Respiratory Research

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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 (EFL_T) 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 EFL_T.

Methods: This prospective, cross-over, open-label study randomized patients to one night of fixed-EPAP and one night of EFL_T-abolishing-EPAP. The primary outcome was transcutaneous carbon dioxide pressure ($PtcCO_2$). Secondary outcomes were: peripheral oxygen saturation (SpO_2), 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 EFL_T-abolishing-EPAP and the fixed-EPAP night (median (IQR) = 7.0 (6.0, 8.8) cmH_2O during night vs 7.5 (6.5, 10.5) cmH_2O, p = 0.365). We found no differences in mean $PtcCO_2$ (44.9 (41.6, 57.2) mmHg vs 54.5 (51.1, 59.0), p = 0.365), the percentage of night time with $PtcCO_2 > 45$ 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 EFL_T-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 EFL_T has the potential to reduce hypercapnia and ineffective efforts in stable COPD patients receiving nocturnal NIV.

Trial registration: ClicalTrials.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 (EFL_T) [1]. This method,

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which uses the difference between inspiratory and expiratory reactance (ΔXrs) measured by the forced oscillation technique (FOT) [2, 3] to assess the presence of EFL_T, 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 EFL_T 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 EFL_T-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 EFL_T 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 EFL_T-abolishing-EPAP.

Population
We enrolled moderate to severe COPD patients [6], with FEV1 $\leq$ 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 EFL_T in the supine position at EPAP $= 4$ cmH$_2$O [1]. Exclusion criteria were COPD exacerbation within the past two months, acute illness, or clinical instability.

Outcomes
The primary outcome was PtcCO$_2$, 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 PtcCO$_2$ and the percentage of the night spent in hypercapnia would be lower during the EFL_T-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 EFL_T by FOT [1, 2, 7] and, in EFL_T-abolishing-EPAP mode, it continuously adjusted EPAP to the minimum level able to abolish EFL_T [1], with a minimum EPAP of 4 cmH$_2$O 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 PtcCO$_2$ and oxygen saturation (SpO$_2$) (TOSCA, Radiometer) continuously. Airway opening pressure, flow and volume tracings were exported from the ventilator for offline analysis. We calculated the following parameters: mean PtcCO$_2$ and SpO$_2$; the percentage of night time spent in hypercapnia (PtcCO$_2 > 45$ mm Hg) and with SpO$_2 < 90\%$ (T90); mean tidal volume (V_T), respiratory rate (RR), minute ventilation (V_E), inspiratory resistance and reactance (R_{INSP} and X_{INSP}, 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.
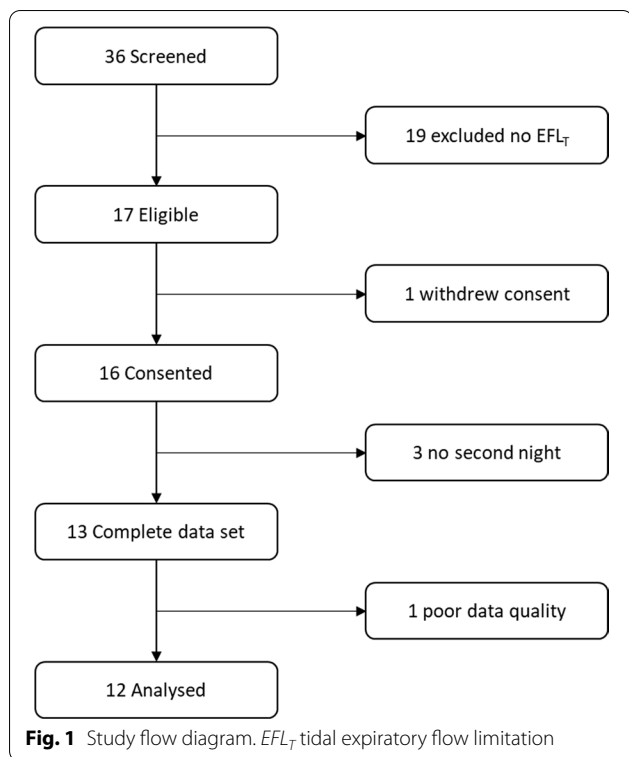
Statistical analysis
We compared parameters from the two nights using Wilcoxon signed-rank test. p-Values < 0.05 were considered statistically significant. Statistical analyses were performed using SigmaPlot v11 (Systat Software, Inc., San Jose, CA, USA).

