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Predictive performance of bedside physiological parameters for the failure of prophylactic non-invasive ventilation after extubation

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Abstract

Background Extubation failure is associated with increased mortality. Whether bedside physiological variables can identify patients at risk of reintubation during prophylactic NIV after extubation is unknown.

Methods In this post hoc analysis of a multicenter physiological study, 60 hypoxemic adults at high risk of extubation failure underwent two 1-hour NIV sessions after planned extubation, with oronasal and full-face masks in randomized crossover order. We assessed the magnitude of airway occlusion pressure (Pocc), the esophageal pressure swing (ΔPes), SpO_2/FiO_2, respiratory rate, tidal volume, dynamic lung elastance (EL,dyn), ROX index [(SpO_2/FiO_2)/respiratory rate] and the pressure-oxygenation index (POX, SpO_2/FiO_2 divided by Pocc). Prophylactic NIV failure was reintubation for respiratory failure within 7 days. Discrimination was assessed by ROC analysis.

Results Fourteen patients (23%) experienced NIV failure. Pocc yielded areas under the curve (AUCs) of 0.83 (95% CI, 0.71–0.95) with the oronasal mask and 0.83 (95% CI, 0.72–0.95) with the full-face mask, showing greater discriminative performance than tidal volume (AUCs, 0.55 and 0.53), respiratory rate (0.54 and 0.38), SpO_2/FiO_2 (0.51 and 0.50), and the ROX index (0.54 and 0.38; all $p < 0.05$). By contrast, the discriminative performance of Pocc did not differ from that of EL,dyn (AUCs, 0.72 and 0.73; $p = 0.08$ and 0.11), POX (AUCs, 0.82 and 0.81; $p = 0.68$ and 0.29), or |ΔPes| (AUCs, 0.83 and 0.82; $p = 1.00$ and 0.64).

Conclusions During prophylactic NIV, Pocc discriminated NIV failure better than conventional bedside variables, with no detectable difference from directly measured inspiratory effort. External validation is required.

Keywords Non-invasive ventilation, Inspiratory effort, Airway occlusion pressure

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Background

In patients at high risk of reintubation, current guidelines suggest implementing prophylactic non-invasive ventilation (NIV) to enhance weaning success [1–3]. Compared to other strategies, NIV improves oxygenation and unloads the respiratory muscles, thereby reducing patient's inspiratory effort [4]. However, continuing NIV despite worsening respiratory failure may delay reintubation, which detrimentally impacts outcomes [5]. This underscores the need for early recognition of treatment failure.

At the bedside, the early response to NIV is routinely assessed using oxygenation, respiratory rate, and tidal volume [6]. The early changes in esophageal pressure swing, a more direct measure of inspiratory effort, have also been shown to discriminate NIV outcome [7]. Although these variables are indirect markers of treatment response, their discriminative performance has been evaluated only in patients with de novo acute hypoxemic respiratory failure [8]. Whether these indices provide similar prognostic information during prophylactic NIV after extubation remains uncertain. Importantly, the pathophysiology of post-extubation respiratory failure may significantly differ from other clinical scenarios [9, 10].

We recently demonstrated that end-expiratory occlusions to measure the magnitude of airway occlusion pressure (Pocc), a non-invasive bedside estimate of inspiratory effort, are feasible during facemask NIV [11]. In this post hoc analysis, we aimed to determine which physiological parameter measured during the first hour of each prophylactic NIV session, including noninvasive estimates of inspiratory effort and lung mechanics, best discriminated treatment failure.

Methods

Study design

This is a post hoc analysis of a multicenter physiological study conducted in five general intensive care units in Italy between November 2023 and September 2025 designed to establish the feasibility of airway occlusion maneuvers during NIV [11] (approved by the Ethics Committee of Bari University Hospital, approval No. 7748-0049191; ClinicalTrials.gov NCT06344234). The discriminative performance of Pocc and its comparative performance against conventional bedside indices were not previously investigated and constitute the object of this analysis. Written informed consent was obtained from all enrolled patients.

Study population

Adult patients who had received invasive mechanical ventilation for at least 48 hours and were considered ready for planned extubation after successfully completing a spontaneous breathing trial (SBT) were screened for inclusion. Eligible patients were hypoxemic and non-hypercapnic, defined by PaO_2/FiO_2 <300 mmHg and $PaCO_2$ ≤45 mmHg, and had at least one established risk factor for extubation failure. Exclusion criteria included tracheostomy, neuromuscular disease, pregnancy, acute exacerbation of chronic respiratory disease, refusal of consent, and air leak > 30% during NIV before study initiation.

