

# End-tidal arterial CO<sub>2</sub> partial pressure gradient in patients with severe hypercapnia undergoing noninvasive ventilation

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**Background:** Patients with severe hypercapnia represent a particularly serious condition in an emergency department (ED), requiring immediate attention. Noninvasive ventilation (NIV) is an integral part of the treatment for acute respiratory failure. The present study aimed to validate the measurement of end-tidal CO<sub>2</sub> (EtCO<sub>2</sub>) as a noninvasive technique to evaluate the effectiveness of NIV in acute hypercapnic respiratory failure.

**Methods:** Twenty consecutive patients admitted to the ED with severe dyspnea were enrolled in the study. NIV by means of bilevel positive airway pressure, was applied to the patients simultaneously with standard medical therapy and continued for 12 hours; the arterial blood gases and side-stream nasal/oral EtCO<sub>2</sub> were measured at subsequent times: T0 (admission to the ED), T1h (after 1 hour), T6h (after 6 hours), and T12h (after 12 hours) during NIV treatment.

**Results:** The arterial CO<sub>2</sub> partial pressure (PaCO<sub>2</sub>)–EtCO<sub>2</sub> gradient decreased progressively, reaching at T6h and T12h values lower than baseline ( $P < 0.001$ ), while arterial pH increased during the observation period ( $P < 0.001$ ). A positive correlation was found between EtCO<sub>2</sub> and PaCO<sub>2</sub> values ( $r = 0.89$ ,  $P < 0.001$ ) at the end of the observation period.

**Conclusion:** In our hypercapnic patients, the effectiveness of the NIV was evidenced by the progressive reduction of the PaCO<sub>2</sub>–EtCO<sub>2</sub> gradient. The measurement of the CO<sub>2</sub> gradient could be a reliable method in monitoring the effectiveness of NIV in acute hypercapnic respiratory failure in the ED.

**Keywords:** arterial end-tidal CO<sub>2</sub> gradient, noninvasive ventilation, bilevel positive airway pressure, acute respiratory failure

## Introduction

Acute respiratory failure usually presents at emergency departments (EDs) with dyspnea, generally associated with chest pain, cough, and palpitations. It is estimated that approximately 3% of ED admittances are related to dyspnea<sup>1</sup> due to hypoxia or hypercapnia; common causes are pneumonia, acute exacerbation of chronic obstructive pulmonary disease (COPD), and acute cardiogenic pulmonary edema, which lead to gas-exchange impairment.

Noninvasive ventilation (NIV) is now an integral part of the treatment for acute respiratory failure, such as acute exacerbation of COPD<sup>2–4</sup> and acute cardiogenic pulmonary edema<sup>5,6</sup> during the postoperative period after abdominal<sup>7</sup> and thoracic surgery,<sup>8</sup> and its efficacy has been demonstrated in ED settings<sup>9–11</sup> to prevent intubation and invasive ventilation, and to reduce hospital mortality.<sup>12,13</sup> The use of NIV has spread widely within a decade, thanks to its advantageous cost/benefit ratio, easy monitoring, and rapid results.

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Bilevel positive airway pressure (BiPAP) is a method of NIV that combines the application of an inspiratory ventilatory support with positive end-expiratory pressure, in order to obtain alveolar recruitment during inspiration and prevent alveolar collapse during expiration;<sup>14,15</sup> important physiological effects include improved O<sub>2</sub> partial pressure delivery (by increasing O<sub>2</sub> and reducing left ventricular afterload) and reduced respiratory effort (by unloading the respiratory muscles).<sup>16</sup>

