Autotitrating external positive end-expiratory airway pressure to abolish expiratory flow limitation during tidal breathing in patients with severe COPD: a physiological study

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An automated ventilator algorithm, using the forced oscillation technique to detect tidal breathing expiratory flow limitation (EFL_T), identifies the optimum EPAP at which EFL_T is abolished without causing unnecessary lung hyperinflation https://bit.ly/2WNyhWP

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ABSTRACT

Background: The optimal noninvasive application of external positive end-expiratory pressure (EPAP) to abolish tidal-breathing expiratory flow limitation (EFL_T) and minimise intrinsic positive end-expiratory pressure ($PEEP_i$) is challenging in COPD patients. We investigated whether auto-titrating EPAP, using the forced oscillation technique (FOT) to detect and abolish EFL_T, would minimise $PEEP_i$, work of breathing and neural respiratory drive (NRD) in patients with severe COPD.

Methods: Patients with COPD with chronic respiratory failure underwent auto-titration of EPAP using a FOT-based algorithm that detected EFL_T. Once optimal EPAP was identified, manual titration was performed to assess NRD (using diaphragm and parasternal intercostal muscle electromyography, EMG_{di} and EMG_{para}, respectively), transdiaphragmatic inspiratory pressure swings (ΔP_{di}), transdiaphragmatic pressure–time product (PTP_{di}) and $PEEP_i$, between EPAP levels 2 cmH_2O below to 3 cmH_2O above optimal EPAP.

Results: Of 10 patients enrolled (age 65±6 years; male 60%; body mass index 27.6±7.2 $kg.m^{-2}$; forced expiratory volume in 1 s 28.4±8.3% predicted), eight had EFL_T, and optimal EPAP was 9 (range 4–13) cmH_2O. NRD was reduced from baseline EPAP at 1 cmH_2O below optimal EPAP on EMG_{di} and at optimal EPAP on EMG_{para}. In addition, at optimal EPAP, $PEEP_i$ (0.80±1.27 cmH_2O *versus* 1.95± 1.70 cmH_2O; p<0.05) was reduced compared with baseline. PTP_{di} (10.3±7.8 $cmH_2O{\cdot}s^{-1}$ *versus* 16.8±8.8 $cmH_2O{\cdot}s^{-1}$; p<0.05) and ΔP_{di} (12.4±7.8 cmH_2O *versus* 18.2±5.1 cmH_2O; p<0.05) were reduced at optimal EPAP+1 cmH_2O compared with baseline.

Conclusion: Autotitration of EPAP, using a FOT-based algorithm to abolish EFL_T, minimises transdiaphragmatic pressure swings and NRD in patients with COPD and chronic respiratory failure.

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Introduction

Expiratory flow limitation in tidal breathing (EFL_T), defined as an inability to increase expiratory flow despite an increase in expiratory pressure, is a hallmark of COPD and a major cause of the dynamic hyperinflation that leads to dyspnoea [1] and exercise limitation [2, 3].

Externally applied expiratory positive airway pressure (EPAP) during noninvasive ventilation (NIV) reduces the adverse effects of intrinsic positive end-expiratory pressure ($PEEP_i$), thus reducing the work of breathing and improving patient–ventilator synchrony [4, 5]. However, the optimal EPAP is unknown and clinical judgement is usually applied in setting its level. Although studies in invasively ventilated patients have suggested an EPAP level of ~85% of the measured inspiratory threshold load [6], $PEEP_i$ may alter substantially with changes in breathing pattern or posture [7, 8]. Therefore, a single constant level of EPAP may not optimally alleviate an individual patient's $PEEP_i$ under all circumstances. In order to deliver effective NIV, EPAP should be titrated dynamically, adjusting to the varying conditions of the patient to reduce $PEEP_i$, work of breathing, neural respiratory drive and dyspnoea.

Continuous titration of EPAP according to directly measured $PEEP_i$ would be the ideal way of optimising EPAP in COPD patients; however, available methods for assessing $PEEP_i$ require the use of an oesophageal pressure catheter, which is invasive and impractical in patients with acute respiratory failure and those using domiciliary NIV. Moreover, this approach requires continuous monitoring by a skilled operator, both to maintain oesophageal catheter position when the diaphragm moves as a consequence of the natural fluctuation of end expiratory lung volume [9], and for proper interpretation of tracings.

An alternative target for autotitration of EPAP is the abolition of EFL_T, which leads to a reduction in $PEEP_i$. A method based on the forced oscillation technique (FOT) has been developed to detect EFL_T noninvasively during tidal breathing [10]. FOT involves the application of low-frequency and small-amplitude pressure oscillations to the mouth to determine the resistance and reactance (X_{rs}) components of the impedance of the respiratory system (Z_{rs}). Dellacà and colleagues [10, 11] demonstrated that changes in reactance between inspiration and expiration (ΔX_{rs}) are greater for flow-limited breaths than for non-flow-limited breaths; specifically, the application of a single threshold to ΔX_{rs} allows accurate classification of each single breath as affected by EFL_T or not in patients with COPD both in the stable state [10, 11] and during exacerbations [12]. This approach is also accurate when applied through a nasal mask [13, 14]. Moreover, it can be incorporated in a device delivering NIV to titrate EPAP automatically to the minimum value needed to abolish EFL [15].

We hypothesised that autotitrating EPAP to the lowest value that abolishes tidal EFL by FOT criteria would reduce $PEEP_i$, transdiaphragmatic inspiratory pressure swings, the pressure–time product of transdiaphragmatic pressure and neural respiratory drive (NRD) in patients with severe COPD and chronic respiratory failure.

