Original Research

Hypercapnic Respiratory Failure in Obesity-Hypoventilation Syndrome: CO$_2$ Response and Acetazolamide Treatment Effects

Joan-Maria Raurich MD, Gemma Rialp MD, Jordi Ibañez MD, Juan Antonio Llompart-Pou MD, and Ignacio Ayestarán MD

OBJECTIVE: In obesity-hypoventilation syndrome patients mechanically ventilated for hypercapnic respiratory failure we investigated the relationship between CO$_2$ response, body mass index, and plasma bicarbonate concentration, and the effect of acetazolamide on bicarbonate concentration and CO$_2$ response. METHODS: CO$_2$ response tests and arterial blood gas analysis were performed in 25 patients ready for a spontaneous breathing test, and repeated in a subgroup of 8 patients after acetazolamide treatment. CO$_2$ response test was measured as (1) hypercapnic drive response (the ratio of the change in airway occlusion pressure 0.1 s after the start of inspiratory flow to the change in $P_a$CO$_2$), and (2) hypercapnic ventilatory response (the ratio of the change in minute volume to the change in $P_a$CO$_2$). RESULTS: We did not find a significant relationship between CO$_2$ response and body mass index. Patients with higher bicarbonate concentration had a more blunted CO$_2$ response. Grouping the patients according to the first, second, and third tertiles of the bicarbonate concentration, the hypercapnic drive response was 0.32 ± 0.17 cm H$_2$O/mm Hg, 0.22 ± 0.15 cm H$_2$O/mm Hg, and 0.10 ± 0.06 cm H$_2$O/mm Hg, respectively (P < .01), and hypercapnic ventilatory response was 0.46 ± 0.23 L/min/mm Hg, 0.48 ± 0.36 L/min/mm Hg, and 0.22 ± 0.16 L/min/mm Hg, respectively (P < .04). After acetazolamide treatment, bicarbonate concentration was reduced by 8.4 ± 3.0 mmol/L (P < .01), and CO$_2$ response was shifted to the left, with an increase in hypercapnic drive response, by 0.14 ± 0.16 cm H$_2$O/mm Hg (P < .02), and hypercapnic ventilatory response, by 0.11 ± 0.22 L/min/mm Hg (P = .33). CONCLUSIONS: Patients with obesity-hypoventilation syndrome and higher bicarbonate concentrations had a more blunted CO$_2$ response. Body mass index was not related to CO$_2$ response. Acetazolamide decreased bicarbonate concentration and increased CO$_2$ response. Key words: obesity-hypoventilation syndrome; hypercapnia; mechanical ventilation; respiratory center; respiratory function test; acetazolamide; metabolic alkalosis. [Respir Care 2010;55(11):1442–1448. © 2010 Daedalus Enterprises]

Introduction

Obesity-hypoventilation syndrome is under-recognized and under-treated in hospitalized patients\(^1\) and its prevalence increases as body mass index (BMI) increases.\(^2,3\) These patients have a higher rate of intensive care unit (ICU) admission than do obese patients without hypoventilation. No standardized guidelines exist for the treatment of hypercapnic respiratory failure in obesity-hypoventilation syndrome.\(^4\)

The exact mechanism that leads to alveolar hypoventilation in patients with obesity-hypoventilation syndrome is controversial.\(^5\) Proposed mechanisms include abnormal respiratory system mechanics secondary to obesity, impaired central response to hypercapnia and hypoxia, sleep-disor-

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The authors have disclosed no conflicts of interest.

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HYPERCAPNIC RESPIRATORY FAILURE IN OBESITY-HYPOVENTILATION SYNDROME

In a spontaneous breathing test were: hemodynamic sta-

bled breathing, and neurohormonal abnormalities such as decreased leptin level or leptin resistance. Recently, Nor-
man et al. proposed a model that combines sleep-disor-
dered breathing, central respiratory drive, and renal buff-
ering to explain the transition from acute to chronic hypercapnia.

Frequently, when these patients are admitted to the ICU for acute hypercapnic respiratory failure, they have a high plasma bicarbonate concentration. This fact introduces the controversy regarding whether it is appropriate to reduce the bicarbonate concentration with acetazolamide, a car-
bonic anhydrase inhibitor that aims to increase CO₂ re-

In obesity-hypoventilation-syndrome patients mechani-
cally ventilated for hypercapnic respiratory failure we in-
vestigated the relationship between CO₂ response, BMI,
and plasma bicarbonate concentration, and the effect of acetazolamide on plasma bicarbonate and CO₂ response.

Methods

Patients

In 2 medical-surgical ICUs, during a 5-year period, we prospectively studied 25 nonconsecutive patients with obe-

sity-hypoventilation syndrome recovering from hypercap-
nic respiratory failure after ≥ 2 days of invasive mechanical ventilation. The study was approved by the review boards of both hospitals, and informed consent was ob-
tained from patients or relatives.

