7. Kim D, Park Y, Choi KH, Park TK, Lee JM, Cho YH, *et al.* Prognostic implication of RV coupling to pulmonary circulation for successful weaning from extracorporeal membrane oxygenation. *JACC Cardiovasc Imaging* 2021;14:1523–1531.
8. Petit M, Mekontso-Dessap A, Masi P, Legras A, Vignon P, Vieillard-Baron A. Evaluation of right ventricular function and driving pressure with blood gas analysis could better select patients eligible for VV ECMO in severe ARDS. *Crit Care* 2021;25:220.
9. Kon ZN, Bittle GJ, Pasrija C, Pham SM, Mazzeffi MA, Herr DL, *et al.* Venovenous versus venoarterial extracorporeal membrane oxygenation for adult patients with acute respiratory distress syndrome requiring precannulation hemodynamic support: a review of the ELSO registry. *Ann Thorac Surg* 2017;104:645–649.
10. Cavayas YA, Munshi L, Del Sorbo L, Fan E. The early change in Pa_{CO_2} after extracorporeal membrane oxygenation initiation is associated with neurological complications. *Am J Respir Crit Care Med* 2020;201:1525–1535.
11. Abbas AE, Franey LM, Marwick T, Maeder MT, Kaye DM, Vlahos AP, *et al.* Noninvasive assessment of pulmonary vascular resistance by Doppler echocardiography. *J Am Soc Echocardiogr* 2013;26:1170–1177.

Accuracy of Nasal Pressure Swing to Predict Failure of High-Flow Nasal Oxygen in Patients with Acute Hypoxemic Respiratory Failure

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To the Editor:

The risk of deterioration during acute hypoxemic respiratory failure (AHRF) treated by noninvasive respiratory support demands monitoring of the patient's inspiratory effort (1, 2) to avoid delay to mechanical ventilation (MV) (3–5). Despite the fact that respiratory rate (RR) and composite indices such as respiratory rate-oxygenation (ROX) (6) and heart rate, acidosis, consciousness, oxygenation, and respiratory rate (HACOR) (7) might recognize patients at major failure risk, these only indirectly account for the inspiratory effort. Esophageal manometry provides an accurate quantification of effort; however, it is unpractical in real life (8, 9). The nasal pressure swing (ΔP_{nose}) during tidal breathing is highly correlated with the esophageal pressure swing (ΔP_{es}) in patients with AHRF (10). The aim of this *post hoc* analysis of a prospective study (www.clinicaltrials.gov, NCT 03826797) was to assess the accuracy of ΔP_{nose} in predicting early (24-h) failure of high-flow nasal oxygen (HFNO) to treat AHRF.

Consecutive patients with AHRF who were admitted into the respiratory intensive care unit (RICU) of the University Hospital of Modena in Modena, Italy, between January 1, 2021 and June 30, 2022 and started on HFNO were eligible for enrollment (Optiflow and AIRVO, Fisher and Paykel Healthcare Ltd.). Verbal or written informed consent was obtained as appropriate. An age >18 years, peripheral Sp_{O_2} <90% under conventional oxygen supply by Venturi mask with an inspiratory fraction of 0.5 and consent to receive nasal manometry were criteria for inclusion. The need for immediate intubation, use of noninvasive ventilation (NIV) or MV within the same admission, concomitant hypercapnia, cardiogenic pulmonary edema, chronic obstructive pulmonary disease, chest wall neuromuscular diseases, parenchymal interstitial abnormalities, nasal tract anatomical alterations, and long-term oxygen regimen were criteria for exclusion.

Patients' characteristics were collected on admission into the RICU when all patients started HFNO (Time 1 [T1]). ΔP_{nose} was measured by attending staff who were blinded to the purpose of the study. In 69 patients (68%) out of the total, ΔP_{es} recording was simultaneously taken. At T1 and 2 hours after HFNO initiation (Time 2 [T2]), ΔP_{nose}, ΔP_{es}, arterial blood gases, Pa_{O_2}/Fi_{O_2} ratio, RR, HACOR, and ROX were assessed.

The decision to escalate from HFNO either to helmet/facemask NIV or MV (i.e., failure) was taken by the attending physician (8), who was blinded to the results for ΔP_{nose}.

The primary outcome was the accuracy of ΔP_{nose} in predicting failure of HFNO at T2. The comparison between ΔP_{nose} and the ROX index in predicting failure and the correlation between ΔP_{nose} and ΔP_{es} at different time points were also considered.

