality (1). Acute hypercapnia may produce a decrease of awareness, desensitization of neurotransmitters, myocardial contractility depression, an increase of brain blood flow and cranial pressure (2). The increase of $PaCO_2$ necessary to produce this response is wide, in healthy individuals there is no consciousness compromise up to 60-70 mmHg of $PaCO_2$, but patients with chronic hypercapnia develop symptoms when $PaCO_2$ reaches levels of 90 to 100 mmHg (3). On the other hand, obesity produces structural changes on the chest wall leading to restriction and pathological adaptation of the diaphragm. Also, there is a decrease of pulmonary distensibility, by a double mechanism: first an increase of pulmonary blood volume and second by an alveolar collapse due to the closure of the small airway, especially in pulmonary bases (4,5).

Most of the available studies that evaluate changes of $PaCO_2$ with oxygen supply were performed at sea level. British Thorax Society recommends the identification of patients with hypoventilation related to obesity syndrome as a group in whom the prescription of high concentration oxygen in ER department may generate hyperoxia, increase carbon dioxide (CO_2) and diminish pH (6). A study performed at sea level, on patients with hypoventilation related to obesity syndrome, found that supply of oxygen at 100 % worsened hypercapnia. This physiological response is explained by the decrease in minute ventilation in response to a minor stimulus of peripheral receptors, perceiving higher oxygen concentrations and increase of alveolar hypoventilation leading to higher dead space. For these reasons, oxygen therapy must be administered with precaution, given the fact that it can increase $PaCO_2$ over 4 mmHg (95 % CI, 3.3-6.7; P<0.01) (2). Patients with obesity and alveolar hypoventilation syndrome at high altitudes, the effect of oxygen administration was evaluated, finding that, with a inspired oxygen fracction of 50%, there was a significant increase of 3 mmHg (95 % CI, 0.13-0.49; P = 0.012) in $PaCO_2$ and reduction in pH -0.014 (95 % CI, -0.023-0.005; P < 0.011) (7).

At a higher altitude, the level of PaCO2 above which the administration of oxygen in obese patients becomes a deleterious treatment is unknown. Understanding the ventilation and oxygenation in obese patients living over 2 500 above sea level, may modify therapeutically and follow up management, as previous studies have determined at different altitude.

METHODOLOGY

Randomized crossover clinical trial, in patients with BMI ≥ 30 kg/m² and arterial blood gases at the start with a $PaCO_2$ over 35 mmHg to the ambient air, currently living over 2 500 m above sea level (at least a month). Two samples were processed with a FiO_2 of 28 % and 50 % to watch the changes of $PaCO_2$ in the arterial blood gases with a time interval of 30 minutes between both samples. The study was performed at Clínica Universidad de La Sabana physiology laboratory on the patients meeting these criteria on the time-lapse of august 2014 and October 2015.

Participants

Inclusion criteria were patients older than 18 years, obese (> 30 kg/m^2), initial arterial blood gases with $PaCO_2$ over 35 mmHg breathing room air, residents for at least the last month over 2 500 above sea level and accepting the participation on the study. Patients were excluded if they had a history of the chronic pulmonary obstructive disease (relation FEV_1/FVC post β_2 < 0.7 or a relation under the below limit), other causes of hypoventilation as neuromuscular diseases, patients with positive pressure management, recent (less than 15 days) infections, current smoking, imaging (X-ray or CT scan) demonstrating structural pulmonary pathology, previous renal pathology, decompensated heart failure, arteriovenous fistula, infection or vascular disease at the puncture site, use of anticoagulant or coagulation disease.

Sample size

Based on previous studies observing baseline $PaCO_2$ on subjects with FiO_2 of 21 %, 28 %, 50 %, and 100 % of 48.7±3.8 mmHg, 53.25±4.5 mmHg, 57.75±7.5 mmHg, and 52.7±6.5 mmHg respectively. We consider a clinically relevant worsening of hypercapnia of 4 mmHg with a power of 95 % and an alfa error of 0.05, the number of required individuals was 34 (2,7).

Statistical analysis

Study variables were age, gender, body mass index, abdominal perimeter, weight, body fat percent, height, hemoglobin, PaO_2, $PaCO_2$, pH, HCO_3, fraction of inspired oxygen, saturation, respiratory rate, thorax expansibility, EKG abnormalities were the variables included. A descriptive statistical analysis was initially performed and the qualitative variables were summarized as frequencies and percent, and the quantitative variables in average and standard deviations or median and interquartile rank, previous normality test, the qualitative variables were compared to with Chi^2 and quantitative ones were compared according to or their distribution with student T or Mann Whitney, it was performed the analysis of the effect of treatment, period and interaction for a crossed clinical experiment, taking into account as statistically significant as $P<0.05$.