Obesity-hypoventilation syndrome is defined as a com-
bination of obesity (BMI > 30 kg/m²) and awake arterial hypercapnia (PₐCO₂ > 45 mm Hg) in the absence of other causes of hypoventilation. Frequently, obesity-
hypoventilation syndrome is accompanied by sleep-disor-
dered breathing or COPD. Essential to the diagnosis is the exclusion of other common causes of hypercapnia, such as chest-wall restrictive disorders (eg, scoliosis), severe in-
terstitial lung disease, severe COPD (FEV₁ < 35% of predicted), severe hypothyroidism, neuromuscular disease, and other central hypoventilation syndromes.

Patients were eligible for the study if they had acute hypercapnic respiratory failure that required invasive me-

chanical ventilation for hypercapnic encephalopathy or failure of noninvasive mechanical ventilation, BMI > 30 kg/ 
m², previous basal stable PₐCO₂ > 45 mm Hg, and bicarbonate concentration > 27 mmol/L, in the absence of other known causes of hypoventilation.

Protocol

All the patients underwent a daily screening by the phy-

sician in charge. The routine clinical criteria for consider-
ing a spontaneous breathing test were: hemodynamic sta-

bility; awake and able to obey oral commands; FIO₂ ≤ 0.5; 

PEEP ≤ 8 cm H₂O; and PₐO₂/FIO₂ > 150 mm Hg.

The first day that the patient was ready for a spontane-
ous breathing test, respiratory neuromuscular function was evaluated, during pressure support of 7 cm H₂O, via mea-

surement of airway occlusion pressure 0.1 s after the be-

ginning of inspiration (P₀.₁), and CO₂ response test. All these measurements were carried out with the patient in the semirecumbent position, immediately following endo-

tracheal suctioning. We continuously recorded electrocar-
diogram, heart rate, pulse oximetry, and invasive systemic blood pressure.

In a subgroup of these patients, who had plasma bicar-

bonate > 34 mmol/L, a second CO₂ response test was performed several days after acetazolamide treatment, when plasma bicarbonate was reduced.

The physician in charge was responsible for applying a spontaneous breathing test with T-piece 15–30 min after the respiratory neuromuscular measurements, or weaning the patient from mechanical ventilation with progressive reduction of the pressure-support ventilation. The decision to extubate or to reconnect the patient to the ventilator was made by the physician in charge.

Measurements and Procedures

Airway Occlusion Pressure. P₀.₁ was measured with 

the built-in system of the ventilator (Evita 2 Dura or Evita 4, Dräger, Lübeck, Germany), and P₀.₁ was calculated as 

the mean of 5 measurements at each point of the study. Normal P₀.₁ in healthy volunteers is 0.75 ± 0.32 cm H₂O.

CO₂ Response Test. The CO₂ response test has been 
detailed elsewhere. Our CO₂ response test method in-
volved the re-inhalation of expired air by inserting a 
corrugated tube between the Y-piece and the endotracheal tube, which increased the dead space by a volume similar to the tidal volume obtained with pressure support of 7 cm H₂O.

Baseline values for the hypercapnia test were obtained 
after applying 5 min of pressure-support ventilation with a pressure of 7 cm H₂O, without PEEP, and P₁₇, was set at 1.0 to prevent hypoxemia, for patient safety, and to avoid hypoxic stimuli. Then the respiratory rate, P₀.₁, and minute volume (Vₑ) were recorded from the ventilator, and an arterial blood sample was drawn to measure PₐCO₂ with a blood gas analyzer (IL-1650, Instrument Laboratory, Izasa, Spain). Then we conducted the CO₂ response test by in-
creasing the dead space while maintaining the same ven-

tilatory support, and when the exhaled CO₂ (measured via capnography) had increased by approximately 10 mm Hg, we again measured respiratory rate, P₀.₁, and Vₑ, and took another arterial blood sample. After the CO₂ response test
the added dead space was removed and the patient was
returned to the original assisted ventilation mode.

We studied the following hypercapnia indexes:

• The hypercapnic drive response, defined as the ratio of
  the change in $P_{0.1}$ ($\Delta P_{0.1}$) to the change in $P_{aCO_2}$ ($\Delta P_{aCO_2}$)

• The hypercapnic ventilatory response, defined as the
  ratio of the change in $V_E$ ($\Delta V_E$) to $\Delta P_{aCO_2}$

The $\Delta V_E$, $\Delta P_{0.1}$, and $\Delta P_{aCO_2}$ were calculated as the
difference between the value at the end of the hypercapnia
and the baseline value. Normal values in healthy vol-
unteers are: hypercapnic drive response 0.6 ± 0.5 cm H2O/
mm Hg, and hypercapnic ventilatory response 2.6 ± 1.2 L/
min/mm Hg.23,24

We recorded the following variables: age, weight, height,
BMI, pulmonary function test results, polysomnography
results, and arterial blood gas values while in stable
condition and with hypercapnic respiratory failure before
mechanical ventilation, Simplified Acute Physiological Score
(SAPS) II, duration of mechanical ventilation, and out-
come. Duration of mechanical ventilation was defined as
the number of days between the beginning of mechanical
ventilation and the day of successful weaning. The patients
were followed until hospital discharge.

