ORIGINAL ARTICLE

What are the most reliable predictive factors of non-invasive ventilation failure in paediatric intensive care units?[☆],[☆☆]

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Abstract
Introduction: Despite there being limited evidence, non-invasive ventilation (NIV) has become a common treatment for acute respiratory failure (ARF). The aim of this study was to identify the predictive factors of NIV failure, in order to enable early detection of patients failing the treatment.
Patients and methods: Prospective cohort study was conducted that included all ARF patients that received NIV as the initial treatment between 2005 and 2009 in a fourteen-bed Paediatric Intensive Care Unit (PICU) of a tertiary university hospital. Information was collected about the NIV, as well as clinical data prior to NIV, at 2, 8, 12, and 24 h. The haemoglobin saturation (SpO_2)/fraction of inspired oxygen (FiO_2) ratio (S/F) was retrospectively calculated. NIV failure was defined as the need for intubation or requiring rescue with bi-level pressure (BLPAP). Univariate and multivariate statistical analyses were performed.
Results: A total of 282 patients received non-invasive support, with 71 receiving Continuous Pressure (CPAP), and 211 with BLPAP treatment. The overall success rate was 71%. Patients receiving BLPAP vs. CPAP, patients with higher S/F ratios at 2 h (*odds ratio* [OR] 0.991, 95% CI: 0.986–0.996, *P* = .001), and patients older than 6 months (Hazard ratio [HZ] 0.375, 95% CI: 0.171–0.820, *P* = .014), were also more likely to fail. Patients with higher heart rates (HR) at 2 h (OR 1.021, 95% CI [1.008–1.034], *P* = .001) and higher inspiratory positive airway pressure (IPAP) at 2 h were more prone to failure (HZ 1.214, 95% CI [1.046–1.408], *P* = .011).

Conclusions: Age below 6 months, S/F ratio, HR, and IPAP at 2 h are independent predictive factors for initial NIV failure in paediatric patients with ARF admitted to the PICU.

¿Cuáles son los factores predictores de fracaso de ventilación no invasiva más fiables en una unidad de cuidados intensivos pediátricos?

Resumen
Introducción: La ventilación no invasiva (VNI) se ha convertido en un tratamiento habitual de la insuficiencia respiratoria aguda (IRA). Nuestro objetivo ha sido identificar factores predictores de fracaso de VNI para detectar precozmente a los pacientes en los que no tendrá éxito.
Pacientes y métodos: Estudio de cohortes prospectivo que incluyó a todos los pacientes con IRA que recibieron VNI como tratamiento inicial entre 2005 y 2009, en una unidad de cuidados intensivos pediátricos de 14 camas de un hospital universitario de tercer nivel. Se recogieron datos clínicos e información sobre la VNI, previamente a su inicio, a las 2, 8, 12 y 24 horas. La razón entre saturación de hemoglobina y fracción de oxígeno inspirada (S/F) se calculó retrospectivamente. Se definió fallo de VNI como necesidad de intubación o necesidad de rescate con presión binivel (BLPAP). Se realizaron análisis estadísticos univariable y multivariable.
Resultados: Un total de n = 282 pacientes recibieron soporte no invasivo, presión continua = 71, BLPAP = 211. El porcentaje de éxito de la muestra global fue 71%. Los pacientes tratados con BLPAP vs. presión continua, aquellos con S/F más elevados a las 2 horas (*odds ratio* 0,991, IC 95%: 0,986-0,996, p = 0,001) y los mayores de 6 meses (*hazard ratio* 0,375, IC 95% 0,171-0,820, p = 0,014), presentaron menor riesgo de fracaso. Los pacientes con frecuencias cardíacas más altas y mayor presión positiva inspiratoria en vía aérea a las 2 horas (*odds ratio* 1,021, IC 95%: 1,008-1,034, p = 0,001; *hazard ratio* 1,214, IC 95%: 1,046-1,408, p = 0,011) presentaron mayor riesgo de fracaso.
Conclusiones: La edad < 6 meses, S/F, frecuencia cardíaca y presión positiva inspiratoria en la vía aérea a las 2 horas son factores predictores independientes de fracaso de VNI inicial en pacientes con IRA admitidos en una unidad de cuidados intensivos pediátricos.

Introduction

Non-invasive ventilation (NIV) has become a widely accepted therapy for management of acute respiratory failure (ARF) in paediatric patients. To date, only one randomised controlled trial has been performed in the paediatric population in patients admitted to a single paediatric intensive care unit (PICU),[1] which found a reduction in the proportion of patients that required endotracheal intubation in the group managed with NIV. However, there is evidence that maintenance of NIV in adult patients that do not respond to this treatment increases the risk of complications and even death.[2] Thus, it is essential to identify predictors for NIV failure to allow the early identification of patients in whom NIV will fail in order to avoid prolonging an inappropriate treatment. Some of the risk factors identified to date are hypoxaemia,[3–6] acute respiratory distress syndrome,[7] a high score in severity scales (PELOD, PRISM II),[6–10] work of breathing,[1,6,10,11] age,[4,10] hypercapnia,[4,7–9] blood pressure[12] and the use of nasal prongs or ventilators without an air/oxygen blender in hypoxic patients.[13]

The primary objective of our study was to identify predictors for failure of initial NIV in the PICU patient population. The secondary objective was to describe the characteristics of NIV as first-line treatment in children with ARF.

