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BRIEF COMMUNICATION

A novel non-invasive index of oxygenation and prediction of outcomes for patients on high-flow nasal cannula: a pilot study

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Key words
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Abstract

Predicting success of a therapy in acute respiratory failure is clinically important. The FOx index (high-flow rate × FiO_2)/SpO_2 was retrospectively applied to 70 patients who required high-flow nasal prongs for hypoxaemic and hypercapnic respiratory failure. The FOx index could predict between success and failure of high-flow nasal prongs at 6 hours, using non-invasive markers. This adds to the clinician's toolbox in managing respiratory failure and represents important proof of concept for a prospective study.

Acute hypoxaemic respiratory failure (AHRF) is an adverse clinical state, with outcomes ranging from cellular maladaptation to death.[1] There are multiple methods of addressing this, ranging from simple face masks, positive pressure ventilation and high-flow nasal prongs (HFNPs). HFNPs have purported physiological benefits, including reduction in physiological dead space, delivery of mild positive end-expiratory pressure and accurate delivery of oxygen.[2,3] Its role in AHRF was demonstrated with the FLORALI (Clinical Effect of the Association of Non-invasive Ventilation and High Flow Nasal Oxygen Therapy in Resuscitation of Patients with Acute Lung Injury) paper, and its use has expanded to post-extubation settings, the immunocompromised and even hypercapnic respiratory failure.[4]

HFNPs should not replace appropriate and timely intubation and ventilation.[5] Delays to intubation are associated with increased mortality.[5,6] Risk prediction scores have evolved to help clinicians mitigate this threat. However, there are limitations. Roca and colleagues prospectively validated the ROX index (ratio of oxygen saturation as measured by pulse oximetry (SpO_2)/fraction of inspired oxygen (FiO_2) to respiratory rate (RR) in patients with AHRF caused by pneumonia.[7] This well-designed trial identified a threshold value that predicted those patients who would avoid intubation with a high degree of accuracy. Another strength was its ability to be easily applied at multiple time points. However, it was dependent on accurate measurement of the RR, which has limitations outside of intensive care and is vulnerable to human error.[8]

We propose an alternative, non-invasive index, to predict the likelihood of failure of HFNP in patients with respiratory failure: high-flow rate (L/min) × oxygenation (FiO_2)/SpO_2 (FOx) index. In this proof-of-concept retrospective study, we describe the utility of this index in predicting failure of HFNP in patients with acute hypoxaemic and hypercapnic respiratory failure in a general ward admitted under a respiratory specialist team. The hypothesis was that this index, applied at sequential time points, would numerically highlight the patient's deteriorating (or improving) physiology. The primary outcome was the ability of the FOx index to predict treatment failure using a composite outcome of requirement for escalation of ventilatory support to non-invasive or invasive mechanical ventilation, admission to an intensive care unit (ICU) or death.

The delivery of high-flow via nasal cannula is equivalent to low-level positive airway pressure and thus an indirect

Conflict of interest: None.

marker for the degree of positive pressure support required.[9] This formed the physiological basis of our index.

The current investigation was completed via a single-site, retrospective, outcome-driven clinical cohort study from June 2018 to 2019. The project had local ethics approval (LNR/2019/QMS/55474). Consecutive patients were analysed from electronic medical record. Included patients were aged 18 to –85 years, treated by a respiratory physician, who had presence of AHRF with a documented $SpO_2 < 92\%$ and HFNP used to treat the respiratory failure. Hypercapnic respiratory failure was included. Patients with postoperative HFNP and those in whom the indication of HFNP was not clear were excluded from the study. Patients whose treatment intent was palliation were also excluded.

Demographic data were collected, as well as the indication for HFNP and SpO_2, RR, FiO_2 and high-flow rate at time points 0, 2, 6, 12 and 24 hours from initiation of HFNP. HFNP was delivered by a Fisher and Paykel Airvo2 device. HFNP settings and titration were at the treating physician's discretion. Escalation of ventilatory support was also at the treating physician's discretion. Failure was defined as the requirement for non-invasive or mechanical ventilation, intensive care admission or death during index admission within 30 days. The 'success' of HFNP was defined by the ability to deescalate to nasal prongs or room air at 72 hours, or discharge. The primary outcome was the ability of the FOx index to predict treatment failure using this composite outcome measure.

