Neural versus pneumatic control of pressure support in patients with chronic obstructive pulmonary diseases at different levels of positive end expiratory pressure: a physiological study

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Abstract

Introduction: Intrinsic positive end-expiratory pressure (PEEPi) is a “threshold” load that must be overcome to trigger conventional pneumatically-controlled pressure support (PSp) in chronic obstructive pulmonary disease (COPD). Application of extrinsic PEEP (PEEPe) reduces trigger delays and mechanical inspiratory efforts. Using the diaphragm electrical activity (EAdi), neurally controlled pressure support (PSN) could hypothetically eliminate asynchrony and reduce mechanical inspiratory effort, hence substituting the need for PEEPe. The primary objective of this study was to show that PSN can reduce the need for PEEPe to improve patient-ventilator interaction and to reduce both the “pre-trigger” and “total inspiratory” neural and mechanical efforts in COPD patients with PEEPi. A secondary objective was to evaluate the impact of applying PSN on breathing pattern.

Methods: Twelve intubated and mechanically ventilated COPD patients with PEEPi ≥ 5 cm H2O underwent comparisons of PSp and PSN at different levels of PEEPe (at 0 %, 40 %, 80 %, and 120 % of static PEEPi, for 12 minutes at each level on average), at matching peak airway pressure. We measured flow, airway pressure, esophageal pressure, and EAdi, and analyzed neural and mechanical efforts for triggering and total inspiration. Patient-ventilator interaction was analyzed with the NeuroSync index.

Results: Mean airway pressure and PEEPe were comparable for PSp and PSN at same target levels. During PSp, the NeuroSync index was 29 % at zero PEEPe and improved to 21 % at optimal PEEPe (P < 0.05). During PSN, the NeuroSync index was lower (<7 %, P < 0.05) regardless of PEEPe. Both pre-trigger (P < 0.05) and total inspiratory mechanical efforts (P < 0.05) were consistently higher during PSp compared to PSN at same PEEPe. The change in total mechanical efforts between PSp at PEEPe0% and PSN at PEEPe0% was not different from the change between PSp at PEEPe80% and PSN at PEEPe80%.

Conclusion: PSN abolishes the need for PEEPe in COPD patients, improves patient-ventilator interaction, and reduces the inspiratory mechanical effort to breathe.

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Introduction
Intrinsic positive end-expiratory pressure (PEEPi) refers to the increase in the end-expiratory elastic recoil pressure associated with an increase in lung volume above resting lung volume at end expiration consequent to dynamic hyperinflation. PEEPi impairs patient-ventilator interaction and efficiency of ventilatory assistance, increases inspiratory effort, causes dyspnea, and alters hemodynamics [1, 2].

In spontaneously breathing patients on conventional ventilatory assistance, PEEP typically reveals itself as a delayed onset of assistance relative to the onset of neural inspiratory effort, where if ventilatory assistance is triggered on pressure, flow, or volume (i.e., pneumatic trigger), the PEEPi-induced threshold load must be overcome to initiate assistance [3]. Work in patients with chronic obstructive pulmonary disease (COPD) has demonstrated that application of external PEEP (PEEPe) can reduce the mechanical inspiratory effort [3–5].

In COPD patients receiving pressure support (PS) with pneumatic triggering and cycling-off, (PSp), the increased airway resistance prolongs the time constant and delays the cycling-off of ventilator support. Studies suggest a higher than conventional percentage of peak flow is required to adequately terminate assist; inappropriate settings for the cycling-off criteria are known to worsen dynamic hyperinflation and increase PEEPi [6, 7].

The effects of neural cycling-off of assistance in patients with COPD and PEEPi have not been evaluated during PS ventilation. Controlling ventilatory assistance by the diaphragm electrical activity (EAdi) - a neural signal - successfully improves patient-ventilator interaction during neurally adjusted ventilatory assistance (NAVA) compared to PSp [8, 9]. A recent study has shown that the use of NAVA also leads to a decrease in the effort to trigger the ventilator, when compared to (PSp) [10]. These previous studies, however, compared a pressure-targeted mode (PSN) to a proportional mode (NAVA). Therefore, in the present study, we used neurally controlled PS (PSN), where the EAdi was used to initiate and terminate the breath, but with a targeted, fixed pressure. The primary objective was to show that PSN can reduce the need for PEEPe to improve patient-ventilator interaction and to reduce both the pre-trigger and total inspiratory neural and mechanical efforts in COPD patients with PEEPi. A secondary objective was to evaluate the impact of applying PSN on breathing pattern.

Methods
The study was conducted in a 30-bed general intensive care unit (ICU) of a teaching hospital affiliated with Southeast University in China. The protocol was approved by Institutional Ethics Committee of Zhongda hospital (Approval Number: 2010ZDLL018.0), and informed consent was obtained from the patients or next of kin. The trial was registered at clinicaltrials.gov (NCT02114567).

Patients
Twelve adult intubated and mechanically ventilated patients with early COPD and acute respiratory failure due to pneumonia were studied. COPD was defined as the patient having chronic cough, sputum or progressive dyspnea, and forced vital capacity rate of one second (FEV1/FVC) < 0.7 after bronchodilation. Acute respiratory failure was defined as oxygenation index (PaO2/FiO2) < 300 mmHg with or without elevated arterial carbon dioxide tension (PaCO2).

The inclusion criteria were: (1) static PEEPi ≥ 5 cm H2O (see below); (2) hemodynamic stability (heart rate < 140 beats/minute, no vasopressors required, or < 5 μg/kg/min dopamine); (3) no sedation or minimal analgesia with low dose of morphine (< 3 mg/h, by continuous intravenous infusion); (4) breathing spontaneously but in need of partial ventilatory assistance; and (5) awake and able to positively cooperate, defined as the ability to follow an instruction (e.g., open their eyes, raise thumbs up, move limbs).

