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Physiological comparison of noninvasive ventilation and high-flow nasal oxygen on inspiratory efforts and tidal volumes after extubation: a randomized crossover trial

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Abstract

Background Extubation failure leading to reintubation is associated with high mortality. In patients at high-risk of extubation failure, clinical practice guidelines recommend prophylactic non-invasive ventilation (NIV) over high-flow nasal oxygen (HFNO) immediately after extubation. However, the physiological effects supporting the beneficial effect of NIV have been poorly explored. We hypothesized that NIV may reduce patient inspiratory efforts to a greater extent than HFNO after extubation.

Methods In a prospective physiological study, patients at high-risk of extubation failure (> 65 years old or underlying cardiac or respiratory disease) were included to receive after planned extubation prophylactic NIV and HFNO in a randomized crossover order, followed by standard oxygen. Inspiratory efforts were assessed by calculation of the simplified esophageal pressure–time-product per minute ($sPTP_{es}$ in cmH_2O s/min). Tidal volumes, distribution and homogeneity of ventilation were estimated using electrical impedance tomography.

Results Twenty patients were retained in the analysis. Inspiratory efforts were lower with NIV than with HFNO ($sPTP_{es}$ 196 cm H_2O s/min [116–234] vs. 220 [178–327], $p < 0.001$) whereas tidal volumes were larger with NIV than with HFNO (8.4 mL/kg of predicted body weight [6.7–9.9] vs. 6.9 [5.3–8.6], $p = 0.005$). There was a non-significant increase in dorsal region ventilation under NIV compared to HFNO.

Conclusions In patients at high-risk of extubation failure, prophylactic NIV significantly decreased inspiratory efforts with increased tidal volumes compared to HFNO. The clinical benefits of NIV to prevent reintubation in patients at high-risk may be mediated by these physiological effects.

Trial registration Clinicaltrials.gov: ID NCT04036175), retrospectively registered 17 June 2019.

Keywords Ventilator weaning, Airway extubation, Noninvasive ventilation, Work of breathing

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Background

In intensive care units (ICUs), the decision to extubate remains challenging. Approximately 20–30% of patients experience post-extubation respiratory failure, and half of them, *i.e.* 10–15%, require subsequent reintubation [1]. Reintubation is associated with particularly high mortality rates, and is likely the main patient-centered outcome during the post-extubation period [1–3]. Both prophylactic application of noninvasive ventilation (NIV) and high-flow nasal oxygen (HFNO) therapy immediately after extubation reduce the risk of reintubation as compared to standard oxygen [4–7]. In a few studies assessing the physiological effects of noninvasive respiratory supports after extubation, both NIV and HFNO reduced inspiratory efforts as compared to standard oxygen [8–10]. In patients at high-risk of extubation failure, NIV further reduces the risk of reintubation as compared to HFNO [11, 12], and the most recent clinical practice guidelines suggest the use of NIV over HFNO in this setting [13, 14]. However, no study has compared the effects of NIV and HFNO on inspiratory efforts after extubation. A better understanding of the physiological effects of these noninvasive respiratory supports would improve understanding of their clinical effects in this setting. As compared to acute respiratory failure [15, 16], inspiratory efforts may be lower with NIV than with HFNO, which may be particularly beneficial in the post-extubation period due to frequent respiratory muscle weakness, alveolar derecruitment or impaired alveolar ventilation. Additionally, larger tidal volumes and higher levels of PEEP could contribute to re-aeration of posterior regions and lung recruitment. Thereby, we hypothesized that as compared to HNFO, prophylactic NIV applied immediately after extubation in patients at high-risk of extubation failure reduces inspiratory efforts and increases tidal volumes.

Methods

We conducted a randomized crossover physiological study including patients admitted to the medical ICU at the university hospital of Poitiers in France. The study was approved by the ethics committee (Comité de Protection des Personnes, CPP Est III) with registration number 2017-A02838-45. In keeping with our national regulations, consent from patients or agreement from their surrogate was obtained orally with a written record maintained by the researcher. The second and final version of the study protocol was retrospectively recorded at clinicaltrials.gov (ID: NCT04036175) on the 17th of June, 2019. Initial and final versions of the protocol are available in the Supplement. Enrollment, protocol intervention and measures were performed by the clinical investigator.

Patients

Patients were eligible if they had undergone intubation for more than 24 h, had a high risk of extubation failure, had PaO_2/FiO_2 below 300mmHg under mechanical ventilation prior to extubation, and were considered to be ready for extubation after a successful spontaneous breathing trial. Patients had a high risk of extubation failure if they were older than 65 years of age or had any underlying chronic cardiac or respiratory disease [11, 17]. Patients with contraindication to nasogastric tube insertion or to NIV, and those with a do-not-reintubate order at the time of extubation, were not eligible.

Interventions

After informed consent was obtained by a clinical investigator, a spirometer was placed on the endotracheal tube and an esophageal balloon was inserted and filled with 4 mL of air (NutriVent®, Sidam, Mirandola, Italy). Its adequate position and inflation were ensured using an occlusion maneuver [18]. The spirometer and the balloon were connected to a pressure transducer (FluxMed GrT®, MBMED, Martinez, Argentina). Airway pressure, flow and esophageal pressure signals were sampled at 256 Hz, stored in a dedicated computer and then analyzed offline using dedicated software (Acqknowledge, BIOPAC, Goleta, CA, USA). A size-adjusted electrical impedance tomography (EIT) belt with 16 electrodes was placed around the fifth or sixth intercostal space and connected to a dedicated device to detect tidal changes in lung impedance (PulmoVista®, Dräger, Lübeck, Germany). EIT signals were sampled at 50 Hz, and then analyzed offline using a dedicated software (Dräger EIT Data analysis tool, Dräger).

