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ROX (Respiratory rate-OXygenation) index to predict early response to high-flow nasal cannula therapy in infants with viral bronchiolitis

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September 1, 2023

Abstract

Introduction High flow nasal cannula (HFNC) is commonly used as first step respiratory support in infants with moderate-to-severe acute viral bronchiolitis (AVB). This device, however, fails to effectively manage respiratory distress in about a third of patients, and data are limited on determinants of patient response. The respiratory rate-oxygenation (ROX) index is a relevant tool to predict the risk for HFNC failure in adult patients with lower respiratory tract infections. The primary objective of this study was to assess the relationship between ROX indexes collected before and 1 hour after HFNC initiation, and HFNC failure occurring in the following 48 hours in infants with AVB. **Method:** This is an ancillary study to the multicenter randomized controlled trial TRAMONTANE 2, that included 286 infants of less than 6 months with moderate-to-severe AVB. Collection of physiological variables at baseline (H0), and 1 hour after HFNC (H1), included heart rate (HR), respiratory rate (RR), fraction of inspired oxygen (FiO_2), respiratory distress score (mWCAS), and pain and discomfort scale (EDIN). ROX was calculated as SpO_2/FiO_2 to RR. Predefined HFNC failure criteria included increase in respiratory distress score or respiratory rate, increase in discomfort, and severe apnea episodes. The accuracy of ROX index to predict HFNC failure was assessed using receiver operating curve analysis. **Result:** HFNC failure occurred in 111/286 (39%) infants, and for 56 (50% of the failure) of them within the first 6 hours. The area under the curve of ROX indexes at H0 and H1 were, respectively, 0.56 (95% CI 0.48-0.63, p =0.14), 0.56 (95% CI 0.49- 0.64, p =0.09). HFNC failure was associated with higher mWCAS score at H1 ($p<0.01$) and lower decrease in EDIN scale during the first hour of HFNC delivery ($p = 0.02$), but none of the physiological variables were predictive of HFNC failure. **Conclusion:** In this study, neither ROX index, nor physiological variables usually collected in infants with AVB had early discriminatory capacity to predict HFNC failure.

ROX (Respiratory rate-OXygenation) index to predict early response to high-flow nasal cannula therapy in infants with viral bronchiolitis

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Key words: bronchiolitis, high-flow nasal cannula, infant, failure, risk prediction.

Word counts: text: 1758; Abstract: 320; Tables: 2; Figures: 1

Conflict of interest statement: The authors have no financial relationships and no potential conflicts of interest relevant to this article to disclose.

Abbreviations:

AUC: area under the curve.

AVB: acute viral bronchiolitis

CPAP: continuous positive airway pressure.

HFNC: high-flow nasal cannula.

EDIN [*Echelle de douleur et d'inconfort du nouveau-né*]: neonatal pain and discomfort scale.

FiO_2: fraction of inspired oxygen.

HR: heart rate.

mWCAS: modified Wood's clinical asthma score.

$pvCO_2$: partial pressure of carbon dioxide.

ROC: receiver operating curve.

ROX: respiratory rate-oxygenation index.

RR: Respiratory rate.

ABSTRACT

Introduction

High flow nasal cannula (HFNC) is commonly used as first step respiratory support in infants with moderate-to-severe acute viral bronchiolitis (AVB). This device, however, fails to effectively manage respiratory distress in about a third of patients, and data are limited on determinants of patient response. The respiratory rate-oxygenation (ROX) index is a relevant tool to predict the risk for HFNC failure in adult patients with lower respiratory tract infections. The primary objective of this study was to assess the relationship between ROX indexes collected before and 1 hour after HFNC initiation, and HFNC failure occurring in the following 48 hours in infants with AVB.

Method:

This is an ancillary study to the multicenter randomized controlled trial TRAMONTANE 2, that included 286 infants of less than 6 months with moderate-to-severe AVB. Collection of physiological variables at baseline (H0), and 1 hour after HFNC (H1), included heart rate (HR), respiratory rate (RR), fraction of inspired oxygen (FiO_2), respiratory distress score (mWCAS), and pain and discomfort scale (EDIN). ROX was calculated as SpO_2/FiO_2 to RR. Predefined HFNC failure criteria included increase in respiratory

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distress score or respiratory rate, increase in discomfort, and severe apnea episodes. The accuracy of ROX index to predict HFNC failure was assessed using receiver operating curve analysis.