Receiver operating characteristic curves and the area under the curve (AUC) were calculated to test accuracy. The optimal cutoff of ΔP_{nose} was chosen according to Youden's J statistic to maximize the sum of sensitivity and specificity.

The comparison of accuracy between ΔP_{nose} and the ROX index tailed was assessed using Delong's test. Correlation analysis using Pearson's *r* or Spearman's ρ coefficient, as appropriate, was conducted at different time points.

Post hoc, we tested the accuracy and the optimal cutoff of ΔP_{nose} in predicting escalation to MV and the correlations between ΔP_{nose}, and ΔP_{es}, and the ROX index. A two-sided test

Table 1. Characteristics of the Study Population and Measurements (Baseline and 2 h after High-flow Nasal Oxygen Initiation) Grouped by Outcome (Failure or Success)

Variable	Overall (*N* = 102; 100%)	Outcome		*P* Value
		Failure (*n* = 35; 34.3%)	Success (*n* = 67; 65.7%)	
Age, yr, median (IQR)	69 (56–75)	67 (56–78)	70 (56–75)	0.6
Male, *n* (%)	71 (67)	26 (74.3)	45 (67.2)	0.5
BMI, kg/m^2, median (IQR)	23 (19–27)	24 (21–27)	22.5 (18–26)	0.3
Diagnosis and test				
COVID-19, *n* (%)	91 (89.2)	33 (94.3)	58 (86.6)	0.3
Non–COVID-19, *n* (%)	11 (10.7)	2 (5.7)	9 (13.4)	0.3
GCS, score, median (IQR)	15 (15–15)	15 (15–15)	15 (15–15)	0.9
APACHE II score, median (IQR)	11 (7–15)	11 (7–14)	11 (9–15)	0.8
SAPS II score, median (IQR)	28 (23–33)	29 (24–33)	28 (23–34)	0.9
SOFA score, median (IQR)	3 (3–3)	3 (3–3)	3 (3–3)	0.6
Baseline (Time 1)				
HACOR score, median (IQR)	4 (3–5)	5 (4–6)	4 (3–5)	0.1
ROX index score, median (IQR)	6.9 (5.8–8.6)	6.6 (5.5–7.7)	7.4 (6.1–9.1)	0.1
Pa_{O_2}/Fi_{O_2}, mm Hg, median (IQR)	133 (115–152)	125 (102–141)	140 (123–160)	0.1
Fi_{O_2}, %, median (IQR)	50 (45–60)	55 (50–60)	50 (40–60)	0.1
Pa_{O_2}, mm Hg, median (IQR)	66 (60.4–72)	64 (62.5–71.4)	66 (60–72)	0.7
Pa_{CO_2}, mm Hg, median (IQR)	32.7 (31.2–34)	32 (29.9–34.1)	33 (31.2–34.5)	0.1
HR, bpm, median (IQR)	93 (78–102)	95 (76–102)	93 (72–98)	0.6
RR, bpm, median (IQR)	26 (24–28)	26 (25–30)	26 (24–28)	0.1
ΔP_{es}, cm H_2O, median (IQR)	13.5 (11–16.3)	15.2 (12.6–18)	12.2 (10–15.8)	0.04
ΔP_{nose}, cm H_2O, median (IQR)	6 (4.6–8)	6.8 (5.6–8.2)	5.6 (4.2–7)	0.03
2 h after HFNO (Time 2)				
HACOR score, median (IQR)	4 (3–5)	5 (4–5)	4 (3–4)	<0.0001
ROX index score, median (IQR)	7.9 (5.9–10.9)	5.6 (5.2–6)	9.2 (8–11.6)	<0.0001
Pa_{O_2}/Fi_{O_2}, mm Hg, median (IQR)	131 (112–152)	111 (101–127)	144 (130–175)	<0.0001
Fi_{O_2}, %, median (IQR)	50 (45–60)	65 (60–70)	45 (35–55)	<0.0001
Pa_{O_2}, mm Hg, median (IQR)	67.4 (62.2–72.6)	72 (64–77)	67 (62–70)	0.01
Pa_{CO_2}, mm Hg, median (IQR)	34.5 (32.4–36.7)	32 (30–34)	36.1 (33.7–37)	<0.0001
HR, bpm, median (IQR)	90 (78–100)	96 (78–102)	88 (80–100)	0.7
RR, bpm, median (IQR)	24 (21–26)	26 (25–27)	21 (20–24)	<0.0001
ΔP_{es}, cm H_2O, median (IQR)	8 (6–14)	16 (14–17)	6.5 (5–8)	0.01
ΔP_{nose}, cm H_2O, median (IQR)	3.2 (2.7–6)	7 (6–8)	3 (2.1–3.2)	<0.0001

