Fluid Balance Predicts Need for Intubation in Subjects With Respiratory Failure Initiated on High-Flow Nasal Cannula

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BACKGROUND: High-flow nasal cannula (HFNC) has gained widespread use for acute hypoxemic respiratory failure on the basis of recent publications that demonstrated fewer intubations and perhaps lower mortality in certain situations. However, a subset of patients initiated on HFNC for respiratory failure ultimately do require intubation. Our goal was to identify patient-level features predictive of this outcome. METHODS: This was a retrospective cohort study of subjects with hypoxemic respiratory failure treated with HFNC. Individuals were described as having succeeded (if weaned from HFNC) or failed (if they required intubation). A variety of easily measurable variables were evaluated for their ability to predict intubation risk, analyzed via a multivariate logistic regression model. RESULTS: Of a total of 74 subjects, 42 succeeded and 32 failed. The mean ± SD net fluid balance in the first 24 h after HFNC initiation was significantly lower in the success group versus the failure group (–33 ± 80 mL/h vs 72 ± 117 mL/h; *P* < .01). An adjusted model found only fluid balance and the previously described respiratory rate (breathing frequency [f]) to oxygenation (ROX) index ([S_{pO_2}/F_{IO_2}]/f) at 12 h as significant predictors of successful weaning (negative fluid balance adjusted odds ratio 0.77 [95% CI 0.62–0.96] for −10 mL/h increments [*P* = .02]; ROX adjusted OR 1.72 [1.15–2.57], *P* < .01). CONCLUSIONS: A negative fluid balance while on HFNC discriminated well between those who required intubation versus those who were successfully weaned. *Key words: high-flow nasal cannula; hypoxemic respiratory failure; critical care.* [Respir Care 2021;66(4):566–572. © 2021 Daedalus Enterprises]

Introduction

High-flow nasal cannula (HFNC) is a widely used, safe, and effective therapy for the treatment of hypoxemic respiratory failure. It improves oxygenation, breathing frequency (f), and patient comfort compared with a traditional face mask.[1,2] A recent clinical trial demonstrated a 90-d mortality benefit in subjects treated with HFNC as opposed to conventional oxygen therapy in subjects with non-hypercapnic acute hypoxemic respiratory failure.[3] In addition, intubation rates were reduced in the subset of subjects with P_{aO_2}/F_{IO_2} of <200 mm Hg. In supporting this finding, a recent meta-analysis that compared conventional oxygen versus HFNC or noninvasive ventilation (NIV) for hypoxemic respiratory failure found reduced intubation rates with the use of HFNC, although with conflicting results with regard to subject mortality.[4,5]

Several questions have emerged with the more widespread use of HFNC. Among them are ideal patient selection, optimal device settings, and timing of a transition to mechanical ventilation in a patient who is not responding. One concern is that HFNC may, in certain situations, delay intubation and worsen patient outcomes,[6,7] similar to what has been observed with NIV.[8,9] There have been efforts to determine which patients are at risk for failure of HFNC (ie, need rescue mechanical ventilation). One group recently demonstrated that S_{pO_2}/F_{IO_2} to breathing frequency (termed by the investigators as the respiratory rate to oxygenation or the ROX index) while on HFNC can identify patients who will ultimately require intubation.[7,10] Conceptually, lower values generally indicate tachypnea,

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hypoxemia, and higher F_{IO_2}, and a corresponding greater risk of intubation. The clear advantage is that all included variables are easily obtained immediately at the bedside.

In patients mechanically ventilated for ARDS, conservative fluid administration and the use of diuretics to maintain euvolemia have been associated with increased ventilator-free days in one large prospective clinical trial[11] and a recent meta-analysis.[12] In addition, early crystalloid administration is independently associated with the development of ARDS in trauma patients.[13] In our review of the literature, we found that fluid status has not previously been examined with regard to predicting failure of HFNC in the treatment of hypoxemic respiratory failure; therefore, our goal was to identify risk factors that predict the need for intubation in patients initiated on HFNC. We carefully selected easily measured variables, with the hope of providing clinicians pragmatic guidance on the management of these patients.

