Effect of nocturnal EPAP titration to abolish tidal expiratory flow limitation in COPD patients with chronic hypercapnia: a randomized, cross-over pilot study

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Abstract

Background: Tidal expiratory flow limitation (EFLT) promotes intrinsic PEEP (PEEPi) in patients with chronic obstructive pulmonary disease (COPD). Applying non-invasive ventilation (NIV) with an expiratory positive airway pressure (EPAP) matching PEEPi improves gas exchange, reduces work of breathing and ineffective efforts. We aimed to evaluate the effects of a novel NIV mode that continuously adjusts EPAP to the minimum level that abolishes EFLT.

Methods: This prospective, cross-over, open-label study randomized patients to one night of fixed-EPAP and one night of EFLT-abolishing-EPAP. The primary outcome was transcutaneous carbon dioxide pressure ($P_{tcCO_2}$). Secondary outcomes were: peripheral oxygen saturation (SpO2), frequency of ineffective efforts, breathing patterns and oscillatory mechanics.

Results: We screened 36 patients and included 12 in the analysis (age 72 ± 8 years, FEV1 38 ± 14%Pred). The median EPAP did not differ between the EFLT-abolishing-EPAP and the fixed-EPAP night (median (IQR) = 7.0 (6.0, 8.8) cmH2O during night vs 7.5 (6.5, 10.5) cmH2O, p = 0.365). We found no differences in mean $P_{tcCO_2}$ (44.9 (41.6, 57.2) mmHg vs 54.5 (51.1, 59.0), p = 0.365), the percentage of night time with $P_{tcCO_2} > 45$ mm Hg was lower (62(8,100)% vs 98(94,100)%, p = 0.031) and ineffective efforts were fewer (126(93,205) vs 261(205,351) events/hour, p = 0.003) during the EFLT-abolishing-EPAP than during the fixed-EPAP night. We found no differences in oxygen saturation and lung mechanics between nights.

Conclusion: An adaptive ventilation mode targeted to abolish EFLT has the potential to reduce hypercapnia and ineffective efforts in stable COPD patients receiving nocturnal NIV.

Trial registration: ClinicalTrials.gov, NCT04497090. Registered 29 July 2020—Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT04497090.

Keywords: Non-invasive ventilation, Chronic obstructive pulmonary disease, Forced oscillation technique, Intrinsic PEEP

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Background

We have recently introduced a novel automatic ventilation mode that continuously titrates expiratory positive airway pressure (EPAP) to the lowest value that abolishes tidal expiratory flow limitation (EFLT) [1]. This method,
which uses the difference between inspiratory and expiratory reactance (ΔXrs) measured by the forced oscillation technique (FOT) [2, 3] to assess the presence of EFLT, minimizes the neural respiratory drive and transdiaphragmatic pressure swings in COPD patients receiving non-invasive ventilation (NIV) [4].

We hypothesized that this adaptive ventilation mode would reduce hypercapnia during sleep in COPD patients with chronic hypercapnic respiratory failure. Moreover, since EFLT is associated with the development of intrinsic positive end-expiratory pressure (PEEPi)—which acts as an inspiratory threshold for the generation of inspiratory flows and can produce ineffective breath triggering [5]—we further hypothesized that the EFLT-abolishing respiratory support mode would reduce the triggering load imposed by PEEPi reducing the probability of ineffective efforts.

This pilot study aimed to evaluate the effects of a novel ventilation mode that automatically adjusts EPAP at the minimum level able to abolish EFLT compared to the standard fixed-EPAP mode in stable COPD patients receiving nocturnal NIV.

**Materials and methods**

**Study design**

In this prospective, randomized, cross-over, open-label pilot study, patients were studied in the hospital over two non-consecutive nights while using either fixed-EPAP or EFLT-abolishing-EPAP.

**Population**

We enrolled moderate to severe COPD patients [6], with FEV1 ≤ 50%Pred, a history of more than 3 exacerbations per year or more than 1 hospitalization per year. Patients were well established on nocturnal NIV for chronic hypercapnic respiratory failure for longer than 6 months. Inclusion criteria were age below 85 years and presence of EFLT in the supine position at EPAP = 4 cmH2O [1]. Exclusion criteria were COPD exacerbation within the past two months, acute illness, or clinical instability.