The exclusion criteria were: (1) tracheostomy; (2) treatment abandonment; (3) history of esophageal varices; (4) gastroesophageal surgery in the previous 12 months or gastroesophageal bleeding in the previous 30 days; (5) coagulation disorders (international normalized ratio > 1.5 and activated partial thromboplastin time > 44 s); (6) history of acute central or peripheral nervous system disorder or neuromuscular disease, and (7) lack of informed consent.

Measurements
After obtaining consent, enrolled patients were switched to a Servo-i ventilator (Maquet, Solna, Stockholm, Sweden). A 16-F nasogastric feeding tube (NeuroVent Research Inc.; Toronto, ON, Canada) with electrodes measuring EAdi and balloons measuring esophageal (Pes) and gastric (Pga) pressures was inserted through the nose and secured after confirming positioning according to guidelines for NAVA catheter positioning (Maquet, Solna, Stockholm, Sweden). Flow and airway pressure (Paw) were acquired from the Servo-i ventilator whereas Pes and Pga were obtained via pressure transducers; all signals were digitized at 100 Hz and stored for offline analysis (NeuroVent Research Inc.; Toronto, ON, Canada). Mean arterial pressure (MAP) was measured with a blood pressure cuff (Philips G60).

PSp and PSN
Pneumatically controlled PS
Conventional pneumatically controlled PS (PSp) was used with the ventilator in the pressure support mode and was pneumatically triggered (flow-trigger 1 L/min) and cycled.
off (30% of peak inspiratory flow). The rate of rise in pressure was set to 0.05 s in all patients.

**Neurally controlled PS**

Neurally controlled PS (PSN) was used with the ventilator in the NAVA mode, however, the NAVA level was set to maximum (NAVA level 15 cmH2O/μV) with upper pressure limits adjusted to achieve the targeted PS above PEEPe (same as PSN). PSN was neurally triggered (EAdi before sedation. To suppress = T i μ P Trig 2 with PEEPe of zero using the end-expiratory airway occlusion method [2]. PEEPe levels of 0%, 40%, 80%, and 120% were applied targeting 6 ml/kg PBW with PEEPe with = 6 0 / T t P × T P L LT 15 0% P P P × B f was applied targeting 6 ml/kg PBW with PEEPe with the EAdi recovered, patients were returned to PS spontaneous breathing (abolish EAdi), patients received continuous intravenous (IV) sedation by Propofol up to the dose of 2 mg/kg/h. If at this propofol dose the respiratory drive was not totally suppressed, Remifentanil was also infused at the dose of 6–15 μg/kg/h just before the measurement of compliance, resistance and static PEEPi. Static PEEPi was assessed during VCV at PEEPe of zero using the end-expiratory airway occlusion method [2]. PEEPe levels of 0%, 40%, 80%, and 120% of static PEEPi were then calculated and noted (subsequently referred to as PEEPe0%, PEEPe40%, PEEPe80%, and PEEPe120%). PEEPe was increased to determine the presence of expiratory flow limitation (EFL) [2].

**Spontaneous breathing and return to PS at different levels of PEEPe**

Sedation was discontinued and as spontaneous breathing and EAdi recovered, patients were returned to PS0, and adjusted to target 6 ml/kg (of PBW) and PEEPe of 5 cmH2O until a Ramsay score of 2–3 was obtained. This was followed by eight different ventilation periods: PS0 and PSN at PEEPe0%, PEEPe40%, PEEPe80%, and PEEPe120%. First PS0 was applied targeting 6 ml/kg PBW with PEEPe levels randomized to be applied with either ascending or descending order. This was then repeated during PSN with same PEEPe levels (as used with PS0) randomized to either ascending or descending order (independent of the order used during PS0). Assistance pressure above PEEPe was obtained by adjusting the upper pressure limit to the same assistance pressure (above PEEPe) that was observed for the corresponding PEEPe during the PS0 period. The average duration per PEEPe level was 12 (±1 SD) minutes. Arterial blood gases were measured at the end of each PEEPe level. Inspired fraction of oxygen (FiO2) was set similar to that at inclusion (Table 1) and not altered throughout the study.

**Data analysis**

**Parameters during volume control ventilation (and no spontaneous breathing)**

Compliance was calculated from the formula:

\[
\text{Tidal volume/(Plateau pressure-total PEEP).}
\]

Resistance was calculated from the formula:

\[
\text{Resistance = (Peak pressure-Plateau pressure)/Flow.}
\]

EFL was determined from peak airway pressure during increase of PEEPe [2].

**Respiratory parameters during spontaneous breathing on PS0 or PSN**

The last 3 minutes of each condition were analyzed for the EAdi-derived, ventilator, and Pes-derived variables.

**EAdi-derived variables**

Neural inspiratory time (TIN) was calculated between the onset of EAdi and the return to 70% of peak EAdi. Neural expiratory time (TEN) was calculated as the time between the return to 70% of peak EAdi and the onset of the next EAdi. We also calculated the neural duty cycle (TIN/TEN, where TIN = TIN + TEN), and neural breathing frequency (BFN = 60/TEN). The peak inspiratory EAdi (EAAdi) was calculated for the pre-trigger phase (EAAdiTRIG), and for the entire inspiration (EAAdiTOT).

**Ventilator variables**

PEEP was measured as mean airway pressure in the expiratory state. VT was obtained by flow integration. Mean airway pressure (Paw) was calculated during neural inspiration. Pneumatic inspiratory and expiratory times (TIN and TEP) were calculated from the airway pressure signal.

**Pes-derived variables**

The mean inspiratory change in Pes was calculated from onset of each inspiration (based on EAdi) for both the pre-trigger phase (ΔPSTRIG), as well as the total inspiratory (pre-trigger effort included, ΔPSTOT). Transpulmonary pressure (Pt) was calculated as Paw-Pes, and is presented for the total inspiration PL (ΔPLTOT). Pre-trigger inspiratory pressure time product per minute was calculated for Pes (PTPESTRIG) as (ΔPSTRIG × TRIG × BFN), and for the total inspiration (PTPSTOT) as (ΔPSTOT × TIN × BFN). Neumomechanical efficiency (NME) was calculated for total inspiration as ΔPes/EAdi.