Result:

HFNC failure occurred in 111/286 (39%) infants, and for 56 (50% of the failure) of them within the first 6 hours. The area under the curve of ROX indexes at H0 and H1 were, respectively, 0.56 (95% CI 0.48-0.63, p =0.14), 0.56 (95% CI 0.49- 0.64, p =0.09). HFNC failure was associated with higher mWCAS score at H1 (p<0.01) and lower decrease in EDIN scale during the first hour of HFNC delivery (p = 0.02), but none of the physiological variables were predictive of HFNC failure.

Conclusion:

In this study, neither ROX index, nor physiological variables usually collected in infants with AVB had early discriminatory capacity to predict HFNC failure.

INTRODUCTION

Acute viral bronchiolitis (AVB) is a leading cause of lower respiratory tract infection and hospitalization in young infants, notably those aged less than 1 year [1]. Management of moderate-to-severe AVB is based on respiratory support, with as the first step administration of a heated and humidified mixture of air and oxygen with high-flow nasal cannula (HFNC) [2]. While several studies have confirmed HFNC effectiveness to reduce the work of breathing in AVB [3-5], failure occurs in 30-40% of these patients [6-8]. In these infants, evolving respiratory failure requires escalation in therapeutic measures, including transition to continuous positive airway pressure (CPAP), then if necessary to noninvasive ventilation or intubation [9].

Early identification of patients who are most likely to fail with HFNC is critical for care organization in the pediatric emergency department [10]. Indeed, these infants will need to be referred to a pediatric intensive care unit, necessary for the monitoring of any non-invasive ventilation technique including CPAP and bilevel positive airway pressure, while those who will improve with HFNC can potentially be transferred to a general pediatric ward [11]. Currently, some patient characteristics have been individualized as predictors of respiratory deterioration, notably younger age or initial severity [12, 13]. However, neither isolated physiologic parameters, such as respiratory rate (RR), fraction of inspired oxygen (FiO_2), or venous/capillary partial pressure of carbon dioxide ($pvCO_2$), nor clinical scales that incorporate different vital signs have demonstrated a consistent association with the risk of HFNC failure and are discriminating enough to be used as triage tools [14-18].

Recently, Roca *et al.* developed a tool to assess the risk for HFNC failure in adult patients with hypoxemic acute respiratory failure [19]. ROX (Respiratory rate-OXygenation) index corresponds to the ratio of patient oxygenation, which has been associated to HFNC success, over RR, which has been associated to HFNC failure. Subsequent studies confirmed it was a good predictor of HFNC failure in lower respiratory tract infections, including those caused by virus [20, 21]. In pediatric patients with acute respiratory failure, ROX index application 24 and 48 hours after hospital admission also appeared a good marker for predicting the risk of HFNC failure [22]. In the specific context of AVB in <2 years infants managed in a pediatric emergency department, patients with ROX index in the lowest quartile at HFNC initiation were three times more likely to require CPAP compared to those in the highest quartile [23]. The single-center nature of this study, with lack of standardization for failure criteria, incited to test the relevance of ROX index in an homogeneous population of <6 months infants requiring HFNC for severe AVB, recruited in the framework of a multicenter study with predefined HFNC failure criteria [24].

The primary objective of this study was to assess the relationship between ROX index collected early (*i.e.* before HFNC initiation and 1 hour after), and HFNC failure occurring in the following 48 hours in patients admitted for severe AVB.

METHODS

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This is an ancillary study to the multicenter randomized controlled trial TRAMONTANE 2, which compared two settings, (3 versus 2 L/kg/min), in young infants with severe AVB (defined by a modified Wood's clinical asthma score (mWCAS) >3) supported with HFNC [24]. The study protocol was approved by the South Mediterranean IV Ethics Committee (2016-A00900-51), and recorded on the National Library of Medicine registry (NCT02824744). Written authorization was obtained from the two parents.

The study, performed in 16 French university hospital centers between November 2016 and March 2017, enrolled 142 infants in the 2 L-group, 144 infants in 3 L-group, and found the same failure rate of 39% in each group, allowing to include the 286 TRAMONTANE 2 patients in the current analysis.

Data collection

Heart rate (HR), RR, FiO_2, venous/capillary pH and $pvCO_2$, mWCAS, and the neonatal pain and discomfort scale (EDIN) were collected at baseline (H0), in the 15 minutes following admission, while the infant received a blend of air/oxygen using nasal cannula at a maximal flow rate of 1 L/min. The same physiological variables, except for capillary blood gas analysis, were collected 1 hour after HFNC initiation at the flow rate allocated by randomization (H1).

