Predictive factors for the outcome of noninvasive ventilation in pediatric acute respiratory failure*

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Objectives: To identify success and failure prognostic signs of noninvasive ventilation in pediatric acute respiratory failure. Noninvasive ventilation constitutes an alternative treatment for pediatric acute respiratory failure. However, tracheal intubation should not be delayed when considered necessary.

Design: Prospective, noncontrolled, clinical study.

Setting: Pediatric intensive care unit in a university hospital.

Patients: Children (age range, 1 month – 16 yrs) with moderate-to-severe acute respiratory failure who received noninvasive ventilation during a 4-year period. Failure was defined as the need for tracheal intubation.

Interventions: None.

Measurements and Main Results: Nine (19.1%) of 47 patients needed tracheal intubation between the third and 87th hour after the start of treatment (33.6 ± 29.6 hrs). Failure was associated with the younger age group (4 ± 3.3 yrs vs. 7.7 ± 5 yrs, p < .04), acute respiratory distress syndrome (4 of 37, p = .013), and worsening radiographic images taken at 24 hrs and/or 48–72 hrs (p = .001 and p < .001, respectively). A significant reduction in heart rate was observed between the second and fourth hour after starting noninvasive ventilation (130 ± 25.8 bpm vs. 116 ± 27.7 bpm, p < .001) and PaO2 (54.1 ± 19.5 torr vs. 48.6 ± 14.3 torr; 7.21 ± 2.6 vs. 6.48 ± 1.91 kPa, p < .007) in the success group. The failure group had a higher rate of breathing assistance, both initial and maximal. In the multivariate analysis, only maximum mean airway pressure and FiO2 formed part of the success/failure discriminant function with a cutoff point of 11.5 and 0.57, respectively.

Conclusions: Modifications in a patient’s respiratory assistance were made depending on the clinical, blood gas, and radiologic evolution of the patient. Mean airway pressure and FiO2 values of >11.5 and 0.6, respectively, predict failure and possibly set the limit above the patient’s risk of delayed intubation increases. (Pediatr Crit Care Med 2010; 11:675–680)

Key Words: noninvasive ventilation; children; acute respiratory failure; acute respiratory distress syndrome; predictive factors; mean airway pressure

Acute respiratory failure (ARF) is one of the main reasons for admission to a pediatric intensive care unit (PICU). Tracheal intubation and conventional mechanical ventilation (CMV) are frequently necessary to treat these patients. Noninvasive ventilation (NIV) has been developed to reduce complications associated with these techniques. Numerous controlled studies and meta-analysis have shown its efficiency in different forms of ARF in adults (1–5), but experience in pediatric ARF is limited, showing a favorable outcome in patients with postextubation ARF (6), acute exacerbation of chronic respiratory failure (7), and hypoxemic ARF (8, 9). The aim of NIV is to gain control of ARF, avoiding intubation; however, when intubation is required, its application should not be delayed, as this may result in a worse prognosis. This is the main reason to look for reliable failure signs of the technique. In adults, several retrospective (10, 11) and prospective (12, 13) studies have identified some factors which can predict the success of NIV. Less information is available regarding children (14–17). The aim of this study is to identify prognostic signs related to the application of NIV in pediatric ARF, which would allow us to use the technique appropriately and detect early on which patients need tracheal intubation and CMV.

MATERIALS AND METHODS

We carried out a prospective, noncontrolled, clinical study on children admitted to the PICU, who were treated with NIV over a period of 4 yrs. This unit is a multivariant PICU composed of six beds at a tertiary university hospital. The study was approved by the Institutional Review Board, and informed parental written consent was obtained. We applied NIV to pediatric patients with ARF, aged 1 month to 16 yrs, when the attending pediatric intensive care physician considered that the patient was likely to require tracheal intubation. All patients included in the study fulfilled the following clinical or blood gas criteria:

1. Increased respiratory rate for their age (18) and moderate-to-severe signs of respiratory distress, reading >4 on the Clinical Score chart used (Table 1), and/or
2. Hypoxemic ARF (type 1): PaO2 <60 torr (< 8 kPa) or arterial oxygen saturation (Sao2) < 90% with FiO2 >.5 (19), and/or
4. Mix form of ARF: Includes criteria from hypoxemic and hypercapnic ARF.