Methods

Patients and setting

We conducted a prospective cohort study in the 14-bed PICU of a tertiary care hospital between January 2005 and December 2009. We used consecutive sampling to recruit patients aged 0–18 years with a diagnosis of ARF admitted to the PICU that received NIV as initial treatment. Non-invasive ventilation was initiated in patients that met the clinical criteria for ARF and at high probability of intubation in the next 6 h. This decision was made by the clinician in charge of the patient if the patient presented any of the following signs: respiratory rate (RR) more than 2 standard deviations (SDs) above normal, need of a fraction of inspired oxygen (FiO_2) greater than 0.5 to maintain the percentage of oxygenated haemoglobin

Table 1 Criteria used to select the interface and ventilator.

	Device and interface used for CPAP	Device and interface used for BiPAP
0–6 months	Benveniste with NPA	<1 m: Giulia (GINEVRI) with nasal prongs
	Bubble CPAP (Fisher & Paykel) with nasal prongs	0–3 m: Servo-i (Maquet) with NPA
		>3 m: BiPAP Vision (Philips) with nasal used as oronasal interface (Profile)
>6 months	BiPAP Vision (Philips) o Carina (Dräger) with nasal interface (Comfort Classic) or nasal interface used as oronasal (Profile)	BiPAP Vision or Carina (Dräger) oronasal (Performatrak, Hans Rudolph 7500, Mirage), nasal (Comfort Classic) or nasal as oronasal (Profile) interface

NPA, nasopharyngeal airway.
The Benveniste valve (used in our unit in 64% of patients aged 0–6 months) is an adaptation crafted by hand of a water seal connected to the interface (usually a NPA) by means of an open ring that helps reduce the work of breathing in the expiratory phase.

(peripheral capillary oxygen saturation, SpO_2) above 94% or progressive dyspnoea at rest. We categorised respiratory failure as type I (changes in ventilation/perfusion without impairment of gas exchange at the alveolar level) or type II (changes accompanied by impaired gas exchange in alveoli) based on the classification proposed by Newth.[14] The exclusion criteria were the presence of any contraindication for the use of NIV[15]: cardiac arrest, haemodynamic instability requiring inotropic therapy, severe arrhythmia, Glasgow coma scale score of less than 10, facial trauma, surgery, vocal cord paralysis, undrained pneumothorax and active upper gastrointestinal bleeding. We also excluded patients that were intubated or ventilated through a tracheostomy tube at the time of admission, as well as patients that received NIV after extubation or palliative NIV (such as patients with diseases where intubation is considered a futile intervention). The study was approved by the Ethics and Research Committee of the Hospital Sant Joan de Déu and considered exempt of the need for informed consent, as NIV is a routine treatment in the PICU and consent for the use of this type of data was not necessary at the time of the study.

Non-invasive ventilation technique

The physician in charge of the patient was responsible for the decision to choose between continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP). Continuous positive airway pressure was used in patients with apnoea or mild dyspnoea, and BiPAP in patients with moderate to severe dyspnoea, significantly increased work of breathing (based on lung sounds and diaphragmatic excursion) despite the use of CPAP, low inspiratory capacity or progressive hypercapnia.

Materials

We used the following interfaces: nasal prongs for the Bubble CPAP system (Fisher & Paykel Healthcare Ltd., New

Zealand) and the Giulia™ ventilator (GINEVRI, Italy); Profile Lite™ and Comfortclassic™ Philips Respironics nasal masks (Philips Respironics, Netherlands) used as oronasal masks; the Mirage™ (ResMed, California, USA), PerformaTrak® (Philips Respironics, Netherlands) and 7500® (Hans Rudolph Inc., Kansas, USA) oronasal masks; and endotracheal tubes used as nasopharyngeal tubes. Table 1 details the criteria used to select the interface and ventilator. Comfeel™ hydrocolloid dressings (Coloplast, Denmark) and Mepentol™ hyperoxygenated fatty acid solution (Bama-Geve, Spain) were used to prevent pressure ulcers. Active humidification (Fisher & Paykel) was used in every patient starting in 2007.

Ventilation strategy

The ventilation strategy was selected according to the protocol established by the Working Group on Respiratory Care of the Sociedad Española de Cuidados Intensivos Pediátricos (Spanish Society of Paediatric Intensive Care).[15] The initial pressure set for CPAP was 4–5 cmH_2O. In patients that did not experience improvement in work of breathing or apnoea, the pressure was increased to up to 8 cmH_2O. The initial settings for BiPAP were an inspiratory positive airway pressure (IPAP) or maximum inspiratory pressure of 6–8 cmH_2O and an expiratory positive airway pressure (EPAP) or positive pressure at the end of expiration of 4 cmH_2O. The IPAP was increased in 2 cmH_2O increments to up to 22 cmH_2O in case of an inadequate tidal volume, insufficient improvement of work of breathing or hypercapnia. The EPAP was increased to up to 8 cmH_2O to improve alveolar recruitment and oxygenation. There was no set maximum FiO_2.