This study meets the Declaration of Helsinki and the local rules in research subjects as outlined in resolution 8430 of 1993 of the Republic of Colombia. It is considered that this is research with greater risk than the minimum and that an intervention was evaluated. The above considerations, it was evaluated by the Clínica Universidad de la Sabana institutional ethics Committee and required the signature of informed consent as well as the protection and privacy of information obtained according to the regulation of habeas data.

RESULTS

A total of 86 obese patients (BMI equal to or over 30 kg/m^2) were evaluated, 42 patients were excluded for different considerations. Figure 1 specifies the reasons for not participating.

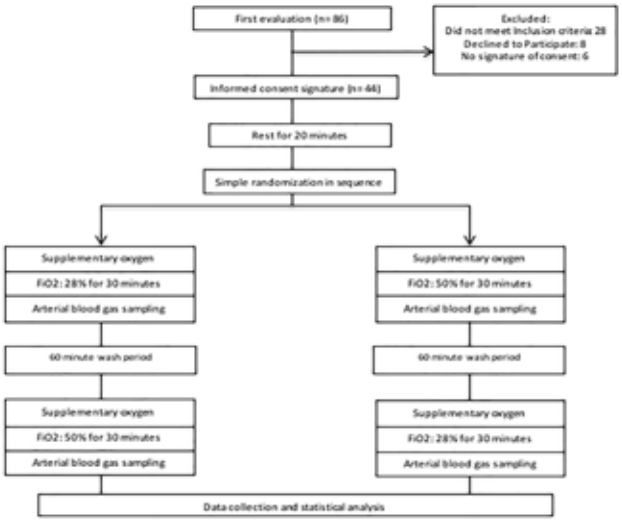

Figure 1. The flow of subjects through the study. FiO_2: Fraction of inspired oxygen.

Clinical characteristics

Average (x) age was 57.36±13.8 years, female 59.1 %, average (x) weight 97.9±19.37 kg, average height 1.59±0.09 m, BMI 38.38±6.31 kg/m^2, abdominal perimeter: 119.2±16.05 cm, SBP 128.5±16.04 mmHg, BP 81.5±10.4 mmHg, HR 74.3±12.1 bpm, RR 18.39±1.96 rpm. Table 1 summarizes the characteristics of the population.

Arterial blood gases

The baseline $PaCO_2$ was 39.8±4.95 mmHg, the baseline PaO_2 was 53.1±8.59 mmHg, the mean baseline HCO_3 was 24.4±3.32, and baseline saturation were 87.43±5.3 %. Arterial gas values at different oxygen-inspired fractions are summarized in Table 2, and the analysis of effective treatment, period, and interaction is given in Table 3.

Table 1

Clinical and demographic characteristics of the population

Age in years x (SD)	57.36 (13.8)
Female n (%)	26 (59.1)
Weight (kg) x (SD)	97.9 (19.3)
Height (m) x (SD)	1.59 (0.09)
Abdominal perimeter cm x (SD)	118.6 (16)
Obesity grade 1 n (%)	18 (40.9)
Obesity grade 2 n (%)	11 (25)
Obesity grade 3 n (%)	15 (34.1)
Systolic blood pressure mmHg x (SD)	128.5 (16.04)
Diastolic blood pressure mmHg x (SD)	81.5 (10.4)
Heart rate (bpm) x(SD)	74.3 (12.1)
Respiratory rate (rpm) x(SD)	18.39 (1.96)

Table 2

Values of Arterial Blood Gases at different Inspired Fraction

Variable	FIO2 21 %	FIO_2 28 %	Difference	FIO_2 50 %	Difference
pH x(SD)	7.40 (0.025)	7.39 (0.031)	-0.008 (0.029)	7.38 (0.027)	-0.019 (0.03)
$PaCO_2$ mmHg x(SD)	39.8 (4.95)	38.78 (5.96)	-1.04 (3.79)	39.8 (5.65)	-0.04(3.29)
PaO_2 mmHg x(SD)	53.1 (8.59)	70.4 (15.17)	17.3 (14.3)	87.03 (25.67)	33.9 (22.6)
HCO_3 mmol/L x(SD)	24.4 (3.32)	23.3 (3.07)	-1.14 (2.14)	23.3 (2.55)	-1.08 (2.06)
SO_2 % x(SD)	87.43 (5.3)	93.3 (3.91)	5.87 (4.62)	94.9 (4.57)	7.5 (4.7)