In normal subjects, end-tidal CO<sub>2</sub> pressure (EtCO<sub>2</sub>) is slightly lower than arterial CO<sub>2</sub> partial pressure (PaCO<sub>2</sub>) at rest, but becomes higher than PaCO<sub>2</sub> during exercise as the workload increases.<sup>17,18</sup> On the contrary, in patients with obstructive or restrictive lung diseases and with silent pulmonary embolism, EtCO<sub>2</sub> is below normal at rest and during exercise.<sup>19,20</sup> The arterial–EtCO<sub>2</sub> (P[a–Et]CO<sub>2</sub>) difference is dependent on several factors that include the physiological dead space/tidal volume ratio, respiratory rate, cardiac output, and mixed venous carbon dioxide partial pressure (PCO<sub>2</sub>).<sup>21</sup> These findings suggest that EtCO<sub>2</sub> is decreased in some pathophysiologic conditions associated with ventilation–perfusion mismatch and decreased cardiac output,<sup>22</sup> and thus in these conditions EtCO<sub>2</sub> is not a good estimate of PaCO<sub>2</sub> and a CO<sub>2</sub> gradient can be found.

We hypothesized that the assessment of the difference between PaCO<sub>2</sub> and EtCO<sub>2</sub> (CO<sub>2</sub> gradient) over time could be a reliable method to evaluate patients' response to NIV treatment. The present study aimed to validate the measurement of EtCO<sub>2</sub> as an instrumental noninvasive technique for monitoring the effectiveness of the noninvasive BiPAP in hypoxemic–hypercapnic patients admitted to the ED.

## Materials and methods

This was a prospective, observational and noncomparative clinical trial conducted in the ED of the Riuniti Hospital in Foggia. Ethical approval for this study was provided by the ethical committee of Foggia University Hospitals, and written informed consent was obtained from all patients.

## Patients

Twenty consecutive patients admitted to the ED with severe dyspnea were enrolled from February to September 2012. Our inclusion criteria were severe dyspnea (respiratory rate >24/minute), contraction of accessory respiratory muscles, Glasgow Coma Scale >12, acidosis (pH <7.35), and PaCO<sub>2</sub> >70 mmHg. Exclusion criteria were deterioration in neurologic status (Glasgow Coma Scale <12), respiratory rate <12/min or respiratory arrest, severe hemodynamic

instability (systolic blood pressure <90 mmHg), arrhythmias, pneumothorax, mask non adaptable to the patient's face or mask intolerance, uncooperative patient, and need for orotracheal intubation.<sup>2</sup>

## NIV treatment procedure

BiPAP was started simultaneously with medical therapy, and set in the spontaneous-timed mode; all patients were ventilated by a facial mask. The level of pressure support (inspiratory positive airway pressure) was adjusted to obtain an expired tidal volume of >8 mL/kg, a respiratory rate <25 breaths/minute and a clinical disappearance of accessory muscle activity; expiratory positive airway pressure was set at 5 cmH<sub>2</sub>O, as a starting value. The fraction of inspired oxygen was adjusted to achieve a level of oxygen saturation >90%.<sup>3</sup> The patients were not sedated. The treatment was continued for 12 hours in an adult intermediate care unit within the ED, and throughout their stay the patients' comfort and level of consciousness was carefully assessed. At the end of the observation period, an assessment was performed to decide if the patient had to be transferred to the local respiratory intensive care unit, or whether the NIV could be stopped and the patient discharged.

## Pharmacological treatment

Patients were treated with a beta2-adrenergic agonist administered by aerosol (500 mcg of salbutamol within 5 mL of saline) as a first choice, repeated after 30–60 minutes as appropriate; intravenous theophylline was used as a second-choice drug at the discretion of the medical staff.<sup>23–27</sup> The administration of O<sub>2</sub> was never discontinued.

Systemic steroids were administered to support the improvement of the respiratory failure in patients with acute exacerbation of COPD (n = 12) and with pneumonia (n = 2) (methylprednisolone up to 100–125 mg intravenously followed by 40–80 mg/day intravenously for the first 72 hours, every 6–8 hours).<sup>28–30</sup> Antibiotic treatment was administered according to international guidelines, as appropriate.<sup>31–35</sup>

## Measurements

Arterial blood gases and EtCO<sub>2</sub> were measured at subsequent times: T0 (admission to the ED), T1h (after 1 hour), T6h (after 6 hours), and T12h (after 12 hours) during NIV treatment. Arterial blood was collected from the radial artery, and the examination was performed using a blood gas analyzer. Routine monitoring during the entire period included pulse oximetry, five-lead electrocardiography, and noninvasive blood pressure measurement.