Postextubation ARF was defined as the appearance of clinical ARF with the above criteria, in the immediate postextubation period. Acute respiratory distress syndrome (ARDS)
Table 1. Clinical scores

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Intercostal/sternal retraction</td>
<td>No</td>
</tr>
<tr>
<td>Thoraco-abdominal dissociation</td>
<td>No</td>
</tr>
<tr>
<td>Nasal flaring</td>
<td>No</td>
</tr>
<tr>
<td>Expiratory groan of chest</td>
<td>No</td>
</tr>
<tr>
<td>Cyanosis (SaO2)</td>
<td>No (&gt;92%)</td>
</tr>
<tr>
<td>Conscious level</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Clinical score was applied a synthesis of Silverman and Wood-Downes test, applicable to any type of pediatric acute respiratory failure. We used the Silverman test, utilizing the evolution of the costal and sternal retraction as the only parameter, and we included the evaluations of the level of consciousness and of cyanosis of the Wood-Downes score. This last parameter was evaluated by pulseoximetry, instead of Po2 and clinical evaluation.

Scores: <4, mild; 4–6, moderate; >6, severe.

and pneumonia were diagnosed, using criteria according to the American-European Consensus (21) and Centers for Disease Control (22), respectively. Newborns were excluded, along with those who had: a need for immediate intubation or incapacity to protect the airway; hemodynamic instability in spite of blood volume expansion (>60 mL/kg); and the use of vasoactive drugs (except dopamine <10 μg/kg/min); malformations, traumatisms, and facial burns; undrained pneumothorax; severe digestive hemorrhage; serious obstruction of the superior airway; abundant respiratory secretions; and absolute absence of collaboration (23–27).

A volumetric ventilator with a specifically fitted NIV module was used (Evita 2 Dura, Dräger Medical, Lübeck, Germany) with active humidification in all cases (Fisher and Paykel Healthcare, Auckland, New Zealand). The starting ventilatory mode was used as continuous positive airway pressure with pressure support (CPAP + PS) in patients post extubation and in type 1 moderate ARF patients, and bilevel positive airway pressure with pressure support (BiPAP + PS) in the remaining patients. This mode was also applied on patients where CPAP + PS was initially used but the patient’s evolution was not favorable. Nonventilated mouth-nasal mask interface were used: Mirage model (Resmed, Poway, CA), Perfomatrach (Respironics, Murrysville, PA), or Hans Rudolph masks (Hans Rudolph, Kansas City, MO). Clorazepate dipotassium (0.5–1 mg/kg/day) or midazolam (0.05–0.1 mg/kg/hr) was administered to all patients to improve mask tolerance and adaptation to mechanical ventilation, according to medical criteria. Nasogastric tube decompression was used, according to the attending pediatric physician criteria. All patients remained without enteral feedings until the need for intubation was ruled out. Oral feeding was started when the patient’s situation allowed the temporary withdrawal of NIV.

Treatment failure criteria were determined by withdrawal due to major complications, poor tolerance, and/or inability to stabilize the progression of respiratory failure requiring tracheal intubation (28).

The following variables were analyzed to determine the success/failure prognostic signs:

1. Nominal and Ordinal Variables
   a. Sex
   b. Underlying disease
   c. Cause and type of ARF
   d. Need for sedation
   e. Method of initial mechanical ventilation used (CPAP + PS vs. BiPAP + PS)
   f. Hemodynamic support: defined by the need for vasoactive drugs above dopamine 5 μg/kg/min and/or blood volume expansion of >20 mL/kg in the first 24 hrs
   g. Appearance of complications brought on by the use of NIV
   h. Respiratory evolution before 0 hr, 2 hrs, and 6 hrs assessed using the Clinical Score chart (Table 1)
   i. Chest radiography carried out at the beginning, after 24 hrs and 48–72 hrs. The evaluation was performed by a pediatric radiologist who had no previous knowledge of the patient’s clinical evolution.

