



Editorial

Guidelines for Chronic Non-invasive Ventilation in COPD: From Experience to Evidence



Guías para la ventilación crónica no invasiva en la EPOC: de la experiencia a la evidencia

The indication of chronic non-invasive mechanical ventilation (NIV) in patients with chronic obstructive pulmonary disease (COPD) has been controversial for the past 30 years. Despite the lack of support from high quality controlled studies, the number of prescriptions for NIV in patients with COPD was growing progressively. A consensus based on experts criteria appeared in 1999¹ with an essentially regulatory purpose of the prescriptions. Few years later, the Eurovent study demonstrated how heterogeneous the prescription of NIV in COPD in different European countries was. While in Italy or Austria, the prescription percentage of chronic NIV in COPD reached 50%, in others remained around 10%.²

Twenty years after the publication of the regulatory consensus, the number of prescriptions in COPD has continued to grow exponentially. The main reasons given by the clinicians for its use have been recurrent exacerbations or the impossibility of NIV withdrawal after a severe exacerbation.³ On the other hand, the evidence, although still far from solid, has increased considerably after the publication of some (few) high quality (but complex), controlled studies. The complexity of such studies to be performed can be summarized as follows:

- The primary main of the studies, that not always had been focussed to either exacerbation or hospitalizations
- The duration of follow-up: it is not uncommon to find studies with a duration greater than five years, including recruitment and follow-up period.^{4,5} Otherwise, a long duration is completely necessary if you look at mortality. Under these conditions, the economic burden can be really high. Some recent studies, however, used composite endpoints (mortality or time until the next exacerbation) that have significantly shortened the follow-up period.^{6,7}
- Inclusion criteria: traditionally, hypercapnia in the stability phase was the main inclusion criterion, since it was considered a marker of severity and short or medium-term mortality after the hypoxemia has been corrected. But the PaCO₂ threshold for initiating NIV has also been a matter of controversy. Studies including patients with PaCO₂ values farther from normal have shown greater differences between the arms of the study (NIV vs conventional therapy). Thus, in a situation of stability, it seems reasonable to recommend a threshold value around 50 mm Hg to consider NIV therapy.⁸ It is also especially important to rule out

other factors that may contribute to the development of hypercapnia, such as the coexistence of apnea-hypopnea syndrome (overlap syndrome). More recent controlled studies used a different approach, including patients with persisting hypercapnia after an exacerbation that needed NIV in the acute phase. Similarly to severe hypercapnia in the stable phase, this phenotype identifies a particularly fragile population with a reduced ventilatory reserve. The fact of having received and tolerated NIV in the acute phase can even reduce the difficulties in the shift to the chronic use. However, a key point of this design is the appropriateness of the time frame to define the persistence of post-exacerbation hypercapnia. The experience of the Rescue study⁶ showed that if too short periods of time are used (around 48 h of NIV withdrawal in the acute phase), many patients tend to normalize their PaCO₂ spontaneously. For this reason, the use of a time frame between 2 and 4 weeks^{5,7} seems more appropriate to exclude patients with spontaneous normalization of PaCO₂, thus avoiding an over-prescription of NIV after an exacerbation.

- The experience of recruiting centers and the procedure of the therapy: Whether stable or post exacerbated patients are included, the required sample needs clearly a multicenter approach. The heterogeneity in the experience of recruiting centers requires a strict protocol on how to carry out and control the therapy. In this regard, monitoring of PaCO₂ during adaptation and follow up and adjustment of parameters based on these results should be mandatory. A recent meta-analysis has already suggested that the use of high pressure support values (high intensity ventilation), with the aim to decrease PaCO₂ significantly (at least 20%) was associated with better outcomes.⁹ As a consequence, more recent studies used pressure support values much higher than their predecessors.^{4,5,7,10} Finally, it is also necessary to take into account the growing interest in automatic modes (volume assured pressure support or automatic expiratory pressure modes). Theoretically these modes are able to adapt to changes in ventilatory pattern or coexistence of upper airway obstructions during the use of therapy.
- Assessment of patient centered outcomes: Patient centered outcomes such as dyspnea, health-related quality of life and sleep quality are critically important for the effectiveness of NIV. However, the assessment methods varied widely across studies ending up with heterogeneous results.^{4,5,10} The impact of NIV on

sleep is still uncertain as sleep quality has been studied to a lesser extent with different methods which were mostly subjective. Ideally, we need to use validated and specific tools to measure the effect of NIV in these critically important outcomes in COPD patients with chronic respiratory failure.