QUICK LOOK

Current knowledge

High-flow nasal cannula (HFNC) has been used successfully in management of hypoxemic respiratory failure. In certain situations, HFNC may delay intubation and lead to excess mortality. Predicting which patients will fail HFNC can be challenging and imprecise. The respiratory rate to oxygenation index, or ROX index, has been previously shown to predict failure of HFNC in patients with pneumonia.

What this paper contributes to our knowledge

Fluid balance predicted HFNC failure in subjects with hypoxemic respiratory failure. It outperformed a variety of metrics, including the SOFA score, as well as any single physiologic variable, including the ROX index. When combined with the ROX index, our model accurately predicted which subjects treated with HFNC would require intubation. This knowledge can aid clinicians in predicting which patients treated with HFNC may require intubation.

Methods

Subjects

This was a retrospective cohort study of subjects from the medical ICU at Medstar Georgetown University Hospital, a tertiary-care center. The study was approved by the institutional review board of Georgetown University. All patients admitted to the medical ICU are anonymously included in a prospectively maintained database in which demographic information, admission diagnosis, medical history, and variables pertinent to their ICU course are recorded. We included as subjects those patients from July 2017 to July 2019 with acute hypoxemic respiratory failure who were newly initiated and maintained on HFNC for at least 6 h, and whose code status allowed for intubation. The success group were subjects weaned off HFNC, whereas the failure group ultimately required invasive mechanical ventilation. The decision to intubate was ultimately determined by the treating clinician. Subjects who transitioned to NIV were excluded. The study center uses a Optiflow HFNC system manufactured by Fisher & Paykel Healthcare (Auckland, New Zealand) with the MR850 heated humidifier and RT232 tubing.

Data

We recorded variables thought to be potentially related to one's ability to be weaned from HFNC, based on clinical relevance and previous studies.[7,10,14-16] Basic demographic and clinical information collected included age, sex, body mass index, medical history, and the cause of respiratory failure. At the initiation of HFNC, we recorded breathing frequency (f), device settings (flow and F_{IO_2}) and information from the arterial blood gas results (pH, lactate and P_{aO_2}/F_{IO_2}). For the first 24 h on HFNC (or for the duration on HFNC if less than that), we calculated the Sequential Organ Failure Assessment (SOFA) score,[17] net fluid balance, furosemide use (the use of other diuretics was rare), and whether the subject had acute kidney injury or significant vasopressor use. These subjects were defined as having a SOFA component score of ≥3 in the kidney and the cardiovascular system. Fluid balance was expressed per hour because the time on HFNC varied.

While the subjects were on HFNC, we measured frequency, S_{pO_2}, and HFNC settings (flow and F_{IO_2}) at the 3-, 6-, and 12-h marks. We also calculated the ROX index as previously described,[10] which is $(S_{pO_2}/F_{IO_2})/f$ at the 6- and 12-h marks. This tool has been derived and validated in separate patient populations and provides a reasonably accurate distinction between patients who will wean from HFNC and those who will ultimately require intubation.[7] Finally, we measured the total continuous time on HFNC and whether the subject died in the hospital (in the ICU or otherwise).

Analysis

Summary statistics describe the frequency of each categorical variable and either the mean ± SD or median and interquartile range (IQR) for parametric and nonparametric continuous variables, respectively. In a comparison of those who were successfully weaned and those who were not successfully weaned, continuous variables were analyzed by

Table 1. Baseline Subject Characteristics

	Total Subjects ($N = 74$)	HFNC Success ($n = 42$)	HFNC Failure ($n = 32$)	*P*
Age, mean ± SD y	59.7 ± 15.7	57.0 ± 17.1	63.4 ± 12.9	.20
BMI, median (IQR) kg/m^2	25 (23–31)	26 (22–34)	25 (23–28)	.73
Female, *n* (%)	39 (52.7)	24 (57.1)	15 (46.9)	.38
Comorbid conditions, *n* (%)				.98
Underlying lung disease	18 (24.3)	10 (23.8)	8 (25.0)	
Preexisting oxygen dependence	10 (13.5)	6 (14.3)	4 (12.5)	
Cirrhosis	14 (18.9)	8 (19.0)	6 (18.8)	
Cancer	21 (28.4)	11 (26.2)	10 (31.3)	
Systolic heart failure	5 (6.8)	2 (4.8)	3 (9.4)	
Cause of respiratory failure, *n* (%)				.62
Pulmonary edema	16 (21.6)	7 (16.7)	9 (28.1)	
Pneumonia	37 (50.0)	20 (47.6)	17 (53.1)	
Other*	21 (28.4)	15 (35.7)	6 (18.8)	