Table 3

Analysis of treatment effect, period, and interaction

	Treatment effect	95 % IC	P	Period effect (P value)	Interaction effect (P value)
pH x(SD)	-0.011	(-0.004- -0.018)	0,003	0.235	0.768
pCO_2 mmHg x(SD)	1.0	(0.08-1.92)	0,039*	0.092	0.056
PO_2 mmHg x(SD)	16.6	(10.66-22.4)	<0.001*	0.001*	0.275
HCO_3 mmol/L x(SD)	0.07	(-0.43-0.56)	0.795	0.322	0.277
SO_2 % x(SD)	1.62	(0.21 – 2.97)	0.029*	0.279	0.055

*P < 0.05, Statistically significant

Patiens were assesed at room air with baseline $PaCO_2$ levels, when fraction of inspired oxigen were given to reach at maximum level of 50 %, variable changes in $PaCO_2$ was observed. In general terms when incresing factors of inspired oxigen. Overall results showed 1 mmHg change $PaCO_2$. Figures 2A and 2B show the behavior of $PaCO_2$ per subject.

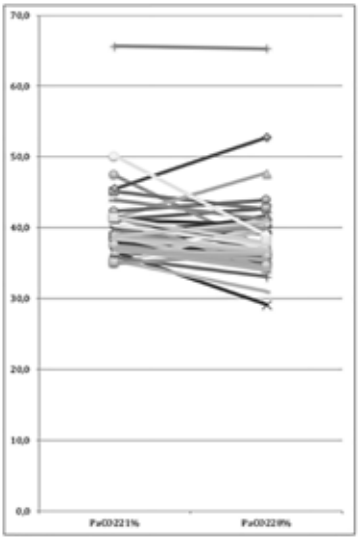

Figure 2A. Individual behavior of $PaCO_2$ with an inspired fraction of 21 % to 28 %.

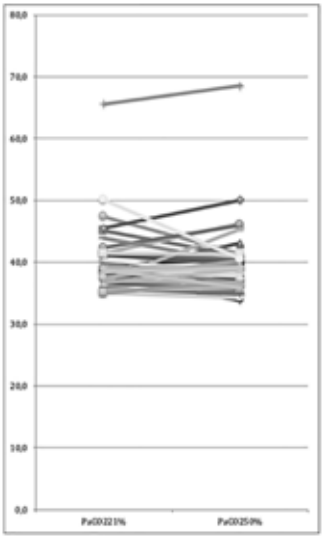

Figure 2B. Individual behavior of $PaCO_2$ with an inspired fraction of 21 % to 50 %.

A total of 13 adverse events were reported by seven subjects, three episodes of headache with the administration of 50 % inspired fraction oxygen, one 1 x 1.5 cm puncture site hematoma, six episodes of drowsiness, and three patients with electrocardiographic manifestations where one had limited supraventricular arrhythmia, the subjects who presented electrocardiographic changes had a mean $PaCO_2$ at 21 % of 41.63±0.58 mmHg, mean $PaCO_2$ at 28 % of 44.7±2.6 mmHg, and mean $PaCO_2$ at 50 % of 43.9±3.6 mmHg, with differences from 21 % to 28 % of 3.07 mmHg and from 21 % to 50 % of 2.27 mmHg. As for drowsiness, the mean $PaCO_2$ of the 21 % was 45.58±9.8 mmHg, the mean $PaCO_2$ of the 28 % was 45,0±11 mmHg, and the mean $PaCO_2$ of the 50 % was 46.9±11 mmHg, with differences from 21 % to 28 % -0.58 mmHg and from 21 % to 50 % a difference of 1.32 mmHg.

DISCUSSION

This randomized crossover clinical trial demonstrated that breathing oxygen at 28 % and 50 % causes an increase in $PaCO_2$ levels of 1.00 mmHg (95 % CI, 0.08-1.92; $P = 0.039$), in obese patients with $PaCO_2 > 35$ mmHg at an altitude above 2.500 meters above sea level. This increase in $PaCO_2$ did not reach the threshold of 4 mmHg previously stipulated as a clinically significant change according to Wijesinghe et al. (2). In our study, patients with somnolence, $PaCO_2$ increased between 2.27 and 3.07 mmHg, those findings also reported by Böing et al., found differences in the state of consciousness with a rise of $PaCO_2$ levels between 2 to 8 mmHg in obese patients (8). This response in obese subjects has been explained by different mechanisms that occur in the central nervous system as well as in the lung tissue. At the central nervous system, the development of hypercapnia is associated with increased glutamine in the brain and gamma-aminobutyric acid (GABA), as well as reductions in glutamate and aspartate (9). This change in the environment of the central nervous system can negatively impact the level of consciousness and depress MV and inspiration. The occlusion pressure (P_0), which is a parameter used to determine the state of the impulse generated by the respiratory centers, is elevated in obese

patients with alveolar hypoventilation, most likely secondary to the increase in elastic resistance of the thorax (4,5,10). But there are other patients, also obese, who demonstrate low P_0 before the chemical stimulus, explaining in this way a low sensitivity of the central chemoreceptors. However, this response of certain obese patients is still in controversy, since no nerve damage has been demonstrated because of obesity (10,11).