Study protocol and measurements

After the clinical decision to extubate, patients were reventilated for 1 hour according to their pre-SBT ventilation setting [12]. After extubation, prophylactic NIV was immediately initiated using an ICU ventilator connected through a dual-limb circuit and heat-and-moisture exchanger. NIV was delivered by face mask in pressure support mode [11]. Initial settings included positive end-expiratory pressure (PEEP) of 5–7 cmH_2O and pressure support of 5 cmH_2O, subsequently titrated to achieve a tidal volume of 6–8 mL/kg predicted body weight [1]. FiO_2 was adjusted to maintain SpO_2 between 92 and 96% [1].

At study initiation, patients were randomized 1:1 to receive either oronasal or full-face NIV first, followed by the alternate interface, according to the parent study protocol [11]; sessions were separated by 1 hour of high-flow nasal oxygen. All physiological variables were assessed during the first hour of each NIV session. Three non-consecutive end-expiratory occlusions were performed to measure Pocc. Because Pocc is recorded as a negative deflection in airway pressure [13, 14], throughout the present analysis it was expressed and analyzed as its absolute magnitude (|Pocc|), so that higher values denote greater inspiratory effort. Tidal volume and respiratory rate were recorded from the ventilator display and averaged over the preceding 5-minute period of stable, nonoccluded breathing. Airway occlusion pressure at 100 ms (P0.1) was read directly from the ventilator display. Esophageal pressure was recorded in all patients through a dedicated catheter (Nutrivent, Sidam, Mirandola, Italy) positioned and calibrated before extubation [11]; the magnitude of the esophageal pressure swing of non-occluded breaths (|ΔPes|) was measured over the same 5-minute period. Dynamic lung elastance (EL,dyn) was calculated as the ratio of dynamic transpulmonary driving pressure (pressure support + K × |Pocc|, where K = 0.71 for the oronasal mask and 0.80 for the full-face mask) to expiratory tidal volume normalized to predicted body weight [11]. The respiratory rate–oxygenation (ROX) index was calculated as the ratio of SpO_2/FiO_2 to respiratory rate [15, 16]. For the purposes of this post hoc analysis, we introduced the pressure–oxygenation index (POX), calculated as the ratio of SpO_2/FiO_2 to |Pocc|.

POX was not prespecified in the parent protocol or trial registry. Its directionality was defined on physiological grounds before examining its association with reintubation, with lower values indicating a less favorable balance between oxygenation and inspiratory effort.

After completion of the study sessions, patients continued prophylactic NIV using the interface they found most comfortable. NIV and HFNO were subsequently alternated in 12-hour periods for a total of 48 hours [3]. Thereafter, the choice and duration of respiratory support were left to the discretion of the treating clinicians. Study measurements, including Pocc and the results of the occlusion maneuvers, were not available to the attending physicians, who decided on reintubation in case of post-extubation respiratory distress independently of the study data.

Study objective

The primary objective was to compare the ability of bedside physiological indices measured during the first hour of prophylactic NIV to discriminate NIV failure, defined as reintubation for new-onset respiratory failure within 7 days after extubation.

Statistical analysis

Continuous variables are reported as median [interquartile range] and categorical variables as n (%). NIV success and NIV failure were compared using the Mann-Whitney U test or Fisher's exact test, as appropriate; physiological analyses were performed separately for each interface. Descriptive comparisons were exploratory and unadjusted. ROC analysis assessed the discrimination for NIV failure. AUCs with 95% confidence intervals were estimated and compared using DeLong's test. *p* values from pairwise AUC comparisons were adjusted using the Holm method. Cutoffs were selected using the Youden index, and diagnostic performance was reported with exact binomial 95% confidence intervals. The relationship between |Pocc| and the time from extubation to reintubation was assessed in the patients who required reintubation using the Spearman rank correlation coefficient. Tests were two-sided, with $p < 0.05$ considered significant.

Results

NIV failure occurred in 14 of the 60 patients included in the analysis (23.3%) at a median of 70 [39–122] hours after extubation. Clinical characteristics of the success and failure groups are reported in Table 1, and the physiological variables measured during prophylactic NIV in Table 2.