Encounters were assessed for exclusion/inclusion criteria. For recurrent presentations requiring HFNP, only the first encounter was analysed. Quantitative variables were expressed as median (interquartile range) and categorical variables were expressed as frequency (percentage). Appropriate statistical methods were employed, including Mann–Whitney *U* test for nonparametric comparisons of independent variables, independent *t* test for normally distributed variables and summary data for continuous variables were analysed via independent samples *t* test and chi-square test. A power calculation was not performed.

A total of 70 patients were included in the final analysis. Their characteristics are outlined in Table 1. Hypercapnic respiratory failure accounted for most indications for use of HFNP. The mean age was 65 years. Smoking was prevalent amongst the population studied (75%), likely reflecting the patient demographics of the institution's catchment. About 27% of patients were obese and 37% of patients had chronic liver disease – a higher proportion than expected (Table 1).

Across the whole population, flow rates ranged from 30 to 60 L/min, with a mean ranging from 46.2 to 44.8 L/min over the sequential time points. FiO_2 ranged from 21 to 60% with a mean ranging from 28.7% to 29.6% over the different time points. At times 0, 2, 6, 12 and 24 h, there were, respectively, 70, 70, 68, 64 and 51 patients analysed (due to cessation of HFNP), and two deaths were reported. Chronic obstructive pulmonary disease was the most common diagnosis amongst the cohort studied, followed by community-acquired pneumonia and then step-down from non-invasive ventilation (NIV) (Figure 1). Very few patients with interstitial lung disease, congestive cardiac failure and pulmonary embolism were analysed. Arterial blood sampling was obtained for 37 patients. Mean $PaCO_2$ was 46.4 mm Hg in the failure group and 53.8 mm Hg in the success arm ($P = 0.188$). Mean PaO_2 was 61.1 mm Hg in the failure arm and 79.3 mm Hg in the success arm ($P = 0.019$).

Nine patients had failed HFNP in our cohort. Of those patients, six required non-invasive ventilation (NIV), one required ICU support and two died. The FOx index could discriminate between failure and success from 6 hours and continued to 24 hours, reaching the primary end point. A FOx index of ≥19 from 6 hours, continuing out to 24 hours was associated with HFNP failure ($P < 0.05$ via independent samples *t* test) (Table 2 and Figure 2). There was a reassuring trend in values, becoming smaller with improving physiology in the success arm, and vice

Table 1 Baseline cohort demographic information

Demographic	Results		
Population	$n = 70$		
Age, mean (SD), years	65.2 (17.6)		
Women (%)	48.6		
HFNP indication (%)			
Hypoxaemic respiratory failure	45.7		
Respiratory failure	50		
Undetermined respiratory failure	4.3		
Comorbidities (%)			
Smoker (>10 pack years)	75.7		
Immunocompromised	8.6		
Diabetes (1 or 2)	22.9		
Chronic kidney disease	21.4		
Ischaemic heart disease	28.6		
Congestive cardiac failure	28.6		
Obesity	27.1		
Chronic liver disease	37.1		
Subgroup analysis			
	Success	Failure	*P* value
Outcome	61	9	n/a
$PaCO_2$ (mean), mm Hg	52.8	47.2	0.34
Duration of HFNP (mean), h	42.9	52.6	0.49
Age (mean), years	60.8	65.9	0.42
Obesity (%)	29.5	11.1	0.43
Smoker (%)	80	55.6	0.19
HF (%)	27.9	33.3	0.71

HF, heart failure; HFNP, high-flow nasal prong; n/a, not applicable.