Methods

Patients

Patients established on domiciliary NIV for chronic respiratory failure due to COPD were recruited from at a UK regional ventilation service. The study was approved by the London Bentham research ethics committee 10/H0705/66. Inclusion criteria were 1) age ⩾35 years; 2) >10 pack-year smoking history; and 3) exacerbation-free for ⩾6 weeks prior to enrolment. Exclusion criteria were 1) significant cardiac or respiratory comorbidity; 2) other serious medical condition, as defined by the responsible clinician; 3) allergies to latex, metals or local anaesthetic agents; and 4) psychosocial factors that would impair compliance with the study protocol.

Study protocol

Patients were asked not to eat or drink for 4 h prior to the study, and to avoid using their bronchodilators on the day of the study. Baseline anthropometric data, spirometry and arterial blood gas measurements were recorded. A multipair electrode oesophageal catheter incorporating a gastric and an oesophageal balloon (combined electrode catheter; Top Pine Technology Development Ltd, Hong Kong, China) was inserted *via* the nares and positioned optimally for recording the diaphgram electromyogram (EMG_{di}) signals, with the patient in a semi-recumbent position, as described previously [16]. The occlusion test was performed to confirm correct positioning of the oesophageal balloon [17]. Patients were monitored continuously by transcutaneous oximetry and capnography. Parasternal EMG electrodes were applied at the second intercostal space, as described previously [18].

Details of the ventilator algorithm and the mask interface used to apply EPAP are given in the supplementary material.

Patients were initially settled in tidal breathing at a baseline EPAP level of 3 cmH_2O (the minimum EPAP level required to allow effective exhaled breath washout from the whisper swivel) for 5–10 min for baseline measurements. The ventilator was then set to the FOT-based autotitration mode, so that EPAP would rise or fall according to the presence of EFL, and autotitration was carried out for up to 45 min, until a stable optimal EPAP ($EPAP_{opt}$) was reached.

In order to investigate the effects of EPAP settings higher and lower than $EPAP_{opt}$, the autotitration mode was switched off and EPAP manually set at a fixed level of 3 cmH_2O above $EPAP_{opt}$ ($EPAP_{opt}$+3) for 10 min. EPAP was then reduced by 1 cmH_2O every 10 min until $EPAP_{opt}$−3 was reached (figure 1). The modified Borg scale was used to record dyspnoea at each level of EPAP.

Measurements

Pressure and flow at the airway opening were measured using a differential pressure transducer (PXLA0025DN, full scale range ±0–25 cmH_2O; Sensym, Milpitas, CA, USA) and a pneumotachometer connected to a pressure transducer (PXLA02X5DN, full scale range 0–2.5 cmH_2O; Sensym). The pneumotachometer was placed proximally to the patient, between the whisper swivel exhalation valve and the mask, in order to avoid measurement of the intentional airflow leaked through the valve. Pressure and flow data were sampled at 200 Hz using an analogue-to-digital acquisition board (DAQCARD 6036-E; National Instruments, Austin, TX, USA) and recorded on a personal computer.

NRD was quantified using EMG_{di} and second intercostal space parasternal muscle EMG (EMG_{para}). EMG_{di} signals were pre-amplified with a gain of 100. EMG_{para} signals were pre-amplified with a gain of 1000. EMG_{di}, EMG_{para}, mouth pressure, oesophageal pressure and gastric pressure measurements were sampled at 2000 Hz *via* a Powerlab analogue-to-digital converter (AD Instruments, Chalgrove, UK). The modified Borg scale was used to assess dyspnoea at each level of EPAP during the manual titration phase.

Data processing and analysis

Respiratory system impedance was calculated offline from flow and pressure measurements made at the mask using a least-squares algorithm [19] as an independent measure of Z_{rs}. Dynamic $PEEP_i$ was calculated at each level of EPAP as the difference in oesophageal pressure from the onset of inspiratory effort to the onset of inspiratory flow, averaged over 1 min [4]. Inspiratory transdiaphramatic pressure swings (ΔP_{di}) were identified and averaged over 1 min at each step on the EPAP titration ladder. The pressure–time product of transdiaphragmatic pressure (PTP_{di}) was calculated by integrating the P_{di} signal with respect to time for each breath; the mean PTP_{di} of all breaths in 1 min was reported [20]. EMG_{di} signals were analysed as follows: the mean inspiratory peak root mean square (RMS) EMG_{di} value over breaths taken in 1 min were normalised to the mean RMS EMG_{di} value at $EPAP_{opt}$ and expressed as $EMG_{di\%opt}$. Similarly, parasternal EMG was expressed as a percentage of the value obtained at $EPAP_{opt}$, *i.e.* $EMG_{para\%opt}$.

Data obtained at the EPAP level of 3 cmH_2O during the initial settling phase were considered to be the baseline level for comparison during the manual titration phase.

Data were analysed with the Friedman test for repeated measures, the Wilcoxon signed-ranks test for paired data and the Mann–Whitney U-test for independent samples. Data are expressed as mean±SD.

Results

13 patients were recruited. Two patients were excluded as they were in acute respiratory failure upon arrival for their study and required acute NIV. One patient had otherwise unreported diaphragm weakness on oesophageal pressure monitoring and was therefore excluded from the analysis. The baseline characteristics of the 10 remaining patients are shown in table 1. Nine patients had transcutaneous capnography and oximetry. Parasternal EMG signals were analysable in eight (80%) patients.