If any sign of treatment failure was detected, NIV was discontinued and the patient underwent intubation and started conventional mechanical ventilation. The following were considered signs of failure: $SpO_2 < 85\%$ and a partial pressure of carbon dioxide (pCO_2) greater than 65 mmHg despite application of maximum settings in NIV, increase in work of breathing, apnoea or development of exclusion criteria. Patients were weaned of NIV gradually, with

stepwise decreases in IPAP by 2 cmH$_2$O and in EPAP by 1 cmH$_2$O when the patient experienced a decrease in RR and work of breathing and the FiO$_2$ was less than 0.4. The patients underwent placement of a nasogastric tube to avoid abdominal distension and for administration of enteral feedings.

Monitoring

All patients underwent continuous monitoring of heart rate, RR and SpO$_2$. Peripheral venous blood gas analysis was only performed when the physician in charge considered it necessary.

Sedation

When nonpharmacological measures were insufficient to prevent patient-ventilator asynchrony, the patient received sedatives (in monotherapy or as combination therapy), such as oral levomepromazine (1 mg/kg/dose), continuous intravenous infusion of midazolam (0.05–0.1 mg/kg/h) or propofol (1–2 mg/kg/h) for less than 24 h.

Data collection

For each episode, we recorded the age and sex of the patient, the underlying disease and the severity score (Paediatric Risk of Mortality Score II [PRISM II]). We also collected data on variables related to NIV: aetiology of ARF, type of respiratory failure, mode of ventilation, ventilatory parameters (FiO$_2$, IPAP, EPAP), physiological variables (HR, RR and SpO$_2$) prior to initiation of NIV and at 2, 8, 12 and 24 h of treatment, changes (numerical difference in values) in HR and RR relative to baseline, peripheral venous blood gas values (when obtained), changes in the mode of ventilation, ventilator or interfaces used, administration of sedatives, development of complications or contraindications, mortality, duration of NIV, outcome of NIV (success/failure) and length of stay in the PICU.

We defined NIV failure as the need for intubation or rescue with BiPAP in the group initially treated with CPAP. The very strong correlation between the SaO$_2$/FiO$_2$ (S/F) and PaO$_2$/FiO$_2$ (P/F) ratios was confirmed in the paediatric population in 2009.[16] Therefore, we calculated the S/F ratio retrospectively and assessed its potential usefulness as a predictor of NIV failure. We calculated the S/F ratio for the baseline before initiation of NIV and at 2, 4, 8, 12 and 24 of NIV, excluding any values of SpO$_2$ greater than 97%.

Statistical analysis

We performed a descriptive analysis, expressing qualitative variables as percentages and 95% confidence intervals (CIs) and quantitative variables as mean or median as a measure of central tendency, and standard deviation or interquartile range (IQR) as a measure of dispersion, depending on whether or not the data distribution was normal. We assessed the correlation of outcome measures with different variables under study by means of the chi square test, the Student t test or the Mann–Whitney U test, depending on
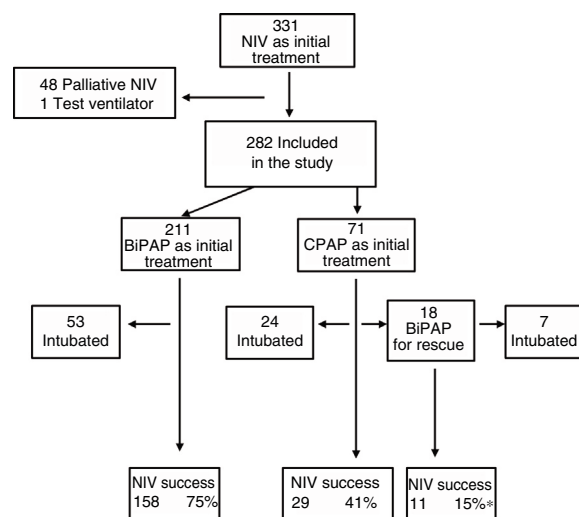

Figure 1 Flow chart of patients included in the study.

the shape of the distribution. We performed a multivariate analysis fitting forward stepwise binary logistic regression and Cox regression models to identify potential predictors of NIV success or failure, calculating the odds ratios and hazard ratios, respectively, with their corresponding 95% CIs. The variables selected for the model were those corresponding to p-values of less than 0.1 in the univariate analysis or which had been found to be significant in the previous literature. In case of potential colinearity, we selected the variable for which there was data earlier in time. We provide a measure of the predictive power of the model, the -2 log-likelihood statistic (-2LL), which is better the lower the value of the statistic, to better inform the reader.

Results

Descriptive analysis

In the period under study, 5101 patients were admitted to the PICU, of who 2238 (43.9%) required ventilatory support. Within this subset, 331 (14.8%) received NIV as the initial mode of ventilation. We excluded 48 patients that received NIV for palliative care and 1 case where a test ventilator was used. Thus, the final sample comprised 282 patients (12.6%), of who 71 were managed with CPAP and the rest with BiPAP (Fig. 1). In the CPAP group, 14% of patients had type I respiratory failure, compared to 40% in the BiPAP group.