Measurements were first recorded for a 20 min period just before extubation while patients were still under mechanical ventilation. Patients were then assessed immediately after extubation under standard oxygen; and then under NIV or HFNO in a computer-generated randomized crossover order, and lastly once again under standard oxygen. Each period of treatment lasted 20 min and was fully recorded.

Invasive and noninvasive respiratory supports were delivered according to our weaning protocol. Before extubation, all patients were ventilated in pressure-support ventilation with a pressure-support level targeting a tidal volume at least 6 ml/kg of predicted body weight and a respiratory rate below 35 breaths per minute. A first spontaneous breathing trial was considered as early as patients met the following weaning criteria: awake (with a Richmond agitation-sedation scale RASS between −2

and + 1) without any continuous sedation, no vasopressors, respiratory rate ≤ 35 breaths per minute and PaO_2/FiO_2 > 150 cm H_2O under $FiO_2 \leq 40\%$ and PEEP up to 8 cm H_2O. Extubation was then decided by the physician in case of SBT success in patients having adequate cough. At the beginning of the study (until 2021), SBT was systematically performed using a T-piece, and then using PSV 8 cm H_2O without PEEP, according to the results of a large-scale clinical trial coordinated by our center [24]. After extubation, HFNO was delivered with a flow set at least 40 L/min (Optiflow®, Fisher & Paykel Healthcare, Auckland, New Zealand) and NIV through facemask connected to a ventilator with a NIV-dedicated mode (Carescape R860®, General Electric Healthcare, Chicago, USA), with a pressure-support (PS) level targeting expired tidal volumes between 6 and 8 ml/kg of predicted body weight and a positive end-expiratory pressure (PEEP) level of at least 5 cm H_2O. Standard oxygen was administered via nasal cannula at a flow of at least 4L/min. FiO_2 and oxygen flow were adjusted to maintain SpO_2 between 94 and 98% regardless of the noninvasive respiratory support, except for chronic respiratory disease patients for whom the target was between 88 and 92%.

Measurements

Baseline characteristics were collected at enrollment. Blood pressure, heart rate, respiratory rate, transcutaneous pressure of CO_2 and SpO_2 were monitored continuously, and an assessment of respiratory comfort with a visual analogue scale was performed.

At each step, 20 representative breaths recorded during the last 5 min were analyzed and averaged. Representative breaths were selected by visually analyzing the impedance and esophageal signals. The chosen cycles were consecutive, regular, and homogeneously shaped, without cough or esophageal spasms for esophageal pressure.

Inspiratory efforts were estimated using the esophageal pressure swings at each breath (ΔP_{es}) and the esophageal simplified pressure–time-product ($sPTP_{es}$), *i.e.* the area above the esophageal pressure curve over time from the onset of negative deflection of the esophageal pressure to its return to baseline, not considering the elastic recoil pressure of the chest wall or the beginning and the end of inspiration, as surrogate of the esophageal pressure–time product [19, 20]. $sPTP_{es}$ was expressed by breath, by minute and by liter. Swings of transpulmonary pressure ΔP_L were assumed to be equal to the swings of esophageal pressure as airway pressure is considered to be stable under standard oxygen and HFNO; and were estimated for NIV using $\Delta P_{es} + PS$.

Tidal volumes (V_T) during the post-extubation periods were obtained using impedance variation throughout time (ΔZ, arbitrary unit), converted to mL with a correlation coefficient determined for each patient by simultaneous measurement of impedance variation and tidal volume under invasive ventilation before extubation. Minute ventilation was calculated as the estimated tidal volume times the respiratory rate.

A surrogate of dynamic compliance was calculated as the estimated tidal volume divided by the esophageal pressure swings plus pressure support during NIV ($V_T/(\Delta P_{es} + PS)$) [21].

Outcomes

The primary outcome was inspiratory efforts measured by the $sPTP_{es}$ per min. Secondary outcomes included other indices of inspiratory efforts ($sPTP_{es}$ per liter, ΔP_{es} per breath), tidal volumes expressed in mL and in mL per kilogram of predicted body weight, minute ventilation, swings of transpulmonary pressure ΔP_L and estimated dynamic compliance using the $V_T/(\Delta P_{es} + PS)$ ratio per breath.

Following the completion of the planned analyses, we incorporated exploratory outcomes derived from EIT results. We calculated global and regional end-expiratory lung impedance (EELI), change of global and regional EELI from mechanical ventilation (ΔEELI), center of ventilation, global inhomogeneity index and percentage of pendelluft, using a previously described method [22].

Statistical analysis

Based on previous studies [9, 21], enrollment of 22 patients was determined to detect a 100 ± 80 cm H_2O s/min reduction in $sPTP_{es}$ (from 200 cm H_2O s/min with HFNO to 100 cm H_2O s/min with NIV) at a two-sided alpha level of 0.05 and with power of 80%. Categorical data were expressed as number (percentage) and continuous data were expressed as median [interquartile range, IQR 25th-75th percentiles]. Outcomes were compared between standard oxygen, HFNO and NIV using the Friedman test for repeated measures. Dunn's post-hoc test for multiple comparisons was performed in a paired analysis, if the results of the Friedman test yielded significant results. To avoid any residual effect of mechanical ventilation, the results presented for standard oxygen correspond to those obtained during the second period. Statistical analyses were performed using GraphPad Prism 8.0.1 (GraphPad Software, San Diego, CA, USA). Two-tailed p values < 0.05 were considered statistically significant.