2. Scale Variables (Quantitative)
   a. Age
   b. Respiratory assistance (initial and maximum): peak inspiratory pressure, positive end-expiratory pressure, pressure support (PS), mean airway pressure (MAP) and FiO2. Oxygen was administered by a Venturi mask, reservoir mask, or nasal prongs before starting NIV. When nasal prongs were used, FiO2 was calculated by using the formula: FiO2 = 20 + 4 × oxygen flow in L/min (29). The following FiO2 value was measured by a mechanical ventilator.
   c. NIV application time and length of PICU stay
   d. Respiratory rate, heart rate, and blood pressure measured (0 hr and 2–4 hrs)
   e. Blood gases and pH (0 hr and 2–4 hrs): capillary samples were taken from most patients (arterialized blood by heating the peripheral extremity); the attending pediatric physician determined the need to obtain arterial samples.
   f. SaO2 as determined by pulseoximetry through the use of Masimo technology (Radical, Datascop, Irvine, CA) at 0 hr and 2–4 hrs
   g. Pediatric logistic organ dysfunction mortality score during the first 24 hrs

Statistical Analysis

The SPSS statistic package 14.0 for Windows (SPSS Inc., Cary, NC) was used to analyze statistics. Analyses of variance were used for continuous variables between subjects and t tests were used for related values. Repeated-measured designs were also used (intrasubject). In the case of multiple comparisons, Type I errors were corrected, using the Bonferroni adjustment. To assess the prognostic value in the case of ordinal variables, the Wilcoxon matched-pairs ranks test for related values was applied, and the Kruskal-Wallis test was used for comparisons within groups. Fisher’s exact test was used for dichotomous variables and the Ji-square for 2 × 3 tables. For the scale variables, a discriminant analysis was used along with an analysis of the receiver operating characteristic curve. A p .05 was considered statistically significant.

RESULTS

During the study period, there were 208 episodes of ARF in our PICU. Of these, 98 (47.1%) required positive-pressure respiratory assistance: 51 (52.1%) were treated with CMV. In the remaining 47 episodes (47.9%), we applied NIV. This group included 37 patients, 25 boys and 12 girls aged between 1 month and 16 yrs of age (average age, 7.1 ± 4.9 yrs). The technique was used four times in one patient, three times in another, and twice in five patients. Twelve patients suffered from psychomotor delay and 10 patients suffered from immunosuppression. The most frequent causes of ARF were pneumonia in 20 (42.5%) patients, followed by postextubation ARF in 11 (23.4%) patients and ARDS in 10 (21.3%) patients. The remaining diagnoses were: lung atelectasis (n = 2), acute lung injury (n = 2), asth-
The radiologic evolution of the seven patients with normal initial radiograph did not show any alterations. Improvement was observed at 24 hrs (n = 39) in 26 (66.6%) patients, worsening in three (7.6%) patients, and there was no change in ten (25.6%) patients. Improvement was noted in 26 (70.2%) patients (Fig. 1), within 48–72 hrs (n = 37) worsening in five (13.5%) patients, and no change was observed in six (16.2%) patients.

Worsening of radiographic images at 24 hrs and/or between 48 hrs and 72 hrs was mainly associated with NIV failure (p = .001 and p < .001, respectively), all patients requiring tracheal intubation and CMV.

Complications were minor and linked to the use of the interface, although in none of the patients was it necessary to withdraw NIV. The most frequent complication was minor erosion and irritant dermatitis of nasal bridge (29.8%). Three patients had signs of irritative conjunctivitis (6.4%). There was no relationship between complications and outcome.

CPAP + PS was used initially in 14 patients and proven successful in seven of these patients. The other seven patients needed to be switched over to BIPAP + PS. Two of these patients required tracheal intubation. BIPAP + PS was the first method used in 33 patients. However, no correlation was found between the first method used and the result. Initial and maximum assistance is shown in Table 4. More assistance was needed for patients for whom the technique had failed in both the initial as well as maximum parameters (Table 5). They also required significantly stronger breathing assistance after intubation (Fig. 2).

In the multivariate analysis of scale variables (Tables 3 and 5), only maximum MAP and P/F formed part of the discriminant function to predict outcome. The results were correctly predicted in 85.1% of cases.
of patients when using this function. When the leave-one-out cross-validation with forward stepwise was used, the percentage remained identical.

With the receiver operating characteristic curve analysis, we established as cut-off points for failure an MAP of 11.5 cm H2O (sensibility, 89%; specificity, 82%) and an FIO2 of 0.57 (sensibility, 78%; specificity, 84%). Understandably, the time needed for NIV was significantly less in those patients in whom the technique had failed (36.6 ± 29.6 hrs vs. 80.8 ± 62.2 hrs, p < .05). On the other hand, they required longer breathing assistance (285.3 ± 150.1 hrs vs. 80.8 ± 62.2 hrs, p < .03) as well as a lengthier PICU stay (23 ± 16.9 days vs. 13.1 ± 9.9 days, p < .03). Only one patient from the failure group died during hospital stay, after 1 month of NIV treatment, due to complications of the underlying disease.