The most frequent relevant medical conditions in the sample were congenital heart disease (12.4%), chronic neuromuscular disease (9.1%), cardiovascular postoperative period (8.7%), history of preterm birth (3.2%) and Down syndrome (2%); 47% of the patients were previously healthy. The diagnoses associated with ARF most frequently were bronchiolitis (31%), pneumonia (15%), viral respiratory infection (9%) and asthma (7%).

Sedation was used in 47% of cases to promote patient-ventilator synchronisation, and oral levomepromazine was the drug used most frequently for the purpose. Fifteen patients required a change of interface due to leaks.

Table 2 Baseline characteristics of patients by success or failure of NIV.

	NIV ($n = 282$)	Success ($n = 200$)	Failure ($n = 82$)	P
Age (months)[a]	12 [1.9; 49]	21 [4; 82]	3.4 [1; 14]	.0001
	33–47	42–61	10–26	
Bronchiolitis (%)	31	23	61	.00001
	28–40	17–29	50–72	
Type II respiratory	58	51	75	.0003
failure (%)	52–64	44–58	64–84	
Male sex[a] (%)	64.5	63.5	69	.466
	59–70	57–70	59–80	
FiO_2	0.49 ± 0.25	0.50 ± 0.25	0.44 ± 0.24	.400
	0.46–0.52	0.46–0.53	0.39–0.49	
SpO_2 (%)	95 ± 6	93 ± 7	94 ± 6	.870
	94–96	92–94	93–95	
RR (breaths/min)	46 ± 18	44 ± 17	50 ± 25	.700
	44–48	42–46	44–55	
HR (beats/min)	154 ± 25	149 ± 27	147.5 ± 31	.529
	151–157	145–153	141–154	
S/F ($n = 124$)	236 ± 144	231 ± 119	255 ± 99	.351
	210–261	214–248	233–277	
pCO_2 (mm Hg)	48 ± 13	49 ± 13	49 ± 12	.911
($n = 121$)	46–50	47–51	46–52	
pH ($n = 121$)	7.34 ± 0.08	7.35 ± 0.07	7.30 ± 0.1	.037
	7.339–7.341	7.34–7.36	7.28–7.32	
PRISM II[a]	6 [4.75; 10]	5.5 [4; 8]	8 [5; 12]	.019
	6–8	4–6.5	6–12	

FiO_2, fraction of inspired oxygen; HR, heart rate; pCO_2, partial pressure of carbon dioxide; PRISM II, Paediatric Risk Score of Mortality II; RR, respiratory rate; S/F, haemoglobin saturation/fraction of inspired oxygen; SpO_2, haemoglobin saturation.

[a] The age and PRISM II, whose distribution was not normal, are expressed as median and interquartile range; sex, presence of bronchiolitis and presence of type II respiratory failure as absolute frequencies and percentages, and the rest of the variables, which followed a normal distribution, as mean $\pm$ standard deviation. For all these statistics, the 95% confidence interval for the sample is given below the value.

Complications were mild and infrequent: pressure ulcers ($n = 11$), pneumomediastinum ($n = 1$), gastric distention ($n = 1$), hypercapnia ($n = 1$) and conjunctivitis ($n = 1$). Four patients died, and none of these deaths could be attributed to the previous use of NIV. The proportion of success in our study was 71%, although there were differences based on the initial treatment, with the lowest proportion (55%) in the group treated exclusively with CPAP (Fig. 1). As Fig. 1 shows, 18 patients required rescue with BiPAP, which succeeded in preventing intubation in 11 (61%). Table 2 presents the baseline data for the total sample comparing the NIV success and NIV failure subsets. We found significant differences between the success and failure subsets at baseline for age (21 vs. 3.4 months), blood pH, type of respiratory failure and frequency of bronchiolitis diagnosis, and in the PRISM score at 24 h (5.5 vs. 8).

Table 3 compares the patients treated with CPAP versus BiPAP, highlighting that patients that received CPAP were significantly younger and had lower oxygen requirements compared to patients treated with BiPAP.

Tables 4 and 5 present the differences between the NIV success and NIV failure subsets of patients in the CPAP group and the BiPAP group, respectively. Although we ought to highlight the difference in efficacy between NIV devices (Benveniste, 55%; BiPAP Vision® 71%) it was not statistically significant. In the BiPAP group, patients in whom NIV failed were significantly younger (10 vs. 28.5 months, $P = .001$), had significantly higher RRs (51 vs. 41 bpm, $P = .010$) and had significantly lower blood pH values (pH 7.30 vs. 7.35, $P = .014$) prior to initiation of NIV compared to patients that did not require intubation. As can be seen in Fig. 2, approximately 70% of patients were intubated in the first 24 h. The most frequent causes of intubation were the presence of clinical signs of respiratory muscle fatigue (absence of improvement in HR and RR, thoracoabdominal asynchrony) and persistent hypoxaemia.

Lastly, the length of stay in the PICU was significantly longer in patients that experienced BiPAP failure.

Multivariate analysis (Table 6)

We performed a multivariate analysis of the data for the total sample by means of binary logistic regression (BLR). We analysed the following variables: mode of ventilation, type of respiratory failure, age 6 months (greater than/less than), RR, HR and S/F ration at 2 h of treatment and bronchiolitis (yes/no) (predictive power, $-2LL = 232$). We also performed a multivariate analysis of the subset of patients that received BiPAP at some point during the course of disease by means of Cox regression. We analysed the following variables: mode of ventilation age 6 months (greater

Table 3 Characteristics of patients before initiation of NIV. Comparison of CPAP and BiPAP modes.