**Outcomes**

The primary outcome was PtCO2, expressed as mean overnight value and the percentage of night time spent in hypercapnia. Secondary outcomes were oxygen saturation, ineffective efforts, breathing pattern, and oscillatory mechanics. We hypothesized that mean PtCO2 and the percentage of the night spent in hypercapnia would be lower during the EFLT-abolishing-EPAP than during the fixed-EPAP night.

**Ventilation strategy**

Pressure support NIV was delivered using a non-commercial version of BiPAP Synchrony Ventilator (Philips-Respironics) via an unvented facial mask (AMARA, Philips-Respironics). The ventilator measured EFLT by FOT [1, 2, 7] and, in EFLT-abolishing-EPAP mode, it continuously adjusted EPAP to the minimum level able to abolish EFLT [1], with a minimum EPAP of 4 cmH2O and keeping the pressure support (ΔP) constant.

**Measurements**

Full laboratory polysomnography (Alice5, Philips-Respironics) was performed according to the American Academy of Sleep Medicine recommendations [8]. During each study night, we recorded PtCO2 and oxygen saturation (SpO2) (TOSCA, Radiometer) continuously. Airway opening pressure, flow and volume tracings were exported from the ventilator for offline analysis. We calculated the following parameters: mean PtCO2 and SpO2; the percentage of night time spent in hypercapnia (PtCO2 > 45 mm Hg) and with SpO2 < 90% (T90); mean tidal volume (Vt), respiratory rate (RR), minute ventilation (VE), inspiratory resistance and reactance (RINSP and XINSP, respectively), ΔXrs, and the number of ineffective efforts (IE) per hour. We identified ineffective efforts by the presence of a positive deflection in expiratory flow without a concomitant breath delivered by the ventilator, as previously described [9]. At the end of the night, we asked the patients to report about their comfort on the ventilator.

**Statistical analysis**

We compared parameters from the two nights using Wilcoxon signed-rank test. p-Values < 0.05 were considered statistically significant. Statistical analyses were performed using SigmaPlot v11 (Systat Software, Inc., San Jose, CA, USA).

**Results**

We screened thirty-six patients from April 2015 to April 2017. Of these patients, 19 did not satisfy the inclusion criteria as they did not present EFLT, one withdrew consent after the screening, two did not perform the second night trial because they got acutely sick, one was excluded from the analysis because of poor data quality, and 12 were included in the analysis (Fig. 1). Table 1 reports the characteristics of the patients included in the analysis.

Some patients acknowledged the presence of the oscillations, but they got acclimated after just few minutes. No patients reported discomfort during the EFLT-abolishing-EPAP night. We observed
large within-night fluctuations in EPAP during the EFLT-abolishing-EPAP night: the minimum within-night IQR was 1.8 cmH2O, the maximum within-night IQR was 8.8 cmH2O. Figure 2 shows the airway pressure and $P_{tc\text{CO}_2}$ of a representative patient during both nights.

The EPAP applied by the EFLT-abolishing mode was not significantly different from the prescribed EPAP (median (IQR) 7.0 (6.0, 8.8) cmH2O during the EFLT-abolishing-EPAP night vs 7.5 (6.5, 10.5) cmH2O during the fixed-EPAP night, $p = 0.365$), despite its larger within-night variability. $\Delta Xr$ values clustered around the EFLT threshold during the EFLT-abolishing-EPAP night (Fig. 3).

Figure 4 shows gas exchange parameters during the EFLT-abolishing-EPAP and the fixed-EPAP nights. The percentage of time spent in hypercapnia was lower (median (IQR) = 62 (8, 100)% vs. 98 (94, 100)% $p = 0.031$) during the EFLT-abolishing-EPAP than during the fixed-EPAP night. We found no differences in mean $P_{tc\text{CO}_2}$ between the EFLT-abolishing-EPAP and the fixed-EPAP night (44.9 (41.6, 57.2) mmHg vs 54.5 (51.1, 59.0), respectively; $p = 0.365$). Mean $Sp\text{O}_2$ and $T90$ did not differ between nights.