**Analysis of patient-ventilator interaction**

EAdi-to-trigger time difference in ms (TTRIG) was calculated between onset of EAdi and early initial rise in Paw. Cycling-off timing-difference in milliseconds (TCYCOFF) was calculated between time points for early decrease in Paw and 30% decline from EAdi peak.

Patient-ventilator interaction was evaluated by the NeuroSync Index, comparing Paw and EAdi waveforms.
with automated computer algorithms [11] and quantifying the error between them. Briefly, trigger and cycling-off errors were classified as either too early (negative values) or too late (positive values). Early and late triggering was defined as assistance starting before or after the onset of EAdi. Early and late cycling-off was defined as assistance starting before or after the return of EAdi to 70 % of its peak. Early trigger and cycling-off errors were normalized to the associated neural expiratory or inspiratory periods, respectively and presented in percent with a negative sign. Late trigger and cycling-off errors were normalized to related neural inspiratory or expiratory periods, respectively, and presented in percent with a positive sign. EAdi without associated assistance (ineffective effort) was defined as entire neural breathing cycles taking place without triggering assistance, and was assigned 100 % error. Assistance without associated EAdi (auto triggering) was defined as entire assistance cycles taking place without associated EAdi, and was assigned 100 % error. The NeuroSync index was calculated by averaging the errors for all events, the higher the NeuroSync index, the greater the error between EAdi and Paw.

**Statistics**

Statistical analysis was performed with Sigma-Stat 3.5 (Jandel Scientific, California, USA). (Jandel Scientific, California, USA) Three types of comparisons were made: (i) within a mode, the impact of increasing PEEPe, (ii) at a given PEEPe, the impact of PS\textsubscript{P} versus PS\textsubscript{N}, (iii) PS\textsubscript{N} at PEEPe\textsubscript{0} versus PS\textsubscript{P} at PEEPe\textsubscript{80} (considered to be optimal PEEP). Due to non-normally distributed data, we opted for within-subject comparison of all eight conditions using one-way repeated measures analysis of variance (ANOVA) on ranks and Student-Newman-Keuls test for post hoc analysis of multiple comparisons. Significant difference was defined as \( P < 0.05 \). Power calculation suggested that a reduction of inspiratory effort by 50 % required 12 patients for a power of 1.0 with alpha of 0.05. To test if mechanical respiratory efforts were reduced similarly during PS\textsubscript{N} without PEEPe and during PS\textsubscript{P} with optimal PEEPe linear regression and Pearson product–moment correlation was used.

**Results**

A total of 17 patients were screened; 5 did not meet the inclusion criteria of 5 cm H\textsubscript{2}O static PEEPi. Characteristics of the remaining 12 patients are described in Table 1.
Table 2 Ventilation parameters, arterial blood gases, and mean arterial pressure at different PEEPe for PSF and PSE.

| Parameter | Mode | PEEPe0% | PEEPe40% | PEEPe80% | PEEPe120% | P* |
|-----------|------|---------|----------|----------|-----------|----|
| Paw (cm H2O) | PSF | 10.9 (10.3, 11.3) | 12.9 (12.3, 13.3)a | 15.0 (14.8, 16.3)ab | 17.4 (16.8, 18.3)abc | <0.001 |
| PSN | 11.4 (10.8, 11.6)a | 13.1 (12.1, 13.3)a | 15.2 (14.4, 16.4)ab | 17.5 (16.9, 18.6)abc | <0.001 |
| PEEPe (cm H2O) | PSF | 0.6 (0.4, 1.0)b | 2.3 (2.2, 2.5)c | 4.7 (4.2, 5.4)ab | 7.1 (6.5, 7.5)abc | <0.001 |
| PSN | 1.0 (0.5, 1.2)c | 2.5 (2.3, 3.0)d | 4.7 (4.4, 5.4)c | 7.0 (6.6, 7.5)abc | <0.001 |
| Vt (ml/kg) | PSF | 5.4 (4.2, 6.7)c | 5.8 (4.9, 6.8)c | 5.9 (5.0, 6.6)c | 5.5 (5.2, 7.0)c | <0.001 |
| PSN | 4.6 (4.3, 5.8)c | 5.0 (4.4, 5.9)c | 4.9 (4.6, 6.7)c | 5.0 (4.6, 7.1)c | <0.001 |
| BI (breaths/min) | PSF | 20.2 (17.7, 29.3)c | 20.5 (17.6, 28.9)c | 21.5 (17.2, 26.9)c | 20.9 (17.9, 30.3) | 0.003 |
| PSN | 26.4 (17.3, 30.7)c | 24.4 (17.2, 33.2) | 22.1 (18.1, 31.5)c | 20.5 (16.0, 29.6)c | <0.001 |
| Ve (l/min) | PSF | 6.05 (5.25, 8.13)c | 6.54 (5.47, 8.01)c | 7.05 (5.67, 9.02)c | 7.07 (5.70, 11.62)c | <0.001 |
| PSN | 6.43 (5.31, 9.54)c | 6.92 (5.53, 9.98)c | 7.14 (5.50, 9.20)c | 7.79 (5.74, 9.66)c | <0.001 |
| Vt/Te (ml/s) | PSF | 424 (390, 462)c | 429 (389, 472) | 436 (386, 458) | 438 (396, 466) | 0.013 |
| PSN | 414 (302, 491)c | 443 (334, 508)c | 452 (338, 526)c | 479 (361, 513)c | <0.001 |
| Ti/Tot (% | PSF | 0.90 (0.72, 1.03) | 0.90 (0.74, 0.94) | 0.84 (0.73, 0.98) | 0.87 (0.69, 0.93) | NS |
| PSN | 0.84 (0.71, 0.96) | 0.77 (0.71, 0.86) | 0.81 (0.74, 0.86) | 0.84 (0.73, 0.95) | NS |
| Te (s) | PSF | 2.12 (1.43, 2.60)c | 2.22 (1.45, 2.93) | 2.17 (1.58, 3.14)c | 2.13 (1.53, 2.58) | 0.050 |
| PSN | 1.76 (1.16, 2.66)c | 2.09 (1.20, 2.77)c | 2.02 (1.24, 2.59)c | 2.14 (1.33, 2.92)c | <0.001 |
| Ti/Tot (% | PSF | 29.6 (27.5, 36.5) | 28.7 (24.5, 39.0) | 27.1 (23.4, 36.3) | 26.1 (23.0, 36.7) | NS |
| PSN | 31.4 (25.6, 37.8) | 29.4 (23.9, 38.5) | 29.7 (24.6, 38.3) | 30.6 (22.5, 36.8) | NS |
| pH | PSF | 7.36 (7.33, 7.41) | 7.38 (7.36, 7.41)c | 7.39 (7.34, 7.44)c | 7.39 (7.33, 7.42)c | 0.009 |
| PSN | 7.37 (7.33, 7.40)c | 7.39 (7.34, 7.42)c | 7.38 (7.32, 7.45)c | 7.38 (7.35, 7.42)c | NS |
| PaCO2 (mm Hg) | PSF | 37.9 (32.0, 48.6) | 35.9 (32.1, 46.1) | 36.3 (32.1, 46.8) | 33.5 (32.9, 43.3) | NS |
| PSN | 40.4 (29.8, 47.5) | 34.2 (31.2, 42.1) | 35.4 (32.8, 41.8) | 36.5 (30.7, 41.9) | NS |
| PaO2 (mm Hg) | PSF | 840.0 (799.9, 113.9) | 94.8 (84.9, 116.7) | 98.7 (90.0, 124.3) | 103.9 (84.0, 117.2) | NS |
| PSN | 897.7 (835.7, 122.9) | 106.6 (81.2, 124.1) | 99.4 (91.0, 123.9) | 109.0 (95.0, 125.8) | NS |
| MAP (mm Hg) | PSF | 89.0 (76.0, 92.7) | 88.0 (77.0, 92.7) | 86.7 (77.7, 91.7) | 89.3 (79.0, 91.3) | NS |
| PSN | 88.3 (77.5, 91.3) | 88.0 (75.3, 90.4) | 88.7 (78.3, 91.0) | 86.7 (80.3, 92.0) | NS |