Throughout the treatment, fluids were administered as appropriate. Side-stream EtCO<sub>2</sub> measurements were performed during NIV by means of a capnograph and a nasal/oral sample line, which has proven to be reliable in reading EtCO<sub>2</sub> during BiPAP utilization.<sup>36</sup>

## Statistics and data analyses

Data are given as mean values  $\pm$  standard deviations. P(a–Et)CO<sub>2</sub> and arterial blood pH values from subsequent assessments were compared with one-way analysis of variance for repeated measures; in order to identify significant differences, Fisher's exact test was applied for post hoc comparison between values at different times. We used Pearson's coefficient to assess the correlation between EtCO<sub>2</sub> and PaCO<sub>2</sub> for each time.  $P < 0.05$  was the minimum value accepted as statistically significant. All calculations were performed with Statistica version 10 software package (StatSoft, Tulsa, OK, USA).

## Results

A total of 20 patients were included in the study, (eight males, 12 females; mean age  $77 \pm 9$  years). The causes of acute respiratory failure included acute exacerbation of COPD in twelve cases (60%), pneumonia in two cases (10%), and acute cardiogenic pulmonary edema in six cases (30%). Tolerance to NIV was good in all the patients. Table 1 shows the demographic characteristics and NIV settings of the population studied. Initial inspiratory positive airway pressure and expiratory positive airway pressure settings were  $16.5 \pm 3$  cmH<sub>2</sub>O and  $6.1 \pm 1.3$  cmH<sub>2</sub>O, respectively.

**Table 1** Patient characteristics

Demographic details	
Male/female	8/12
Age (years, mean $\pm$ SD)	$77 \pm 9$
Preexisting disease*	
COPD	15 (75)
Hypertensive heart disease	3 (15)
Chronic heart failure	6 (30)
Diabetes mellitus type 2	9 (45)
Cause of acute respiratory failure*	
Acute exacerbation of COPD	12 (60)
Pneumonia	2 (10)
Acute cardiogenic pulmonary edema	6 (30)
Initial pressure setting, cm water (mean $\pm$ SD)	
IPAP	$16.5 \pm 3$
EPAP	$6.1 \pm 1.3$

**Note:** \*Number of patients, with percentages in parentheses.

**Abbreviations:** SD, standard deviation; COPD, chronic obstructive pulmonary disease; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure.

The mean baseline value of P(a–Et)CO<sub>2</sub> was  $60.7 \pm 17.7$  mmHg due to high PaCO<sub>2</sub> levels (Figure 1), and after the introduction of the medical therapy and NIV, it decreased to  $8.4 \pm 8$  mmHg at T6h and to  $4.7 \pm 6.7$  mmHg at T12h ( $P < 0.001$  versus T0). Arterial pH was  $7.22 \pm 0.06$  at T0 (Figure 2) and increased to  $7.33 \pm 0.04$  at T6h ( $P < 0.001$ ) and to  $7.39 \pm 0.04$  at T12h ( $P < 0.001$ ).