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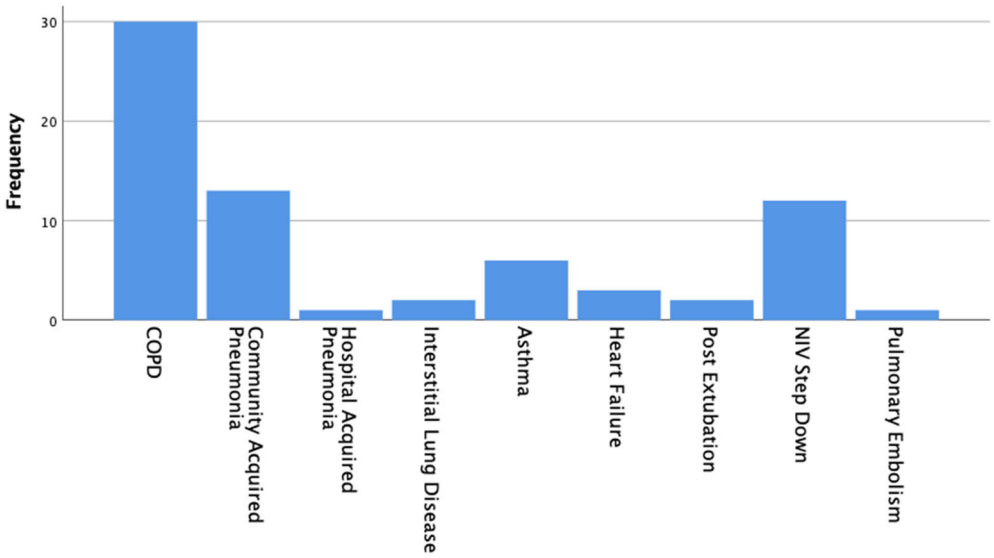

Figure 1 Frequency of diagnoses in the total FOx index cohort. COPD, chronic obstructive pulmonary disease; NIV, invasive ventilation.

Table 2 FOx index values at sequential time points

Index time point	Outcome	*n*	Mean	Standard deviation	*P* value
0	Success	61	14.85	5.49	0.299
	Failure	9	16.91	5.71	
2	Success	61	14.66	5.80	0.096
	Failure	9	18.14	5.50	
6	Success	60	14.10	5.63	0.020
	Failure	8	19.20	6.33	
12	Success	59	13.93	5.52	0.008
	Failure	5	20.85	4.15	
24	Success	47	13.60	5.13	<0.001
	Failure	4	23.89	2.41	

versa in the failure arm. Furthermore, at no point was the mean in the success arm higher than the mean in the failure arm (Table 2).

On chi-square analysis, the presence of type 2 respiratory failure, ischaemic heart disease, heart failure, obesity or smoking status were not significantly different between the failure and success groups (Table 1). A multivariate analysis was not performed because of low numbers in the failure arm.

Discussion

The current study demonstrates a proof-of-concept regarding the performance of this novel non-invasive index at forecasting failure of HFNP. Previously reported indices have performed well in predicting success or failure in respiratory failure.[7] However, they have largely all been limited to patients with hypoxaemic respiratory failure or were dependent on invasive measures (peak airway pressure in intubated patients or PaO_2 from arterial blood gases). The ROX index is novel because of its reliance on non-invasive features; however, it is limited by the requirement for RR. RR is a vital clinical sign and one of the most sensitive markers of deterioration. Despite its importance, there is significant variability in accuracy of RR recordings in clinical practice, particularly outside the ICU.[8,10] Given that the denominator of the equation was based on a very observer-dependent variable, we sought to explore the utility of an index utilising clinical parameters less susceptible to observer variability. An added benefit of the FOx index is that it considers the physiological factors leading to patient deterioration.