Statistical Analysis

Categorical data are expressed as numbers and percent-
ages. Continuous variables are expressed as mean ± SD or
as median and interquartile range. Differences between
patients with and without COPD were analyzed with the
Mann-Whitney test. BMI and plasma bicarbonate were
coded by tertiles, and the differences between tertiles were
compared with the Kruskal-Wallis test. BMI was coded by
tertiles (not by obesity standard classification) to maintain
a homogeneous categorization criteria as with plasma bi-
carbonate. The associations between BMI and plasma bi-
carbonate were analyzed with Pearson’s correlation. Dif-
fences between the first and second CO2 response tests
were analyzed with the Wilcoxon signed-rank test. Statis-
tical analysis was performed with statistics software (SPSS
15.0, SPSS, Chicago, Illinois).

Results

We studied 25 patients with obesity-hypoventilation syn-
drome. Eight patients (32%) had associated both COPD
and obstructive sleep apnea (Table 1). Data not available
were: pulmonary function tests in 5 patients, polysomnog-
raphy in 2 patients, and arterial blood gases while in stable
condition in 1 patient (see Table 1). The arterial blood gas
analysis before mechanical ventilation in 22 of 25 patients
showed respiratory acidosis: pH 7.18 ± 0.08 and $P_{aCO_2}$

102 ± 25 mm Hg. The mean SAPS II score at ICU ad-
mission was 35 ± 10. The total duration of mechanical
ventilation was 6.7 ± 5.3 d (median 5 d, interquartile
range 3-8 d). Two patients (8%) died during their hospital
stay.

The mean duration of invasive mechanical ventilation at
CO2 response test was 3.3 ± 2.1 d (median 2 d, interquar-
The mean P0.1 was increased, and the mean CO2 response test levels were low (Table 2), compared to reference normal values.

Comparing patients with and without COPD, no differences were found in the mean values of FEV1, plasma bicarbonate, hypercapnic drive response, or hypercapnic ventilatory response. Only the FEV1/FVC ratio showed statistically significant difference between the groups (Table 3).

We did not find statistically significant differences in the mean hypercapnic drive response and ventilatory response of patients grouped according to BMI tertiles (Table 4 and Fig. 1). However, there was a nonsignificant trend of increased CO2 response and BMI (see Table 4). When BMI was grouped by obesity standard classifications, we found no significant differences (data not shown).

We did find significant differences in hypercapnic drive response and ventilatory response of patients grouped according to plasma bicarbonate tertiles (see Table 4 and Fig. 1). The higher the plasma bicarbonate, the more blunted the CO2 response.

There was no correlation between BMI and plasma bicarbonate (r² = 0.04, P = .36).

The second CO2 response test was performed in 8 patients (4 of them with COPD) 5.9 ± 6.9 d after the first test. Six patients were included in the third plasma bicarbonate tertile and 2 patients in the second plasma bicarbonate tertile. Acetazolamide was administered via nasogastric tube 1–4 days before the second CO2 response test, with a dose range of 500–2,750 mg. Plasma bicarbonate was reduced by 8.4 ± 3.0 mmol/L (P = .01), hypercapnic drive response was increased by 0.14 ± 0.16 cm H2O/mm Hg (P = .02), and hypercapnic ventilatory response was increased by 0.11 ± 0.22 L/min/mm Hg (P = .33) (Table 5). CO2 response was shifted to the left in the PaCO2 axis (Fig. 2).

During the CO2 tests, no clinical complications occurred that required interruption of the test.

**Discussion**

This study in obesity-hypventilation-syndrome patients mechanically ventilated for acute-on-chronic hypercapnic respiratory failure demonstrated an association between CO2 response and plasma bicarbonate, but not between CO2 response and BMI. The patients with the highest plasma bicarbonate had the most blunted CO2 response. Moreover, in the patients with the highest plasma bicarbonate, acetazolamide decreased the plasma bicarbonate and increased the hypercapnic drive response.
Patients with higher plasma bicarbonate showed decreased CO₂ response, compared to the others. This decreased response could not be explained by the COPD. This fact highlights the importance of the respiratory-renal interaction. In a mathematical model, Norman et al. showed that the respiratory-renal interactions create a cumulative effect over subsequent periods of sleep, which eventually results in a self-perpetuating state of chronic hypercapnia, through increased plasma bicarbonate and blunting of ventilatory drive. A hyperbolic relationship between ventilatory response and bicarbonate concentrations was demonstrated, indicating blunting of the ventilatory CO₂ response with elevated bicarbonate. The reason is that elevated bicarbonate is associated with smaller decreases in pH for a given change in PₐCO₂, and results in blunting of ventilatory response. We believe that the same model could explain some episodes of acute respiratory failure and high plasma bicarbonate in patients with obesity-hypoventilation syndrome.