At H0 and H1, ROX was calculated as SpO_2/FiO_2 to RR.

Predefined HFNC failure criteria included the occurrence, within 48 hours of randomization, of one or more of the following: increase, compared to H0, in respiratory distress score (*i.e,* 1 point in mWCAS) or respiratory rate (*i.e,* >10 breath per min with RR> 60 bpm), increase in discomfort (1 point in EDIN score), and severe apnea episodes requiring bag and mask ventilation.

Outcome

The primary study outcome was discriminatory capacity of ROX index values, at H0 and H1, and their change during the first hour of HFNC delivery (H1-H0), to predict HFNC failure.

We also tested, as secondary outcomes, the predictive values of the physiological variables collected at H0 and H1 and their changes between the 2 time-points.

Statistical analyses

Groups, defined as HFNC failure or success, were compared using Student or Wilcoxon Mann-Whitney test for continuous variables and Chi-square or Fisher test for categorical ones.

The accuracy of ROX index and physiological variables to predict HFNC failure was assessed using receiver operating curve (ROC) analysis. The area under the curve (AUC) was calculated by the Hanley method and compared to the value 0.5 using Wilcoxon's W statistic. For the analyses at H1 and for changes during the first hour of HFNC delivery, all HFNC failure patients at H1 or before were excluded.

Statistical tests were performed 2-tailed and p-values <0.05 were considered significant test results. Statistical analyses were conducted with SAS (version 9.4, SAS Institute, Cary, NC) and R software (R 2.3.4 for Windows). Patients' characteristics were presented using mean and standard deviation (SD) for the quantitative variables and frequencies with proportions for categorical ones.

RESULTS

HFNC failure occurred in 111/286 (39%) infants, after a mean (SD) delay of 11.36 (11.98)

hours (Figure 1). In 96/111 (86%), failure occurred within 24 hours, including 56 (50%) within the first six hours.

Primary outcome:

ROX indexes at H0 and H1, and their changes during the first hour were not different according to HFNC failure or success (Table 1). Their respective AUC were 0.56 (95% CI 0.48-0.63, p =0.14), 0.56 (95% CI

0.49- 0.64, p =0.09), and 0.54 (95% CI 0.45-0.62, p =0.34) (Table 2). These results didn't support that early ROX indexes predicted HFNC failure.

Secondary outcome

HFNC failure was associated with higher mWCAS score at H1 ($p<0.01$) and lower decrease in EDIN scale during the first hour of HFNC delivery ($p = 0.02$) (Table 1). However, none of the physiological variables collected at H0 and H1 and their changes during the first hour of HFNC delivery were predictive of HFNC failure, according to their respective AUC (Table 2).

DISCUSSION

In this multicentre population of young infants with severe AVB, the failure rate of HFNC was 39%. Failure of this first step of respiratory support occurred early, within 6 hours after HFNC initiation for half of failing patients and within 24 hours for nearly 90% of them. Neither ROX index, nor physiological variables usually collected in infants with acute respiratory failure had early discriminatory capacity to predict failure of management with HFNC.

In a previous study, Kannikeswaran *et al.* observed an association between ROX index and HFNC failure, in other words the need for positive pressure ventilation, in <2 years infant with bronchiolitis [23]. This result was particularly relevant from the perspective of directing these patients to the most suitable units downstream of the emergency department. In this perspective, our study aimed to identify a threshold for this index, associated with actual predictive capacities. Our AUC results suggested a weak and non-significant relationship between ROX and HFNC failure, which currently does not confirm the interest of this tool in a clinical decision rule. The main difference with studies suggesting that ROX index may be a good marker to predict the risk of HFNC failure probably comes from different patient's characteristics [22, 23]. Our trial involved much younger patients and, as our results indicate, age is a key risk factor for respiratory failure in this population [12, 13]. In addition, the TRAMONTANE 2 study included patients probably affected by more severe forms of the disease, as mWCAS > 3 was required to be eligible, which signals unambiguous respiratory distress. In Kannikeswaran*et al.* study, the regression model to estimate the odds ratio of PPV requirement was based on the highest ROX quartile, suggesting marked heterogeneity in the severity of bronchiolitis [23].

The ROX index takes into account only two characteristics of a respiratory distress, namely oxygenation and tachypnea. While these parameters are critical in patients with acute hypoxemic respiratory failure, they do not take into account all of the determinants of HFNC failure in AVB. Indeed, AVB present different phenotypes: sometimes as a restrictive parenchymal disease, but a majority of these infants demonstrate a severe obstructive lung disease, with markedly increased work of breathing and frequent apneas [4, 5, 25]. These two elements, as well as comfort, are not integrated in the ROX index, whereas they often intervene in the clinician's decision to upgrade respiratory support in a patient with AVB.