	BiPAP ($n = 211$)	CPAP ($n = 71$)	P
Age (months)[a]	22 [7; 80]	1.2 [0.7; 2.2]	.0001
	43–60	0.8–11	
Bronchiolitis (%)	21	73	.0001
	15–27	62–84	
Type II respiratory failure (%)	54	69	.045
	48–61	58–80	
Male sex[a] (%)	59	64.5	.40
	52–65	56–71	
FiO_2	0.50 [0.36; 0.64]	0.30 [0.26; 0.35]	.0001
	0.47–0.53	0.28–0.39	
SpO_2 (%)	96 [92; 99]	98 [93; 100]	.056
	93–95	94–97	
RR (breaths/min)	45 ± 18	60 ± 17	.686
	43–48	41–52	
HR (beats/min)	153 ± 26	158 ± 18	.082
	148–156	53–166	
S/F ($n = 124$)	207 ± 93	320 [265; 357]	.0001
	188–227	283–346	
pCO_2 (mm Hg) ($n = 121$)	43 [38; 49]	51 ± 9	.005
	44–50	48–55	
pH ($n = 121$)	7.36 [7.31; 7.40]	7.34 [7.28; 7.38]	.309
	7.35–7.37	7.32–7.36	
PRISM II[a]	7.1 ± 4.5	7.5 ± 4.7	.734
	6–8	6–8	

HR, heart rate; FiO_2, fraction of inspired oxygen; pCO_2, partial pressure of carbon dioxide; PRISM II, Paediatric Risk Score Mortality II; RR, respiratory rate; S/F, haemoglobin saturation/fraction of inspired oxygen; SpO_2, haemoglobin saturation.

[a] Age, the PRISM II score and other variables that did not have a normal distribution are expressed as median and interquartile range; sex as percentages, and the rest of the variables, which met the normality assumption, as mean ± standard deviation. For all these statistics, the 95% confidence interval for the sample is given below the value.

than/less than) and HR, S/F ad IPAP at 2 h. Good predictive power (−2LL = 22).

Another multivariate analysis involved the group treated exclusively with BiPAP.

- BLR: the variables analysed were age 6 months (greater than/less than), values of IPAP, S/F ratio and HR and the decrease in the RR at 2 h. Good predictive power (−2LL = 131).
- Cox regression analysis: the variables analysed were age 6 months (greater than/less than), values of IPAP, HR and S/F ratio at 2 h. Lesser predictive power (−2LL = 240).

Although we also performed a multivariate analysis in the CPAP group, we did not find statistically significant differences due to the small size of this subset of patients.

Discussion

Our analysis identified 2 important predictors of NIV failure. The first and most strongly correlated was age, which is consistent with previous studies.[4,11] More specifically, we found that age less than 6 months predicted NIV failure. This could be explained by the anatomical and physiological characteristics of this age group, which would result in a higher incidence of severe respiratory failure. Furthermore, these children have apnoeic episodes more frequently,[17] and those born preterm in particular are more likely to experience patient-ventilator asynchrony[18] compared to patients aged more than 7 months.[19] On the other hand, the technical limitations of the ventilators and interfaces used in this age group complicate the use of NIV.

Another important predictor identified in the total sample was initial use of CPAP, which contradicts the findings of James et al.[12] Since severe apnoea was not the reason for NIV failure in patients treated with CPAP with the exception of 2 cases, this difference could be due to the use of the Benveniste valve in most patients in the CPAP group, a device that is less effective (and is no longer used in our unit) because it does not allow measurement of pressures or volumes or compensating for leaks. On the other hand, the use of conventional ventilators in younger children,[3] as was done in the study by James et al, has been shown to have poorer outcomes compared to the use of ventilators specifically designed for NIV.[6,10,20] Thus, both their and our study probably reflect the technical limitations of the devices used, as opposed to whether the mode of ventilation is an actual predictor.[21]

The S/F ratio performed as a predictor of NIV failure, especially the lowest values at 2 h of treatment. The largest study conducted to date in the paediatric population (390 episodes) that used the S/F ratio as a monitoring measure

Table 4 Study variables in the group treated with CPAP based on the success or failure of NIV.