Values are presented as median (25–75 % interquartile range). *P values for one-way repeated measures analysis of variance on ranks for the eight conditions: within the same mode; **P < 0.05 compared to PEEPe0%. P < 0.05 compared to PEEPepeak. Between modes: §P < 0.05 compared to PSF at same PEEPe. Comparison of PSF zero PEEP to PSF optimal PEEP: §P < 0.05 PEEPe0%. at PSF vs. PEEPe20% at PSF. PSF pneumatically triggered and cycled-off pressure support, PSF neurally triggered and cycled-off pressure support ventilation, Paw mean airway pressure (including PEEPe), PEEPe extrinsic PEEP, VT tidal volume, Ve minute ventilation, Te0 neurol respiratory time, Te01 neural expiratory time, Ti/Ttot neural duty cycle, BF neural breathing frequency, PEEPeStar static intrinsic positive end-expiratory pressure, MAP mean arterial pressure, NS not significant.
Fig. 1 (See legend on next page.)
Figure 2 shows the topographic distribution of timing errors for triggering (y-axis) and cycling-off (x-axis), respectively, for all patients. The red area indicates 80% of the most frequent patient-ventilator interactions for all breaths in all subjects during PS$_N$ (left panels) and PS$_P$ (right panels) during PEPP$_{E0\%}$, PEPP$_{e40\%}$, PEPP$_{e80\%}$, and PEPP$_{e120\%}$ (top to bottom). During PS$_N$ at PEPP$_{E0\%}$, triggering was concentrated within an area ranging from minus 5% to 25% for triggering error (y-axis) and minus 5% to 5% error during cycling-off (x-axis) regardless of PEPP$_{e}$ (indicated by box).

During PS$_P$, there was a widespread variability ranging from about minus 10% to 60% for triggering error (y-axis) and about minus 30% to 30% error for cycling-off (x-axis), regardless of PEPP$_{e}$. Regardless of PEPP$_{e}$, less than 10% of breaths landed within the box during PS$_P$ compared to more than 80% during PS$_N$ (Table 3).

During PS$_N$ at PEPP$_{E0\%}$, 52% (SD ± 30%) of all breaths were terminated by neural cycling-off at 70% of peak EAdi and at this point the inspiratory flow had decreased to 46% (SD ± 19%) of peak flow. The remaining 48% (SD ± 30%) of breaths were terminated earlier due to pressure exceeding the upper pressure limit by 3 cm H$_2$O causing the −5% cycling-off errors indicated in Fig. 2, left panel.

During PS$_N$, the NeuroSync index was consistently lower, indicating improved patient-ventilator interaction, at all levels of PEPP$_{e}$. Increasing PEPP$_{e}$ improved patient-ventilator interaction i.e., decreased NeuroSync index during PS$_P$, but had no effect during PS$_N$ (Table 3). Regarding severe asynchronies, EAdi without trigger (ineffective efforts) exceeded 10% in three patients (12%, 12% and 20%) during PS$_P$ (Table 3). Other asynchronies were not frequent during either PS$_P$ or PS$_N$.