* Includes pulmonary embolism, COPD exacerbation, cancer, significant abdominal distention, acute chest syndrome, and unknown.
BMI = body mass index
IQR = interquartile range

using the Student *t* test for parametric data and the Mann-Whitney U test for nonparametric data. Categorical variables were analyzed with the chi-square test or the Fisher exact test as appropriate.

A model was developed to predict HFNC failure by using it as the dependent variable in multivariate logistic regression, developed in a stepwise fashion, with a stopping rule based on minimum Bayesian Information Criterion. Candidate predictor variables showed a statistically significant difference in a univariate comparison or were of particular clinical interest (SOFA score and P_{aO_2}/F_{IO_2}). A traditional survival analysis technique was not used because there are no censored data and time is not intrinsic to the research question, which was about predicting the intubation rate rather than the time to intubation. The predictive utility of the model was summarized by receiver operating characteristic curve technique (area under the curve or C statistic). The analysis was performed with JMP 15 Pro (SAS Institute, Cary, North Carolina).

Results

Subjects

One hundred twenty-six patients newly initiated on HFNC for acute hypoxemic respiratory failure were identified during the study period: 25 had a do not intubate (or had code status changed to do not intubate after initiation of HFNC), 10 were on HFNC for <6 h, and 17 were transitioned to NIV at some point during their course, which left 74 unique patients eligible for analysis. There were no differences in basic demographic features, comorbid conditions, or cause of respiratory failure between the subjects who were successfully weaned and those who ultimately required intubation (Table 1). Notably, 50% of the subjects were initiated on HFNC for diagnoses other than pneumonia. These included pulmonary edema, non-hypercapnic COPD exacerbations, pulmonary embolism, and acute onset pulmonary infiltrates of equivocal cause among others (Table 1).

Respiratory Indices

Although there was a trend toward higher upfront frequency in the failure group not meeting statistical significance, by 12 h on HFNC, the frequency remained constant in the subjects successfully weaned, whereas it increased in those who required intubation, (34 vs 27, $P < .001$). In addition, the F_{IO_2} was significantly higher (0.5 vs 0.85; $P < .001$) (Table 2). The previously described ROX index,[7] which is a combination of these variables and S_{pO_2}, (S_{pO_2}/F_{IO_2})/f, similarly was significantly lower in the subjects who required intubation at both 6 and 12 h (Table 3).

There were no statistically significant differences in the initial HFNC settings between the groups, although there was a higher F_{IO_2} in individuals who were intubated (F_{IO_2}: 0.8 vs 0.6 [$P = .12$]; flow: 40 vs 38 L/min [$P = .96$]). In addition, a stratified analysis of the initial HFNC settings revealed that a higher initial flow and F_{IO_2} did not lead to an increased intubation rate when using 40 L/min (40% intubation rate in subjects with flow > 40 L/min and 46% in those with flow < 40 L/min $P = .76$) and F_{IO_2} of 0.6 (32% and 49%, $P = .16$) as cutoffs.

Fluid Balance

The mean ± SD fluid balance markedly differed in the subjects who required intubation (–33 ± 80 mL/h vs 72 ±