The IE were fewer (126 (93, 205) vs. 261 (205, 351) events/hour, $p = 0.003$) during the EFLT-abolishing-EPAP than during the fixed-EPAP night. Additionally, mean $V_T$ was lower ($p = 0.029$), and RR was higher ($p = 0.035$) during the EFLT-abolishing-EPAP than during the fixed-EPAP night. $V_E$, $R_{INS\text{P}}$, and $X_{INS\text{P}}$ did not differ between nights, even if the statistical power was too low to exclude an effect of the ventilation mode on these variables (Table 2).

**Discussion**

This is the first report of the nocturnal application of an adaptive NIV mode that continuously adjusts EPAP to the minimum level that abolishes EFLT in hypercapnic COPD patients. This ventilation mode was well tolerated, reduced the frequency of ineffective efforts and the percentage of night time spent in hypercapnia. We found no differences in $R_{INS\text{P}}$, $X_{INS\text{P}}$, and $\Delta Xr$s between the two modes. The median EPAP did not significantly differ between nights; however, on an individual basis, some patients received significantly different (either higher or lower) EPAP levels during the EFLT-abolishing-EPAP and the fixed-EPAP nights. During the EFLT-abolishing-EPAP night, the EPAP presented large fluctuations, suggesting that the ventilator automatically adapted the EPAP level to the changes in lung mechanics associated with changes in posture and sleep stage.

The individual responses to abolishing EFLT were highly heterogeneous, and this heterogeneity may have contributed to the lack of statistically significant differences in gas exchange between nights. In several subjects, we noticed a clinically relevant improvement in either $P_{tc\text{CO}_2}$ or $Sp\text{O}_2$ during the EFLT-abolishing-EPAP night. One patient presented a markedly higher mean $P_{tc\text{CO}_2}$ during the EFLT-abolishing-EPAP than during the fixed-EPAP night. This patient was very flow-limited, received a median EPAP of 12 cmH2O during the EFLT-abolishing-EPAP night vs 6 cmH2O during the fixed-EPAP night, and presented a much higher $V_E$ during the EFLT-abolishing-EPAP than during the fixed-EPAP night. We did not identify any parameter able to predict the gas exchange response of a given patient to the EFLT-abolishing ventilation mode. Larger studies are needed.
needed to draw conclusions about the clinical benefits of this novel adaptive mode and to identify phenotypes that may better benefit from it.

NIV is used in stable COPD patients with hypercapnic respiratory failure to reduce arterial partial pressure of CO\textsubscript{2} [10]. In our study improvements in P\textsubscript{tcCO\textsubscript{2}} and in the percentage of night time spent in hypercapnia were not associated with increases in pressure support or V\textsubscript{E}, highlighting the relevant role of EPAP in the control of hypercapnia in COPD patients. Titrating EPAP to abolish EFL\textsubscript{T} may reduce CO\textsubscript{2} via several mechanisms [5, 11, 12]: (1) reducing work of breathing by improving patient-ventilator synchronization, (2) unloading the inspiratory muscles by counteracting the intrinsic PEEP, (3) reducing the ventilation-perfusion mismatch by eliminating choke-points. Moreover, EFL\textsubscript{T} is highly variable within the same patient, e.g. it changes with body posture [1] and sleep stage. Therefore, an adaptive ventilation mode that continuously adjusts EPAP based on patient respiratory mechanics increases the time spent with the optimal EPAP compared with a fixed-EPAP mode, even if the average EPAP applied by the two ventilation modes is similar.

This study has several limitations. Since it was a short-term study, we could not assess long-term effectiveness and safety. Moreover, this was a pilot study on a
**Fig. 3** EPAP and tidal expiratory flow limitation index during the night with EFLT-abolishing-EPAP vs. fixed-EPAP. Data are reported as individual values (open symbols dotted lines) and as mean ± SD of all subjects (closed symbols). Dashed-line: tidal expiratory flow limitation threshold. EPAP: expiratory positive airway pressure. ∆Xrs: difference between mean inspiratory and expiratory reactance (tidal expiratory flow limitation index). ∆Xrs data for 11 subjects.