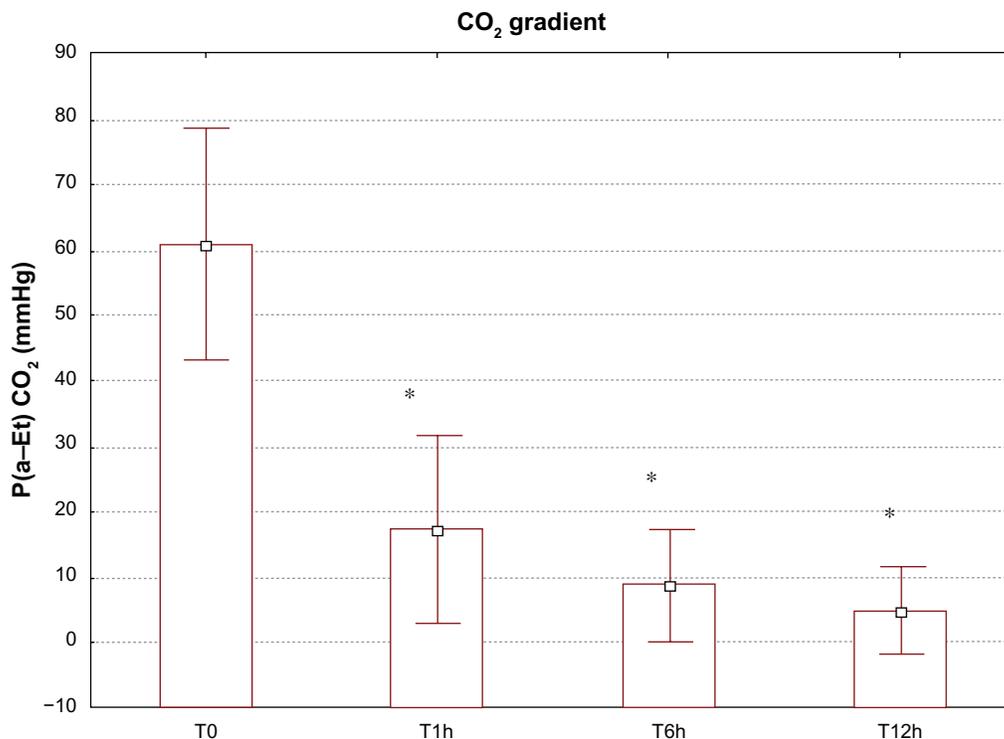
In Figure 3, the relationships between the EtCO<sub>2</sub> and PaCO<sub>2</sub> values are shown at T0, (Figure 3A), T1h (Figure 3B), T6h, (Figure 3C), and T12h (Figure 3D). At T0, EtCO<sub>2</sub> was lower than PaCO<sub>2</sub>, and there was no significant relationship between EtCO<sub>2</sub> and PaCO<sub>2</sub> ( $r = 0.12$ ). At T1h, EtCO<sub>2</sub> was more closely correlated with PaCO<sub>2</sub> ( $r = 0.56$ ,  $P < 0.01$ ), and at T6h and T12h we found a strong linear relationship between the two variables ( $r = 0.81$  and  $r = 0.89$ , respectively,  $P < 0.001$ ).

There was an improvement in respiratory rate, heart rate, and arterial oxygen saturation throughout the study (Table 2): respiratory rate decreased from an initial  $27.5 \pm 3$  to  $19 \pm 3$  (T12h) breaths/minute ( $P < 0.001$ ), heart rate decreased from  $107.6 \pm 14$  (T0) to  $83.5 \pm 9$  (T12h) beats per minute ( $P < 0.001$ ) and oxygen saturation improved from  $80.2\% \pm 7\%$  at T0 to  $91.5\% \pm 2\%$  at T12h ( $P < 0.001$ ).

At the end of the study period, twelve patients (60%) were discharged, while eight (40%) had to be transferred to the local respiratory intensive care unit because of persisting respiratory impairment, but no patient required intubation. No difference in the etiology of acute respiratory failure was found between discharged and transferred patients.