Results

Patients

Across five distinct periods between April 2018 to April 2023 for a total of 19 months, 22 patients were included

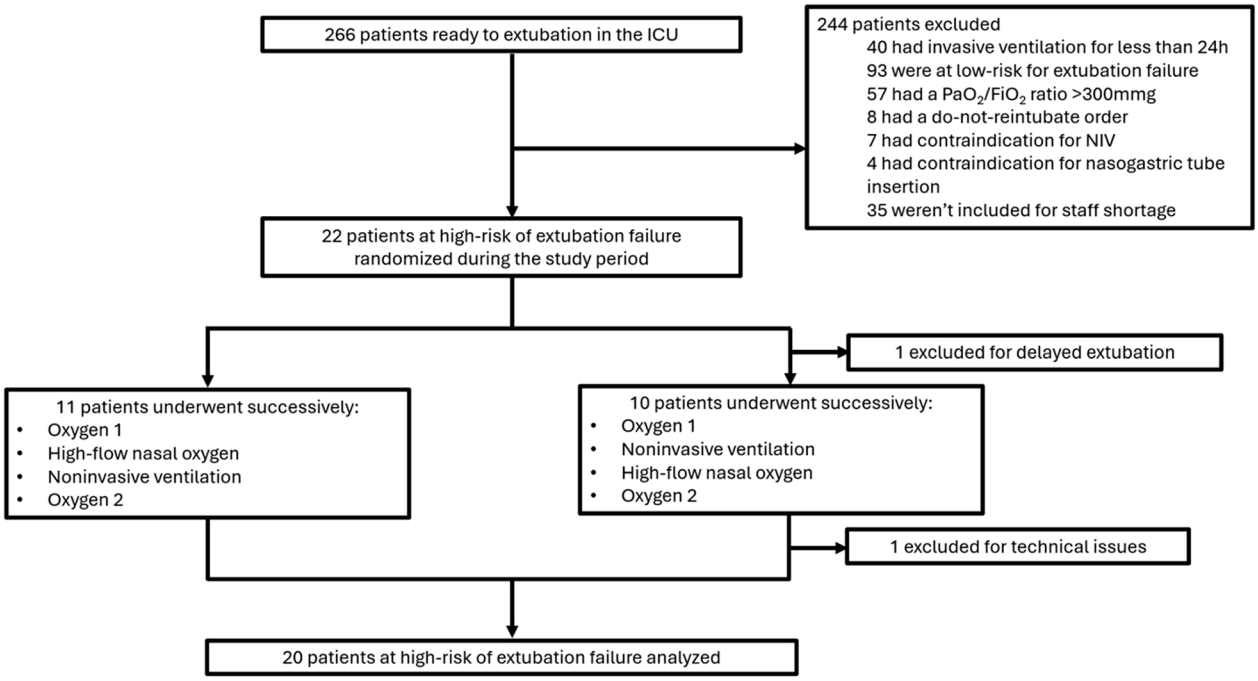

Fig. 1 Flow-chart. Patients were included across five distinct periods between 2018 and 2023 for a total of 19 months

in the study and 20 of them were retained in the analysis (one excluded because of a delayed extubation, and one for technical issues) (Fig. 1). Baseline characteristics of patients are shown in Table 1. Patients were 69 years old in median [60–71] and most of them were males (85%). A majority were intubated for acute respiratory failure (65%), and their median duration of invasive mechanical ventilation before extubation was eight days [3–13]. Five patients (25%) required reintubation within the seven days following extubation. None of the patients died in the ICU.

Clinical parameters, ventilatory settings and weaning details on the day of extubation are presented in Table 2. All patients were ventilated in pressure-support mode, with a median pressure-support level of 8 cm H_2O [6–10], a median PEEP of 6 cm H_2O [6–8] and a median FiO_2 of 30% [30–40]. Median PaO_2/FiO_2 ratio was 257 [209–280] and median pH was 7.50 [7.45–7.51].

Noninvasive respiratory support settings

Patients received standard oxygen using nasal cannula immediately after extubation with an oxygen flow rate of 5 L/min [5, 6]. Thereafter, eleven patients were randomized to receive first HFNO and then NIV, whereas the nine others received first NIV and then HFNO (Fig. 1). HFNO was delivered with a flow rate of 40 L/min [40–50] and FiO_2 of 40% [40–50]. NIV was delivered with a median pressure-support level of 4 cm H_2O [4, 5], a PEEP level of 4 cm H_2O [4], and FiO_2 of 40 [40–40]. Assessment of respiratory comfort under the different devices was available for only five patients due to difficulties in collecting a reliable evaluation from the other patients; therefore, this data has not been included.

Evaluation of inspiratory efforts

The results are displayed in Table 3 and Fig. 2.

Inspiratory efforts varied significantly between NIV, HFNO and standard oxygen with respect to the primary outcome, $sPTP_{es}$ in cmH_2O s/min (respectively 196 [116–234], 220 [178–327] and 256 [170–355] cmH_2O s/min, $p < 0.001$). When directly comparing NIV to HFNO, there was a significant reduction in the inspiratory effort under NIV ($p = 0.021$). There was no significant difference between HFNO and standard oxygen ($p > 0.999$).