Compared with patients with NIV success, those with NIV failure had higher |Pocc| (oronasal: 16 [12–18] vs 8 [6–11] cm H_2O; full-face: 15 [12–18] vs 8 [6–11] cm

Table 1 Clinical characteristics and physiological variables at the end of the spontaneous breathing trial according to NIV outcome

Clinical characteristics	Overall (n=60)	NIV success (n=46)	NIV failure (n=14)
Age, years	64 [57-72]	64 [57-72]	64 [58-71]
Male, n (%)	43 (72)	34 (74)	9 (64)
Body mass index, kg/m^2	27 [26-29]	27 [25-29]	28 [26-29]
APACHE II at ICU admission	17 [13-20]	16 [13-20]	18 [17-20]
APACHE II on the day of extubation	12 [9-16]	11 [9-16]	13 [10-16]
Duration of mechanical ventilation before extubation, days	5 [4-6]	5 [4-6]	4 [4-6]
Physiological variables at the end of SBT			
PEEP, cmH_2O	0 [0-0]	0 [0-0]	0 [0-0]
Pressure support, cmH_2O	7 [7-7]	7 [7-7]	7 [7-7]
V_T, mL/kg PBW	8.1 [7.3-8.5]	8.2 [7.5-8.6]	7.5 [7.1-8.2]
FiO_2	0.35 [0.30-0.40]	0.35 [0.30-0.40]	0.35 [0.30-0.40]
Respiratory rate, breaths/min	21 [18-24]	21 [19-23]	23 [20-24]
RSBI	49 [42-61]	49 [42-58]	53 [42-61]
P0.1, cmH_2O	2.7 [2.4-3.0]	2.7 [2.5-3.1]	2.9 [2.5-3.1]
|Pocc|, cmH_2O	12 [9-14]	10 [9-13.8]	14 [12-18]
Arterial pH	7.43 [7.40-7.44]	7.42 [7.40-7.44]	7.44 [7.43-7.45]
PaO_2, mmHg	101 [98-105]	101 [98-105]	94 [91-104]
$PaCO_2$, mmHg	42 [41-44]	43 [41-44]	41 [40.2-43.8]
Systolic arterial pressure, mmHg	127 [118-134]	127 [120-134]	125 [111-130]
Diastolic arterial pressure, mmHg	77 [74-83]	78 [74.2-83]	75 [73-79]
Heart rate, beats/min	78.5 [76-83]	78 [77-82]	78.5 [75-83]

Data are median [interquartile range] or n (%). NIV, noninvasive ventilation; SBT, spontaneous breathing trial; APACHE II, Acute Physiology and Chronic Health Evaluation II; PBW, predicted body weight; PEEP, positive end-expiratory pressure; FiO_2, fraction of inspired oxygen; RSBI, rapid shallow breathing index; PaO_2, arterial oxygen partial pressure; $PaCO_2$, arterial carbon dioxide partial pressure; P0.1, airway occlusion pressure at 100 ms; |Pocc|, airway occlusion pressure, reported as an absolute magnitude. All variables in the second section were recorded at the end of the spontaneous breathing trial, during invasive ventilation and before extubation

Table 2 Physiological characteristics during prophylactic NIV according to NIV outcome

Variable	Overall (n=60)		NIV success (n=46)		NIV failure (n=14)	
	Oronasal NIV	Full-face NIV	Oronasal NIV	Full-face NIV	Oronasal NIV	Full-face NIV
PaO_2/FiO_2, mmHg	212 [184-260]	223 [188-255]	208 [174-215]	187 [154-195]	213 [185-202]	195 [172-211]
SpO_2, %	96 [95-97]	96 [94-97]	96 [95-96]	96 [93-97]	96 [96-97]	97 [96-97]
SpO_2/FiO_2 ratio	241 [213-275]	241 [214-275]	242 [213-274]	242 [214-275]	228 [214-276]	228 [214-275]
Respiratory rate, breaths/min	15 [12-20]	15 [12-21]	15 [12-20]	15 [13-20]	16 [12-25]	13 [10-19]
V_T, mL/kg PBW	7.8 [7.1-9.5]	8.7 [8.1-9.4]	7.8 [6.9-9.5]	8.0 [7.3-9.4]	9.5 [7.9-10.2]	9.0 [8.4-11.5]
PEEP, cmH_2O	5 [5-6]	5 [5-6]	5 [5-6]	5 [5-6]	5 [5-6]	5 [5-6]
Pressure support, cmH_2O	6 [5-6]	5 [5-6]	6 [5-6]	5 [5-6]	5 [5-6]	6 [5-6]
P0.1, cmH_2O	2.1 [1.9-2.2]	2.6 [2.5-2.8]	2.1 [1.8-2.2]	2.6 [2.5-2.8]	2.2 [2.0-2.3] *	2.5 [2.4-2.6]
|Pocc|, cmH_2O	9 [7-14]	9 [7-14]	8 [6-11]	8 [6-11]	16 [12-18] *	15 [12-18] *
|ΔPes|, cmH_2O	6.4 [4.4-10.1]	6.8 [5.0-11.7]	5.7 [4.0-8.5]	5.8 [4.3-9.4]	11.4 [8.5-13.9] *	12.8 [9.4-13.4] *
ROX index	15 [12-20]	16 [11-21]	15 [13-20]	15 [11-20]	14 [9-22]	19 [14-22]
POX index	27 [17-35]	25 [16-36]	30 [20-41]	28 [19-39]	16 [14-18]*	15 [14-18]*