Table 2. Dynamic Respiratory Variables

	Time on HFNC, h		
	0	6	12
Frequency, mean ± SD breaths/min			
Succeeded	26 ± 7	27 ± 10	27 ± 6
Failed	29 ± 8	29 ± 7	34 ± 13
Heart rate, mean ± SD beats/min			
Succeeded	100 ± 21	92 ± 23	91 ± 22
Failed	97 ± 20	96 ± 20	94 ± 25
S_{PO_2}, median (IQR) %			
Succeeded	96 (93–99)	98 (96–99)	99 (97–100)
Failed	96 (92–98)	98 (95–99)	97 (94–99)
F_{IO_2}, median (IQR)			
Succeeded	0.6 (0.5–0.9)	0.58 (0.5–0.65)	0.5 (0.4–0.75)
Failed	0.8 (0.5–1)	0.78 (0.5–1)	0.85 (0.58–1)
Flow, median (IQR) L/min			
Succeeded	38 (30–46)	35 (30–45)	39 (25–49)
Failed	40 (21–49)	40 (30–45)	40 (30–50)
ROX index score, mean ± SD			
Succeeded	6.4 ± 3.4	6.5 ± 2.4	6.2 ± 2.8
Failed	5.3 ± 2.4	5.8 ± 2.5	4.4 ± 1.6

HFNC = high-flow nasal cannula
IQR = interquartile range
ROX index = breathing frequency (f) to oxygenation, calculated as $(S_{pO_2}/F_{IO_2})/f$

Table 3. Clinical Features

	Total Subjects (*N* = 74)	HFNC Success (*n* = 42)	HFNC Failure (*n* = 32)	*P*
Arterial pH, median (IQR)	7.42 (7.35–7.47)	7.4 (7.34–7.45)	7.43 (7.36–7.49)	.14
Serum lactate, median (IQR) mmol/L	1.6 (1–2.6)	1.6 (1–2.3)	1.7 (1.1–2.6)	.42
Frequency, mean ± SD breaths/min	28 ± 8	26 ± 7	29 ± 8	.11
HFNC settings				
Flow, median (IQR) L/min	40 (30–47)	38 (30–46)	40 (21–49)	.96
F_{IO_2}, median (IQR)	0.6 (0.5–1.0)	0.6 (0.5–0.9)	0.8 (0.5–1.0)	.12
P_{aO_2}/F_{IO_2}, median (IQR) mm Hg	106 (59-152)	113 (77–160)	103 (82–142)	.57
Acute kidney injury, *n* (%)	27 (36.5)	15 (36.5)	12 (38.7)	.85
Significant upfront vasopressor use, *n* (%)	11 (14.9)	3 (7.3)	8 (25.8)	.048
Time on HFNC, median (IQR) h	31 (14–64)	36 (18–68)	30 (8–55)	.23
ROX index, mean ± SD				
At 6 h		6.8 ± 2.5	5.3 ± 2.5	.01
At 12 h		7.2 ± 2.9	4.3 ± 1.7	<.001
Fluid balance for first 24 h, mean ± SD mL/h		–33 ± 80	72 ± 117	<.001
Furosemide in the first 24 h, median (IQR), mg		20 (10–40)	20 (0–40)	.15
SOFA score at the first 24 h, mean ± SD	4.8 ± 3.2	4.3 ± 2.9	5.5 ± 3.4	.07
In-patient mortality, *n* (%)	15 (20.3)	3 (7.1)	12 (37.5)	

IQR = interquartile range
HFNC = high-flow nasal cannula
ROX index = breathing frequency (f) to oxygenation, calculated as $(S_{PO_2}/F_{IO_2})/f$
SOFA = Sequential Organ Failure Assessment

117 mL/h; $P < .01$). We explored reasons that the treating clinician could or could not potentially successfully diurese subjects: there was no between-group difference in the rate of acute kidney injury (38.7% vs 36.5%; $P = .87$) or median (IQR) furosemide administered (20 [10–40] mg vs 20 [0–40] mg; $P = .15$), but there were more subjects with significant

upfront vasopressor use (25.8% vs 7.3%; $P = .048$), along with a trend toward an increased SOFA score (5.5 vs 4.3; $P = .07$).

A greater negative fluid balance is more impactful. As an example, only 12.5% of individuals (3/24) who achieved a negative fluid balance of 50 mL/h were ultimately intubated. These subjects had similar mean ± SD SOFA scores and median (IQR) P_{aO_2}/F_{IO_2} as did the remainder of the subjects: 5.1 ± 3.4 and 110 (80–158) mm Hg, respectively. Of note, the median (IQR) furosemide dosage did not differ by presenting diagnosis (20 [10–40] mg in those with pulmonary edema vs 20 [0–40] mg for all others; $P = .30$).