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 EFL_T, 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 EFL_T-abolishing-EPAP night. We observed

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Fig. 1 Study flow diagram. *EFL$_T$* tidal expiratory flow limitation

Table 1 Characteristics of study participants

N	12
Sex, %males	67%
Age, years	73 (66, 79)
BMI, kg/m^2	29.2 (27.7, 32.9)
FEV1, % predicted	33 (25, 47)
FEV1/FVC, %	43 (32, 60)
Prescribed EPAP, cmH$_2$O	7.5 (6.0, 9.0)

BMI body mass index, *FEV1* forced expiratory volume in one second, *FVC* forced vital capacity, *EPAP* expiratory positive airway pressure

large within-night fluctuations in EPAP during the EFL$_T$-abolishing-EPAP night: the minimum within-night IQR was 1.8 cmH$_2$O, the maximum within-night IQR was 8.8 cmH$_2$O. Figure 2 shows the airway pressure and *P*tcCO$_2$ of a representative patient during both nights.

The EPAP applied by the EFL$_T$-abolishing mode was not significantly different from the prescribed EPAP (median (IQR) 7.0 (6.0, 8.8) cmH$_2$O during the EFL$_T$-abolishing-EPAP night vs 7.5 (6.5, 10.5) cmH$_2$O during the fixed-EPAP night, p = 0.365), despite its larger within-night variability. ΔXrs values clustered around the EFL$_T$ threshold during the EFL$_T$-abolishing-EPAP night (Fig. 3).
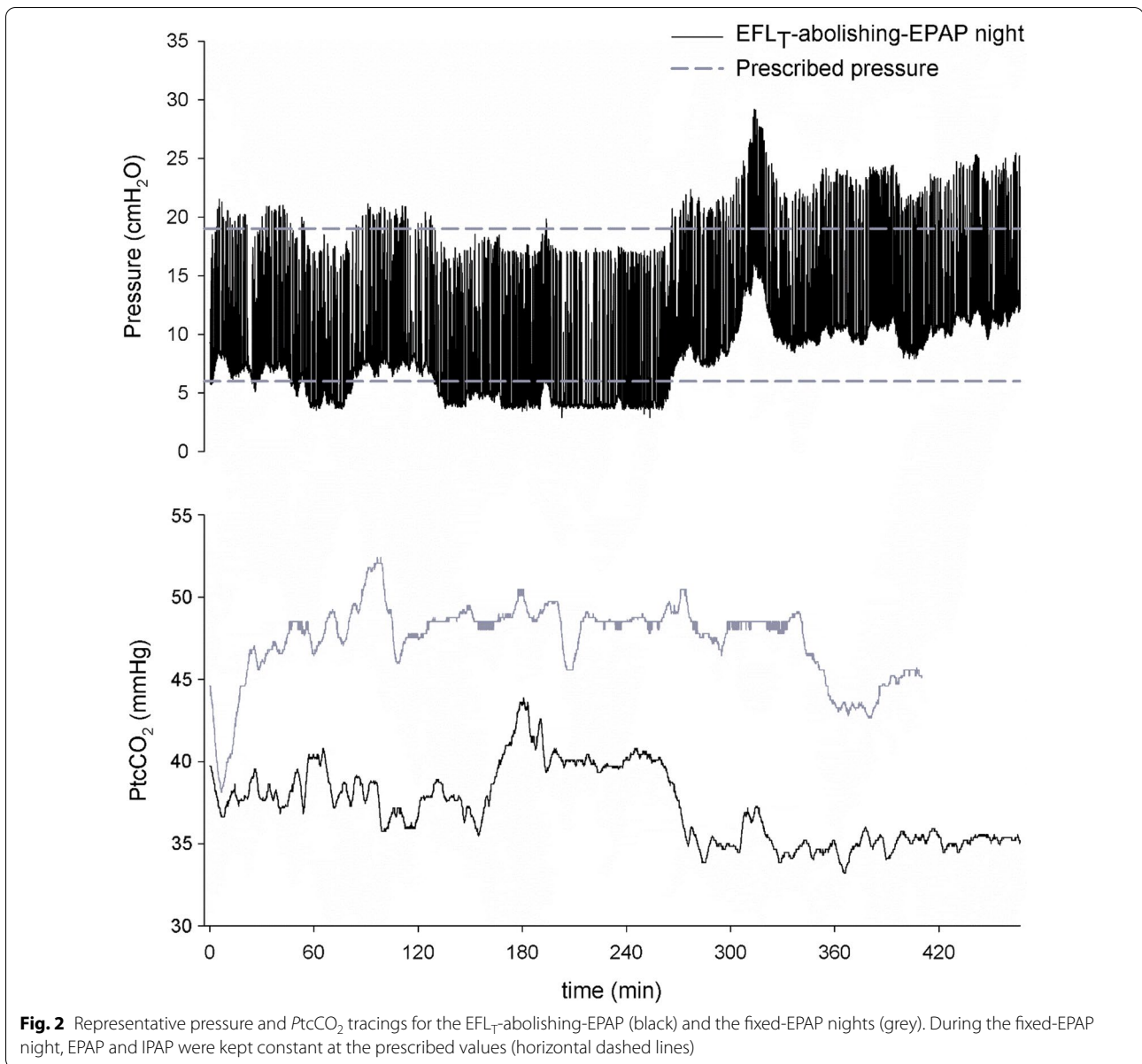
Figure 4 shows gas exchange parameters during the EFL$_T$-abolishing-EPAP and the fixed-EPAP nights. The percentage of time spent in hypercapnia was lower (median (IQR) = 62 (8, 100)% vs. 98 (94, 100)%, p = 0.031) during the EFL$_T$-abolishing-EPAP than during the fixed-EPAP night. We found no differences in mean *P*tcCO$_2$ between the EFL$_T$-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 SpO$_2$ 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 EFL$_T$-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 EFL$_T$-abolishing-EPAP than during the fixed-EPAP night. V$_E$, R$_{INSP}$, and X$_{INSP}$ 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 EFL$_T$ 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$_{INSP}$, X$_{INSP}$, and ΔXrs 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 EFL$_T$-abolishing-EPAP and the fixed-EPAP nights. During the EFL$_T$-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 EFL$_T$ 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*tcCO$_2$ or SpO$_2$ during the EFL$_T$-abolishing-EPAP night. One patient presented a markedly higher mean *P*tcCO$_2$ during the EFL$_T$-abolishing-EPAP than during the fixed-EPAP night. This patient was very flow-limited, received a median EPAP of 12 cmH$_2$O during the EFL$_T$-abolishing-EPAP night vs 6 cmH$_2$O during the fixed-EPAP night, and presented a much higher V$_E$ during the EFL$_T$-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 EFL$_T$-abolishing ventilation mode. Larger studies are