This difference between NIV and HFNO remained significant in each of the treatment sequence groups ($p = 0.016$ in the NIV then HFNO group, and $p = 0.027$ in the HFNO then NIV group), thereby excluding a carryover effect. Results were also consistent in $sPTP_{es}$ per liter. There was a significant difference across the three groups in $sPTP_{es}$ per breath and ΔP_{es} per breath, with a numerically, but not significant reduction in the inspiratory effort under NIV compared to HFNO.

We also compared invasive ventilation and noninvasive ventilation and found no differences in any markers of inspiratory effort (Table 1).

Table 1 Baseline characteristics and outcomes of patients included

Baseline characteristics	***N*** **= 20**
Age, years	69 [60–71]
Sex, male (%)	17 (85%)
Body mass index, kg/m^2	26 [24–32]
Simplified Acute Physiology Score II on admission, points	47 [38–60]
Main reason for intubation	
Acute respiratory failure, n (%)	13 (65%)
Hypoxemic respiratory failure	9 (45%)
Hypercapnic respiratory failure	4 (20%)
Coma, *n* (%)	3 (15%)
Shock, *n* (%)	2 (10%)
Surgery, *n* (%)	2 (10%)
Risk factors for extubation failure	
Age > 65y, *n* (%)	13 (65%)
Underlying chronic cardiac disease, *n* (%)	7 (35%)
Ischemic heart disease, *n* (%)	4 (20%)
Atrial fibrillation, *n* (%)	3 (15%)
Left ventricular dysfunction, *n* (%)	3 (15%)
History of cardiopulmonary oedema, *n* (%)	4 (20%)
Underlying chronic lung disease, *n* (%)	10 (50%)
Chronic obstructive pulmonary disease, *n* (%)	9 (45%)
Obesity-hypoventilation syndrome, *n* (%)	3 (15%)
Chronic restrictive pulmonary disease, *n* (%)	1 (5%)
Characteristics on the day of extubation	
Duration of invasive ventilation, days	8 [3–13]
Difficult or prolonged weaning, *n* (%)	10 (50%)
Outcomes	
Reintubation at day 7	5 (25%)

Continuous variables were expressed as median [interquartile range, 25th-75th percentile] and categorical variables as number (percentage)

Table 2 Clinical parameters, ventilator settings and weaning details on the day of extubation

Type of spontaneous breathing trial	
T-piece	9 (45%)
Low-level of pressure-support without PEEP	11 (55%)
Ventilator settings before the spontaneous breathing trial	
Pressure-support mode	20 (100%)
Pressure-support, cm H_2O	8 [6–10]
Positive end-expiratory pressure, cm H_2O	6 [6–8]
FiO_2, %	30 [30–40]
Clinical characteristics before the spontaneous breathing trial	
Respiratory rate, breaths per min	24 [22–29]
Heart rate, beats per minute	90 [84–96]
Systolic arterial pressure, mmHg	128 [113–145]
SpO_2, %	96 [95–98]
Arterial blood gas analysis before extubation	
pH, units	7.50 [7.45–7.51]
$PaCO_2$, mm Hg	37 [33–41]
PaO_2/FiO_2, mm Hg	257 [209–280]
Ineffective cough	6 (30%)
Abundant secretions	10 (50%)

Continuous variables were expressed as median [interquartile range, 25th-75th percentile] and categorical variables as number (percentage)

Cough strength and amount of respiratory secretions were assessed using a clinical semi-quantitative 4-point scale. Ineffective cough included absent cough and weak cough categories. Abundant secretions included productive and very productive categories

Abbreviations: FiO_2 = fraction of inspired oxygen; SpO_2 = pulse oximetry; PaO_2 = partial pressure of arterial oxygen; $PaCO_2$ = partial pressure of arterial carbon dioxide

Evaluation of tidal volumes

The results are displayed in Table 3 and Fig. 3.

Tidal volume in ml/kg of PBW was 8.4 [6.7–9.9] under NIV, 6.9 [5.3–8.6] under HFNO and 7.0 [6.2–9.6] under standard oxygen (p = 0.006). Tidal volume was significantly larger under NIV than under HFNO ($p = 0.002$) (Table 3 and Fig. 3). Results were consistent with tidal volume in absolute values and estimated minute ventilation.

Interestingly, tidal volumes were greater under NIV than under invasive ventilation (Table 1).

Evaluation of respiratory mechanics

The results are displayed in Table 3.

There was no difference between the three noninvasive methods on estimated dynamic compliance (NIV 38 [29–44], HFNO 36 [26–48] and standard oxygen 41 [29–46] ml/cmH_2O, p = 0.819). Swings of transpulmonary pressures were significantly different across the groups (15 [13–16] cm H_2O under NIV, 13 [10–15] under HFNO, and 14 [10–16] under standard oxygen, $p = 0.013$), with a significant reduction under HFNO when directly compared to NIV ($p = 0.010$).

Greater pressure support with comparable inspiratory effort led to greater transpulmonary pressure under invasive ventilation compared to NIV, ultimately resulting in lower dynamic compliance (Table 1).

Vital signs and adverse effects

Vital signs (SpO_2, respiratory rate, heart rate and systolic blood pressure) did not differ between the different noninvasive respiratory supports, or between NIV and HFNO. Transcutaneous pressure of CO_2 could not be performed due to technical issues (defective device).