Failure Prediction Model

To further explore these univariate observations, we generated a logistic regression model with HFNC failure as the outcome by using variables with statistically significant univariate associations, along with the SOFA score and P_{aO_2}/F_{IO_2} (given their relevancy toward clinical deterioration and oxygenation). After this multivariate adjustment, only 2 variables, the ROX index and fluid balance, remained significant predictors of successful weaning. A model with the ROX index measured at 12 h (adjusted odds ratio [OR] 1.72 [1.15–2.57]; $P < .001$) and fluid balance (adjusted OR 0.77 [0.62–0.96] for –10 mL/h increments; $P = .02$) had an overall R^2 value of 0.45 and a C statistic of 0.86. The C statistic for a model composed of ROX alone was 0.77, for fluid balance alone, it was 0.82. These terms did not demonstrate significant collinearity (variance inflation factor of 1.38).

Notably, despite increased significant vasopressor use and a strong trend toward a higher mean SOFA score in the subjects who were intubated, the addition of those 2 variables to the aforementioned model did not improve its predictive ability and individually did not contribute significantly to predicting the intubation risk (SOFA score adjusted OR 0.88 [95% CI 0.59–1.30] ($P = .34$) and vasopressor use ($P = .18$)). The data are not shown, but these conclusions were also true for the ROX index measured at 6 h as well.

Analysis stratified by diagnosis yields similar results. For both individuals with ($n = 37$) versus those without pneumonia ($n = 37$), ROX index at 12 h (adjusted OR 1.82 [$P = .038$] and 1.66 [$P = .049$], respectively) and negative fluid balance (adjusted OR 0.97 [$P = .042$] and 0.88 [$P = .033$] respectively) remained the only significant independent predictors of intubation risk. A simplified scheme of this information for clinicians to consider is proposed in Table 4.

Table 4. Simplified Intubation Prediction Model*

	ROX Index Score	
	≤5	≥5
Fluid balance		
Positive	68.4%	50.0%
Negative	50.0%	18.5%

* Intubation rates predicted were based on fluid balance positivity and ROX index score at 12 h >5 or <5 as binary terms.
ROX = breathing frequency (f) to oxygenation, calculated as $(S_{pO_2}/F_{IO_2})/f$

Discussion

HFNC has emerged as a helpful tool for clinicians in the treatment of hypoxemic respiratory failure, with demonstrated efficacy in avoiding mechanical ventilation and perhaps reducing mortality.[3] However, many subjects started on HFNC still need to be intubated, and there is concern that delaying intubation may lead to excess mortality.[18] In our analysis of 74 subjects with hypoxemic respiratory failure treated with HFNC, a series of easily measured variables, including fluid balance, were highly predictive of the need for intubation. The causes of respiratory failure in these individuals were diverse compared with many previous studies confined to those with pneumonia. We elected to include this varied population, given that the specific etiology of severe acute respiratory failure is often equivocal or multifactorial, and the upfront impression may ultimately be incorrect. Thus, given this diversity, our study offers a pragmatic tool to predict failure of HFNC in undifferentiated hypoxemic respiratory failure.

This was the first study we are aware of that specifically evaluated fluid balance in predicting the success of HFNC. We chose to study this given the demonstrated utility in other disease states[11,19-21] and our own anecdotally observed correlation. In supporting a direct relationship, the more net negative an individual was predicted successful weaning to a greater degree (eg, only 12.5% of individuals with a negative fluid balance of 50 mL/h were intubated). In addition, this association held true, regardless of the initially suspected cause of respiratory failure.

Whether fluid balance is simply a risk predictor or a parameter specifically worth targeting remains an open question. Mechanistically, during acute lung disease, smaller increases in pulmonary arterial pressure result in greater extravascular lung water (ie, pulmonary edema) than in heath, partly driven by the loss of the protective glycocalyx layer (an extracellular glycoprotein and lipid matrix between the capillary endothelium and the alveolar epithelium), which mitigates vascular permeability.[22] In patients intubated for ARDS, a strategy of conservative fluid management[11] results in fewer days on the ventilator. It is not clear in our cohort whether certain subjects achieved a negative fluid balance because of the clinician's decision to diurese or because the patient's level factors were hindering his or her ability to do so (ie, sicker patients).

