Respiratory CO₂ response depends on plasma bicarbonate concentration in mechanically ventilated patients

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Abstract

Objective: There is controversy about the effects of high plasma bicarbonate concentration ([HCO₃⁻]) and the CO₂ response test. We analyzed the relationship between [HCO₃⁻] and the variation in hydrogen ion concentration (pH) for a given change in PaCO₂, and its effects upon CO₂ response.

Design: A retrospective study was carried out.

Setting: Two intensive care units.

Patients: Subjects with and without chronic obstructive pulmonary disease (COPD), at the beginning of weaning from mechanical ventilation.

Interventions: The CO₂ response was evaluated by the re-inhalation of expired air method, measuring the hypercapnic ventilatory response (ΔVₑ/ΔPaCO₂) and hypercapnic drive response (ΔP₀₁/ΔPaCO₂), where Vₑ is minute volume and P₀₁ is airway occlusion pressure 0.1 s after the initiation of inspiration.

Main outcome measures: [HCO₃⁻] and CO₂ response.

Results: A total of 120 patients in the non-COPD group and 48 in the COPD group were studied. COPD patients had higher mean [HCO₃⁻] than non-COPD patients (33.2 ± 5.4 vs. 25.7 ± 3.7 mmol/l, p < 0.001). In both non-COPD and COPD patients we observed a significant inverse linear relationship between [HCO₃⁻] and pH change per mmHg of PaCO₂ (p < 0.001), ΔVₑ/ΔPaCO₂ (p < 0.001) and ΔP₀₁/ΔPaCO₂ (p < 0.001).

Conclusions: There is an inverse linear relationship between [HCO₃⁻] and the variation of pH for a given change in PaCO₂ and the CO₂ response.

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La respuesta respiratoria al CO₂ depende de la concentración plasmática de bicarbonato en pacientes sometidos a ventilación mecánica

Resumen
Objetivo: Existe controversia en si las diferencias en la concentración plasmática de bicarbonato (CO₃⁻⁻) modifican la respuesta al incremento de CO₂. Hemos analizado la relación entre la CO₃⁻⁻ y la variación en la concentración de iones de hidrógeno (pH) por un incremento agudo de la PaCO₂ y entre la CO₃⁻⁻ y la respuesta del sistema respiratorio al incremento de CO₂.

Diseño: Estudio retrospectivo.
Ámbito: Dos unidades de cuidados intensivos.

Pacientes: Pacientes con y sin enfermedad pulmonar obstructiva crónica (EPOC) en el inicio de la desconexión de ventilación mecánica.

Intervenciones: La respuesta del sistema respiratorio al incremento de CO₂ fue evaluada por el método de reinhalación del aire espirado, midiendo la respuesta ventilatoria a la hiperbicapnia (ΔVₑ/ΔPaCO₂) y la respuesta del centro respiratorio a la hiperbicapnia (ΔP₀₁/ΔPaCO₂), donde Vₑ es el volumen minuto y P₀₁ es la presión de oclusión de la vía aérea a 0,1 s del inicio de la inspiración.

Variables de interés principales: CO₃⁻⁻ y respuesta al CO₂.

Resultados: Fueron estudiados 120 pacientes sin EPOC y 48 con EPOC. Las CO₃⁻⁻ medias en los pacientes sin y con EPOC fueron de 25,7 ± 3,7 y 33,2 ± 5,4 mmol/L, respectivamente (p < 0,001).

Hallamos, en ambos grupos de pacientes, una relación lineal inversa entre la CO₃⁻⁻ y el cambio de pH por mmHg de PaCO₂ (p < 0,001), el ΔVₑ/ΔPaCO₂ (p < 0,001) y el ΔP₀₁/ΔPaCO₂ (p < 0,001).

Conclusiones: Hay una relación lineal inversa entre la CO₃⁻⁻ y la variación en el pH por un incremento agudo de la PaCO₂ y entre la CO₃⁻⁻ y la respuesta al CO₂.