The median $EPAP_{opt}$ reached during the autotitration phase was 9 cmH_2O (range 4–13 cmH_2O). $EPAP_{opt}$ correlated inversely with forced vital capacity (FVC) and FVC % predicted (r=−0.69, p=0.026 and r=−0.64, p=0.047), and correlated positively with baseline $\Delta X_{rs,5Hz}$ (r=0.82, p=0.004) during tidal breathing at EPAP 3 cmH_2O (figure 2). Using the FOT-based criterion of Dellacà *et al.* [10] ($\Delta X_{rs,5Hz}$ >2.8 $cmH_2O{\cdot}s{\cdot}L^{-1}$), eight patients had EFL detected during tidal breathing at baseline EPAP 3 cmH_2O. No clear pattern emerged in terms of changes in dyspnoea during the manual EPAP titration phase, and most patients reported the same degree of breathlessness throughout (supplementary table E1). This may be a reflection of the limitations of the modified Borg scale in detecting changes in dyspnoea in patients with stable severe COPD undergoing EPAP titration at rest.

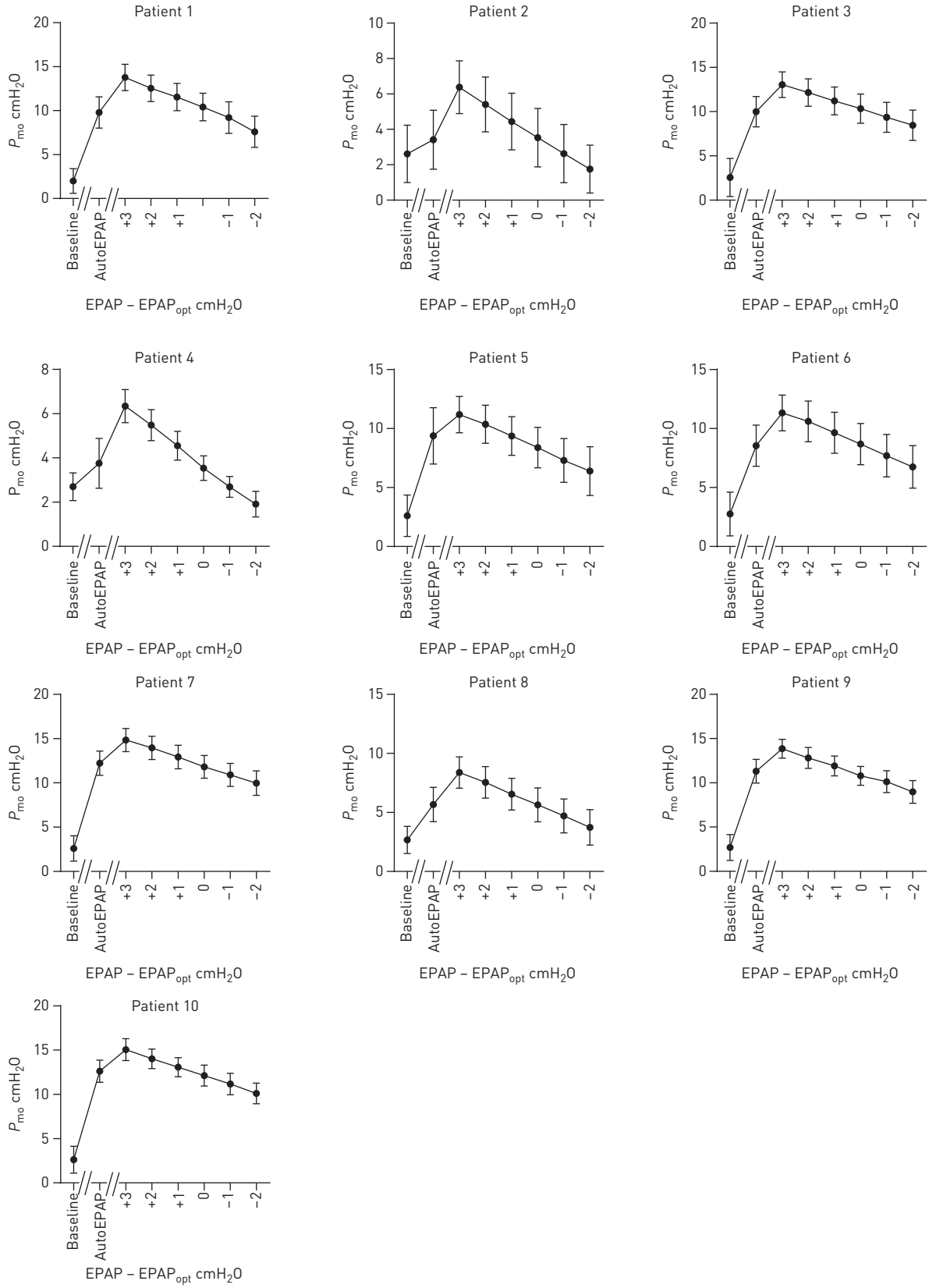

FIGURE 1 Expiratory positive airway pressure (EPAP) titration protocol for each patient. Patients were settled at baseline EPAP 3 cmH_2O, then underwent autotitration of EPAP to find the optimal EPAP (autoEPAP). Manual downtitration of EPAP was then performed from optimal EPAP +3 cmH_2O to optimal EPAP–2 cmH_2O. P_{mo}: pressure at the mouth (airway opening); EPAP$_{opt}$: optimal EPAP at which expiratory flow limitation in tidal breathing is abolished.