## Discussion

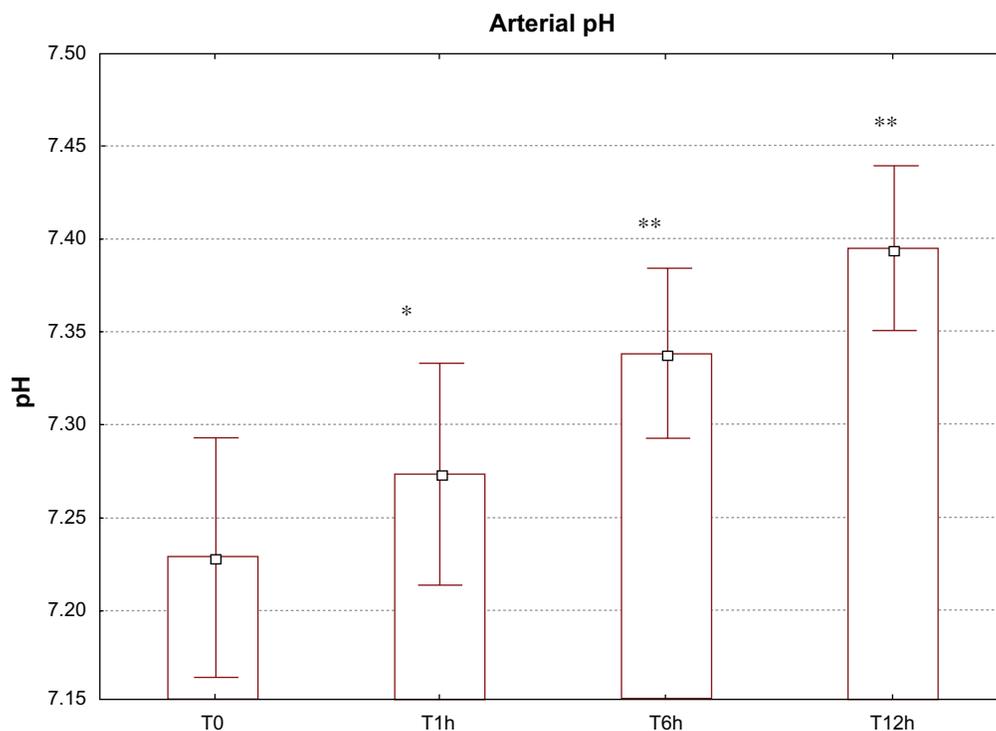
The main result of the present study is that in patients with hypoxemic–hypercapnic respiratory failure, the effectiveness of early application of BiPAP in the ED could be monitored by means of the measurement of EtCO<sub>2</sub> and arterial EtCO<sub>2</sub> gradient. Among our patients, a high percentage were successfully treated, with 60% discharged and no tracheal intubation required. The reduction of the acidosis after the introduction of BiPAP was correlated with an improvement of respiratory function, and as a consequence, the relief of the subjective feeling of dyspnea. This result is in agreement with published data.<sup>2,4,37</sup> Moreover, the recruitment of non-ventilated alveolar spaces, thus improving the ventilation/perfusion ratio, is evidenced by the progressive reduction of the difference between directly measured (PaCO<sub>2</sub>) and estimated PaCO<sub>2</sub> (EtCO<sub>2</sub>); at the end of the observation period, the EtCO<sub>2</sub> becomes a good estimate of PaCO<sub>2</sub>, although it doesn't reflect the exact PaCO<sub>2</sub> value. The novelty of the present study is the introduction of the CO<sub>2</sub> gradient as a



**Figure 1** Differences between directly measured and estimated arterial CO<sub>2</sub> partial pressure at different times.