Data are median [interquartile range]. All variables were measured during the first hour of each NIV session. *p<0.05 vs NIV success within the same interface. ROX index = [(SpO_2/FiO_2)/respiratory rate]; POX index = [(SpO_2/FiO_2)/|Pocc|]. NIV, noninvasive ventilation; PBW, predicted body weight; PEEP, positive end-expiratory pressure; FiO_2, fraction of inspired oxygen; PaO_2, arterial oxygen partial pressure; SpO_2, peripheral oxygen saturation; V_T, tidal volume; P0.1, airway occlusion pressure at 100 ms; |Pocc|, magnitude of airway occlusion pressure; |ΔPes|, magnitude of the esophageal pressure swing of non-occluded breaths

H_2O), higher |ΔPes| (oronasal: 11.4 [8.5–13.9] vs 5.7 [4.0–8.5] cm H_2O; full-face: 12.8 [9.4–13.4] vs 5.8 [4.3–9.4] cm H_2O) and lower POX (oronasal: 16 [14–18] vs 30 [20–41]; full-face: 15 [14–18] vs 28 [19–39]; all $p < 0.001$). P0.1 was slightly higher in patients who failed NIV during oronasal ventilation (2.2 [2.0–2.3] vs 2.1 [1.8–2.2] cm H_2O, $p = 0.03$), but did not differ during full-face ventilation (2.5 [2.4–2.6] vs 2.6 [2.5–2.8] cm H_2O, $p = 0.35$). No differences between groups were observed in tidal volume ($p = 0.55$ and $p = 0.76$), SpO_2/FiO_2 ($p = 0.96$ and $p = 0.97$), respiratory rate ($p = 0.69$ and $p = 0.19$), or ROX index ($p = 0.63$ and $p = 0.17$) during oronasal and full-face NIV, respectively.

The discriminative performance of each bedside physiological variable for NIV failure is summarized in Table 3 and Fig. 1. During both oronasal and full-face NIV, |Pocc| yielded the highest AUC (oronasal: 0.83 [95% CI, 0.71–0.95]; full-face: 0.83 [95% CI, 0.72–0.95]), showing greater discriminative performance than tidal volume ($p = 0.03$ and $p = 0.04$), respiratory rate ($p = 0.04$ and $p < 0.01$), SpO_2/FiO_2 ($p = 0.02$ and $p < 0.01$), and the ROX index ($p = 0.04$ and $p < 0.01$) during oronasal and full-face NIV, respectively. The discriminatory capacity of |Pocc| did not differ significantly from that of POX (oronasal: 0.82 [95% CI, 0.69–0.94], $p = 0.68$; full-face: 0.81 [95% CI, 0.68–0.93], $p = 0.29$), EL,dyn (oronasal: 0.72 [95% CI, 0.57–0.87], $p = 0.08$; full-face: 0.73 [95% CI, 0.57–0.90], $p = 0.11$), and |ΔPes| (oronasal: 0.83 [95% CI, 0.70–0.95], $p = 1.00$; full-face: 0.82 [95% CI, 0.70–0.95], $p = 0.64$). Conversely, P0.1 discriminated NIV failure only modestly during oronasal NIV (0.70 [95% CI, 0.54–0.86], $p = 0.17$) and did not discriminate during full-face NIV (0.40 [95% CI, 0.20–0.60], $p < 0.01$).

Across the failure group, one patient required reintubation within the first day, 4 patients between day 1 and day 2, and 9 patients between day 2 and day 7. No association was found between |Pocc| measured during the first hour of NIV and the time from extubation to reintubation (oronasal: $r = -0.32$, $p = 0.27$; full-face: $r = -0.05$, $p = 0.86$) (Fig. 2).