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; BMI = body mass index; bpm = beats per minute; COVID-19 = coronavirus disease; GCS = Glasgow Coma Scale; HACOR = heart rate, acidosis, consciousness, oxygenation, and respiratory rate; HFNO = high-flow nasal oxygen; HR = heart rate; IQR = interquartile range; ROX = respiratory rate-oxygenation; RR = respiratory rate; SAPS II = Simplified Acute Physiology Score II; SOFA = Sequential Organ Failure Assessment; ΔP_{es} = esophageal pressure swing; ΔP_{nose} = nasal pressure swing.
Data are presented as *n* (%) for dichotomous values or median (IQR) for continuous values. Continuous variables were compared using the Student's *t* test or Mann-Whitney *U* test, as appropriate. Differences in categorical variables were assessed with the chi-square test or Fisher exact test, as appropriate.

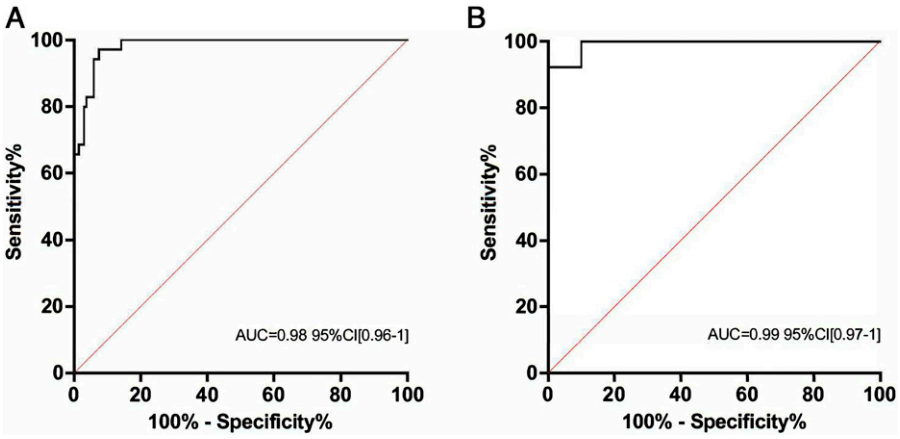

Figure 1. Receiver operating characteristic analyses for high-flow nasal oxygen (HFNO) early failure (24 h). ΔP_{nose} 2 hours after HFNO initiation in the whole population (*A*) and in those patients without esophageal pressure assessment (*B*). AUC = area under the curve; CI = confidence interval; ΔP_{nose} = nasal pressure swings.

$P < 0.05$ was considered statistically significant (SPSS package, version 25.0; IBM Corp.).

Of 210 eligible patients, 102 were enrolled in accordance with the exclusion criteria. Of these, 91 (89.2%) were diagnosed with coronavirus disease (COVID-19)–related pneumonia, and 43 had been included in a previous publication (10). Of the enrolled patients, 35 (34.3%) failed HFNO within 24 hours (between 6 and 12 h).

Table 1 shows the patients' characteristics. At any time, those who failed showed higher ΔP_{nose} and ΔP_{es} compared with those who succeeded; at T2, group differences were observed in HACOR, ROX, Pa_{O_2}/Fi_{O_2} ratio, Pa_{CO_2}, RR, and breathing effort.

ΔP_{nose} at T2 accuracy of prediction was high (Figure 1A), being 5.1 cm H_2O, the cutoff value of risk. At T2, no difference was found when comparing the AUC of ΔP_{nose} with ROX (AUC = 0.98; 95% confidence interval [CI], 0.96–1, $P < 0.0001$), whose threshold value of risk for failure was 6.52. Among patients without esophageal manometry ($n = 69$), ΔP_{nose} still showed a high accuracy of prediction (Figure 1B).