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Patients were retrospectively and non-consecutively studied in two medical-surgical ICUs, at the beginning of the weaning of mechanical ventilation. Hospital research committee approved the study. Informed consent was obtained in all cases from patients or closest relatives. Most of the patients of this study have been included in previous studies of our group.15-15

Protocol

Patients were studied when the physician in charge considered that they had clinical stability and fulfilled criteria for a spontaneous breathing trial. These criteria included that the patient was hemodynamically stable, without sedation awake and able to obey oral commands, had core temperature below 38.3 °C and a ratio of the partial pressure of arterial oxygen (PaO2) to the fraction of inspired oxygen (FiO2) above 150 mm Hg with a positive end-expiratory pressure (PEEP) of <8 cm H2O.

When the patients were clinically stable and ready for a spontaneous breathing trial, respiratory neuromuscular function was evaluated by measurement of maximal inspiratory pressure (Pimax), maximal expiratory pressure (Pemax), and CO2 response test. All these measurements were carried out in the semirecumbent position at 30 degrees. We continuously recorded electrocardiogram, heart rate, pulse oximetry, and invasive systemic blood pressure.

Measurements and procedures

Maximal inspiratory and expiratory pressure
Muscular respiratory strength was assessed with the Pmax and Pmax measurements. Pmax and Pmax were measured, after 1-2 min of spontaneous breathing, with an external pressure transducer via a unidirectional valve (Hans Rudolph, Kansas City, MO) connected to the endotracheal tube. Pmax was obtained at residual volume, by occluding the inspiratory port of the unidirectional valve, whereas Pmax was measured at total lung volume, by occluding the expiratory port.16 After 20-25 s of occluded inspiration or expiration, the most negative or positive pressure values were recorded for Pmax or Pmax test. Two measurements were performed and the highest value was used for analysis.

CO2 response test

To increase the CO2 we used the method of the re-inhalation of expired air15,11) by inserting a corrugated tube between the Y-piece and the endotracheal tube that increased the dead space with a volume similar to the tidal volume (VT) obtained with a pressure support of 7 cm H2O in each patient. The increase of dead space was made with a continuous corrugated tube (CORR-A-FLEX II® 22 mm Tubing, Hudson RCI®, Temecula, USA).

Baseline values for CO2 response test were obtained after applying 5 min of pressure support ventilation with a pressure of 7 cm H2O without PEEP, and FiO2 was set at 1.0 to prevent hypoxemia for patients’ security and to avoid hypoxic stimuli. Then, respiratory rate, airway occlusion pressure 0.1 s after the beginning of inspiration (P0.1), and minute volume (VE) were recorded from the ventilator, and an arterial blood sample was withdrawn. Thereafter, we initiated the CO2 response test by increasing dead space maintaining the same ventilatory support, and when the exhaled CO2 (measured through capnography) had increased by above 10 mm Hg, we measured again the respiratory rate, P0.1 and VE, and withdrew another arterial blood sample. Once the CO2 response test was finished the added dead space was removed and the patient was returned to his original assisted ventilation mode.

We studied the following derived indexes of CO2 response test: the hypercapnic ventilatory response (ΔVT/ΔPaCO2), defined as the ratio of the change in VT (ΔVT) to the change in PaCO2 (ΔPaCO2) and the hypercapnic drive response (ΔP0.1/ΔPaCO2), defined as the ratio of the change in P0.1 (ΔP0.1) to ΔPaCO2. The changes in VE, P0.1, and PaCO2 were calculated as the difference between the value at the end of the CO2 response test and the baseline value. P0.1 was measured by means of the built-in system of the Dräger ventilator (Evita 2 Dura or Evita 4, Dräger, Lübeck, Germany),18,19 and Pa0.1 was calculated as the mean of 5 measurements at each point of the study. Arterial blood gases were measured with a blood gas analyzer (IL-1650, Instrument Laboratory, Izasa, Spain).

Data collection and definitions

We recorded the following clinical variables: gender, age, height, weight, the Simplified Acute Physiological Score (SAPS) II, length of mechanical ventilation before the study day, ICU and in-hospital length of stay, and in-hospital mortality.