**DISCUSSION**

The main aim of NIV is to control ARF and to avoid tracheal intubation and its complications. In our study, this objective was achieved in 81% of patients. Furthermore, NIV application only caused minor complications, which were interface related. These results are similar to other studies (15, 30–32). Therefore, we think that it should be used early, as long as its use is not contraindicated. Early application is especially important for patients suffering from psychomotor delay (9) and immunosuppression (5, 15, 33–35), because the application of NIV could especially benefit them.

Our results are also in agreement with those of other authors (14, 16, 17, 30). The risk of failure is higher in patients at younger ages and also among those with more severe conditions at the time of admission, as our results indicate and has been observed by other authors (15, 17). Therefore, extra vigilance is required for these patients.

As in other pediatric ARF studies (9, 14, 28, 30), pneumonia was reported to be the main cause of NIV, followed by postextubation ARF (14, 15, 30, 32, 36). There is some controversy about the use of NIV on adult patients for these indications (10, 13, 37). There is also controversy about its use in adult patients with ARDS (38, 39). In pediatrics, only Essouri et al (15) studied its use in these patients, showing a failure rate of 78%, which in our study dropped to 50% (5 of 10 patients). On the other hand, tracheal in-

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**Table 4. Initial and maximum assistance (n = 47)**

<table>
<thead>
<tr>
<th></th>
<th>Initial Assistance (Range)</th>
<th>Maximum Assistance (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIO2</td>
<td>0.5 ± 0.2 (0.21–0.9)</td>
<td>0.5 ± 0.2 (0.3–1)</td>
</tr>
<tr>
<td>PIP, cm H2O</td>
<td>17.7 ± 2.9 (14–23)</td>
<td>19 ± 2.7 (15–25)</td>
</tr>
<tr>
<td>PEEP, cm H2O</td>
<td>5.4 ± 1.1 (4–9)</td>
<td>6 ± 1.2 (4–9)</td>
</tr>
<tr>
<td>PS over PEEP, cm H2O</td>
<td>9.7 ± 2.1 (5–14)</td>
<td>10.6 ± 2.5 (5–18)</td>
</tr>
<tr>
<td>MAP, cm H2O</td>
<td>8.7 ± 1.7 (6–12)</td>
<td>10 ± 2.2 (6–15)</td>
</tr>
</tbody>
</table>

PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; PS, pressure support; MAP, mean airway pressure.

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**Table 5. Respiratory assistance according to noninvasive ventilation result**

<table>
<thead>
<tr>
<th></th>
<th>NIV Failure</th>
<th>NIV Success</th>
<th>p</th>
<th>Effect Size (%)</th>
<th>Strength of Test (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial breathing assistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEEP, cm H2O</td>
<td>6.2 ± 1.5</td>
<td>5.2 ± 0.9</td>
<td>&lt;.015</td>
<td>19.7</td>
<td>89.6</td>
</tr>
<tr>
<td>PIP, cm H2O</td>
<td>19.4 ± 2.9</td>
<td>17.2 ± 2.7</td>
<td>.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS, cm H2O</td>
<td>10.8 ± 1.1</td>
<td>9.5 ± 2.2</td>
<td>.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, cm H2O</td>
<td>9.8 ± 1.9</td>
<td>8.5 ± 1.6</td>
<td>&lt;.04</td>
<td>13.3</td>
<td>73.8</td>
</tr>
<tr>
<td>FIO2</td>
<td>0.59 ± 0.15</td>
<td>0.52 ± 0.18</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum assistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEEP, cm H2O</td>
<td>6.9 ± 1.2</td>
<td>5.8 ± 1.1</td>
<td>&lt;.02</td>
<td>17.3</td>
<td>85</td>
</tr>
<tr>
<td>PIP, cm H2O</td>
<td>20.5 ± 2.1</td>
<td>18.5 ± 2.7</td>
<td>.053</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS, cm H2O</td>
<td>12 ± 1.5</td>
<td>10.2 ± 2.5</td>
<td>&lt;.005</td>
<td>8.3</td>
<td>50.8</td>
</tr>
<tr>
<td>MAP, cm H2O</td>
<td>12.5 ± 1.2</td>
<td>9.4 ± 2.1</td>
<td>&lt;.001</td>
<td>32</td>
<td>99.4</td>
</tr>
<tr>
<td>FIO2</td>
<td>0.64 ± 0.13</td>
<td>0.45 ± 0.17</td>
<td>&lt;.005</td>
<td>17.3</td>
<td>85</td>
</tr>
</tbody>
</table>

NIV, noninvasive ventilation; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; PS, pressure support; MAP, mean airway pressure.