No adverse events were observed during the time of the study, from the insertion of the nasogastric tube and EIT belt until the end of the post-extubation noninvasive respiratory support periods.

Exploratory outcomes

The results are displayed in Table 4.

Table 3 Primary and secondary outcomes

	Invasive ventilation	Noninvasive ventilation	High-flow nasal oxygen	Standard oxygen‡	*p* value
Primary Outcome					
$sPTP_{es}$ per minute, cmH_2O s/min	124 [92–238]	196 [116–234]*,†	220 [178–327]	256 [170–355]	0.001
Secondary Outcomes					
$sPTP_{es}$ per litre, cm H_2O s/L	12.8 [8.8–18.8]	12.8 [8.5–17.5]*,†	19.7 [13.2–28.3]	19.4 [13.6–30.0]	< 0.001
$sPTP_{es}$ per breath, cm H_2O s/breath	5.5 [3.5–8.8]	6.8 [5.4–9.1]*	9.1 [6.8–12.2]	9.4 [7.6–13.7]	0.002
ΔP_{es} per breath, cm H_2O/breath	9.5 [6.3–13.5]	10.5 [8.6–12.7]*	13.4 [9.9–15.3]	13.5 [9.4–17.5]	0.004
ΔP_{es} per litre, cm H_2O/L	20.3 [14.4–30.1]	19.1 [15.0–26.4]†	27.6 [20.8–38.9]	25.7 [21.7–34.6]	0.019
ΔP_{Lung}, per breath, cm H_2O/breath	18 [14.2–21]	15.0 [13.0–16.0]†	13.4 [9.9–15.3]	13.6 [9.8–16.1]	0.013
Tidal volume, ml/breath	435 [382–488]	549 [463–631]†	433 [339–528]	458 [399–610]	0.004
Tidal volume, mL/kg of PBW	6.8 [6.1–8.4]	8.4 [6.7–9.9]†	6.9 [5.3–8.6]	7.0 [6.2–9.6]	0.006
Minute ventilation, L/min	10.7 [9.1–12.7]	13.7 [10.2–19.0]†	11.1 [7.6–16.4]	11.6 [9.2–17.6]	0.011
Dynamic compliance, mL/cm H_2O	26.0 [20.6–29.7]	38.0 [29.0–44.3]	36.3 [25.7–48.0]	40.9 [28.9–46.2]	0.819
Respiratory rate, breaths/min	24 [21–30]	26 [21–32]	25 [23–32]	24 [22–30]	0.896
SpO_2, %	97 [96–99]	97 [96–98]	96 [94–98]	97 [95–99]	0.239
Heart rate, beats/min	90 [84–96]	92 [87–105]	90 [86–98]	91 [81–96]	0.056
Systolic blood pressure, mm Hg	128 [113–145]	139 [125–156]	139 [121–152]	138 [127–156]	0.850

Continuous variables were expressed as median [interquartile range, IQR 25th-75th percentiles] and compared using the Friedman test for repeated measures (NIV/HFNO/standard oxygen)

Invasive ventilation values are not included in the statistical analysis

‡ The results correspond to the 2nd period of standard oxygen

Abbreviations: $sPTP_{es}$ = simplified esophageal pressure–time product; ΔP_{es} = esophageal pressure swings, ΔP_{Lung} = transpulmonary pressure swings, PBW = predicted body weight

* Adjusted $p < 0.05$ using Dunn's post-hoc test for multiple comparisons between noninvasive ventilation or high-flow nasal cannula oxygen and standard oxygen

† Adjusted $p < 0.05$ using Dunn's post-hoc test for multiple comparisons between noninvasive ventilation and high-flow nasal cannula oxygen

Regarding the distribution of ventilation, the center of ventilation was different across the three different groups (54.5% [50.1–57.3] under NIV, 53.8 [46.5–57.1] under HFNO and 53.5 [50.0–56.9] under standard oxygen) indicating more posterior ventilation under NIV. However, there was no statistical difference between NIV and HFNO.

There was no difference in global or regional EELI across the three groups, despite a median two-fold increase under NIV compared to HFNO and standard oxygen. Moreover, when assessing the change of EELI from mechanical ventilation (ΔEELI), there was a trend toward greater loss of aeration under HFNO and standard oxygen, particularly in the dorsal regions. However, there was no statistical difference in the regional percentages of global ΔEELI.

Regarding ventilation inhomogeneity, there was a significant difference in the percentage of pendelluft among the three groups, with less pendelluft under NIV compared to standard oxygen. No difference was observed between HFNO and NIV. The global inhomogeneity index did not differ among the three groups.

Interestingly, during the NIV phase, there was a weak correlation between efforts in ΔPes and tidal volumes in ml/cycle ($r = 0.2663$).

Discussion

In this randomized crossover physiological study providing a comprehensive assessment of NIV, HFNO and standard oxygen after extubation amongst high-risk patients, while inspiratory efforts were significantly lower with NIV than with HFNO and standard oxygen, tidal volumes and minute ventilation were significantly higher. NIV promoted more posterior ventilation with an appreciable, albeit non-significant, increase in EELI. These results advocate for a strong effect of NIV to relieve the inspiratory workload, and potential re-aeration of lung regions. However, there was no difference in dynamic compliance, and a significant but modest increase in transpulmonary swings occurred under NIV.