TABLE 1 Baseline characteristics of included patients

Subject	Age years	Sex	BMI $kg \cdot m^{-2}$	pH	P_{aCO_2} kPa	P_{aO_2} kPa	HCO_3^- $mEq \cdot L^{-1}$	FEV_1 L	FEV_1 % pred	FVC L	FVC % pred	Baseline $\Delta X_{rs,5Hz}$ $cmH_2O \cdot L^{-1} \cdot s$	$EPAP_{opt}$ cmH_2O	Baseline $PEEP_i$ cmH_2O
1	67	M	42.1	7.39	5.89	10.3	26.1	0.84	27.5	1.27	32.2	4.19	9	1.25
2	66	F	22.9	7.39	6.95	6.1	31.1	1.01	42.3	1.57	55.3	1.61	4	0.72
3	57	M	23.0	7.36	7.12	9.3	29.5	0.57	22.2	1.24	39.2	4.78	11	0.79
4	71	M	24.0	7.39	8.72	8.4	37.2	0.8	23.2	2.6	57.4	1.32	4	1.85
5	52	M	35.6	7.41	6.72	6.9	30.8	1.2	34.0	2.01	45.8	4.01	9	4.35
6	66	F	17.6	7.39	6.08	7.7	27.2	0.66	36.1	1.4	63.1	3.40	9	1.65
7	65	M	22.6	7.37	7.72	6.9	32.8	0.97	34.5	1.68	46.8	5.22	13	5.58
8	68	M	28.2	7.35	6.22	9.9	25.3	0.7	26.1	2.57	74.5	5.48	6	1.74
9	67	F	31.3	7.37	8.54	6.3	36	0.51	23.6	1.06	40.9	6.12	12	0.13
10	69	F	28.5	7.34	8.86	6.3	35.4	0.32	14.1	0.9	33.2	7.10	13	1.43
Average	65±6	6M	27.6±7.2	7.38±0.02	7.28±1.12	7.81±1.58	31.1±4.2	0.76±0.26	28.4±8.3	1.63±0.59	48.8±13.6	4.32±1.84	9 (4–13)	1.95±1.61

Data are presented as mean±SD or median (range), unless otherwise stated. Baseline values refer to those while breathing on the forced oscillation technique device at externally applied positive airway pressure (EPAP) 3 cmH_2O. BMI: body mass index; P_{aO_2}: arterial partial pressure of oxygen; P_{aCO_2}: arterial partial pressure of carbon dioxide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $\Delta X_{rs,5Hz}$: within-breath difference in respiratory system reactance at 5 Hz; $EPAP_{opt}$: optimal EPAP identified by autotitration; $PEEP_i$: intrinsic positive end-expiratory pressure; M: male; F: female.

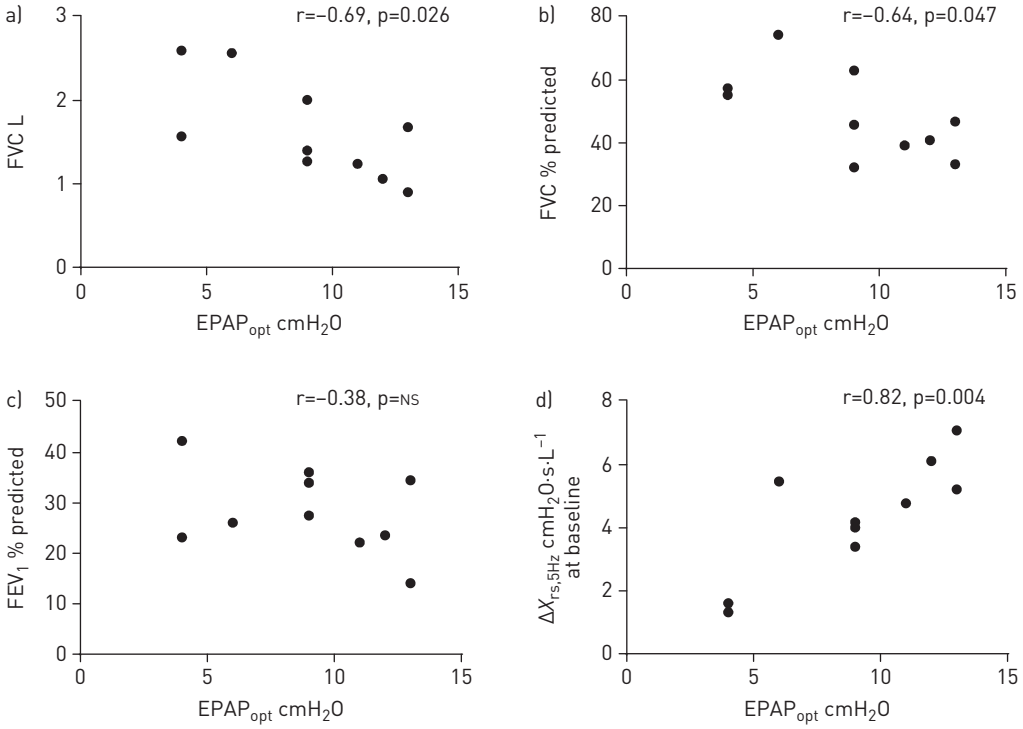

FIGURE 2 Correlations between optimal expiratory positive airway pressure (EPAP) at which expiratory flow limitation in tidal breathing is abolished ($EPAP_{opt}$) and a) forced vital capacity (FVC), b) % predicted FVC, c) % predicted forced expiratory volume in 1 s (FEV_1) and d) within-breath change in respiratory system reactance ($\Delta X_{rs,5Hz}$) during EPAP 3 cmH_2O settling phase. NS: nonsignificant.

Changes in physiological parameters during the autotitration phase from EPAP 3 cmH_2O to $EPAP_{opt}$

NRD, as expressed by $EMG_{di\%opt}$ and $EMG_{para\%opt}$, and peak inspiratory transdiaphragmatic pressure swings (ΔP_{di}) fell significantly at $EPAP_{opt}$ (table 2, figure 3). Respiratory rate increased to a small extent during autotitration, but transcutaneous oxygen and carbon dioxide levels did not change.

EPAP downtitration

All 10 patients provided ΔP_{di}, EMG_{di} data between $EPAP_{opt}$+3 and $EPAP_{opt}$−2 as well as at baseline (EPAP 3 cmH_2O settling phase), eight (80%) patients between $EPAP_{opt}$+3 and $EPAP_{opt}$−3. For clarity, ΔP_{di} and EMG_{di} analyses are presented for data from $EPAP_{opt}$+3 to EPAP $_{opt}$−2.