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**Figure 1.** Significant thorax radiograph improvement after 72 hrs (right) from the beginning of noninvasive ventilation (left) in two patients with acute respiratory distress syndrome and immunosuppression who did not need tracheal intubation.
tubation was avoided in the remaining 50% of patients. This fact is especially relevant when these patients are immunodepressed (6 of 10 in our series) (5, 15, 33–35). For this reason, we believe that diagnosis of ARDS should have no contraindications for the use of NIV. It should be used early in acute lung injury or mild ARDS (Pao2/Fio2 >150 torr; >20 kPA), and with careful monitoring so as not to delay intubation whenever necessary.

Avoiding tracheal intubation delay is, in our opinion, the cornerstone of NIV use in ARF. That is why it is essential to have objective predictive factors to determine which patients should be intubated and when. It is important because this particular period, as we have seen in our study and in others (15, 30, 32), can range from a few hours to days.

Initial evolution of the clinical and blood gas parameters has been put forward as signs of success/failure (10–13, 16, 17). In our study, as in the study of Bernet et al (14), the initial improvement of respiratory rate in both groups (success and failure) suggests that this is an initial sign of adaptation to NIV treatment and not necessarily an indication of success. The same thing occurs with the interpretation of the initial improvement of pH, oxygen saturation, and the clinical score. Although the evolution of heart rate and Pco2 are related to the result, we believe its role is similar. Likewise, the initial improvement of these parameters could be regarded as “adaptation or initial success,” and further progress of disease can condition the failure of NIV. In our opinion, continuous evaluation of these parameters is useful, as it enables us to modify the level of ventilatory assistance and evaluate the need for tracheal intubation.

Radiologic assessment seems especially interesting as a prognostic sign. Although initial affection was not related to the result, the worsening of the radiograph at 24 hrs and then between 48 hrs and 72 hrs is a clear sign of illness progression and is useful in predicting late failure of NIV. Therefore, unfavorable radiograph evolution compelled us to monitor carefully without ruling out tracheal intubation. We have not found any information regarding the use of thoracic radiograph as a prognostic sign in other studies.

Furthermore, we have not found any studies that use the patient’s respiratory assistance as a predictive factor. However, in our study, several ventilatory parameters, at initial and maximal settings, were directly linked to the result. Nevertheless, only two parameters made up the discriminating success/failure function: MAP and Fio2. Maximum MAP represents all the power from the effects of the other pressure parameters. Therefore, an MAP >11.5 cm H2O predicted failure in nearly 90% of patients, regardless of time to disease progression. Although it is possible to see that this value fluctuates slightly in other studies, we believe that it marks the limit that NIV treatment can reach. This is why MAP can be considered as a sign of failure at any point during the progress of ARF. We believe that the second parameter, Fio2 during the maximum assistance period, has an additional purpose. If we cannot reduce Fio2 down to a safe level (≤0.5–0.6) during NIV in spite of intensifying respiratory assistance and other treatment measures, NIV is at high risk of failing. In our study, an Fio2 of > 0.57, during the time of maximum assistance, predicted failure in nearly 80% of patients. Other authors (14, 16) have already observed that evolution of initial Fio2 was defined as a sign of early failure. We observed that this parameter is useful at any moment during the progress of ARF. To be interpreted correctly, it must now be valued together with MAP. These parameters allow us to evaluate illness severity and establish the most convenient therapeutic management at any moment during the progress of ARF.

CONCLUSIONS

We believe that clinical, blood gas, and radiologic evolution results should be used as a guide for modifying respiratory assistance parameters. MAP and Fio2 values allow us to evaluate the required intensity of the treatment. In our study, MAP and Fio2 values of >11.5 and 0.6 respectively, predict failure and possibly set the limit above the patient’s risk of delayed intubation increases.

ACKNOWLEDGMENTS

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REFERENCES


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