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Fig. 2 Representative pressure and $PtcCO_2$ tracings for the EFL_T-abolishing-EPAP (black) and the fixed-EPAP nights (grey). During the fixed-EPAP night, EPAP and IPAP were kept constant at the prescribed values (horizontal dashed lines)

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_2 [10]. In our study improvements in $PtcCO_2$ and in the percentage of night time spent in hypercapnia were not associated with increases in pressure support or V_E, highlighting the relevant role of EPAP in the control of hypercapnia in COPD patients. Titrating EPAP to abolish EFL_T may reduce CO_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_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
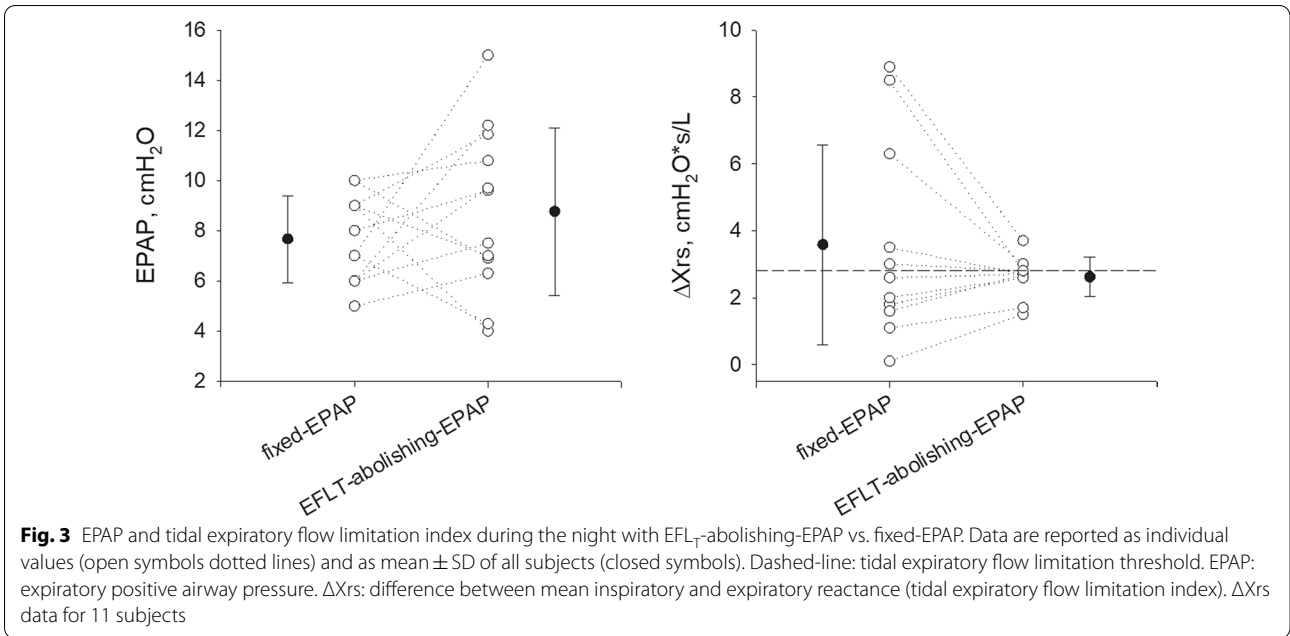