We considered the study day as the day that the CO2 response test was performed. Length of mechanical ventilation before the study day was defined as the number of days between the beginning of mechanical ventilation and the day the CO2 response test was performed. Patients were followed-up until discharge from our two hospitals.

Statistical analysis

Categorical data are expressed as number and percentages. Continuous variables are expressed as mean ± standard deviation or as median and interquartile ranges (IQR). Differences between groups were compared with t test and chi-square test. Non-COPD and COPD patients were grouped into tertiles according to the baseline level of plasma bicarbonate concentration. Trend analysis among the tertiles of plasma bicarbonate concentration and changes of pH by changes of PaCO2, minute volume, CO2 response, tidal volume and respiratory rate, were conducted with Jonckheere–Terpstra test. Statistical analysis was performed with specific statistics software (SPSS 19.0, SPSS, Chicago, IL).

Results

One hundred and sixty-eight patients were studied, 120 patients in the non-COPD group and 48 in the COPD group. The COPD group had a mean FEV1/FVC ratio of 54 ± 12% and of the FEV1 of 37 ± 16%. Compared with non-COPD patients, COPD patients were mostly men, with higher body mass index and lower severity disease (Table 1). The
main diagnoses of non-COPD patients were pneumonia and non-pulmonary sepsis (Table 1). Non-COPD patients had longer duration of ventilation before the study day, and longer ICU and in-hospital length of stay (Table 1).

Between non-COPD and COPD groups there was no difference in the added dead space used to increase the PaCO₂. Mean values were 414 ± 70 mL and 392 ± 68 mL respectively (p = 0.08). The baseline values of CO₂ response test, with pressure support ventilation of 7 cm H₂O and FiO₂ of 1.0 showed a higher plasma bicarbonate concentration and PaCO₂ and lower minute volume, respiratory rate and pH in COPD group compared with the non-COPD group (Table 2). No differences were found in mean PaO₂ and baseline P₀.1 values between groups (Table 2). The ventilatory and central CO₂ response was lower in COPD patients than in non-COPD. No differences were found in respiratory muscle strength assessed by Pimax and Pemax between groups (Table 2).

The tertile ranges of plasma bicarbonate concentration were 17.1 to 24.1, 24.1 to 26.6 and 26.6 to 37.5 mmol/L for non-COPD patients, and 19.7 to 30.9, 30.9 to 35.5 and 35.5 to 43.7 mmol/L for COPD patients. We found a significant inverse linear relationship between plasma bicarbonate concentration grouped in tertiles, in non-COPD and COPD groups of patients, and baseline minute volume (p < 0.001) (Fig. 1). The same inverse linear relationship in both groups of patients were found between the tertiles of plasma bicarbonate concentration and pH change per mm Hg of PaCO₂ induced by CO₂ response test (p < 0.001) (Fig. 2), and between the tertiles of plasma bicarbonate concentration and hypercapnic ventilatory response (p < 0.001) and hypercapnic drive response (p < 0.001) (Fig. 3).

When plotted minute volume and P₀.1 against PaCO₂, in non-COPD and COPD patients grouped by tertiles of plasma bicarbonate concentration, the slope of the CO₂ response flattened with high levels of plasma bicarbonate concentration (Fig. 4). Of note, baseline values of minute volume decreased with the increased level of plasma bicarbonate, without changes in P₀.1. Minute volume decreases through decrease in tidal volume (p = 0.003) and respiratory frequency (P < 0.001) (Fig. 5).

### Discussion

In this study we found an inverse relationship between the plasma bicarbonate concentration and the variation in pH for a given change in PaCO₂. Indeed, the most interesting finding was that the response to CO₂ also inversely depends on the level of plasma bicarbonate concentration,

![Figure 1](image-url)  
**Figure 1** Relationship between plasma bicarbonate concentration grouped in tertiles and baseline minute volume expressed by body weight in mL/min/kg, in non-COPD (white circles) and COPD patients (black circles). Dashed lines show the linear relationship among groups (p < 0.001 for each variable). Values are expressed as mean and standard error.
Table 2  CO₂ response test (baseline and hypercapnia values of arterial blood gases and ventilatory parameters) and respiratory muscle strength (P_{max} and P_{em} values).