	Success (n = 29), 41%	Failure (n = 42)	P
Age (months)[a]	28.5 [11; 106]	10 [3.6; 25]	.0001
RR 2 h (breaths/min)[a]	35 [28; 43]	40.5 [33; 55]	.007
RR 12 h (breaths/min)[a]	32 [25; 40]	42 [27; 56]	.09
RR 24 h (breaths/min)[a]	42 [33; 51]	52 [37; 56]	.058
Decrease in RR at 2 h (breaths/min)[a]	−3 [−9; 15]	−2 [−15; 11]	.45
HR 2 h (beats/min)[a]	134 [116; 152]	143 [32; 161]	.06
HR 12 h (beats/min)[a]	135 [121; 157]	154 [139; 168]	.15
HR 24 h (beats/min)[a]	145 [129; 166]	150 [126; 162]	.07
Decrease in HR at 2 h (beats/min)[a]	11 [−5; 50]	9 [−5; 7]	.47
SpO_2 2 h (%)[a]	99 [98; 100]	97 [94; 100]	.023
SpO_2 8 h (%)[a]	100 [97; 100]	97 [96; 99]	.037
SpO_2 24 h (%)	97 ± 3	98 ± 3	.135
FiO_2 2 h	0.34 ± 7	0.40 ± 12	.009
FiO_2 8 h	0.33 ± 7	0.37 ± 7	.05
FiO_2 24 h	0.30 ± 7	0.35 ± 5	.012
S/F 2 h[a], n = 57	294 [232; 414]	259 [247; 317]	.003
S/F 8 h[a], n = 51	294 [267; 336]	270 [237; 298]	.10
S/F 24 h[a], n = 47	333 [273; 407]	274 [248; 321]	.001
Type II respiratory failure (%)	69	69	.8
Bronchiolitis (%)	59	76	.07
Benveniste valve (%)	55	45	.684[*]
BiPAP vision (%)	71	29	.684[*]
Length of PICU stay (days)[a]	9 [5; 12]	11 [9; 13]	.09

FiO_2, fraction of inspired oxygen; HR, heart rate; RR, respiratory rate; S/F, haemoglobin saturation/fraction of inspired oxygen; SpO_2, haemoglobin saturation.

[a] Expressed as median and interquartile range; the rest of the variables, which followed a normal distribution, expressed as mean ± standard deviation.

[*] We compared the proportion of failure based on the device used using the Fisher exact test.

demonstrated its validity as a predictor of failure at 1 h and 6 h of treatment,[22] and the authors proposed to cut-off point of 200 for this ratio. Along these lines, previous studies had already demonstrated that hypoxaemia was a predictor of failure, with the authors proposing a P/F ratio of less than 175 in adults[23] and an S/F ratio of less than 189 in children[24] for indication of intubation. Based on the cumulative evidence to date, the S/F ratio could be used as a standardised non-invasive marker of oxygen saturation in patients in whom vascular access cannot be established, a situation that is frequent in paediatric patients requiring NIV.

When it came to other variables that are indirect measures of the work of breathing, we also found that higher values of the HR at 2 h of treatment independently predicted failure, a result that was consistent with previous reports,[1,11] a reminder of the importance of closely monitoring HR, especially at the beginning of treatment. Our study also identified high values of the IPAP at 2 h as an independent predictor of failure. This agreed with the findings of a previous study[5] that identified a mean airway pressure (MAP) greater than 11.5 cmH2O in conventional ventilators as a predictor of failure. Since the MAP cannot be measured by ventilators specifically designed for NIV, the IPAP, equivalent to the peak pressure, could be a more useful parameter, as it is measured by all ventilators.

We ought to highlight that the odds ratios and hazard ratios corresponding to the variables HR, S/F ratio and IPAP at 2 h had values close to 1, so that any of them in isolation cannot guide clinical decision-making. Our findings are consistent with the current data and suggest that the early identification of patients at risk of NIV failure must be based on age and the monitoring of hypoxaemia and work of breathing. While previous studies have identified the PRISM II as a predictor,[6–10] we ruled out its use in our study, as this score is obtained at least 24 h after admission, and a large proportion of patients managed with NIV require intubation before this time, which makes this score useless for predicting failure in the first 24 h.

There are several limitations to our study. First of all, our decision to define failure of CPAP not only as endotracheal intubation but also as the need of rescue with BiPAP may be confusing to the reader and be a source of bias through uncontrolled confounders in the multivariate analysis. Another potential weakness is the loss of patients with SpO_2 values of more than 97% in the multivariate analysis, which reduced the power of the S/F ratio as treatment with NIV progressed. However, substituting the FiO_2 (n = 282) for the S/F ratio in this Cox regression model lessened the predictive power (increase in the −2LL), which reinforced the validity of the data obtained using the S/F ratio. Since

Table 5 Study variables in the group treated with bilevel positive airway pressure based on the success or failure of NIV.

	Success group (n = 158) 75%	Failure group (n = 53)	P
Age (months)	28.5 [11; 106]	10 [3.6; 25]	.0001
Age <6 months (%)	14.5	41	.0001
RR 2 h (breaths/min)	35 [28; 43]	40.5 [33; 55]	.007
RR 12 h (breaths/min)	33 ± 11	38 ± 13	.006
RR 24 h (breaths/min)	32 [25; 40]	42 [27; 56]	.029
Decrease in RR 2 h (breaths/min)	2 [−9; 15]	3 [−9; 15]	.269
HR 2 h (beats/min)	134 [116; 152]	143 [32; 161]	.006
HR 12 h (beats/min)	128 [108; 143]	137 [114; 162]	.022
HR 24 h (beats/min)	123 [103; 146]	151 [119; 163]	.852
Decrease in HR 2 h (beats/min)	10 [−5; 25]	4 [−12; 20]	.06
SpO_2 2 h (%)	97 ± 4	96 ± 4	.495
SpO_2 8 h (%)	97 ± 4	96 ± 3	.843
SpO_2 24 h (%)	97 ± 4	96 ± 5	.135
FiO_2 2 h	0.41 [0.35; 0.50]	0.50 [0.41; 0.60]	.011
FiO_2 8 h	0.40 [0.35; 0.44]	0.50 [0.41; 0.55]	.002
FiO_2 24 h	0.35 [0.30; 0.45]	0.45 [0.32; 0.52]	.015
S/F 2 h n = 185	222 [192; 277]	200 [160; 223]	.013
S/F 8 h n = 193	250 [225; 285]	245 [189; 311]	.755
S/F 24 h n = 140	274 [218; 323]	208 [175; 283]	.016
IPAP 2 h	13 ± 3	14 ± 3	.006
Type II respiratory failure (%)	52	62	.25
Length of PICU stay (days)	4 [2; 6]	9.5 [6; 14.5]	.0001

