

## Volume-Targeted Versus Pressure-Limited Noninvasive Ventilation in Hypercapnic Respiratory Failure: What Could Be Established in Real Practice?

To the Editor:

We have read with interest the original article titled "Volume-Targeted Versus Pressure-Limited Noninvasive Ventilation in Subjects with Acute Hypercapnic Respiratory Failure: A Multi-Center Randomized, Controlled Trial."<sup>1</sup> In this study, Cao et al<sup>1</sup> used a prospective, randomized controlled trial in the general respiratory wards to establish whether the ventilatory strategy with volume-targeted noninvasive ventilation (VT-NIV) was more effective than pressure-limited NIV (PL-NIV).

We have some remarks on this study for practical implications. First, regarding methodology, we believe patient selection was inadequate, as only subjects with exacerbations of chronic pathologies (eg, COPD, asthma, bronchiectasis, and obstructive sleep apnea syndrome) were randomized into 2 groups of 29 subjects with similar demographics and blood gas analysis (pH,  $P_{CO_2}$ ,  $P_{aO_2}/F_{IO_2}$ , and  $HCO_3^-$ ). The authors randomized subjects with mild to moderate acute-on-chronic hypercapnic respiratory failure, of which 12% reported previous use of NIV. However, they did not specify the causes or conditions for which these subjects received previous treatment with NIV.

Second, evaluation of key determinants of severity and grading needs to be more precisely defined in three aspects. There is an absence of parameters in the evaluation of acute hypercapnic respiratory failure. The authors did not report on (1) severity of mental status impairment;<sup>2</sup> (2)  $HCO_3^-$ , mmol/L, base excess at 2–6 h and at 12 h after NIV use, without clearly establishing the moment when they reached their compensation; and (3) conventional therapy such as inhaled  $\beta_2$ -agonists, anticholinergic agents, systemic steroids, and antibiotics, along with the method of delivery, dose, and frequency of treatments in both groups.

The third issue relates to the prolonged use of NIV detailed in the study. The authors reported on duration of NIV – median (IQR) of 6.0 d (4.0–9.5) for PL-NIV versus 9.0 (4.0–13.0) d for VT-NIV. Today, it is known that more than half of patients with

acute hypercapnic respiratory failure treated with NIV resolve within the first 24 h, 80% experience resolution within 48 h, and 92% resolve within 72 h. Patients with initial pH values between 7.30 and 7.35 require fewer days of NIV than those with a pH between 7.21 and 7.25.

In accordance with the guidelines, NIV should be first-line therapy in patients with exacerbations of chronic airway diseases, with pH < 7.35 and  $P_{CO_2} > 45$  mm Hg, until pH is normalized to 7.35–7.45. This prolonged use of NIV could indicate that these subjects had chronic hypercapnia, and therefore the reported NIV results may differ from other patient populations.<sup>3,4</sup>

Fourth, the authors used inadequate ventilation settings. In the non-intervention group, the authors tried to obtain a  $V_T$  of 8–10 mL/kg predicted body weight. They noted variations in the exhaled  $V_T$  of approximately 1 mL/kg predicted body weight, with 9.5 mL/kg at the start of the NIV, and 10.3 mL/kg at 6 h. On the other hand, 2 h after the use of NIV, the authors reported an increase in the pressures inspired by the PL-NIV group as shown in Figure 4D, at the moment when a greater decrease of  $P_{CO_2}$  in the VT-NIV group was observed. This pressure increase in favor of PL-NIV was maintained for up to 6 h. The maximum inspiratory positive airway pressure target should have been programmed as much as possible during the first hours of PL-NIV.<sup>5</sup>

We believe that these assessments should be taken into account when analyzing these results for proper clinical practical recommendation.

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## Volume-Targeted Versus Pressure-Limited in Noninvasive Ventilation in Hypercapnic Respiratory Failure. What Could Be Established in Real Practice?—Reply

In Reply:

We thank Drs Briones Claudett and Esquinas for their interest and for commenting on our work.<sup>1</sup> It is our immense pleasure to respond to such comments.

Regarding the methodology, we recruited 58 subjects with mild-to-moderate acute hypercapnic respiratory failure that mainly included COPD, asthma, bronchiectasis, and obstructive sleep apnea syndrome. Despite the small sample size, there were similar demographic and baseline characteristics between the two groups. As noted by Drs Briones Claudett and Esquinas, we included 7 subjects (12%) who had received noninvasive ventilation (NIV) previously, suggesting that in these subjects chronic hypercapnic respiratory failure occurred in the past. However, it is difficult to retrospectively obtain the specific conditions on which the previous NIV treatment was given.

It is of great importance to precisely define the severity of illness. Herein, we defined the eligible subjects as those with arterial pH < 7.35 and  $\geq 7.25$  with  $P_{aCO_2} >$

45 mm Hg and formulated the specific exclusion criteria. Despite no specific data on the severity of mental status impairment, we excluded patients with severe metabolic acidosis and lack of cooperation, which suggests that the subjects had favorable mental status. Considering that the changes of bicarbonates and base excess were not the primary variables, we did not present them in the Results section, even if we did in fact record them and found that there were no between-group and within-group differences over the first 6 h in these two variables. Moreover, the changes of pH and  $P_{aCO_2}$  at 0, 2, and 6 h were provided, which indirectly indicate the metabolic compensation level. In this study, despite no report on conventional therapy concerning COPD, the decision to conduct such treatment was left to the attending physician who was blinded to the study, suggesting that there might be similar treatment processes between the two groups.

We do not agree that the NIV use was prolonged. In this study, to avert respiratory distress after NIV liberation as much as possible, we formulated a rigorous withdrawal protocol for NIV, including the gradual decrease of pressure support level and the daily use of NIV under the conditions of clinical stability, and we established the specific cri-

teria of NIV liberation. As a result, we found that the daily use of NIV was gradually decreased during the first 5 d after randomization, and the median (IQR) duration of NIV was 6.0 d (4.0–9.5 d) in the pressure-limited NIV (PL-NIV) group and 9.0 d (4.0–13.0 d) in the volume-targeted NIV (VT-NIV) group. There was no significant difference between the two groups.

In our protocol, we adjusted the inspiratory positive airway pressure (IPAP) level to obtain a tidal volume ( $V_T$ ) of 8–10 mL/kg predicted body weight for PL-NIV, while the target  $V_T$  was set at 10 mL/kg predicted body weight for VT-NIV. We found that the exhaled  $V_T$  at the beginning of NIV was  $9.5 \pm 2.4$  mL/kg in the PL-NIV group and  $10.1 \pm 1.5$  mL/kg in the VT-NIV group, and the exhaled  $V_T$  at 6 h was  $10.3 \pm 2.3$  mL/kg in the PL-NIV group and  $10.4 \pm 1.3$  mL/kg in the VT-NIV group. There were no significant difference between the groups. We agree that the IPAP level had a tendency to be increased in the PL-NIV group. However, as the target to adjust IPAP level, the actual exhaled  $V_T$  was not significantly different between the groups, and thus the decrement of  $P_{aCO_2}$  was not significantly different between the groups. Certainly, as suggested by Frat and Thille,<sup>2</sup> an adequate tidal volume is the cor-

nerstone of NIV efficiency in acute hypercapnic respiratory failure, whatever mode is used. Accordingly, whether the IPAP level should be increased as much as possible deserves further investigation.

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