The recently published guidelines on Long term Home Non-Invasive Ventilation for Management of COPD by the European Respiratory Society⁸ have tried to cover all these aspects. The content is structured around 4 main PICO questions, suggesting the use of NIV in chronic stable hypercapnic COPD patients and in patients with COPD following a life-threatening episode of acute hypercapnic respiratory failure requiring acute NIV, if hypercapnia persists following the episode. At same time, the target of the procedure should be directed to the normalization or reduction of PaCO₂ values using fixed pressure support mode as a first choice instead of more complex volume-assured modes. Attention has also been given to some questions (narrative) with less evidence in the literature. These questions provide an additional insight into the complexity of the procedure (phenotypic differences such as the presence of comorbidities, heterogeneity in the use of interfaces or even in ventilator models) and, at same time, are focused on important issues for the research in the immediate future, such as the appropriate way of monitoring these patients. Although PaCO₂ monitoring (daytime and overnight continuous by transcutaneous CO₂ sensors) is the recommended way to follow-up patients under NIV, it may lack specificity to determine the ultimate cause of suboptimal ventilation. Therefore, centers with more experience use routinely some advanced monitoring tools, such as polygraphy under NIV or information transfer from the built in software of the ventilators. The influence on outcome of persisting events or asynchronies during ventilation in COPD, classified based on the consensus of experts^{11,12} remains to date unclear.

Finally, although the clinicians using the above guidelines may feel uncomfortable about the low level of evidence of the recommendations, we believe that this only emphasizes on the complexity of their implementation in the daily clinical practice. It should be compulsory that their clinical application is accompanied by high levels of technical and clinical skills and continuous medical education. Ultimately, and as experience was the forerunner of the evidence, the clinical application of evidence requires high levels of experience and expertise.

References

1. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoxemia – a consensus conference report. *Chest*. 1999;116:521–34.
2. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, Escarabil J, Farre R, Fauroux B, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. *Eur Respir J*. 2005;25:1025–31.
3. Crimi C, Noto A, Princi P, Cuvelier A, Masa JF, Simonds A, et al. Domiciliary non-invasive ventilation in COPD: an international survey of indications and practices. *COPD*. 2016;13:483–90.
4. McEvoy RD, Pierce RJ, Hillman D, Esterman A, Ellis EE, Catchpole PG, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. *Thorax*. 2009;64:561–6.
5. Köhnlein T, Windisch W, Köhler D, Drabik A, Geiseler J, Hartl S, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med*. 2014;2:698–705.
6. Struik FM, Sprooten RTM, Kerstjens HAM, Bladner G, Zijnen M, Asin J, et al. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax*. 2014;69:826–34.
7. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA*. 2017;317:2177–86.
8. Ergan B, Oczkowski S, Rochwerg B, Carlucci A, Chatwin M, Clini E, et al. European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. *Eur Respir J*. 2019;54.
9. Struik FM, Lacasse Y, Goldstein RS, Kerstjens HA M, Wijkstra PJ. Nocturnal non-invasive positive pressure ventilation in stable COPD: a systematic review and individual patient data meta-analysis. *Respir Med*. 2014;108:329–37.
10. Casanova C, Celli BR, Tost L, Soriano E, Abreu J, Velasco V, et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. *Chest*. 2000;118:1582–90.
11. Gonzalez-Bermejo J, Perrin C, Janssens JP, Pepin JL, Mroue G, Léger P, et al. Proposal for a systematic analysis of polygraphy or polysomnography for identifying and scoring abnormal events occurring during non-invasive ventilation. *Thorax*. 2012;67:546–52.
12. Gonzalez-Bermejo J, Janssens J-P, Rabec C, Perrin C, Lofaso F, Langevin B, et al. Framework for patient-ventilator asynchrony during long-term non-invasive ventilation. *Thorax*. 2019;74:715–7.

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