Neural (EAdi variables) and mechanical (Pes variables) effort

Figure 3 shows the neural and mechanical effort for triggering and for the whole inspiration in all subjects, at all PEPP$_{e}$ levels, for PS$_N$ and PS$_P$. The corresponding statistics are provided in Table 4 for clarity. EAdi$_{TRIG}$ was lower during PS$_N$ than PS$_P$ at all PEPP$_{e}$ levels. During PS$_N$, EAdi$_{TRIG}$ at PEPP$_{E0\%}$ was also lower compared to PS$_P$ at PEPP$_{e120\%}$ (Table 4). Increasing PEPP$_{e}$ decreased

### Table 3 Patient ventilator interaction indices at different levels of PEPP$_{e}$ for PS$_N$ and PS$_P$

| Parameter                  | Mode   | PEPP$_{E0\%}$ | PEPP$_{e40\%}$ | PEPP$_{e80\%}$ | PEPP$_{e120\%}$ | P$^*$  |
|----------------------------|--------|---------------|----------------|---------------|-----------------|-------|
| T$_{TRIG}$ (ms)            | PS$_N$ | 276 (169, 370)$^a$ | 198 (136, 357)$^{bc}$ | 183 (143, 312)$^{bc}$ | 154 (33, 236)$^{abc}$ | <0.001|
|                           | PS$_P$ | 69 (56, 82)$^c$   | 54 (32, 70)       | 59 (17, 82)    | 76 (54, 90)     |       |
| T$_{CYC-OFF}$ (ms)        | PS$_N$ | 76 (21, 36)$^a$   | 126 (44, 401)$^{bc}$ | 130 (47, 432)$^{bc}$ | 106 (14, 314)$^{abc}$ | <0.001|
|                           | PS$_P$ | 12 (8, 14)$^a$    | 8 (2, 14)         | 5 (2, 12)      | 2 (<7, 10)      |       |
| NeuroSync index (%)       | PS$_N$ | 29.1 (13.9, 46.8)$^a$ | 25.3 (15.5, 40.9)$^{bc}$ | 20.6 (13.5, 37.1)$^{bc}$ | 17.7 (10.5, 38.9)$^{abc}$ | <0.001|
|                           | PS$_P$ | 5.6 (4.2, 7.8)$^a$ | 6.0 (4.9, 8.3)    | 6.2 (5.1, 8.5)  | 6.7 (3.8, 10.3) |       |
| EAdi without assist (%)   | PS$_N$ | 0.8 (0, 10.1)     | 1.1 (0, 18.7)     | 0 (0, 10.8)    | 0 (0, 11.4)     | <0.001|
|                           | PS$_P$ | 0 (0, 0)          | 0 (0, 0)          | 0 (0, 0)       | 0 (0, 0)        | <0.001|
| Synchrony (inside box) (%)| PS$_N$ | 4.7 (0, 16.3)$^a$ | 7.8 (0, 20)$^{bc}$ | 11.5 (0, 37.4)$^{abc}$ | 7 (0.2, 46.3)$^{abc}$ | <0.001|
|                           | PS$_P$ | 89.4 (76.2, 97.9)$^a$ | 91.3 (76, 95.7)   | 88 (78, 93)    | 80 (63.4, 97.4) |       |
| Dysynchrony (outside box) (%)| PS$_N$ | 83.5 (76.3, 92)$^a$ | 79.3 (63, 86.7)$^{bc}$ | 76.9 (62, 87.5)$^{bc}$ | 70.9 (52, 89.3)$^{abc}$ | <0.001|
|                           | PS$_P$ | 9 (2.1, 23.1)$^a$ | 7.3 (1.8, 21.1)   | 10.8 (6.5, 17.4) | 18.6 (2.1, 32.7) |       |

Values are presented as median (25–75% interquartile range). $^a$P$^*$ values for one-way repeated measures analysis of variance on ranks for the eight conditions: within the same mode: $^*P < 0.05$ compared to extrinsic positive end-expiratory pressure (PEPP$_{E0\%}$); $^pP < 0.05$ compared to PEPP$_{e40\%}$; $^pP < 0.05$ compared to PEPP$_{e80\%}$; $^pP < 0.05$ compared to PEPP$_{e120\%}$. Between modes: $^*P < 0.05$ compared to PS$_N$ at same PEPP$_{e}$. Comparison of PS$_N$ zero PEPP to PS$_P$ optimal PEPP: $^*P < 0.05$ PEPP$_{e0\%}$ at PS$_N$ vs. PEPP$_{e80\%}$ at PS$_P$. PS$_P$ pneumatically triggered and cycled-off pressure support, PS$_N$ neurally triggered and cycled-off pressure support ventilation, PEPP$_{e}$ extrinsic PEEP, T$_{TRIG}$ diaphragm electrical activity (EAdi)-to-trigger time difference, T$_{CYC-OFF}$ cycling-off time difference.
\(\Delta \text{Adi}_{\text{TRIG}}\) during both PS\(_P\) and PS\(_N\). \(\Delta \text{Adi}_{\text{TOT}}\) was not significantly between PS\(_P\) and PS\(_N\), nor did it change with changing PEEPe.

Both \(\Delta \text{P}_{\text{es} \text{TRIG}}\) and \(\Delta \text{P}_{\text{es} \text{TOT}}\) were higher during PS\(_P\) compared to PS\(_N\) at the same PEEPe (Fig. 3 and Table 4): \(\Delta \text{P}_{\text{es} \text{TRIG}}\) was consistently and markedly reduced during PS\(_N\) compared to PS\(_P\). Increasing PEEPe reduced \(\Delta \text{P}_{\text{es} \text{TRIG}}\) during PS\(_P\) at PEEPe\(_{80}\%\) but did not change during PS\(_N\). \(\Delta \text{P}_{\text{es} \text{TOT}}\) decreased with increasing PEEPe during both PS\(_P\) and PS\(_N\). Four patients had positive \(\Delta \text{P}_{\text{es} \text{TOT}}\) during PS\(_P\) at PEEPe\(_{80}\%\) and one patient had positive \(\Delta \text{P}_{\text{es} \text{TOT}}\) during PS\(_N\) at PEEPe\(_{0}\%\). Figure 4 shows that the change in total mechanical efforts between PS\(_P\) at PEEPe\(_{0}\%\) and PS\(_N\) at PEEPe\(_{0}\%\) (x-axis) is similar to the change between PS\(_P\) at PEEPe\(_{0}\%\) and PS\(_P\) at PEEPe\(_{80}\%\) (with strong correlation: \(R^2 = 0.77\) for \(\Delta \text{P}_{\text{es} \text{TOT}}\) and \(R^2 = 0.68\) for \(\text{PTP}_{\text{es} \text{TOT}}\)).