HR, heart rate; FiO_2, fraction of inspired oxygen; h, hours/hours of treatment with NIV; IPAP, inspiratory positive airway pressure; PICU, paediatric intensive care unit; RR, respiratory rate; S/F, haemoglobin saturation/fraction of inspired oxygen; SpO_2, haemoglobin saturation.
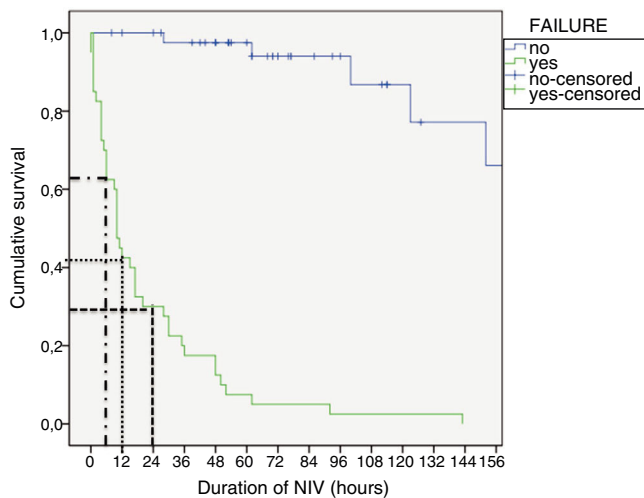
Table 6 Summary of the multivariate analysis.

	Odds ratio (95% CI)	P
Multivariate analysis of the total sample by means of binary logistic regression		
CPAP vs. BiPAP	7.817 (3.5–17.441)	.0001
Higher S/F at 2 h	0.991 (0.986–0.996)	.001
Higher HR at 2 h	1.021 (1.008–1.034)	.001
S/F at 2 h	0.991 (0.984–0.999)	.026
HR at 2 h	1.027 (1.009–1.046)	.004
	Hazard ratio (95% CI)	P
Multivariate analysis of the patient subset managed with BiPAP at some point during their stay by means of Cox regression		
Age greater/less than 6 months	0.375 (0.171–0.820)	.014
IPAP mayor at 2 h	1.214 (1.046–1.408)	.011
Multivariate analysis of the patient subset treated exclusively with BiPAP by means of Cox regression		
S/F at 2 h	0.991 (0.984–0.999)	.026
HR at 2 h	1.024 (1.008–1.040)	.003
IPAP at 2 h	1.030 (1.030–1.351)	.017

peripheral venous blood gas analysis was not routinely performed in every patient before and during NIV, our study was also severely limited in the analysis of monitoring of acidosis/hypercapnia and for the purpose of comparison with other studies.

Lastly, the considerable diversity in the equipment required based on the age of the patient also limits the generalisation of our findings to other hospitals, especially when it comes to the delivery of CPAP with a device handcrafted at the hospital.

Figure 2 Duration of NIV in success and failure groups until NIV discontinuation or endotracheal intubation. PARCHEOS: Cambiar las comas a puntos en los decimales del eje vertical.

Given the introduction of multiple devices for delivery of CPAP and BiPAP, of new modes of ventilation such as neurally adjusted ventilatory assist (NAVA) or interfaces like the full-face mask, and the fact that the data of our study were collected at least 9 years ago, our conclusions may be debatable. However, there are many facilities where these innovations have not been introduced, so our results may still be considered valid and pertinent in those facilities where there have been no substantial changes in the equipment or protocols used.

Conclusions

Our study found that lower S/F ratios and higher HR values at 2 h of treatment were independently associated with an increased risk of failure of NIV both in the total sample and in the group treated with BiBAP, although this increase was minimal. In the group of patients managed with BiPAP at some point during their stay, we also found that a higher inspiratory pressure at 2 h of treatment and age less than 6 months were associated with an increased risk of endotracheal intubation.

Conflicts of interest

None of the authors had conflicts of interest at the time the study was conducted. In the past 5 years, Dr. Pons has given talks for ResMed and Fisher & Paykel and collaborated in the development of a nasal interface for at-home use for Air Liquide Healthcare. The Hospital Sant Joan de Déu has equipment that has been donated by Philips and ResMed.

References

1. Yañez LJ, Yunge M, Emilfork M, Lapadula M, Alcantara A, Fernandez C, et al. A prospective, randomized, controlled trial of noninvasive ventilation in pediatric acute respiratory failure. Pediatr Crit Care Med. 2008;9:484–9.

2. Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apezteguia C, Gonzalez M, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med. 2004;350:2452–60.