Discussion

In this post hoc analysis of high-risk patients receiving prophylactic NIV after planned extubation [11], inspiratory effort quantified by the magnitude of airway occlusion pressure during the initial NIV sessions provided the greatest discrimination for treatment failure. By contrast, oxygenation, respiratory rate, tidal volume, and the ROX index showed limited discrimination.

In clinical practice, NIV is used in selected patients with de novo acute hypoxemic respiratory failure and as prophylactic support after extubation in patients at high risk of reintubation [1–3]. In both settings, the early recognition of treatment failure is essential for patient-centered outcomes [5, 17]. During assisted spontaneous breathing, vigorous inspiratory effort may increase dynamic transpulmonary pressure and contribute to patient self-inflicted lung injury [18]. Transpulmonary pressure reflects the combined contribution of ventilator-delivered pressure support and the pleural pressure swing generated by the patient's inspiratory muscles [20]. Although esophageal manometry is the reference method for estimating inspiratory effort, it is infrequently used in nonintubated patients [14]. Accordingly, bedside monitoring of NIV should integrate tidal volume (when reliably measured), oxygenation, and composite indices of respiratory drive and inspiratory effort, such as the ROX index, to identify patients who may require escalation of respiratory support [6, 8]. In our cohort, however, none of these physiological parameters discriminated

Table 3 Diagnostic performance of respiratory variables and composite indices measured during the first hour of NIV for predicting NIV failure

Variable	Cutoff	AUC (95% CI)	P vs |Pocc|*	Youden index	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
ORONASAL MASK (1st hour)								
V_T, mL/kg PBW	≥ 7.7	0.55 (0.40-0.71)	0.03	0.26	79 (49-95)	48 (33-63)	31 (17-49)	88 (69-97)
RR, breaths/min	≥ 21.1	0.54 (0.32-0.75)	0.04	0.25	43 (18-71)	83 (69-92)	43 (18-71)	83 (69-92)
SpO_2/FiO_2	≤ 239	0.51 (0.32-0.69)	0.02	0.27	64 (35-87)	63 (48-77)	35 (17-56)	85 (69-95)
PaO_2/FiO_2, mmHg	≤ 208	0.47 (0.29-0.65)	<0.01	0.17	50 (23-77)	67 (52-80)	32 (14-55)	82 (66-92)
P0.1, cmH_2O	≥ 2.3	0.70 (0.54-0.86)	0.17	0.35	50 (27-73)	85 (72-92)	50 (27-73)	85 (72-92)
|Pocc|, cmH_2O	≥ 12.0	0.83 (0.71-0.95)	Reference	0.59	79 (49-95)	80 (66-91)	55 (32-77)	92 (80-98)
|ΔPes|, cmH_2O	≥ 10.0	0.83 (0.70-0.95)	1.00	0.58	71 (45-88)	87 (74-94)	62 (39-82)	91 (79-96)
EL,dyn, cmH_2O/mL/kg PBW	≥ 1.5	0.72 (0.57-0.87)	0.08	0.45	93 (66-100)	52 (37-67)	37 (21-55)	96 (80-100)
POX index	≤ 18.1	0.82 (0.69-0.94)	0.68	0.59	79 (49-95)	80 (66-91)	55 (32-77)	92 (80-98)
ROX index	≤ 8.7	0.54 (0.33-0.76)	0.04	0.24	29 (8-58)	96 (85-99)	67 (22-96)	81 (69-91)
FULL-FACE MASK (1st hour)								
V_T, mL/kg PBW	≥ 10.5	0.53 (0.35-0.71)	0.04	0.16	36 (13-65)	80 (66-91)	36 (13-65)	80 (66-91)
RR, breaths/min	≥ 28.1	0.38 (0.19-0.58)	<0.01	0.07	7 (0-34)	100 (92-100)	100 (2-100)	78 (65-88)
SpO_2/FiO_2	≤ 217	0.50 (0.32-0.67)	<0.01	0.20	50 (23-77)	70 (54-82)	33 (15-57)	82 (66-92)
PaO_2/FiO_2, mmHg	≤ 240	0.41 (0.25-0.56)	<0.01	0.08	71 (42-92)	37 (23-52)	26 (13-42)	81 (58-95)
P0.1, cmH_2O	≥ 2.4	0.40 (0.20-0.60)	<0.01	0.07	90 (60-98)	17 (9-31)	19 (10-33)	89 (56-98)
|Pocc|, cmH_2O	≥ 13.5	0.83 (0.72-0.95)	Reference	0.61	79 (49-95)	83 (69-92)	58 (33-80)	93 (80-98)
|ΔPes|, cmH_2O	≥ 11.7	0.82 (0.70-0.95)	0.64	0.58	71 (45-88)	87 (74-94)	62 (39-82)	91 (79-96)
EL,dyn, cmH_2O/mL/kg PBW	≥ 1.9	0.73 (0.57-0.90)	0.11	0.44	57 (29-82)	87 (74-95)	57 (29-82)	87 (74-95)
POX index	≤ 18.0	0.81 (0.68-0.93)	0.29	0.57	79 (49-95)	78 (64-89)	52 (30-74)	92 (79-98)
ROX index	≤ 10.5	0.38 (0.19-0.56)	<0.01	0.02	21 (5-51)	80 (66-91)	25 (5-57)	77 (63-88)