<table>
<thead>
<tr>
<th></th>
<th>Non-COPD n: 120</th>
<th>COPD n: 48</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td><strong>CO₂ response test</strong></td>
<td></td>
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<tr>
<td>Baseline PaO₂ at FiO₂ of 1.0, mm Hg</td>
<td>439 ± 100</td>
<td>410 ± 114</td>
<td>0.10</td>
</tr>
<tr>
<td>Baseline CO₂H mmol/L</td>
<td>25.7 ± 3.7</td>
<td>33.2 ± 5.4</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>pH</strong></td>
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<tr>
<td>Baseline</td>
<td>7.42 ± 0.05</td>
<td>7.38 ± 0.05</td>
<td>&lt;0.001</td>
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<tr>
<td>Hypercapnia</td>
<td>7.31 ± 0.05</td>
<td>7.29 ± 0.05</td>
<td>0.02</td>
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<tr>
<td><strong>PaCO₂, mm Hg</strong></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>39.6 ± 7.4</td>
<td>56.1 ± 12.3</td>
<td>&lt;0.001</td>
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<tr>
<td>Hypercapnia</td>
<td>55.6 ± 10.2</td>
<td>73.2 ± 15.1</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Respiratory rate, bpm</strong></td>
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<tr>
<td>Baseline</td>
<td>28 ± 7.3</td>
<td>23 ± 6.0</td>
<td>&lt;0.001</td>
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<tr>
<td>Hypercapnia</td>
<td>34 ± 7.4</td>
<td>28 ± 7.8</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Minute ventilation, L/min</strong></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>11.2 ± 3.2</td>
<td>9.0 ± 2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>18.3 ± 4.9</td>
<td>13.4 ± 4.1</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>P_{o1}, cm H₂O</strong></td>
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<tr>
<td>Baseline</td>
<td>3.2 ± 1.9</td>
<td>2.9 ± 1.6</td>
<td>0.32</td>
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<tr>
<td>Hypercapnia</td>
<td>9.7 ± 3.9</td>
<td>7.0 ± 3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>∆V_{E} / ∆PaCO₂, L/min/mm Hg</td>
<td>0.52 ± 0.37</td>
<td>0.30 ± 0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>∆P_{o1} / ∆PaCO₂, cm H₂O/mm Hg</td>
<td>0.44 ± 0.26</td>
<td>0.27 ± 0.18</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Respiratory muscle strength</strong></td>
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<tr>
<td>P_{max}, cm H₂O</td>
<td>46 ± 18</td>
<td>47 ± 14</td>
<td>0.80</td>
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<tr>
<td>P_{max}, cm H₂O</td>
<td>26 ± 13</td>
<td>27 ± 13</td>
<td>0.57</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; P_{o1}: occlusion pressure at 100 ms; ∆V_{E} / ∆PaCO₂: hypercapnic ventilatory response; ∆P_{o1} / ∆PaCO₂: hypercapnic drive response; P_{max}: maximal inspiratory pressure; P_{em}: maximal expiratory pressure.

Both in non-COPD and COPD patients, during the weaning of mechanical ventilation.

These results are in agreement with previous studies in healthy subjects and chronic hypercapnia secondary to kyphoscoliosis or skeletal muscle disease. In these studies the variations in plasma bicarbonate concentration were induced by oral administration of sodium bicarbonate and ethacrynic acid, or ammonium chloride. Our results are also in accordance with a previous study with obesity-hypoventilation syndrome patients during the weaning of mechanical ventilation. In that study we found the same inverse relationship between plasma bicarbonate concentration and CO₂ response. We also found that lowering plasma bicarbonate concentration by acetazolamide administration increased the CO₂ response in a small subset of patients.

One possible explanation for several previous studies that did not find the relationship between the plasma bicarbonate concentration and CO₂ response was that the changes in the bicarbonate concentrations were small and in some cases only toward acidosis. Changes in the slope of the CO₂ response are more evident when the patients reach high levels of plasma bicarbonate concentration, as occurred in our study.