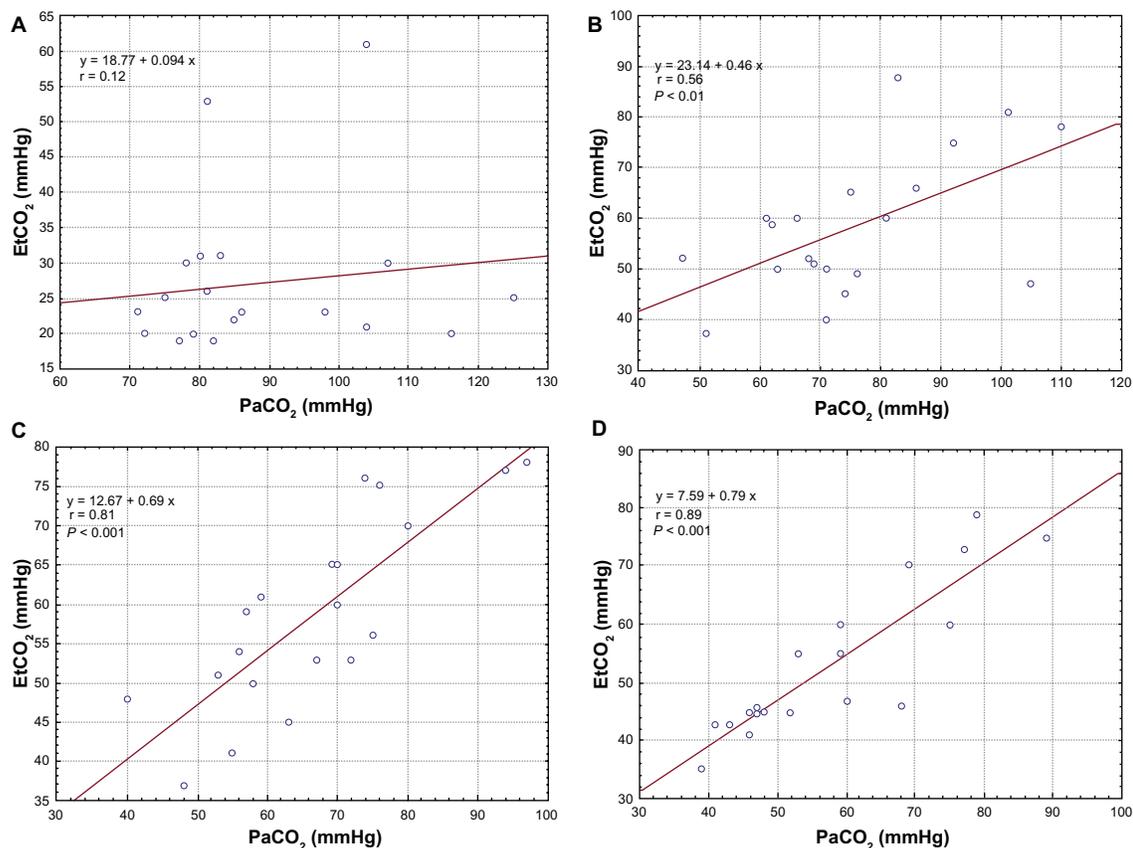
**Note:** \**P* < 0.001 (analysis of variance).

**Abbreviation:** P(a-Et)CO<sub>2</sub>, arterial–end tidal CO<sub>2</sub> difference.



**Figure 2** Arterial pH measured before application of bilevel positive airway pressure (T0) and after 1, 6, and 12 hours of treatment (T1h, T6h, T12h).

**Notes:** \**P* < 0.05, T1h versus (vs) T0; \*\**P* < 0.001, T6h vs T0 and T12h vs T0 (analysis of variance).



**Figure 3** Relationships of end-tidal CO<sub>2</sub> (EtCO<sub>2</sub>) pressure with arterial CO<sub>2</sub> partial pressure (PaCO<sub>2</sub>) at different times: (A) at admission ( $r = 0.12$ ); (B) after 1 hour ( $r = 0.56$ ,  $P < 0.01$ ); (C) after 6 hours ( $r = 0.81$ ,  $P < 0.001$ ); (D) and after 12 hours ( $r = 0.89$ ,  $P < 0.001$ ).

parameter to assess the effectiveness of BiPAP treatment of severe hypercapnic patients in an ED, independently from the underlying pathophysiological mechanism, along with the other methods to monitor patients.

In our study, the severe dyspnea was mainly due to pneumonia, acute exacerbation of COPD, and acute cardiogenic pulmonary edema; the presence of hypercapnic respiratory failure may be explained by respiratory muscle fatigue and associated illness (especially acute respiratory tract infections). As confirmed by previous studies,<sup>9,10</sup> it is important to initiate

early NIV in the ED, since avoiding delays reduces mortality rates and the need for tracheal intubation.