Fig. 3 EPAP and tidal expiratory flow limitation index during the night with EFL_T-abolishing-EPAP vs. fixed-EPAP. Data are reported as individual values (open symbols dotted lines) and as mean $\pm$ SD of all subjects (closed symbols). Dashed-line: tidal expiratory flow limitation threshold. EPAP: expiratory positive airway pressure. ΔXrs: difference between mean inspiratory and expiratory reactance (tidal expiratory flow limitation index). ΔXrs data for 11 subjects
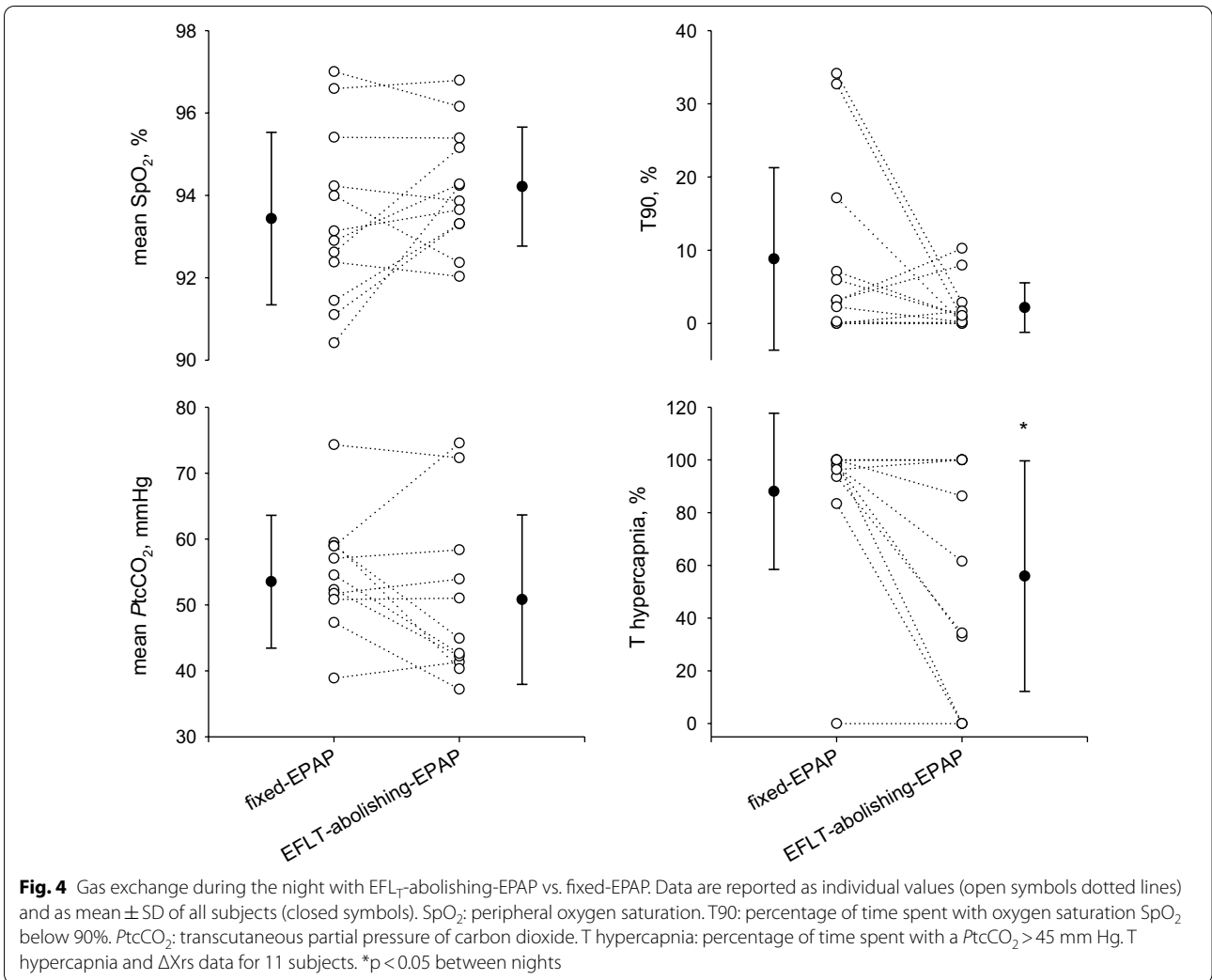
Fig. 4 Gas exchange during the night with EFL_T-abolishing-EPAP vs. fixed-EPAP. Data are reported as individual values (open symbols dotted lines) and as mean $\pm$ SD of all subjects (closed symbols). SpO_2: peripheral oxygen saturation. T90: percentage of time spent with oxygen saturation SpO_2 below 90%. $PtcCO_2$: transcutaneous partial pressure of carbon dioxide. T hypercapnia: percentage of time spent with a $PtcCO_2 > 45$ mm Hg. T hypercapnia and ΔXrs data for 11 subjects. *p < 0.05 between nights