Vasopressor use was more prevalent in the failure group, as were trends toward a higher upfront SOFA score and worse P_{aO_2}/F_{IO_2}. Notably, these variables were not independently predictive of one's intubation risk, whereas fluid balance was predictive. Even if fluid balance is a risk predictor rather than causative, our model suggests that it is at least as important to monitor as frequency or oxygenation in this patient population. If a positive fluid balance is simply a marker of severe disease, then it remains clinically useful by alerting the clinician to those who are more likely to deteriorate. Future study is needed to address whether targeting a negative fluid balance would reduce intubation rates in subjects treated with HFNC.

Similar to previous prospective studies, we also found that the ROX index accurately predicted the need for intubation in subjects initially treated with HFNC.[7,10] This measure significantly outperformed any single upfront or dynamic physiologic respiratory variable. This finding validated the previous work in a separate cohort with diverse causes of respiratory failure. The ROX index and fluid balance may be mechanistically linked insofar as the negative fluid balance improves oxygenation and thus frequency, which are the components of the ROX index. However, in our sample, they are not statistically colinear and, therefore, both individually and independently predicted failures of HFNC. When used together, they form a more-accurate risk prediction tool than either alone.

In contrast to previous studies, the initial flow and F_{IO_2} settings were not standardized but rather titrated to oxygen saturation as well as to subject comfort by the respiratory therapist and treating clinician. This gave us an opportunity to examine the impact of HFNC settings on successful weaning. We hypothesized that lower flow would be associated with higher rates of failure; however, this was not true in our cohort. This potentially suggests that, if a patient is unable to tolerate high flows, then a lower flow may be trialed before moving to a different oxygen delivery modality. Higher initial F_{IO_2} (>0.6) was associated with a trend toward higher intubation rates not meeting statistical significance (32% vs 49%; $P = .16$); this was likely driven by severity of illness (P_{aO_2}/F_{IO_2}: 163 mm Hg vs 113 mm Hg; and SOFA scores: 5.8 vs 4.9). Our institution does not have a strict protocol for initial or titrating HFNC settings, nor are there clear societal guidelines, which represents an area of unmet clinical need.

This analysis has many notable limitations. Data were collected from a retrospective chart review; hence, physiologic parameters were recorded in accordance with appropriate clinical care and not precisely uniform among the subjects. In addition, although intubation is noteworthy, it is ultimately an intermediate outcome in an individual's recovery from critical illness. In contrast to previous studies,[3,7,10] our intubation rate was higher, which may reflect the inclusion of subjects with fewer reversible processes, for example, advanced malignancy.

We elected not to include patients who transitioned to NIV because our goal was to provide a precise, rigorous description of the success and failure of acute hypoxemia-treated HFNC. Patients who are transitioned to NIV are phenotypically different (often having upper-airway obstruction, hypercarbia, or a marked increase in work of breathing) and are often switched back and forth before weaning or intubation. In our current practice, NIV is not used in cases of HFNC failure unless one of the aforementioned conditions is present and, instead, invasive mechanical ventilation is initiated. This approach is in line with the previously published ROX and ROX validation in which NIV was specifically not used in cases of HFNC failure.[7,10] In addition, the 2017 ATS/ERS guidelines[23] for NIV make no recommendation for the use of NIV in de novo acute hypoxemic respiratory failure, do not mention the use of NIV in cases of HFNC failure, and do recommend against using NIV for patients with COPD who are not acidotic. Also, unlike previous studies, we did not have cutoffs that mandated intubation; however, this is likely more reflective of standard practice.

Conclusions

Many patients initiated on HFNC for respiratory failure are ultimately intubated. Negative fluid balance while on HFNC discriminated between subjects who were versus those who were not successfully weaned. This finding needs to be validated in a separate population before being incorporated into routine clinical decision-making.

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