BiPAP ventilation is a relatively new type of respiration-support mode that has characteristics of spontaneous breath and breath control simultaneously. The device has been successfully used to improve exercise tolerance in COPD patients by increasing respiratory muscle strength,<sup>38</sup> and its long term use provides a better ventilation–perfusion match, and better blood gases and lung function through a mass-flow redistribution.<sup>39</sup> The efficacy of BiPAP has been evaluated in acute settings as well: in acute exacerbation of COPD, its use leads to an increase of arterial oxygen partial pressure (PaO<sub>2</sub>), a reduction of intubation rate, an amelioration of respiratory and other vital parameters, and a reduction in in-hospital mortality,<sup>3,4</sup> as regards acute cardiogenic pulmonary edema, the combination of inspiratory assistance with expiratory positive airway pressure can effectively alleviate respiratory distress, and as a consequence bilevel ventilation is considered more effective than continuous positive airway pressure (CPAP).<sup>5,16</sup> Systematic reviews have shown the benefit of BiPAP in the management of acute cardiogenic pulmonary edema, with reduction in the need for invasive mechanical ventilation and reduction of mortality.<sup>40,41</sup>

**Table 2** Changes in physiological variables with NIV

Variables	Before NIV	12 hours after NIV	ANOVA
Respiratory rate (breaths/minute)	27.5 ± 3	19 ± 3	$P < 0.001$
Heart rate (bpm)	107.6 ± 14	83.5 ± 9	$P < 0.001$
Systolic BP (mmHg)	150 ± 45	138 ± 32	NS
Diastolic BP (mmHg)	92 ± 14	84 ± 10	NS
SatO <sub>2</sub> (%)	80.2 ± 7	91.5 ± 2	$P < 0.001$

**Note:** Values are given as means ± standard deviation.

**Abbreviations:** NIV, noninvasive ventilation; ANOVA, analysis of variance; bpm, beats per minute; BP, blood pressure; NS, not significant; SatO<sub>2</sub>, oxygen saturation.

In patients with COPD and severe airflow obstruction, CO<sub>2</sub> retention is mainly associated with shallow breathing and inspiratory muscle weakness,<sup>42</sup> and EtCO<sub>2</sub> does not accurately reflect PaCO<sub>2</sub> at rest or during exercise,<sup>21</sup> because pulmonary diseases are usually associated with uneven distribution of ventilation and perfusion, due to large physiologic dead space. Since decreased cardiac output and pulmonary congestion in cardiac patients cause ventilation–perfusion mismatch, the CO<sub>2</sub> gradient is observed in patients with heart failure as well.<sup>22</sup> In acute settings, we found only a few studies evaluating the concordance between EtCO<sub>2</sub> and PaCO<sub>2</sub>,<sup>43,44</sup> but none assessing the CO<sub>2</sub> gradient changes during the treatment of severe hypercapnic dyspnea by means of NIV. Most studies that found EtCO<sub>2</sub> monitoring useful in nonintubated patients were not performed in circumstances of respiratory distress.<sup>45–47</sup>

Capnography measurements poorly reflect blood gas-analysis measurements in hypercapnic and tachypneic patients;<sup>43</sup> this fact could be explained by the ratio between dead space and tidal volume, which is increased in patients with respiratory distress and abnormal lung function. Furthermore, the higher the respiratory rate, the lower the accuracy of EtCO<sub>2</sub> measurements.<sup>48</sup>

EtCO<sub>2</sub> alone does not reliably reflect ventilation status in nonintubated adult patients with respiratory distress syndrome, but the effectiveness of NIV, with a reduction of dead space and respiratory rate, is reflected in the CO<sub>2</sub> gradient, leading to a better relationship between arterial CO<sub>2</sub> and EtCO<sub>2</sub>.

This study has some limitations: (1) the involvement of a relatively small number of patients, so a widening in sample size will be considered in order to reduce bias; (2) a relative lack in the collection of clinical data and some inhomogeneities due to differences in underlying diseases; and (3) the design of the study as a noncontrolled observational trial. In conclusion, even if further research is necessary to evaluate whether our results are confirmed in different settings, our data suggest that the measurement of the CO<sub>2</sub> gradient could be a reliable method in monitoring the effectiveness of NIV in acute hypercapnic patients in the ED.

## Disclosure

The authors report no conflicts of interest in this work.

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