\(\Delta \text{P}_{\text{es}}/\Delta \text{P}_{\text{L}}\) ranged between 2.2 and 24.5 \%, decreased with increasing PEEPe during both PS\(_P\) and PS\(_N\), and was lower during PS\(_N\) (Table 4).
Neuromechanical efficiency (NME)

Neuromechanical efficiency at the same PEEPe was lower during PS\textsubscript{N} compared to PS\textsubscript{P} and decreased with increasing PEEPe during both PS\textsubscript{P} and PS\textsubscript{N} (Table 4). There was no difference in NME between PS\textsubscript{N} at PEEPe\textsubscript{0\%} and PS\textsubscript{P} at PEEPe\textsubscript{80\%}. The reduction in NME from
Table 4  Neural and mechanical indices of respiratory effort at different levels of PEEPe during PSp and PSN

| Parameter                  | Mode | PEEPe0% | PEEPe20% | PEEPe40% | PEEPe120% | P   |
|----------------------------|------|---------|----------|----------|-----------|-----|
| ΔPes/TRG (cm H2O)          | Psp  | -0.9    | -0.9     | -0.6     | -0.4      | <0.001  |
|                            | PSN  | -0.2    | -0.1     | -0.0     | -0.1      | 0.01   |
| ΔPes/CTR (cm H2O)          | Psp  | -2.2    | -1.7     | -1.0     | -0.4      | <0.001  |
|                            | PSN  | -0.7    | -0.6     | -0.4     | -0.3      | 0.02   |
| PTPes/CTR (cm H2O*s/min)   | Psp  | -5.0    | -3.3     | -2.4     | -1.4      | <0.001  |
|                            | PSN  | -0.2    | -0.2     | -0.0     | -0.1      | 0.01   |
| NME (cm H2O/μV)            | Psp  | 3.1     | 2.6      | 2.1      | 1.8       | <0.001  |
|                            | PSN  | 1.3     | 1.1      | 1.1      | 1.0       | <0.001  |
| ΔPes/ΔP L (%)              | Psp  | 24.5    | 18.2     | 12.5     | 6.6       | <0.001  |
|                            | PSN  | 7.0     | 5.4      | 2.8      | 2.2       | <0.001  |
| NME/ΔPes (μV/ΔPes)         | Psp  | -0.27   | -0.22    | -0.13    | -0.09     | 0.001   |
|                            | PSN  | -0.11   | -0.07    | -0.06    | -0.05     | 0.001   |

Values are presented as median [25–75% interquartile range]. *P values for one-way repeated measures analysis of variance on ranks for the eight conditions: within the same mode: *P < 0.05 compared to PEEPe0%; **P < 0.05 compared to PEEPe20%; ***P < 0.05 compared to PEEPe40%. Between modes: *P < 0.05 compared to Psp at same PEEPe comparison of PSN zero PEEP to Psp; optimal PEEP: *P < 0.05 PEEPe0% at PSN vs. PEEPe0% at Psp. Psp pneumatically triggered and cycling-off pressure support, PSN neurally triggered and cycling-off pressure support ventilation, ΔPes/ΔP L pre-trigger mean deflection of esophageal pressure, ΔPes/TOT total inspiratory mean deflection for esophageal pressure, ΔPes/TRIG total inspiratory pressure time product per minute for esophageal pressure, PTPes/ΔPes pre-trigger pressure time product per minute for esophageal pressure, EAdi inspiratory diaphragm electrical activity (EAdi) for total inspiration, EAdi/ΔPes peak pre-trigger EAdi, ΔPes/ΔPes esophageal pressure contribution to transpulmonary pressure during inspiration, NME neuromechanical efficiency calculated for esophageal pressure.

PEEPe0% to PEEPe80% during SPS was not different (P = 0.699) for patients with EFL (median 28%, 25th–75th percentile 14–46%) and without EFL (41, 14–75%).

Discussion

This study shows that neurally controlled pressure support improves patient-ventilator interaction, nearly abolishes pre-trigger inspiratory neural and mechanical effort, and shows - even when zero PEEP is applied - similar total inspiratory neural and mechanical effort as conventional pressure support with an optimal PEEP. The main strength of the study is that it is the first to show that both neural monitoring and neural control of patient-ventilator interaction in patients with PEEPi are superior to pneumatic triggering.

Patient-ventilator interaction

In agreement with previous studies [5, 10, 12–16], increasing PEEPe during Psp reduced the trigger delay. As hypothesized, the EAdi trigger-synchronization nearly abolished both neural and mechanical pre-trigger efforts regardless of PEEPe. Our results showing that both neural and mechanical pre-trigger efforts were reduced with increasing PEEPe during Psp confirms that application of PEEPe counteracts PEEPi and reduces pre-trigger mechanical effort with pneumatic triggering [5], although not as efficiently as during neural triggering, similar to the recent work of Bellani [10].

Cycling-off assistance in PS mode is conventionally based on the relative reduction in inspiratory flow. This algorithm is an oversimplification and not physiologically sound, as flow during ventilatory assistance is influenced by multiple factors, such as respiratory system time constant, neural inspiratory time, level of pressure support, and inspiratory muscle pressure [17]. In the present study, the cycling-off setting was 30% of peak inspiratory flow (default setting of the ventilator utilized). This choice could be criticized as being too low in sensitivity in COPD patients as percentages from 40 to 70% have been suggested as more feasible [6, 7]. As there are no guidelines on how to adjust cycling-off for each individual patient, we opted to stay within default settings.

In support of cycling-off at 70% of peak EAdi being feasible was our finding that assistance was either EAdi-terminated when flow corresponded to 46% of peak flow or immediately before EAdi termination due to the inspiratory muscle relaxation increasing pressure in the circuit by 3 cm H2O above the targeted pressure (Servo-I manual). Thus the PSN cycling-off in the present study coincides with suggested flow cycling-off at 40–70% of peak flow in COPD [6, 7].