Responses of EMG data to changes in EPAP between baseline and optimal

The changes in $EMG_{di\%opt}$ between baseline (measured at EPAP 3 cmH_2O settling phase) and $EPAP_{opt}$+3 for all patients are shown in figure 4d. There was a reduction in $EMG_{di\%opt}$ (p=0.004) from baseline to

TABLE 2 Physiological parameters at baseline (externally applied positive airway pressure (EPAP) 3 cmH_2O) and optimal EPAP ($EPAP_{opt}$) achieved at the end of the auto-titration phase

	Baseline (EPAP 3 cmH_2O)	$EPAP_{opt}$	p-value
$EMG_{di\%opt}$ %	138.5±27.1	120.9±20.7	0.049
$EMG_{para\%opt}$ %	134.3±27.0	115.6±23.8	0.008
ΔP_{di} cmH_2O	18.2±5.1	13.2±7.0	0.006
Respiratory rate bpm	19.0±3.6	20.8±3.2	0.049
P_{tcCO_2} kPa	7.3±1.2	7.1±1.3	0.82
S_{pO_2} %	91.6±3.9	91.8±3.4	0.57

Data are presented as mean±SD, unless otherwise stated. $EMG_{di\%opt}$: diaphragm electromyogram as a percentage of the value at optimal EPAP; b) $EMG_{para\%opt}$: parasternal electromyogram as a percentage of the value at optimal EPAP; ΔP_{di}: peak transdiaphragmatic inspiratory pressure swing; P_{tcCO_2}: transcutaneous carbon dioxide tension; S_{pO_2}: transcutaneous oxygen saturations.

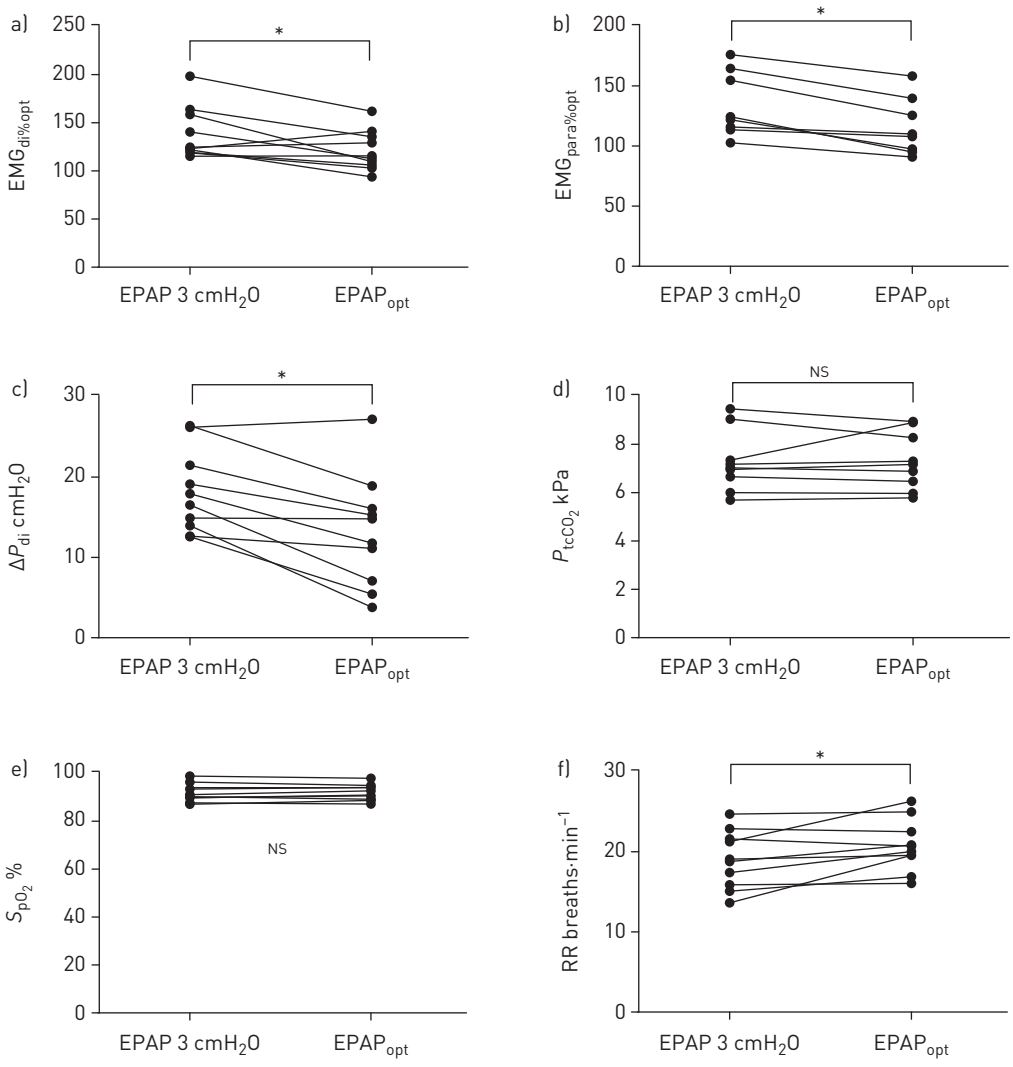

FIGURE 3 Changes in physiological parameters between baseline (expiratory positive airway pressure (EPAP) 3 cmH_2O) and optimal EPAP achieved at the end of the autotitration phase ($EPAP_{opt}$). a) Diaphragm electromyogram as a percentage of the value at optimal EPAP ($EMG_{di\%opt}$); b) parasternal electromyogram as a percentage of the value at optimal EPAP ($EMG_{para\%opt}$); c) transdiaphragmatic inspiratory pressure swing (ΔP_{di}); d) transcutaneous carbon dioxide tension (P_{tcCO_2}); e) transcutaneous oxygen saturations (S_{pO_2}); and e) respiratory rate (RR). NS: nonsignificant. *: p<0.05.