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Table 2 Respiratory parameters and sleep quality during the night with fixed vs. EFL$_T$-abolishing-EPAP

	Fixed-EPAP	EFL$_T$-abolishing-EPAP	p
Gas exchange			
mean *P*tcCO$_2$, 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 SpO$_2$, %	93 (92, 95)	94 (93, 95)	0.204
T90, %	3 (0, 12)	1 (0, 2)	0.175
Respiratory parameters			
R$_{INSP}$, cmH$_2$O*s/L	9.7 (8.5, 12.0)	11.4 (9.3, 12.1)	0.577
X$_{INSP}$, cmH$_2$O*s/L	− 3.6 (− 4.1, − 2.3)	− 3.8 (− 3.9, − 2.9)	0.898
IPAP, cmH$_2$O	15.7 (14.0, 17.1)	16.1 (14.3, 18.1)	0.638
V$_T$, mL	**356 (252, 542)**	**272 (230, 395)**	**0.032**
RR, bpm	**16 (13, 18)**	**17 (14, 20)**	**0.019**
V$_E$, 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 EFL$_T$-abolishing-EPAP nights (Wilcoxon signed-rank test, p < 0.05)

*P*tcCO$_2$ transcutaneous partial pressure of CO$_2$, *T hypercapnia* percentage of time spent with a transcutaneous partial pressure of CO$_2$ > 45 mm Hg, *SpO$_2$* peripheral oxygen saturation, *T90* percentage of time spent with oxygen saturation SpO$_2$ below 90%, *R$_{INSP}$* inspiratory resistance, *X$_{INSP}$* inspiratory reactance, *IPAP* inspiratory positive airway pressure, *V$_T$* tidal volume, *RR* respiratory rate, *V$_E$* minute ventilation, *IE* ineffective efforts

*p < 0.05 vs. fixed-EPAP

small number of patients. Ten to fifteen patients is the typical sample size for pilot studies. This number is not calculated on statistical bases, but it is appropriate to assess the feasibility of a new method, inform possible improvements and collect preliminary data for larger clinical trials. The most reliable method for the assessment of ineffective efforts is to identify tidal swings in trans-diaphragmatic pressure (measured by gastric and oesophageal probes) that are not followed by an assisted breath. Our definition of ineffective efforts may have missed the efforts that did not generate any deflation in the flow signal, underestimating the actual number of events. However, we preferred not to measure the trans-diaphragmatic pressure because it could have disrupted sleep. We used *P*tcCO$_2$ and pulse oximetry as indicators of gas exchange. Arterial blood gas measurements would have been more precise; however, in the ordinary setting of polysomnography, it is not possible to have an invasive continuous measurement of arterial blood gasses. On the other hand, single blood gas measurements are not representative of the gas exchange during sleep, and multiple overnight assessments usually determine sleep disruption.

Conclusion

In conclusion, the use of a NIV mode that continuously auto-titrates EPAP to abolish EFL$_T$ 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.

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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