*Paired two-sided DeLong tests compared the AUC of each variable with that of |Pocc|; P values were Holm-adjusted separately within each interface across the seven comparisons shown. Cutoffs were selected by maximizing the Youden index. Sensitivity, specificity, positive predictive value, and negative predictive value are reported with exact binomial 95% confidence intervals

ROX index = $[(SpO_2/FiO_2)/RR]$; POX index = $[(SpO_2/FiO_2)/|Pocc|]$; EL,dyn = [pressure support + K × |Pocc|]/(V_T/PBW), where K = 0.71 for the oronasal mask and 0.80 for the full-face mask. AUC, area under the receiver operating characteristic curve; CI, confidence interval; EL,dyn, dynamic lung elastance; FiO_2, fraction of inspired oxygen; NPV, negative predictive value; PBW, predicted body weight; |Pocc|, magnitude of airway occlusion pressure; PPV, positive predictive value; RR, respiratory rate; SpO_2, peripheral oxygen saturation; V_T, tidal volume.P0.1, airway occlusion pressure at 100 ms. |ΔPes|, magnitude of the esophageal pressure swing of non-occluded breaths

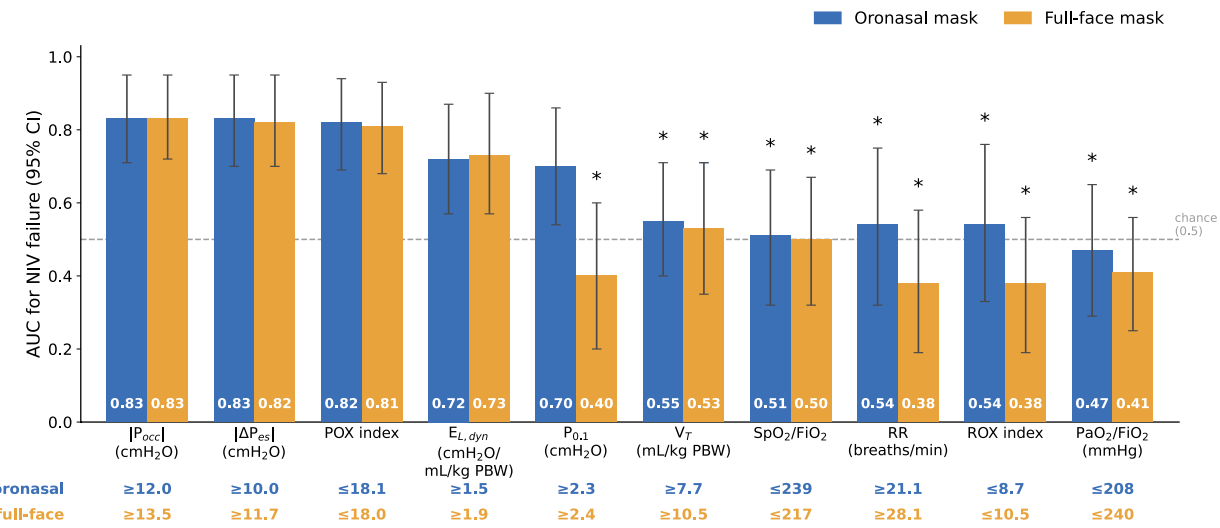

Fig. 1 Discriminative performance for NIV failure of the bedside physiological variables measured during the first hour of NIV, expressed as the area under the receiver operating characteristic curve with its 95% confidence interval, during oronasal (blue bars) and full-face (orange bars) NIV. Variables are ordered by decreasing area under the curve, and the best cut-off of each variable is reported below the corresponding bars. The dashed horizontal line indicates no discrimination (0.5). *$p < 0.05$ versus |pocc| at paired DeLong testing