PSN showed high precision of triggering and cycling-off of pressure relative to the neural effort and centered...
Fig. 4 (See legend on next page.)
80% of breaths within a narrow range of error (Fig. 2). In contrast, $P_{SP}$ showed poor precision of both triggering and cycling-off relative to the neural effort. Although group median values indicated delays (Table 3), the topographical distribution of all breaths and all subjects shows that ventilatory assistance could start and cycle off prematurely. It is questionable if adjustment of trigger and cycling-off settings during $P_{SP}$ could have corrected this extreme heterogeneity of timing of assist relative to neural inspiratory effort.

With regards to the overall patient-ventilator interaction, a low NeuroSync index and little inter-individual variability, confirms the effectiveness of $P_{SN}$ to synchronize assistance in the presence of PEEP. Although improved by increasing PEEPe, the NeuroSync index was at least three times higher (worse patient-ventilator interaction) during $P_{SP}$ mainly due to dys-synchrony i.e., trigger and cycling-off errors, which cannot be determined with pressure-flow-volume waveform analysis without EAdi [11, 18]. The low incidence of other asynchronies e.g., ineffective efforts and auto-triggering is in agreement with previous work by Thille [19] showing that limiting $V_{T}$ (6 ml/kg) - as in the present study - improves patient ventilator interaction during $P_{SP}$. However, three patients (25%) approached a high frequency of EAdi-without-assistance (inefffective efforts) during $P_{SP}$ which is recognized as severe asynchrony and associated with adverse outcomes such as increased duration of mechanical ventilation [20, 21].

With regards to the effort throughout the entire inspiration, our results (Fig. 4) indicating that reductions from PEEPe$_{0\%}$ during $P_{SP}$ to PEEPe$_{0\%}$ during PEEPe; equaled those from PEEPe$_{0\%}$ during $P_{SP}$ to PEEPe$_{0\%}$ during PEEPe; support our assumption that synchronized assist overcomes PEEPi in COPD patients without the need to apply PEEPe. Thus, neural triggering allows a unique starting point for assistance delivery during every breath regardless of hyperinflation and PEEPi; however, the subsequent inspiration requires that the combined patient effort and assistance (i.e., the transpulmonary pressure) is sufficient to overcome the respiratory system’s resistive and elastic forces. In contrast, $P_{SP}$ and fixed PEEPe only compensate for the estimated average increase in elastic recoil at end-expiration due to dynamic hyperinflation and cannot correct for breath-by-breath changes in PEEPi.

Our results that applying PEEPe during $P_{SP}$ reduced mechanical effort for the entire inspiration agree with previous studies [4, 5]. A curious observation of the present study was that the reduction in total inspiratory mechanical effort from PEEPe$_{0\%}$ to PEEPe$_{0\%}$ during PEEPe; was larger than what could be explained by the reductions in pre-trigger mechanical effort. Even more confounding, increasing PEEPe actually reduced total inspiratory mechanical effort during PEEPe; a decrease that could not be attributed to reductions in the pre-trigger mechanical effort, as it was already abolished by the neural triggering. A likely possibility for why the mechanical efforts decreased is that PEEPe induced hyperinflation (increased end-expiratory lung volume) which would explain the reduction in NME (less pressure for a given neural output).

This is the first study measuring the effect of PEEPe on neural effort strictly in COPD patients (the work of Bellani [10] included 50% COPD patients). Although our results showed that pre-trigger neural effort could be reduced by increasing PEEPe during $P_{SP}$ the total neural inspiratory effort did not reach a significant decrease with increasing PEEPe during $P_{SP}$ nor during $P_{SN}$. This supports our thought that reduced total inspiratory mechanical effort with increasing PEEPe were in part associated with hyperinflation-induced respiratory muscle weakness [22], and not de-activation of the muscles. Previous studies indicate that application of CPAP (Continuous Positive Airway Pressure) in COPD patients with PEEPi increases end-expiratory lung volume [4, 23]. However, it has been suggested that application of PEEPe below the level of PEEPi in patients with EFL does not increase hyperinflation [24]. Our results did not indicate a difference for NME between patients with and without EFL. However, the present study showed a reduction in NME with increasing PEEPe during both $P_{SP}$ and $P_{SN}$ which could have been attributed to impaired contractility due to hyperinflation [22]. Thus, our finding that the total inspiratory mechanical effort during $P_{SN}$ at PEEPe$_{0\%}$ matched $P_{SP}$ at PEEPe$_{0\%}$ suggests that neural triggering is at least as efficient as titration of PEEPe to overcome PEEPi, and reduce total inspiratory mechanical effort. However, both methods pay a toll in terms of reduced NME.

It is important to point out that several patients received too high assistance (approximately 10 cm H$_2$O PS above PEEPe), resulting in low values of total inspiratory
mechanical effort (<2.5 cm H₂O Pes), suggesting that the patient's contribution to tidal volume was very low. At this high level of unloading, further reduction in neural inspiratory effort is limited [25–27], which could explain the modest decrease in total neural inspiratory effort.

Despite relatively low V̇T targeted in the present study, which should contradict the notion of over-assistance [19], PaCO₂ values were low, suggesting that certain patients could have been subjected to hyperventilation. Yet, another factor to explain the low total inspiratory mechanical effort could be respiratory muscle weakness. A limitation was that we did not evaluate respiratory effort sensation or dyspnea, which could have added insight to the issue of PEEPe and assistance levels that were too high. Note that with PSN, the amount of pressure support delivered should be greater than PEEPi. If the initial pressure delivery is not adequate to counteract PEEPi, the elastic recoil in the system would cause an increase in airway pressure [10] (see Fig. 4 in that report), and would activate the cycling-off (pressure algorithm) used with neural control of PS (as the safety algorithm).

Despite PEEPe being demonstrated to reduce PEEPi and work of breathing, many factors of how to implement PEEPe are unclear [4]. It is not clear whether PEEPi should be expressed in terms of its dynamic PEEPi or static PEEPi components. In spontaneously breathing, mechanically ventilated patients with active expiration there are currently no methods available to reliably determine the optimal level of static PEEPi and there is ongoing evaluation of reliability in different methods determining dynamic PEEPi [12, 28–30]. Moreover, the implementation of bias flow for the use of flow-trigger creates further complication as it underestimates dynamic PEEPi [31]. Maltais et al. [32] reported that in paralyzed patients, dynamic PEEPi underestimates static PEEPi due to regional differences of mechanical properties within the lungs. We therefore opted to measure static PEEPi during VCV in the absence of spontaneous breathing effort.