$EPAP_{opt}$+3, with statistically significant differences from baseline becoming apparent at $EPAP_{opt}$−1 and being sustained to $EPAP_{opt}$+3. No change in $EMG_{di\%opt}$ was observed with increases in EPAP from $EPAP_{opt}$ up to $EPAP_{opt}$+3 (p=0.08). The changes in $EMG_{para\%opt}$ during EPAP downtitration are shown in figure 4e for eight patients who provided analysable parasternal EMG data. There was a significant difference in $EMG_{para\%opt}$ from baseline at $EPAP_{opt}$ only (p=0.027). There was no significant increase in $EMG_{para\%opt}$ between $EPAP_{opt}$ and $EPAP_{opt}$+3 (p=0.14).

Inspiratory ΔP_{di}, PTP_{di} and $PEEP_i$ responses

As expected, there was a reduction in inspiratory P_{di} swings at higher levels of EPAP (p<0.001) with significant differences from P_{di} swings at baseline becoming apparent from $EPAP_{opt}$ +1 upwards (figure 4b). There was a continued reduction in P_{di} swings up to $EPAP_{opt}$+3. PTP_{di} and dynamic $PEEP_i$ became significantly different from baseline at $EPAP_{opt}$+1 and $EPAP_{opt}$, respectively (p<0.001) (figure 4c and f, respectively). Changes in gastric pressure during expiration at different levels of EPAP are shown in supplementary figures E1 and E2. Individual physiological responses to changes in EPAP are shown in supplementary figure E3.

Transcutaneous carbon dioxide, oxygen saturations, respiratory rate, breathing pattern and dyspnoea

Nine (90%) patients had transcutaneous carbon dioxide tension (P_{tcCO_2}) and transcutaneous oxygen saturation (S_{pO_2}) monitoring. There was no significant change in either of these parameters during