No variable, observed or calculated, was able to predict HFNC failure in this work. However, half of failure occurred within 6 hours, which suggests that such delay may be a relevant criterion for triage. Insofar as the volume of patients in the emergency room allows it, it may be consistent to maintain the infant with HFNC and adapted monitoring during this timeframe before deciding admission to pediatric intensive care unit.

This study has several strengths, including a large, multicentric and homogeneous population, in terms of severity and age, of infants with AVB. In addition, predefined HFNC failure criteria had been validated by a panel of experts providing from the 16 participating centres in the trial.

We acknowledge some limitations. Half of the children received a flow rate of 2 L/min/kg, and the other half 3 L/min/kg, but we are uncertain whether this affects the interpretation of our results because the failure rate was exactly the same in the two groups.

The predictive value of the ROX index beyond the first hour of HFNC delivery could have been evaluated, but it seemed more obvious that the relevance of an urgent triage tool can hardly exceed 1 to 2 hours.

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Conclusion:

In this population of patient with severe AVB supported with HFNC, half of failures occurred within the first 6 hours. Use of ROX index before or 1 hour after delivery of this support was not able to predict this event.

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FIGURE TABLE

Figure 1. Cumulative number of failures according to time in infants with acute viral bronchiolitis included in the TRAMONTANE 2 trial.

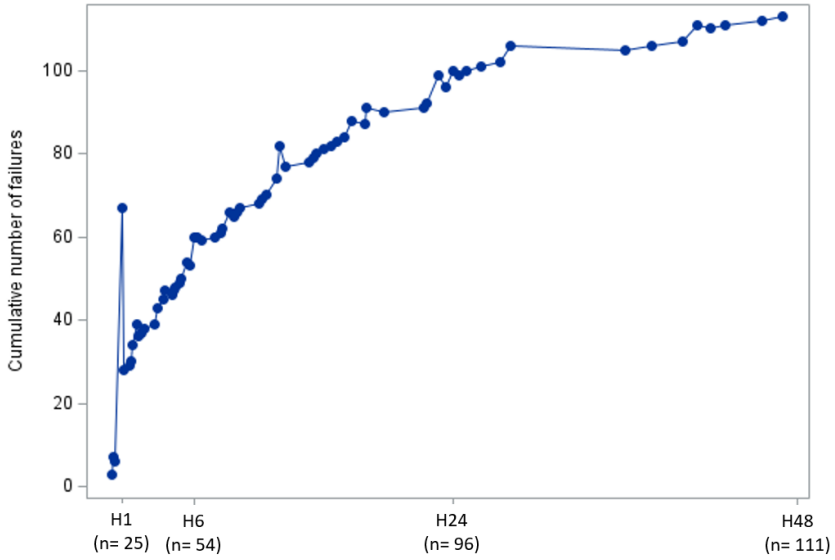

Table 1. Characteristics of the study population, ROX index and physiological variables at baseline (H0) and 1 hour after HFNC initiation (H1).

	Total Population N= 286	HFNC Success N= 175	HFNC Failure N= 111	p
Study population	Study population	Study population	Study population	Study population
Male (%)	170 (59.4)	100 (57.1)	70 (63.1)	0.32
Age, days (±SD)	54 (54)	58 (42)	47 (68)	<0.01
Weight, g (±SD)	4460 (1137)	4547 (1147)	4324 (1112)	0.09
Born preterm (%)	42 (15)	27 (15)	15 (14)	0.66
Baseline (H0)	Baseline (H0)	Baseline (H0)	Baseline (H0)	Baseline (H0)
ROX index (±SD)	N= 250 6.6 (3.3)	N= 158 6.6 (2.8)	N= 92 6.4 (4.1)	0.14
mWCAS (±SD)	N= 286 4.5 (1.1)	N= 175 4.3 (1.0)	N= 111 4.7 (1.3)	0.05
EDIN (±SD)	N= 279 5 (3)	N= 173 5 (3)	N= 106 5 (3)	0.60