From a clinical point of view, it is interesting to find an association between acetazolamide (a carbonic anhydrase inhibitor) and reduced plasma bicarbonate, which explains a leftward shift of the CO₂ response, as has been found in other studies and the increase in CO₂ response, according to the model by Norman et al. The effect of acetazolamide on ventilatory CO₂ sensitivity in humans is less clear, since the CO₂ response ranges from no change to an increase in CO₂ sensitivity. A similar increase in CO₂ response was found in patients with obstructive sleep apnea syndrome treated with continuous positive airway pressure, which reduced bicarbonate concentration.

Applying our results to clinical practice, we believe that patients with obesity-hypoventilation syndrome being mechanically ventilated for acute hypercapnic respiratory failure and who have a high plasma bicarbonate could be treated with acetazolamide, once the acidosis is corrected, to decrease the plasma bicarbonate to the usual level and thus increase the central ventilatory drive. However, it must be underlined that most of these patients will still need noninvasive ventilation after extubation. Therefore, a larger controlled randomized study is necessary to confirm our results, especially on whether there is a reduction of the duration of weaning of mechanical ventilation, and, eventually, a potential implication on outcome.

The lack of relationship between BMI, CO₂ response, and plasma bicarbonate in our study, and with PₐCO₂, in the study by Kessler et al. might indicate that obesity acts as a trigger toward hypoventilation in those patients who already have physiologic abnormalities, similar to what occurs in obstructive sleep apnea-hypopnea syndrome, in which depressed chemoresponsiveness plays a role that is independent of obesity in the development of CO₂ retention. However, the importance of obesity in the pathogenesis of obesity-hypoventilation syndrome is supported by the observation that weight loss alone decreases awake PₐCO₂ and that as much as BMI increases, the prevalence of obesity-hypoventilation syndrome rises.

Table 5. CO₂ Response Test in 8 Patients Before and After Treatment With Acetazolamide

<table>
<thead>
<tr>
<th></th>
<th>Before Acetazolamide (mean ± SD)</th>
<th>After Acetazolamide (mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.38 ± 0.06</td>
<td>7.37 ± 0.03</td>
<td>.55</td>
</tr>
<tr>
<td>Plasma bicarbonate (mmol/L)</td>
<td>39.6 ± 4.3</td>
<td>31.2 ± 3.2</td>
<td>.01</td>
</tr>
<tr>
<td>Hypercapnic drive response (cm H₂O/mm Hg)</td>
<td>0.10 ± 0.05</td>
<td>0.23 ± 0.14</td>
<td>.02</td>
</tr>
<tr>
<td>Hypercapnic ventilatory response (L/min/mm Hg)</td>
<td>0.21 ± 0.17</td>
<td>0.32 ± 0.19</td>
<td>.33</td>
</tr>
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</table>
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Fig. 2. Airway-occlusion pressure 0.1 s after the start of inspiratory flow ($P_{0.1}$) versus $P_{ACO_2}$, and minute volume ($V_e$) versus $P_{ACO_2}$ increase in 8 patients, before (solid lines) and after (dashed lines) acetazolamide treatment. The error bars represent standard errors.

The duration of mechanical ventilation of these patients was short and in-hospital mortality was lower than that previously reported for COPD patients.31,32

Limitations

The first important limitation of this study is the small number of patients studied, in particular after acetazolamide treatment, so the study has limited statistical power. Second, the results of the $CO_2$ response tests performed after acetazolamide treatment are difficult to interpret, as the time elapsed between the 2 tests and the adjunctive treatment received may have differed between patients. A control group could have been useful to address that problem. Third, we did not have pulmonary function and polysomnography tests for all the patients. Finally, the hypercapnia test was performed on an $F_{O_2}$ of 1.0, and we can not exclude the possibility that hyperoxia might have decreased the hypercapnic stimulus; however, hyperoxia-induced hypercapnia may be primarily due to gas-exchange impairment rather than to depression of ventilation.33,34

Conclusions

In patients with obesity-hypoventilation syndrome, invasively ventilated for hypercapnic respiratory failure, those with higher plasma bicarbonate had a more blunted $CO_2$ response than did those with lower plasma bicarbonate. In those patients the BMI was not related to $CO_2$ response. Acetazolamide decreased the plasma bicarbonate and increased the $CO_2$ response.

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