Central chemoreceptors, which account for almost 90 % of the increase in ventilation secondary to changes induced by carbon dioxide (CO_2), are also altered. The increase in $PaCO_2$ causes a greater cellular activation, resulting in greater discharges from the respiratory centers. This is transmitted by the efferent neurons, increasing the respiratory rate, thus reducing the levels of $PaCO_2$ in the initial phases of obesity. In advanced stages, this response is less due to an "adaptation" of chemoreceptors to higher levels of blood $PaCO_2$. Finally, chronic respiratory acidosis occurs when all compensatory mechanisms have been overcome (12). In lung tissue, there are physiological changes, specifically related to increased dead space and imbalance of the ventilation/perfusion (V/Q) ratio by local reversal of hypoxic vasoconstriction in patients with elevated basal $PaCO_2$ submitted to oxygen administration (13), this point has gained importance today as the mechanisms of central decrease in MV at the brain level is usually transient and observations are showing a progressive increase in $PaCO_2$ levels despite the functional recovery of the central nervous system (9).

On the other hand, carbon monoxide diffusion capacity (DLCO) is generally preserved, although studies have reported both high and low values. High levels in DLCO have been explained by an increase in pulmonary blood flow. This is since in obese patients there is an increase in regional blood flow mainly at the bases as a consequence of hypervolemia characteristic of obesity, which increases pulmonary blood flow, favors capillary recruitment, and decreases compliance. The decrease in DLCO occurring in some cases is explained by structural changes in the lipid deposition gap (14,15).

The values of PaO_2 increased with respect to the administration of oxygen, PaO_2 increased 16.6 (95 % CI, 10.66 – 22.4; P <0.001), in obese subjects, there is a basal alteration in gas exchange. Obese patients with hypoventilation are characterized by hypoxemia with a difference in the normal arterial alveolus. However, functional respiratory units that are poorly ventilated by passive atelectasis and normal or increased pulmonary blood flow may appear, leading to the presence of increased pulmonary areas of the alveolar-arterial difference and a greater decrease of PaO_2. Isolated hypoxemia is the most frequent anomaly of gas exchange in obesity, and can be found in up to 30 % of patients, this hypoxemia is usually mild and occurs frequently only in the decubitus or is aggravated by it, this hypoxemia is because of an increased alveolar collapse in obese subjects at these positions, secondary to V/Q inequalities (16).

The higher consumption of substrate in obese subjects is expressed in a greater production of CO_2 by the peripheral tissues which contribute to an increase of the $PaCO_2$ that initially manages to be maintained in normal levels thanks to an increase in MV, the retention of CO_2, and hypoxemia that finally occurs in patients who develop hypoventilation is secondary to the impossibility of increasing MV in response to the increase in $PaCO_2$ (4,16).

When comparing these results with studies conducted at sea level with high O_2 administration with FiO_2 (2,17), our results differ with these studies in the magnitude of the increase in $PaCO_2$ levels, this can be explained because the FiO_2 administered in these studies were 100 % compared to those administered in our study that were 28 % and 50 %; second, there are no studies performed on obese patients with alveolar hypoventilation at high altitudes, therefore there is no reference level to compare our results; third, it should be noted that a study was conducted at the Fundación Neumológica Colombiana of baseline arterial gas values (18) in a healthy resident population at a level of 2.660 meters above sea level, showing $PaCO_2$ levels different from those established as normal in subjects resident at the sea level, the reported values (18) are on average an upper limit for normal $PaCO_2$ in men 36.1 mmHg and in women 37.2 mmHg, so it could be divided for future analyzes groups of patients with $PaCO_2$ less than 37 mmHg and patients with $PaCO_2$ greater than or equal to

37 mmHg (19). Among the weaknesses of the study is that other concomitant diseases that frequently accompany these patients such as arterial hypertension, diabetes, or coronary heart disease (20) were not evaluated, in addition, there is not a significant number of subjects with $PaCO_2 \geq 45$ mmHg and polysomnographic study for a specific analysis for subjects with obesity hypoventilation syndrome (21).

CONCLUSION

The administration of oxygen with 28 % and 50 % inspired fractions in obese subjects with $PaCO_2$ greater than 35 mmHg at a altitude above sea level greater than 2 500 meters, increases $PaCO_2$ levels by 1.0 mmHg.

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