From physiological studies to clinical trials

A physiological study recently showed that inspiratory efforts were significantly lower with HFNO than with standard oxygen after extubation [10]. This may explain the reduced risk of reintubation with HFNO as compared to standard oxygen observed in several clinical trials including patients extubated with mild hypoxemia [6, 7]. Although we observed a trend toward reduced inspiratory efforts with HFNO as compared to standard oxygen,

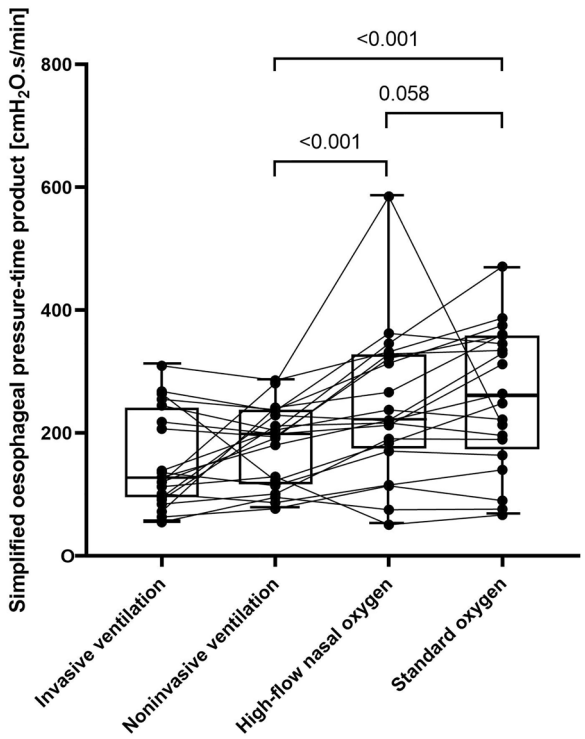

Fig. 2 Comparison of patient inspiratory efforts to the different respiratory supports: patient inspiratory efforts were significantly lower with noninvasive ventilation than with high-low nasal cannula oxygen and standard oxygen

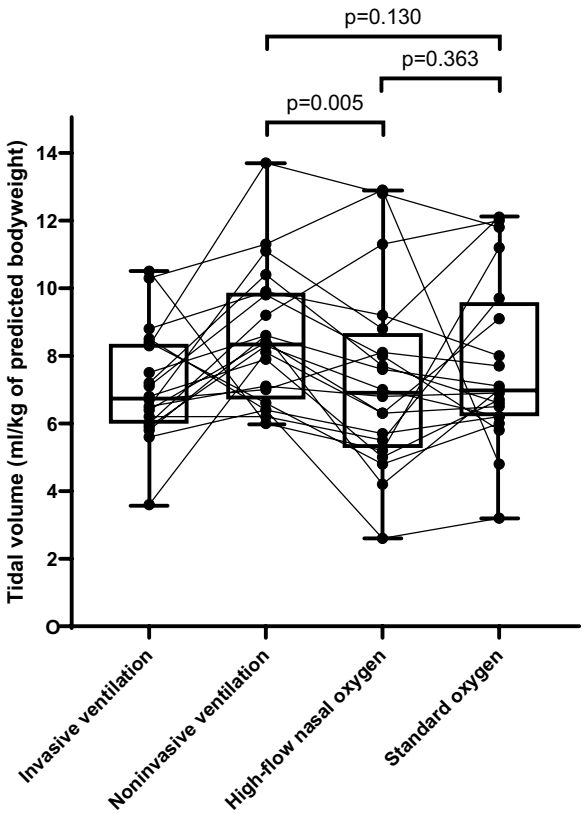

Fig. 3 Comparison of tidal volumes according to the different respiratory supports: tidal volumes were significantly larger with noninvasive ventilation (NIV) than with high-flow nasal oxygen (HFNO)

it did not significantly differ. However, inspiratory efforts in our study were markedly higher than in the above-mentioned physiological study [10], and the beneficial effects of HFNO on inspiratory efforts may be underestimated in large inspiratory efforts. Moreover, we only included patients at low risk. In line with our physiological findings, another clinical trial did not show any difference in the risk of reintubation between patients treated with HFNO and those treated with standard oxygen after extubation [23]. To date, even though prophylactic use of HFNO is recommended by most recent clinical practice guidelines after extubation, the recommendation was conditional with low certainty of evidence [14].

Similarly, older physiological studies showed that inspiratory efforts were significantly lower with NIV than with standard oxygen in the post-extubation period in patients at high risk of extubation failure [8, 9]. In patients with chronic respiratory disease, NIV could even be as effective as invasive ventilation in reducing diaphragm energy expenditure [8]. Similarly, and even if pressure support and PEEP were lower under NIV than under invasive ventilation in our study, we found no difference in inspiratory efforts between NIV and invasive ventilation. Again, this may explain the reduced risks of post-extubation respiratory failure and reintubation with NIV as compared to standard oxygen observed in several studies including patients at high risk of extubation failure [4, 5, 24]. Whereas HFNO is currently widely used after extubation, several clinical trials have shown that the risk of reintubation was lower under NIV than under HFNO in patients at high risk of extubation failure [11, 12]. Thereby, NIV is currently recommended in these patients by most recent clinical practice guidelines, with moderate certainty of evidence [14]. In line with these clinical trials, we reported lower inspiratory efforts under NIV than under HFNO. This physiological effect may be a major contributor to the clinical beneficial effects of NIV.