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	Total Population N= 286	HFNC Success N= 175	HFNC Failure N= 111	p
pH (±SD)	N= 231 7.3 (0.1)	N= 143 7.3 (0.1)	N= 88 7.3 (0.1)	0.46
RR, bpm (±SD)	N= 286 58 (16)	N= 175 57 (15)	N= 111 59 (18)	0.42
HR, bpm (±SD)	N= 286 161 (20)	N= 175 161 (19)	N= 111 162 (21)	0.35
FiO_2, % (±SD)	N= 250 32 (13)	N= 158 31 (13)	N= 92 33 (13)	0.07
PCO_2, mmHg (±SD)	N= 234 58 (13)	N= 145 58 (13)	N= 89 60 (12)	0.28
1 hour after HFNC initiation (H1)	1 hour after HFNC initiation (H1)	1 hour after HFNC initiation (H1)	1 hour after HFNC initiation (H1)	1 hour after HFNC initiation (H1)
ROX index (±SD)	N= 261 7.4 (3.3)	N= 175 7.7 (3.4)	N= 86 7.0 (2.8)	0.09
mWCAS (±SD)	N= 258 3.5 (1.2)	N= 175 3.3 (1.0)	N= 83 4.0 (1.5)	< 0.01
EDIN (±SD)	N= 256 3 (2.3)	N= 173 2.9 (2.2)	N= 83 3.3 (2.5)	0.30
RR, bpm (±SD)	N= 261 51 (14)	N= 175 50 (13)	N= 86 54 (17)	0.05
HR bpm (±SD)	N= 261 155 (19.4)	N= 175 153 (20.3)	N= 86 158 (16.9)	0.03
FiO_2, % (±SD)	N= 261 29.6 (8.5)	N= 175 29.4 (8.9)	N= 86 30.0 (7.8)	0.28
Change during the first hour of HFNC delivery (H1-H0)	Change during the first hour of HFNC delivery (H1-H0)	Change during the first hour of HFNC delivery (H1-H0)	Change during the first hour of HFNC delivery (H1-H0)	Change during the first hour of HFNC delivery (H1-H0)
ROX index (±SD)	N= 230 0.8 (3.3)	N= 158 1.0 (3.3)	N= 72 0.5 (3.4)	0.34
mWCAS (±SD)	N= 258 -0.9 (1.0)	N= 175 -1.0 (1.0)	N= 83 -0.7 (1.0)	0.07
EDIN (±SD)	N= 252 -2.0 (2.4)	N= 171 -2.2 (2.4)	N= 81 -1.5 (2.3)	0.02
RR, bpm (±SD)	N= 261 -6.3 (± 14.4)	N= 175 -7.1 (± 14.4)	N= 86 -4.7 (± 14.2)	0.31
HR, bpm (±SD)	N= 261 -6.4 (± 20.0)	N= 175 -8.0 (± 19.8)	N= 86 -3.2 (± 20.2)	0.17
FiO_2, % (±SD)	N= 247 -1.9 (12.5)	N= 158 -1.6 (12.2)	N= 89 -2.4 (13.0)	0.94

Values are mean (SD) or numbers (%).

BPD: Bronchopulmonary dysplasia; EDIN: neonatal pain and discomfort scale; HR: Heart rate; mWCAS: modified Wood's Clinical Asthma Score; ROX: Respiratory rate OXygenation index; RR: Respiratory rate.

Table 2. Area under the receiver operating curve for ROX index and physiological variables at baseline (H0), 1 hour after HFNC initiation (H1), and their change during the first hour (H1-H0), to predict the risk of HFNC failure in infants with acute viral bronchiolitis.

AUC (95% CI)	H0	p	H1	p	H1-H0	p
ROX index	0.56 (0.48-0.63)	0.14	0.56 (0.49-0.64)	0.09	0.54 (0.46-0.62)	0.34
mWCAS	0.57 (0.50-0.64)	0.05	0.64 (0.57-0.72)	<0.01	0.57 (0.49-0.65)	0.07
EDIN	0.52 (0.45-0.59)	0.60	0.54 (0.46-0.62)	0.30	0.59 (0.51-0.66)	0.02
RR	0.53 (0.46-0.60)	0.39	0.57 (0.50-0.65)	0.05	0.54 (0.46-0.61)	0.31
HR	0.53 (0.46-0.60)	0.35	0.59 (0.51-0.66)	0.02	0.55 (0.48-0.63)	0.17

AUC: Area under the receiver operating curve; CI: confidence intervals; EDIN: neonatal pain and discomfort scale; HR: Heart rate; mWCAS: modified Wood's Clinical Asthma Score; ROX: Respiratory rate OXygenation index; RR: Respiratory rate.

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