Our index captured failure in both hypoxaemic and hypercapnic respiratory failure. Within the limits of the

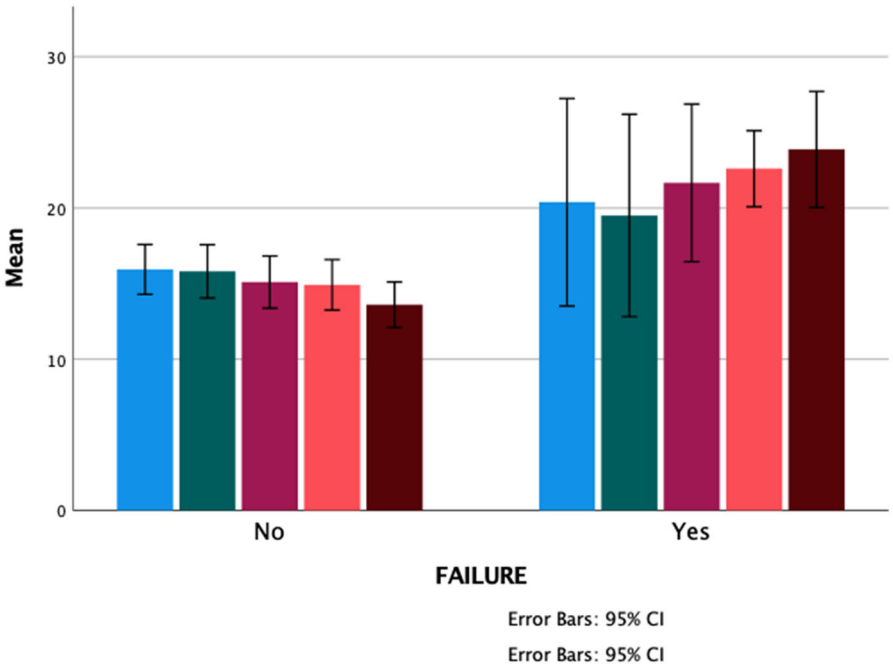

Figure 2 Comparative means of the index at 0, 2, 6, 12, and 24 hours in. (■) Index 0, (■) index 2, (■) index 6, (■) index 12 and (■) index 24.

cohort, there did not appear to be a particular subpopulation in which the FOx index was less accurate. There was no statistical difference between smokers, patients with heart failure and patients with hypercapnic respiratory failure as defined by $PaCO_2$ >50 mm Hg. This represents an important finding and portends to the hopefully broad applicability of this index. However, the study authors acknowledge the limitations of a relatively small sample size. The PaO_2 was significantly lower in the failure arm, reflecting a more unwell cohort.

A value of >19 at 6 hours was associated with failure of HFNC, while a value of <14.1 was associated with a successful outcome of HFNC. It is useful to have a divergence in scores early, so the clinician can make a timely decision regarding changes in care; the 'grey' area being values between 14.1 and 19. This is particularly important, as there is evidence indicating that delay to intubation results in poorer outcomes for patients.[5] While a single calculated variable or index does not and should not replace thorough clinical assessment, this potentially complements the clinician's assessment and helps discriminate a patient's trajectory after presenting with respiratory failure. This has implications for not only morbidity and mortality but could be useful in assisting with resource allocation within hospital systems. With the current limitations of this trial's design, it is unclear whether changes in management would have been made based on the FOx index alone. However, the difference in means between the two groups started at time zero, suggesting that it may be useful earlier on.

There are some limitations to this retrospective cohort analysis. First, there was a relatively small patient sample at 70. There were reduced data points at the 24-hour mark, further limiting the robustness of the index at that point. One of the success criteria was defined as successful weaning from NIV onto HFNP. This represents a subgroup that possibly would have succeeded regardless and may not necessarily represent the clinical benefit of HFNP. Finally, there is an inherent bias using this retrospective methodology, and perhaps the index is only capturing the improving physiology, and not in fact predictive.

This proof-of-concept retrospective review paves the way for future prospective trials utilising this index to help predict failure or success of HFNP in patients. There is an increasing array of oxygen delivery devices available to patients with respiratory failure. Furthermore, a role exists for HFNP in the treatment of hypoxaemic and potentially hypercapnic respiratory failure. It is of critical importance to choose the correct device, as delay to intubation may lead to worse outcomes. Thus, a non-invasive index, based on easily accessible and objective markers of physiology would be useful in assisting clinical decision-making.

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