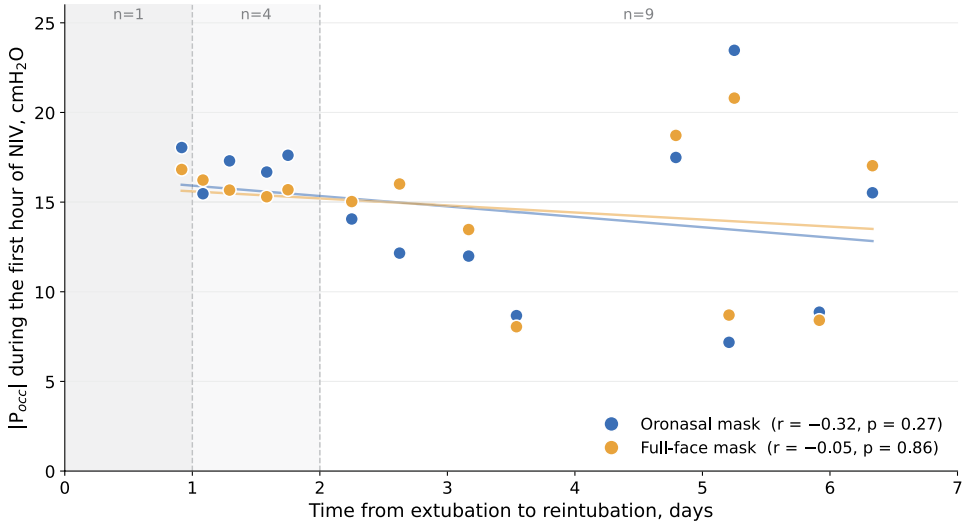

Fig. 2 Relationship between the magnitude of airway occlusion pressure (|pocc|) measured during the first hour of NIV and the time from extubation to reintubation in the 14 patients who required reintubation, during oronasal (blue circles) and full-face (orange circles) NIV. Each patient contributes one value per interface, plotted against the same time to reintubation. Solid lines represent the linear fit for each interface

treatment failure. Several factors may explain this finding. First, most evidence supporting physiological predictors of NIV failure derives from patients with de novo acute hypoxemic respiratory failure; therefore, hypoxemia, tachypnea, and high tidal volume are already manifest and may reflect disease severity [7, 16, 19]. By contrast, prophylactic NIV is initiated before overt postextubation respiratory failure develops in patients who have met extubation criteria and successfully completed an SBT. This prior physiological selection excludes patients with evident respiratory distress or a clearly abnormal breathing pattern, narrowing the range of conventional bedside variables at NIV initiation. Consequently, impending failure may initially manifest as a more subtle imbalance between respiratory load and muscle capacity, with increased inspiratory effort preceding detectable changes in oxygenation, respiratory rate, or tidal volume [21].

Beyond this population difference, each conventional variable has physiological limitations. High tidal volume has been associated with NIV failure in de novo acute hypoxemic respiratory failure [19]. However, during pressure support ventilation, tidal volume reflects a nonlinear interaction among respiratory drive, inspiratory effort, ventilator assistance, respiratory mechanics, leaks, and patient-ventilator interaction rather than effort alone [22]. Respiratory rate may also be uninformative

as respiratory drive can increase through greater inspiratory pressure generation without proportional tachypnea [23]. Also, the heterogeneous outcome effects of different SpO_2 targets indicate that oxygenation should not be interpreted independently of patient context [24]. In patients with de novo hypoxemic respiratory failure, Tonelli and colleagues showed that a reduction in esophageal pressure swing of less than 10 cmH_2O within the first 2 hours of NIV predicted treatment failure with an area under the curve of 0.97 [7]. In our cohort, ΔPes also discriminated NIV failure, although with a lower area under the curve of 0.83 and 0.82 for the oronasal and the full-face interface, respectively. This lower performance is expected, since we assessed absolute inspiratory effort at a single time point during the first hour of prophylactic NIV; moreover, our patients had met extubation criteria and had no established respiratory failure. Most importantly, we found no difference between Pocc and ΔPes in discriminating NIV failure, confirming that a brief end-expiratory occlusion closely reflects esophageal-pressure-derived inspiratory effort [25]. However, the clinical meaning of inspiratory effort appears to differ between the two settings. In de novo hypoxemic respiratory failure, the early change in esophageal pressure swing performed primarily as a positive marker of impending failure [7]. Conversely, our data show that Pocc behaved primarily as a negative predictor: values below the identified thresholds were associated with a lower risk of reintubation (negative predictive value 92 and 93% for the oronasal and the full-face interface), whereas an elevated Pocc did not reliably anticipate failure. This asymmetry may also explain the absence of an association between Pocc and the time to reintubation, suggesting that the mechanisms leading to failure of prophylactic NIV are heterogeneous and only partly related to the inspiratory effort generated immediately after extubation [9].