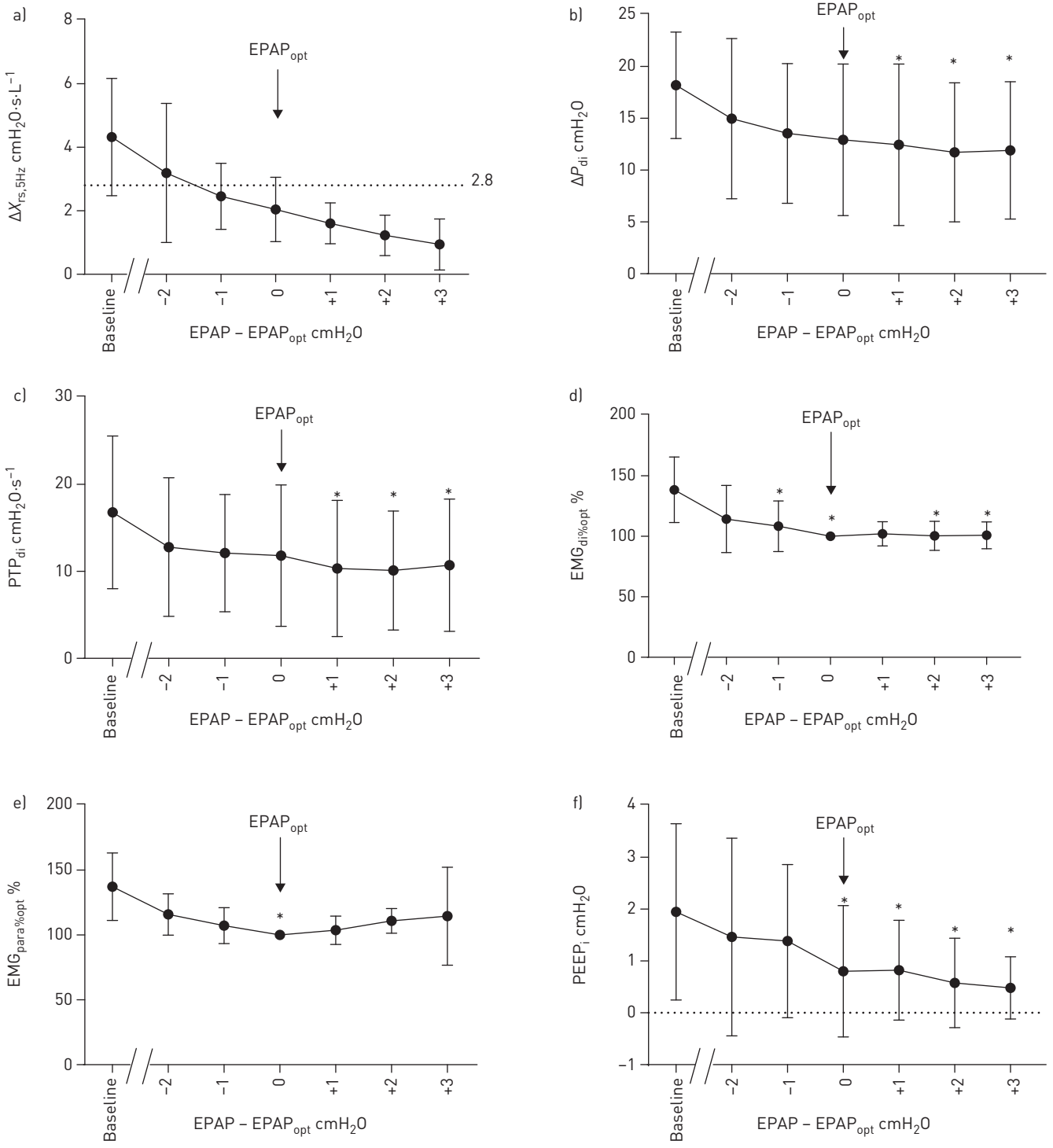

FIGURE 4 Changes in a) within-breath change in respiratory system reactance ($\Delta X_{rs,5Hz}$), b) transdiaphragmatic pressure swings (ΔP_{di}), c) diaphragm pressure–time product (PTP_{di}), d) $EMG_{di\%opt}$ (diaphragm electromyogram as a percentage of the value at optimal expiratory positive airway pressure ($EPAP_{opt}$), e) $EMG_{para\%opt}$ (parasternal EMG as a percentage of the value at $EPAP_{opt}$) and f) intrinsic positive end-expiratory pressure ($PEEP_i$) during manual downtitration of EPAP from $EPAP_{opt}$+3 to baseline EPAP 3 cmH_2O. n=10, except in c) n=9 and e) n=8.

downtitration from $EPAP_{opt}$+3 (P_{tcCO_2} p=0.37, S_{pO_2} p=0.52). Similarly, there was no change in respiratory rate between baseline and $EPAP_{opt}$+3 (p=0.80), in contrast to the autotitration phase. No significant changes in tidal volume, minute ventilation, inspiratory time (t_I), expiratory time and duty cycle (t_I/t_{tot}) were found during EPAP downtitration. Subjects reported little change in their dyspnoea perception as assessed by the modified Borg scale (supplementary table E1).

Discussion

In this detailed physiological study, we have shown that the application of EPAP, titrated to abolish EFL by an automated algorithm based on FOT analysis, was able to significantly reduce neural respiratory drive, transdiaphragmatic inspiratory pressure swings and the pressure-time product of transdiaphragmatic pressure. The data from this study also indicate that increases in EPAP up to 3 cmH_2O beyond the optimal pressure ($EPAP_{opt}+3$), while not causing significant increases in neural respiratory drive (as measured by EMG_{di} and EMG_{para}) or inspiratory transdiaphragmatic pressure swings, offer no additional benefit; therefore, applying EPAP greater than $EPAP_{opt}$ exposes the patient to needless increases in intrathoracic pressure.

Optimal EPAP

A striking finding in this study is the heterogeneity of the optimum EPAP (range 4–13 cmH_2O) that patients with COPD require in order to abolish EFL_T, which has also been noted in the previous study of Lorx *et al.* [12]. The UK Royal College of Physicians guidelines for the use of NIV in COPD patients with acute hypercapnic respiratory failure stipulate an initial setting of 4 cmH_2O, and previous studies of NIV in such patients have used levels of 4–6 cmH_2O [21–23]. NIV is increasingly used to treat COPD patients with chronic hypercapnic respiratory failure; randomised controlled trials of NIV in this situation have employed levels of 2–5 cmH_2O [24–28]. The current study indicates that, in some patients, such EPAP levels are insufficient to abolish EFL, fully oppose $PEEP_i$ and to minimise the work of ventilator triggering.

Autotitration of EPAP by the novel ventilator identified an optimal pressure above which EFL_T could be considered to have been abolished. When the response of the respiratory system was evaluated to manual changes in EPAP above and below $EPAP_{opt}$, diaphragm EMG showed a significant reduction in NRD from 1 cmH_2O below ($EPAP_{opt}-1$) to 3 cmH_2O ($EPAP_{opt}+3$) above this optimal pressure level. This suggests that FOT-based autotitration may find, to within 1 cmH_2O, the minimum level of externally applied PEEP required to produce a significant reduction in NRD through the abolition of EFL_T. It is interesting to note that no further significant changes in $EMG_{di\%opt}$ occurred relative to $EPAP_{opt}$ as the EPAP rose further by up to 3 cmH_2O. Below $EPAP_{opt}$, increases in EPAP would be expected to cause a reduction in $PEEP_i$, without increasing EELV.

Any further increases in EPAP above $EPAP_{opt}$ is expected to cause hyperinflation, an increase in the elastic load, mechanical disadvantage of the diaphragm, and a consequent increase in NRD. That this did not occur in the current study may be due to the fact that EPAP was not increased beyond 3 cmH_2O above the optimal EPAP level, and the respiratory system was therefore not pushed to the nonlinear, low-compliance end of the pressure–volume curve.

Parasternal EMG followed a similar pattern to diaphragm EMG, although a significant reduction compared with baseline was found at $EPAP_{opt}$. Despite there being no statistically significant increase in $EMG_{para\%opt}$ above $EPAP_{opt}$ (figure 4e), there was a trend to an elevation in NRD from $EPAP_{opt}$ to $EPAP_{opt}+3$. This might be expected to occur, because while the diaphragm becomes mechanically disadvantaged at high lung volumes, the force-generating capacity of the parasternal intercostal muscles peak at lung volumes just below total lung capacity. As neural drive to the respiratory muscles is preferentially directed to those with the greatest mechanical advantage [29], parasternal EMG would therefore be expected to rise more prominently at higher lung volumes.

Additionally, inspiratory transdiaphragmatic pressure swings improved significantly from baseline at pressures of $EPAP_{opt}+1$ or higher. However, there is a trend to a continued reduction in P_{di} swings up to $EPAP_{opt}+3$, indicating that while FOT-based EPAP autotitration may identify the minimum level at which NRD and transdiaphragmatic pressure swings are improved compared with baseline, there may be continued decrements in these parameters at even higher levels of EPAP. PTP_{di} trends follow those of ΔP_{di}, confirming that work of breathing is likely to be significantly reduced at or near the optimum EPAP level identified by FOT-based autotitration. Improvements in NRD and ΔP_{di} also occurred during the autotitration phase, confirming that the application of EPAP had a beneficial effect on lung mechanics when the ventilator was operating in its intended automated mode.