The ventilatory adaptation to an increase of plasma bicarbonate concentration is primarily achieved by decrease of tidal volume in subjects without lung disease, while we found a decrease in both tidal volume and respiratory rate. This discordance may be related with the fact that they were studied with a pressure support of 7 cm H₂O. Indeed, Brochard et al. found that the ventilation with a pressure support of 10 cm H₂O during weaning of mechanical ventilation resulted in significant improvements in tidal volume.
with a decreased respiratory rate compared to spontaneous ventilation.

The clinical significance of this relationship between the level of plasma bicarbonate concentration and baseline minute volume and CO₂ response relies on the fact that modifying the plasma bicarbonate concentration can change the baseline minute volume, the CO₂ response, and the work of breathing. Thus, in patients with COPD we could increase the minute volume and the CO₂ response by reducing the plasma bicarbonate concentration. Reducing elevated levels of plasma bicarbonate concentration is simple with the administration of acetazolamide, as observed in our study of patients with obesity-hypoventilation syndrome.12 Ongoing clinical trials evaluating the use of acetazolamide to facilitate the weaning of mechanical ventilation will address this issue. However, one must bear in mind several issues when considering this potential treatment. First, when reducing elevated plasma bicarbonate concentration there is an inherent risk of increasing the work of breathing in excess. Second, in non-COPD patients ventilated with high minute volume and with difficulty of weaning of mechanical ventilation, increasing the plasma bicarbonate concentration can reduce the minute volume and therefore the work of breathing.

Along with the plasma bicarbonate concentration, the CO₂ response depends on other factors such as the family, age, and circadian rhythm. In this regard, we note that approximately 15% of healthy subjects have decreased response to CO₂. These individuals are likely to develop CO₂ retention when additional respiratory problems arise, such as obesity, obstructive lung disease or status asthmaticus. The reduced CO₂ response in COPD patients cannot be attributed to hyperoxia. In these patients, the increase in the PaCO₂ by hyperoxia is due to changes in the ventilation-perfusion distribution and to the increase in dead space by the Haldane effect on PaCO₂. Likewise, the high PaO₂ observed in our patients may be explained by the FiO₂ of 1 used in the study to correct hypoxemia in all lung units regardless of their ventilation-perfusion ratio except with a pure shunt.

The main limitation of this study was the difficulty to interpret the results of the CO₂ response tests due to the wide range of normal values in healthy subjects. In

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**Figure 3** Relationship between plasma bicarbonate concentration grouped in tertiles and hypercapnic ventilatory response (ΔV̇e/ΔPaCO₂) (top), and hypercapnic drive response (ΔP₂,1/ΔPaCO₂) (bottom), in non-COPD (white circles) and COPD patients (black circles). Dashed lines show the linear relationship among groups (p < 0.01 for each variable). Values are expressed as mean and standard error.

**Figure 4** Baseline and response to CO₂ increase of minute volume (V̇e) and occlusion pressure (P₂,1). The patients were grouped according to tertiles of bicarbonate concentration, in non-COPD (white circles) and COPD patients (black circles). Values are expressed as mean and standard error.
addition, the coefficients of variation are also wide, from 17.9% for the ventilatory response (ranged from 8.3 to 26.3%) and about 60% for the P0.1 during CO2 rebreathing trials. Other limitations of our study were the way in which we measured CO2 response with the ventilator, instead of with the conventional method. The Evita ventilator tends to overestimate high P0.1 values and to underestimate low P0.1 values. Another possible limitation is air trapping due to the high minute volume that occurs with hypercapnic stimulation or by effect of bronchoconstriction in patients with COPD. However, Conti et al. found that reliable measurement of P0.1 can be obtained during pressure-support ventilation in patients with variable levels of intrinsic PEEP.

In conclusion, we observed an inverse relationship between the plasma bicarbonate concentration and the variation in hydrogen ion concentration for a given change in PaCO2, and we found that elevated levels of plasma bicarbonate reduced the CO2 response both in COPD and non-COPD critically ill patients during weaning of mechanical ventilation.

Conflict of interest

All authors declare that they have no conflict of interest.

References