Effects of NIV on tidal volume

Tidal volumes were significantly larger with NIV than with HFNO leading to increased minute ventilation. This could be explained by re-aeration of lung regions, as evidenced by the two-fold increase in median EELI under NIV. This increase was more pronounced in the dorsal regions, suggesting a potential effect on reversing

Table 4 Exploratory outcomes

	Invasive ventilation	Noninvasive ventilation	High-flow nasal oxygen	Standard oxygen	*p* value
Distribution of ventilation					
Centre of ventilation, %	53.2 [47.3–58.7]	54.5 [50.1–57.3]*	53.8 [46.5–57.1]	53.5 [50.0–56.9]	0.008
EELI (AU)					
Global	1609 [570–3034]	2209 [791–3404]	1151 [616–3148]	1169 [677–2328]	0.196
Ventral ROI	193 [38–655]	209 [40–508]	141 [92–342]	147 [86–198]	0.949
Midventral ROI	822 [162–1188]	858 [189–1733]	511 [107–1183]	421 [100–905]	0.331
Middorsal ROI	886 [229–886]	692 [234–1315]	623 [247–1101]	438 [68–996]	0.268
Dorsal ROI	148 [64–293]	274 [73–750]	118 [35–367]	201 [21–620]	0.212
ΔEELI (AU)					
Global	Ref.	+268 [−530;+1420]	−173 [−1311;-876]	−315 [−1408;+230]	0.076
Ventral ROI	Ref.	+36 [−338;+179]	−7 [−478;+122]	−33 [−489;+134]	0.949
Midventral ROI	Ref.	−112 [−636;705]+297	−279 [−677;262]	−330 [−830;19]	0.331
Middorsal ROI	Ref.	[−195;+757]	+289 [−472;+750]	+43 [−620;+333]	0.268
Dorsal ROI	Ref.	+80 [−161;+344]	+18 [−341;+191]	+29 [−286;+147]	0.076
Regional ΔEELI (% of global EELI)					
Ventral ROI	Ref.	11.1 [−3,4;59,4]	8.0 [11.3;27.3]*	19.5 [6.6;47.16]	0.012
Midventral ROI	Ref.	38.9 [3.3;63.1]	29.5 [−51.8;52.2]	50.8 [30.8;125.8]	0.211
Middorsal ROI	Ref.	41.4 [−15.3;62.8]	45.8 [21.4;150.4]	30.3 [−54.1;66.8]	0.162
Dorsal ROI	Ref.	17.4 [13.6;32.6]	10.0 [−23.2;26.1]	14.4 [−5.9;21.6]	0.223
Inhomogeneity of ventilation					
Pendelluft, %	10.3 [6.2–15.8]	10.8 [5.2–17.2] *	9.7 [3.9–23.8]	11.15 [7.1–26.7]	0.018
Global inhomogeneity index	0.48 [0.48–0.75]	0.49 [0.46–0.82]	0.50 [0.45–0.79]	0.48 [0.44–0.79]	0.623

Continuous variables were expressed as median [interquartile range, IQR 25th-75th percentiles] and compared using the Friedman test for repeated measures (NIV/HFNO/standard oxygen)

IQR ranges have been expressed as [IQR 25th;75th percentiles] for change of EELI

ΔEELI values indicate the change of EELI compared to invasive ventilation

Invasive ventilation values are not included in the statistical analysis

Abbreviations: EELI: end-expiratory lung impedance, ROI: region of interest, AU: arbitrary units, Ref: reference

* Adjusted $p < 0.05$ using Dunn's post-hoc test for multiple comparisons between noninvasive ventilation or high-flow nasal cannula oxygen and standard oxygen

† Adjusted $p < 0.05$ using Dunn's post-hoc test for multiple comparisons between noninvasive ventilation and high-flow nasal cannula oxygen

atelectasis in patients with frequent underlying respiratory muscle weakness [25]. This effect was significant despite low levels of pressure support under NIV. Indeed, median pressure-support was only 4 cm H_2O, whereas it was 8 cm H_2O in mean in a large clinical trial showing decreased risk of reintubation with NIV compared to HFNO [11]. The beneficial effects of NIV may be even more pronounced using higher levels of pressure support.

Large tidal volumes and higher transpulmonary pressure swings generated under NIV may be associated with increased risk of death in patients admitted to ICUs for acute hypoxemic respiratory failure [26, 27]. However, the tidal volumes under NIV in our study remained modest compared to the "toxic" threshold of 9 to 11 ml/kg PBW that has been observed in acute respiratory failure. Moreover, the weaning process is only possible when the patient has recovered from acute lung injury (i.e. adequate oxygenation and ability to breathe spontaneously without signs of respiratory distress). Therefore, ventilation-induced lung injury could be negligible and large tidal volumes not so harmful after extubation and may even be more beneficial, considering the particularity of respiratory mechanics in this setting.

NIV could also improve the homogeneity of ventilation by mitigating the pendelluft phenomenon, as demonstrated in the context of acute respiratory failure [15]. We observed a significant reduction in pendelluft under NIV compared to standard oxygen, but not compared to HFNO. Moreover, the modest difference in absolute values of pendelluft of less than 2%, may not reflect a clinically significant effect. The absence of difference in the global inhomogeneity index also supports this conclusion.