One limitation of the present study was that we could not randomize PS₀ and PSN, because PS₀ had to be adjusted first (with a target tidal volume of 6 ml/kg), in order to be matched with the upper pressure limits that were obtained during PSN. We did, however, randomize the ascending or descending order of the applied PEEPe in both arms, albeit we acknowledge that randomizing all PEEPe levels would be preferred. Due to risk of the steps between PEEPe levels being too large we decided not to randomize the order in which PEEPe was applied, but to apply PEEPe in either progressively increasing or decreasing order.

Conclusion

The present study shows that PSN overcomes the need for PEEPe to overcome PEEPi in COPD patients. PSN improves patient-ventilator interaction and reduces inspiratory mechanical effort to breathe. Although the present study suggests that PSN (at zero PEEP) can efficiently replace PS₀ with optimal PEEPe, use of PEEPe for other reasons, e.g., alveolar recruitment, would of course still apply. The clinical importance of improving patient-ventilator interaction in COPD remains to be studied.

Key messages

- Neurally controlled pressure support ventilation is feasible in patients with COPD demonstrating intrinsic PEEP
- Neurally controlled pressure support, compared to conventional, pneumatically controlled pressure support, improves patient-ventilator interaction and reduces inspiratory effort, even in the absence of external PEEP
- Neurally controlled pressure support overcomes the need for extrinsic PEEP, in order to overcome intrinsic PEEP in COPD patients

Abbreviations

Bf: breathing frequency; Bf₀: neural breathing frequency; COPD: chronic obstructive pulmonary disease; CV: coefficient of variation; EAdi: diaphragm electrical activity; EAdi: peak inspiratory EAdi; EAdi₀: peak pre-trigger EAdi; EFL: expiratory flow limitation; FEV₁/C15: forced expiratory volume in one second; FEV₁/FVC: forced vital capacity rate of one second; MAP: mean arterial pressure; NAVA: neurally adjusted ventilatory assist; NME: neuromechanical efficiency; PaCO₂: arterial carbon dioxide tension; PaO₂/FiO₂: oxygenation index; PEEPe: extrinsic positive end-expiratory pressure; PEEPe₀: PEEPe levels of 0 % of PEEPi; PEEPe₁20₀: PEEPe levels of 120 % of PEEPi; PEEPe₄₀₀: PEEPe levels of 40 % of PEEPi; PEEPi: intrinsic positive end-expiratory pressure; PEEPi₀: PEEPi levels of 0 % of PEEPi; PEEPi₁₂₀: PEEPi levels of 120 % of PEEPi; PEEPi₄₀₀: PEEPi levels of 40 % of PEEPi; PS₀: pneumatically triggered and cycled-off pressure support; PS₀₀: pneumatically triggered and cycled-off pressure support; PTPes: total inspiratory pressure time product per minute for esophageal pressure; PTPes-lo: pre-trigger pressure time product per minute for esophageal pressure; Ti/Tt: cycling-off timing-difference; Ti: neural inspiratory time; Ti: ventilator (pneumatic) inspiratory time; Tt: neural duty cycle; Ti: neural inspiratory time; Ti: ventilator (pneumatic) inspiratory time; Tt: neural respiratory cycle time; Ti: pre-trigger time difference; Tt: volume control ventilation; Vt: tidal volume; ΔPESPE₀: total inspiratory mean deflection for esophageal pressure; ΔPESPE₀: pre-trigger mean deflection of esophageal pressure; ΔPESPE₀: total inspiratory mean deflection for transpulmonary pressure.

Competing interests

JB and CS have been reimbursed by Maquet Critical Care (Solna, Sweden) for attending several conferences; JB and CS have participated as a speaker in scientific meetings or courses organized and financed by Maquet Critical Care; JB and CS, through Neurovent Research, serve as consultants to Maquet Critical Care. The following disclosure was agreed upon by University of Toronto, Sunnybrook Health Sciences Centre, St-Michael’s Hospital and the RERs of Sunnybrook and St-Michael’s to resolve conflicts of interest: Drs. Beck and Sinderby have made inventions related to neural control of mechanical ventilation that are patented. The patents are assigned to the academic institution(s) where inventions were made. The license for these patents belongs to Maquet Critical Care. Future commercial uses of this technology may provide financial benefit to Drs Beck and Sinderby through royalties. Drs Beck and Sinderby each own 50 % of Neurovent Research Inc (NVR). NVR is a research and development company that builds the equipment and catheters for research studies. NVR has a consulting agreement with...
Maquet Critical Care. St-Michael’s Hospital has a research agreement with Maquet Critical Care AB (Solna, Sweden) and receives royalty and overhead from this agreement. Paolo Navalesi contributed to the development of a new interface (neither used or mentioned in the present work), whose license for patent belongs to Intersurgical S.p.A, and receives royalties for that invention. His research laboratory has received equipment and grants from Maquet Critical Care and Intersurgical S.p.A. He also received honoraria/speaking fees from Maquet Critical Care, Brea, Covidiun AG, and Linde AG. The remaining authors have no competing interests to declare.

**Authors’ contributions**

LL was responsible for conception and design of the study, acquisition, analysis and interpretation of data, and drafting and revising the article for final approval of the version to be published. FX was responsible for design of study, acquisition and analysis of data, and revising the article. YY participated in the design of the study, acquisition and analysis of data, and revising the article for final approval of the version to be published. JB participated in the data analysis, interpretation of the results, and writing of the article. CS participated in the data analysis, interpretation of the results, and writing of the article. PN participated in the data analysis, interpretation of the results and writing of the article. FL participated in the data analysis, interpretation of the results, and writing of the article. HQ was responsible for the conception and design of the study, analysis and interpretation of data, drafting and revising the article for important intellectual content and final approval of the version to be published. All authors read and approved the manuscript.

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