**Fig. 4** Gas exchange during the night with EFLT-abolishing-EPAP vs. fixed-EPAP. Data are reported as individual values (open symbols dotted lines) and as mean ± SD of all subjects (closed symbols). SpO₂: peripheral oxygen saturation. T90: percentage of time spent with oxygen saturation SpO₂ below 90%. PtcCO₂: transcutaneous partial pressure of carbon dioxide. T hypercapnia: percentage of time spent with a PtcCO₂ > 45 mm Hg. T hypercapnia and ∆Xrs data for 11 subjects. *p < 0.05 between nights.
Table 2 Respiratory parameters and sleep quality during the night with fixed vs. EFLT-abolishing-EPAP

|                       | Fixed-EPAP      | EFLT-abolishing-EPAP | p         |
|-----------------------|-----------------|----------------------|-----------|
| **Gas exchange**      |                 |                      |           |
| Mean PtcCO₂, mmHg     | 54.5 (51.1, 59.0) | 44.9 (41.6, 57.2)    | 0.365     |
| T hypercapnia, %      | 98 (94, 100)    | 62 (8, 100)          | 0.031     |
| Mean SpO₂, %          | 93 (92, 95)     | 94 (93, 95)          | 0.204     |
| T90, %                | 3 (0, 12)       | 1 (0, 2)             | 0.175     |
| **Respiratory parameters** |            |                      |           |
| REEP, cmH₉O*s/L       | 9.7 (8.5, 12.0) | 11.4 (9.3, 12.1)     | 0.577     |
| XEEP, cmH₂O*s/L       | −3.6 (−4.1, −2.3) | −3.8 (−3.9, −2.9)    | 0.898     |
| IFAP, cmH₂O           | 15.7 (14.0, 17.1) | 16.1 (14.3, 18.1)    | 0.638     |
| V₅, mL                | 356 (252, 542)  | 272 (230, 395)       | 0.032     |
| RR, bpm               | 16 (13, 18)     | 17 (14, 20)          | 0.019     |
| V₅, L/min             | 5.3 (3.9, 6.4)  | 4.6 (3.8, 5.8)       | 0.123     |
| IE, n/h               | 261 (205, 351)  | 126 (93, 205)        | 0.003     |

Data are reported as median (IQR)

Bold denotes a statistically significant difference between the fixed-EPAP and the EFLT-abolishing-EPAP nights (Wilcoxon signed-rank test, p < 0.05)

PtcCO₂: Transcutaneous partial pressure of CO₂; T hypercapnia: Percentage of time spent with a transcutaneous partial pressure of CO₂ > 45 mm Hg; SpO₂: Peripheral oxygen saturation; T90: Percentage of time spent with oxygen saturation; SpO₂ below 90%; REEP: Inspiratory reactance; XEEP: Inspiratory reactance; IFAP: Inspiratory positive airway pressure; V₅: Tidal volume; RR: Respiratory rate; V₅: Minute ventilation; IE: Ineffective efforts

*p < 0.05 vs. fixed-EPAP

In conclusion, the use of a NIV mode that continuously autotitrates EPAP to abolish EFLT during sleep has the potential to control hypercapnia better and reduce ineffective efforts compared with fixed-EPAP modes in COPD. Larger studies are needed to draw conclusions about the clinical benefits of this novel ventilation mode and to assess its long term effects.

**Abbreviations**

COPD: Chronic obstructive pulmonary disease; EPAP: Expiratory positive airway pressure; EFLT: Tidal expiratory flow limitation; FOT: Forced oscillation technique; IE: Number of ineffective efforts per hour; ΔXrs: Difference between mean inspiratory and expiratory reactance; NIV: Non-invasive ventilation; PtcCO₂: Transcutaneous partial pressure of carbon dioxide; REEP: Mean inspiratory resistance; RR: Respiratory rate; SpO₂: Peripheral oxygen saturation; T90: Percentage of time with SpO₂ < 90%; V₅: Minute ventilation; XEEP: Inspiratory reactance.

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**Authors’ contributions**

EZ participated in data analysis and interpretation and prepared the first version of the manuscript. IM participated in the conception and design of the study, data collection, data analysis and interpretation. RP, LB and SC participated in the data collection and analysis. RT contributed to data analysis. FF participated in data analysis and interpretation and critically revised the manuscript. MV participated in the conception and design of the study, interpretation of the data and critically revised the manuscript. RLD participated in the conception and design of the study, data analysis, interpretation of the data and preparation of the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

The study was approved by the ethics committee of ICS Maugeri (No. 897 CEC/2013) and written informed consent was obtained from all patients.

**Consent for publication**

Not applicable.

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