We recently demonstrated the feasibility and physiological validity of this approach during facemask NIV, including interface-specific conversion factors for estimating ΔPes, dynamic transpulmonary pressure and lung elastance by Pocc [11]. The incremental contribution of the present analysis is the evaluation of discrimination, cohort-derived cut-offs, sensitivity and specificity, and the head-to-head comparison of conventional bedside indices for predicting prophylactic NIV failure. We found that Pocc yielded the highest AUC with both interfaces and discriminated prophylactic NIV failure better than commonly used bedside indices. Interestingly, POX showed nearly identical discrimination, whereas SpO_2/FiO_2 alone was non-discriminative, indicating that its prognostic information was largely driven by inspiratory effort and that adding oxygenation provided no detectable incremental value over the simpler Pocc measurement in this cohort. Although predictors of NIV failure have previously been investigated, to our knowledge, no study has assessed the early prediction of support failure when applied immediately after extubation. These findings identify Pocc as a promising bedside tool for early risk stratification; however, a prospective validation is required before clinical implementation.

Our study has limitations. First, this post hoc analysis included 60 patients and only 14 NIV failures, producing wide confidence intervals and potentially optimistic data-derived thresholds. Second, the cohort comprised selected hypoxemic, nonhypercapnic patients receiving prophylactic facemask NIV, and patients with leaks > 30% were excluded, limiting generalizability. Third, the two interface-specific analyses were based on repeated measurements in the same 60 patients and on the same 14 events and therefore do not represent independent validation. Although randomized interface order balanced time-dependent effects and the 1-hour high-flow nasal oxygen interval limited carry-over, physiological changes during the first hours after extubation may have influenced the absolute measurements and increased within-patient variability. Finally, after the study sessions only the occurrence and timing of reintubation within 7 days were recorded: post-extubation respiratory failure, its causes, the use of rescue NIV and the ventilator settings preceding reintubation were not collected, and their potential influence on the outcome could not be assessed. Reintubation criteria were also not standardized across centers, being left to the attending physicians. However, the present work is a post hoc analysis of a physiological study that was not designed to characterize the mechanisms of post-extubation failure or capture the clinical events preceding reintubation.

Abbreviations

APACHE II	Acute Physiology and Chronic Health Evaluation II
AUC	Area under the receiver operating characteristic curve
CI	Confidence interval
EL,dyn	Dynamic lung elastance
FiO_2	Fraction of inspired oxygen
HFNO	High-flow nasal oxygen
ICU	Intensive care unit
NIV	Non-invasive ventilation
NPV	Negative predictive value
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
PBW	Predicted body weight
PEEP	Positive end-expiratory pressure
Pocc	Airway occlusion pressure
|Pocc|	Magnitude of airway occlusion pressure
POX	Pressure-oxygenation index
PPV	Positive predictive value
ROC	Receiver operating characteristic
ROX	Respiratory rate-oxygenation index
RR	Respiratory rate
SBT	Spontaneous breathing trial
SpO_2	Peripheral oxygen saturation
V_T	Tidal volume

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Author contributions
FM, DLG, and SG conceived and designed the study. FM performed the statistical analysis. FM and DLG drafted the manuscript. MB, TP, SMM, MA, and SG critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript and accept responsibility for the integrity of the work.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The present study is a post hoc analysis of a previously published multicenter trial, which received ethical approval at each participating center (coordinating center: Bari University Hospital, approval No. 7748-0049191) and was registered at ClinicalTrials.gov (NCT06344234). Written informed consent was obtained from all enrolled patients in accordance with the recommendations of the local ethics committees.

Consent for publication
Not applicable.

Competing interests
DLG has received reimbursement for travel expenses from Getinge, Dräger, and Hamilton, personal fees from Dräger, and research grants from Fisher & Paykel and GE. TP has received speaking fees from Getinge. MA has received payments for board participation from Maquet, Air Liquide, and Chiesi, and a research grant from GE. SG has received fees for lectures and board membership from Getinge Critical Care, Estor Critical Care, GE, and AOP Pharma. The remaining authors declare no competing interests.

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