Surprisingly, we observed lower tidal volumes under invasive ventilation compared to NIV, despite lower levels of pressure support and PEEP under NIV. This counterintuitive finding should be interpreted with caution

due to critical differences in experimental conditions between these two situations: resistive pressure due to endotracheal tube (even more after 8 median days of ventilation), reduced mobility, cough, etc.

Limitations

This study has some limitations. First, some outcomes could not be reported, in particular we were unable to properly assess respiratory comfort in all patients. Comfort is an important issue during noninvasive ventilation therapy and intolerance can be associated with treatment failure in acute respiratory failure [28, 29]. However, no patient had to be weaned off noninvasive ventilation because of tolerance issues during the study. Second, we reported transpulmonary pressure swing calculation. Such parameters can be of critical importance to properly understand respiratory mechanics. However, calculation requires an approximate estimate of the end-expiratory airway pressure under HFNO and standard oxygen (usually 2.5 cm H_2O under HFNO and 0 under standard oxygen) [15, 21], and this seems highly questionable, insofar as end-expiratory airway pressure is known to be different depending on patients, work of breathing, flow rate and mouth opening, and generally seems to drop during inspiration [30, 31]. Third, we did not perform any transdiaphragmatic measurement, and therefore cannot partition the effect of the noninvasive respiratory supports on the diaphragmatic function. Fourth, we estimated tidal volumes using EIT, which is an indirect approximate estimate and should be interpreted with caution. However, during the oxygen and HFNO periods, the only method to directly measure tidal volumes involves applying a NIV mask over the oxygenation device, with no PEEP and a low level of inspiratory assistance to offset the augmentation of resistance [32]. We hypothesize that this method significantly alters work of breathing and tidal volumes. In contrast, we believe our method based on EIT and tailored to each patient based on their own invasive measurements, can achieve a higher level of precision. Fifth, there were no hypercapnic patients in our study, and furthermore, median pH prior to extubation was 7.50, and alkalosis may alter respiratory drive. However, recent large-scale clinical trials focusing on weaning have shown similar values of pH and pCO_2 at time of extubation [11, 33, 34]. The beneficial effects of NIV are more pronounced in hypercapnic patients [11], and the fact that we included patients with alkalemia further reinforces the beneficial effects of NIV. Sixth, high PaO_2/FiO_2 ratio and low FiO_2 and PEEP levels at the time of extubation could be interpreted as late extubation. However, blood gases and ventilator settings of ready-to-extubate patients included in recent large randomized trials are comparable to ours [12, 33], even in a recent study focusing on aggressive strategy for early extubation [35]. Seventh, there was no washout period between the different noninvasive techniques, which could have led to a carry-over effect. However, the results remained significant within each treatment sequence group. Lastly, the physiological nature of the study, and the small sample size is an obvious limitation and results, especially secondary and exploratory outcomes, should be interpreted with caution.

Conclusions

In patients at high risk for extubation failure, prophylactic NIV decreased inspiratory efforts and increased tidal volumes, with stable dynamic compliance and potential re-aeration of lung regions, as compared to HFNO and standard oxygen. Our results provide insight of the clinical effects of NIV in the post-extubation settings.

Abbreviations

ΔP_{es}	Esophageal pressure swings
ΔP_{lung}	Transpulmonary pressure swings
CoV	Center of ventilation
EELI	End-expiratory lung impedance
EIT	Electrical impedance tomography
GI	Global inhomogeneity index
HFNO	High-flow nasal oxygen
ICUs	Intensive care units
NIV	Non invasive ventilation
PEEP	Positive end-expiratory pressure
ROI	Region of interest
spO_2	Peripheral oxygen saturation
$sPTP_{es}$	Esophageal simplified pressure–time-product
Vt	Tidal volume

Supplementary Information

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Supplementary materials 1.

Supplementary materials 2.

Supplementary materials 3.

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Not applicable.

Author contributions

Authors contributions: FA, RC, AWT designed the study; FA, APL, CB, RC, AWT included the patients, FA, RC, AWT wrote the manuscript, ST, EE, LR contributed to the exploratory outcomes' calculation, SLP, AB, JPF,ST, EE, LR reviewed the manuscript.

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee (Comité de Protection des Personnes, CPP Est III) with registration number 2017-A02838-45. In keeping with our national regulation, consent from patients or agreement from their surrogate was obtained orally with a written record maintained by the researcher. The study protocol was retrospectively recorded at clinicaltrials.gov (ID: NCT04036175) on the 17th of June, 2019.

Competing interests

JPF receveid grants from the French Ministry of Health; personal fees for lectures, travel expense coverage to attend scientific meetings, grant for randomized clinical trial from Fisher and Paykel Healthcare; personal fees as member of a scientific board and travel expense coverage to attend scientific meetings from SOS Oxygène outside this work. RC received personal fees from Fisher & Paykel Healthcare and Löwenstein, reimbursement for travel expenses from Fisher & Paykel Healthcare, stakeholder of Mayan pharma AT received personal fees for lectures and travel expanse coverage to attend scientific meetings from Fisher&Paykel. FA, SLP, AB, APL, CB, ST, EE, LR declare no competing interests. RC received personal fees from Fisher & Paykel Healthcare and Löwenstein, reimbursement for travel expenses from Fisher & Paykel Healthcare, stakeholder of Mayan pharma. AT received personal fees for lectures and travel expanse coverage to attend scientific meetings from Fisher&Paykel. FA, SLP, AB, APL, CB, EE, LR, ST declare no competing interests.

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