3. Bernet V, Hug MI, Frey B. Predictive factors for the success of noninvasive mask ventilation in infants and children with acute respiratory failure. Pediatr Crit Care Med. 2005;6:660–4.

4. Joshi G, Tobias JD. A five-year experience with the use of BiPAP in a pediatric intensive care unit population. Intensive Care Med. 2007;22:38–43.

5. Munoz-Bonet JI, Flor-Macian EM, Brines J, Rosello-Millet PM, Cruz Llopis M, Lopez-Prats JL, et al. Predictive factors for the outcome of noninvasive ventilation in pediatric acute respiratory failure. Pediatr Crit Care Med. 2010;11:675–80.

6. Lum LC, Abdel-Latif ME, de Bruyne JA, Nathan AM, Gan CS. Noninvasive ventilation in a tertiary pediatric intensive care unit in a middle-income country. Pediatr Crit Care Med. 2011;12:e7–13.

7. Essouri S, Chevret L, Durand P, Haas V, Fauroux B, Devictor D. Noninvasive positive pressure ventilation: five years of experience in a pediatric intensive care unit. Pediatr Crit Care Med. 2006;7:329–34.

8. Larrar S, Essouri S, Durand P, Chevret L, Haas V, Chabernaud JL, et al. Effects of nasal continuous positive airway pressure ventilation in infants with severe acute bronchiolitis. Arch Pediatr. 2006;13:1397–403.

9. Campion A, Huvenne H, Leteurtre S, Noizet O, Binoche A, Diependaele JF, et al. Non-invasive ventilation in infants with severe infection presumably due to respiratory syncytial virus: feasibility and failure criteria. Arch Pediatr. 2006;13:1404–9.

10. Mayordomo-Colunga J, Medina A, Rey C, Diaz JJ, Concha A, Los Arcos M, et al. Predictive factors of non invasive ventilation failure in critically ill children: a prospective epidemiological study. Intensive Care Med. 2009;35:527–36.

11. Mayordomo-Colunga J, Medina A, Rey C, Los Arcos M, Concha A, Menendez S. Success and failure predictors of non-invasive ventilation in acute bronchiolitis. An Pediatr (Barc). 2009;70:34–9.

12. James CS, Hallewell CP, James DP, Wade A, Mok QQ. Predicting the success of non-invasive ventilation in preventing intubation and re-intubation in the paediatric intensive care unit. Intensive Care Med. 2011;37:1994–2001.

13. Antonelli M, Conti G, Moro ML, Esquinas A, Gonzalez-Diaz G, Confalonieri M, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med. 2001;27:1718–28.

14. Newth CJ. Recognition and management of respiratory failure. Pediatr Clin North Am. 1979;26:617–43.

15. Pons-Odena M, Cambra Lasaosa FJ, Sociedad Española de Cuidados Intensivos Pediátricos. Mechanical ventilation in pediatrics (III). Weaning, complications and other types of ventilation. Noninvasive ventilation. An Pediatr (Barc). 2003;59:165–72.

16. Khemani RG, Patel NR, Bart RD 3rd, Newth CJ. Comparison of the pulse oximetric saturation/fraction of inspired oxygen ratio and the PaO_2/fraction of inspired oxygen ratio in children. Chest. 2009;135:662–8.

17. Schroeder AR, Mansbach JM, Stevenson M, Macias CG, Fisher ES, Barcega B, et al. Apnea in children hospitalized with bronchiolitis. Pediatrics. 2013;132:e1194–201.

18. De Waal CG, van Leuteren RW, de Jongh FH, van Kaam AH, Hutten GJ. Patient-ventilator asynchrony in preterm infants on nasal intermittent positive pressure ventilation. Arch Dis Child Fetal Neonatal Ed. 2018, pii:fetalneonatal-2018-315102.

19. Vignaux L, Grazioli S, Piquilloud L, Bochaton N, Karam O, Jaecklin T, et al. Optimizing patient-ventilator synchrony

during invasive ventilator assist in children and infants remains a difficult task. Pediatr Crit Care Med. 2013;14:e316–25.

20. Nunes P, Abadesso C, Almeida E, Silvestre C, Loureiro H, Almeida H. Non invasive ventilation in a pediatric intensive care unit. Acta Med Port. 2010;23:399–404.

21. Park M, Sangean MC, Volpe MS, Feltrim MI, Nozawa E, Leite PF, et al. Randomized, prospective trial of oxygen, continuous positive airway pressure, and bilevel positive airway pressure by face mask in acute cardiogenic pulmonary edema. Crit Care Med. 2004;32:2407–15.

22. Mayordomo-Colunga J, Pons M, López Y, José Solana M, Rey C, Martínez-Camblor P, et al. Predicting non-invasive ventilation failure in children from the SpO_2/FiO_2 (SF) ratio. Intensive Care Med. 2013;39:1095–103.

23. Antonelli M, Conti G, Esquinas A, Montini L, Maggiore SM, Bello G, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med. 2007;35:18–25.

24. Pons-Odena M, Palanca D, Modesto V, Esteban E, González-Lamuño D, Carreras R, et al. SpO_2/FiO_2 (SF ratio) as a predictor of NIV failure in children with hypoxemic respiratory insufficiency. J Pediatr Intensive Care. 2013;2:111–9.