Only three of those patients who failed reported ROX >6.52, whereas all three showed ΔP_{nose} >5.1 cm H_2O (6.7 cm H_2O, 7.5 cm H_2O, and 6.5 cm H_2O). Two patients with ΔP_{nose} <5.1 cm H_2O failed, whereas the reported ROX was <6.52 (4.21 and 6.03, respectively). ΔP_{nose} and ΔP_{es} showed significantly high correlation ($R^2 = 0.91$, $P < 0.0001$) that persisted at any time point (average $\Delta P_{es}/\Delta P_{nos}$ ratio = 2.21, SD = 0.32). Moreover, an inverse correlation was found between ROX and both ΔP_{nose} ($R^2 = 0.34$, $P < 0.0001$) and ΔP_{es} ($R^2 = 0.35$, $P < 0.0001$). ΔP_{nose} accuracy prediction to MV ($n = 12$) was high (0.917; 95% CI, 0.86–0.98, $P < 0.0001$), being 6 cm H_2O, the risk threshold value.

In a real-life cohort of patients with AHRF undergoing HFNO, ΔP_{nose} showed excellent accuracy in predicting early failure, similar to that displayed by ROX. Given that the decision to upgrade to NIV or MV was based on clinical variables, the high accuracy of ROX in predicting failure of HFNO is not surprising. The similar accuracy of ΔP_{nose} (the only measurement to which the staff and attending physician remained blinded in our clinical decision) strengthened the association with outcome, avoiding incorporation bias.

The inverse correlation between the ROX index and both ΔP_{es} and ΔP_{nose} was weak, although the significant level of correlation between ΔP_{nos} and ROX might suggest that they are only partially measuring the same phenomenon. Although ROX can be easily measured without additional equipment, we feel that the integration of ΔP_{nose} as a physiological variable might provide more thorough information in patients with AHRF at risk of deterioration, thus assisting clinicians in their decision-making process. In this line, tidal ΔP_{nose} shows strong correlation with ΔP_{es}, thus making it a valid surrogate marker of the patient's inspiratory effort during spontaneous breathing (10).

Given the limits of the study (monocentric and explorative design, unbalanced population with the majority of patients with COVID-19, *post hoc* analysis, lack of a validation cohort, and issues related to ΔP_{es} assessment), the present findings should be interpreted with caution. Moreover, the role of airflow in influencing ΔP_{nose} during spontaneous breathing needs further investigation. Notwithstanding, should data be confirmed in multicentric and empowered studies, these might pave the way for a novel, minimally invasive, and practical tool that allows real-time monitoring of the breathing effort of patients with AHRF. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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References

1. Pelosi P, Tonelli R, Torregiani C, Baratella E, Confalonieri M, Battaglini D, *et al.* Different methods to improve the monitoring of noninvasive respiratory support of patients with severe pneumonia/ARDS due to COVID-19: an update. *J Clin Med* 2022;11:1704.
2. Grieco DL, Menga LS, Eleuteri D, Antonelli M. Patient self-inflicted lung injury: implications for acute hypoxemic respiratory failure and ARDS patients on non-invasive support. *Minerva Anestesiol* 2019;85:1014–1023.
3. Kang BJ, Koh Y, Lim CM, Huh JW, Baek S, Han M, *et al.* Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. *Intensive Care Med* 2015;41:623–632.
4. Ball L, Robba C, Herrmann J, Gerard SE, Xin Y, Pigati M, *et al.*; GECOVID Group. Early versus late intubation in COVID-19 patients failing helmet CPAP: a quantitative computed tomography study. *Respir Physiol Neurobiol* 2022;301:103889.
5. Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, *et al.*; LUNG SAFE Investigators; ESICM Trials Group. Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. *Am J Respir Crit Care Med* 2017;195:67–77.
6. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, *et al.* An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. *Am J Respir Crit Care Med* 2019;199:1368–1376.
7. Duan J, Han X, Bai L, Zhou L, Huang S. Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxemic patients. *Intensive Care Med* 2017;43:192–199.
8. Tonelli R, Fantini R, Tabbì L, Castaniere I, Pisani L, Pellegrino MR, *et al.* Early inspiratory effort assessment by esophageal manometry predicts noninvasive ventilation outcome in *de novo* respiratory failure. A pilot study. *Am J Respir Crit Care Med* 2020;202:558–567.
9. Mauri T, Yoshida T, Bellani G, Goligher EC, Carteaux G, Rittayamai N, *et al.*; PLeUral pressure working Group (PLUG—Acute Respiratory Failure section of the European Society of Intensive Care Medicine). Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. *Intensive Care Med* 2016;42:1360–1373.
10. Tonelli R, Cortegiani A, Marchioni A, Fantini R, Tabbì L, Castaniere I, *et al.* Nasal pressure swings as the measure of inspiratory effort in spontaneously breathing patients with de novo acute respiratory failure. *Crit Care* 2022;26:70.