Excessive levels of EPAP lead to unnecessary elevation in intrathoracic pressures, which are associated with adverse haemodynamic effects [30, 31], and to hyperinflation in patients with COPD, which is known to disrupt sleep [32, 33]. The increased mechanical stress on the extracellular matrix of the lung parenchyma may also contribute to ongoing lung injury and disease progression [34]. Dynamic titration of EPAP according to the presence of EFL_T may therefore lead to improved sleep quality in patients receiving nocturnal NIV. Furthermore, autotitration of EPAP may improve patient–ventilator synchrony by ensuring that the work of inspiratory triggering of the ventilator is minimised through the reduction of the inspiratory threshold load. Abolishing EFL during sleep may also have the effect of reducing the peripheral airway and parenchymal injury that accelerates the decline of lung function [35].

Limitations of the study

Although all patients had a confirmed diagnosis of severe COPD based on international guidelines [36], three patients were also obese with a body mass index >30 $kg \cdot m^{-2}$ (31.3, 35.6 and 42.1 $kg \cdot m^{-2}$). While EFL_T is a prominent feature of COPD, it is also a recognised finding in obese patients [37, 38], in whom gas trapping arises due to early airway closure at low lung volumes [39]. Our aim was to investigate the effects of FOT-based autotitration of EPAP on EFL_T; therefore, we believe the results remain valid whether the EFL_T in these patients arises from obstructive airway disease or from obesity. Furthermore, with the rising prevalence of obesity among COPD patients [40], our study cohort is likely to be representative of the population of COPD patients with chronic respiratory failure.

We acknowledge that variations in gastric pressure due to abdominal muscle activation in expiration may have influenced the values of dynamic $PEEP_i$ during manual titration of EPAP. Indeed, there was evidence of intermittent active expiration in all patients, which became more prominent at higher levels of EPAP (supplementary figures E1 and E2).

The current study was aimed at identifying the minimum EPAP that would abolish EFL_T during positive airway pressure therapy. Given that EFL_T is a key contributor to the dynamic hyperinflation that leads to dyspnoea in patients with COPD, we termed this minimum level as the optimal EPAP. However, we acknowledge that work of breathing was not directly measured in this study and therefore cannot state that the minimum EPAP required to abolish EFL_T represents the level that minimises work of breathing.

Changes in end-expiratory lung volume would have been valuable to observe during manual EPAP titration. Unfortunately, although efforts were made to measure inspiratory capacity, the measurements were unreliable, particularly at high levels of EPAP in some patients, which led to a high degree of air leak during inspiratory capacity manoeuvres. Transpulmonary pressure (P_L), as an indirect method of assessing lung volume responses to EPAP titration are shown in supplementary figures E4 and E5. It was evident that P_L was negative for many patients at several, if not all, time points. Overall, P_L improves with increasing EPAP and, on average, attains positive values with escalating levels of EPAP.

The small number of patients limits the generalisability of the results of this study. However, the aim of the study was to investigate in detail the physiological responses of the respiratory system to FOT-based EPAP autotitration, rather than to test the clinical efficacy of the new device in a large cohort of patients.

An adequate settling time at each pressure level is required to allow the patient's breathing pattern to stabilise; however, the optimum period is not known [4, 41–44]. The current study protocol provided a period of time for adjustment to changes in the EPAP level which is in keeping with other published data.

Conclusions

FOT-based autotitration of externally applied PEEP, aimed at abolishing expiratory flow limitation in tidal breathing, identified the pressure at which neural respiratory drive and transdiaphragmatic pressure swings were significantly reduced compared with baseline values. Increases in EPAP up to 3 cmH_2O beyond the optimal pressure did not lead to significant elevation of NRD or P_{di} swings. This novel technology has the potential to abolish expiratory flow limitation in tidal breathing while reducing the mechanical stresses on the lung parenchyma that arise due to excessive pressures, and to improve patient comfort in COPD patients requiring NIV. Future randomised controlled trials will establish whether FOT-based autotitration of EPAP leads to improved clinical outcomes, such as sleep quality, quality of life, ventilator adherence and survival among COPD patients receiving domiciliary NIV.

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Conflict of interest: E-S. Suh reports grants and personal fees for educational work from Philips Respironics, grants from Philips Research, during the conduct of the study. P. Pompilio is one of the founders of RESTECH srl, company that designs, manufactures and sells devices for lung function testing based on the forced oscillation technique. S. Mandal reports personal fees for consultancy and educational work from Philips, outside the submitted work. P. Hill is an employee of Philips. G. Kaltsakas has nothing to disclose. P.B. Murphy reports receiving reimbursement for expenses for travel to conferences and lecture fees from Philips Respironics, ResMed, Fisher & Paykel, and B&D Electromedical. R. Romano is an employee of Philips. J. Moxham has nothing to disclose. R. Dellaca reports grants from Acutronic, outside the submitted work; has a patent on the detection of EFL by FOT with royalties paid to Philips Respironics and

Restech srl, a patent on monitoring lung volume recruitment by FOT with royalties paid to Vyaire, and a patent on early detection of exacerbations by home monitoring of FOT with royalties paid to Restech; and is co-founder and shareholder of Restech srl, a spin-off company of the Politecnico di Milano University producing medical devices for lung function testing based on FOT. N. Hart reports personal fees from Fisher & Paykel, grants from Philips Respironics, ResMed and B&D Electromedical, during the conduct of the study; and has a patent pending on the Myotrace technology.

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