

Arterial Blood Lactate in Children Primarily Submitted to Noninvasive Ventilation: A Time-Dependent ROC Analysis

Lactate and noninvasive ventilation in children

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J Child Sci 2020;00:e16–e20.

Abstract

The purpose of this study was to evaluate blood lactate measurements and failure to noninvasive ventilation (NIV) in children admitted to a pediatric intensive care unit. This was a retrospective observational single-center study performed between June 2016 and June 2017. Dynamic lactate indices and failure to NIV in 63 children < 18 years and > 1 month old were examined; we considered blood lactate analyses at time 0, 6, 24, and 48 hours. NIV failure group had a higher pediatric risk of mortality (PRISM) score. Lactate indices decreased over time in the success group ($p < 0.001$). The best area under the curve observed was 69%, at 48 hours. Considering all measurements, the area under the curve for time-dependent receiver-operating characteristic curve was 58.6%. This study demonstrated blood lactate indices evolution over time in children submitted to NIV.

Keywords

- ▶ lactate
- ▶ child
- ▶ critical care
- ▶ ROC curve

Introduction

Ventilatory support is a common treatment for critically ill children. For patients submitted to noninvasive ventilation (NIV), it is important to determine failure as early as possible, based on clinical parameters and laboratory settings. Failure to NIV and delayed intubation could increase morbidity.^{1–3}

Some studies correlated high lactate indices and worse morbidity and mortality, in patients with cardiogenic or septic shock.^{4,5} On the other hand, blood lactate has been related to pulmonary ventilatory thresholds in adult runners, as a marker of physiological response to exercise. In that case, blood lactate is a marker of the aerobic–anaerobic transition and so, it can be used to predict running performance.⁶ It is reasonable to think that in children submitted to NIV, the effort to breath represents a physical exercise and blood lactate indices may correlate to ventilatory failure.^{7,8} To our knowledge, no study yet compared blood lactate indices and failure to NIV in children.

The aim of this study was to investigate blood lactate indices over time and ventilatory failure in children submitted to NIV in a pediatric intensive care unit (PICU).

Materials and Methods

Study Design

We performed a secondary analysis of data from an observational retrospective cohort. Individual chart review was performed on children consecutively admitted from June 2016 to June 2017 at Prontobaby Children's Hospital, a Brazilian tertiary pediatric hospital. The 20-bed PICU was covered 24 hours a day by a team consisting of intensivists (attending physicians, critical care residents, respiratory therapists, and nurses). PICU team rounds were undertaken once a day and orders were registered, according to clinical protocols.

All subjects < 18 years and > 1 month primarily submitted to NIV were included. Those with sepsis,⁹ hemodynamic

received
November 14, 2019
accepted after revision
March 6, 2020

DOI <https://doi.org/10.1055/s-0040-1709718>.
ISSN 2474-5871.

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support or shock (using any vasoactive drugs or needing volume bolus); neurologic impairments (neuromuscular disorder or neurologic impairment affecting respiratory control); cardiac disease (congenital cardiac or myocardial disease); muscular disorder (myopathies); those extubated to NIV; and those with tracheostomy were excluded. Subject characteristics such as age, weight, sex, initial hematocrit, and Pediatric Risk of Mortality III (PRISM III) score were recorded.¹⁰ NIV indications were decided by the doctors in charge. NIV was indicated to children with acute respiratory failure, with respiratory rate above two standard deviations for child's age normal range, without neurological compromise and with hemodynamic stability. Bilevel NIV was delivered by continuous nasal, face, or full-face mask and was overseen 24 hours a day by the PICU team. Maximal NIV settings considered were inspiratory positive airway pressure 25 cm H₂O and expiratory positive airway pressure 12 cm H₂O with fraction of inspired oxygen (FiO₂) 60%. Depending on whether they failed to NIV and had to be intubated, the children were assigned to the success or failure group. Intubation was indicated by the team on clinical basis, when peripheral capillary oxygen saturation was below 85%, with an increase in respiratory effort and/or needing more than the maximum NIV parameters. All subjects were continuously monitored by electrocardiography and pulse oximeter. Peripheral arterial blood gas with lactate analysis was performed whenever the attending physician considered necessary. As severe anemia and blood transfusions could increase lactate indices, we registered hematocrit at baseline.¹¹ Subjects contributed to lactate data for 48 hours or less if one failed to NIV earlier or if NIV was stopped. Blood lactate data corresponding to the beginning of NIV (time 0), 6 hours later (time 6), 24 hours later (time 24), and 48 hours later (time 48) were recorded. We did not consider 12- and 36-hour analysis, when available. Blood lactate was considered normal when <2.2 mmol/L.

Statistical Methods

Data were analyzed using Stata 13.0 (Stata Corp, LC, USA) and the software R. 3.5.3. (r-project.org) Nonparametric tests were required as datasets were not normally distributed. Mann-Whitney U test was used for continuous variables, Fisher's exact test was used for categorical variables, and Kruskal-Wallis test (analysis of variance) was used for lactate medians within group. Interquartile range (IQR), 95% confidence interval (95% CI), and odds ratios (OR) were calculated. Specificity, sensitivity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and accuracy were calculated. We estimated the area under the curve (AUC) for each time and for all the times, using a repeated measures design; using generalized linear mixed model, we estimated the predicted probabilities, then the AUC was estimated by Wilcoxon nonparametric approach by comparing the predicted probability of all discordant pairs of observations. As a time-dependent receiver-operating characteristic (ROC), we used longitudinal lactate indices and calculated the cumulative sensibility and the dynamic specificity beyond time. Thereafter, we defined AUC at each time point.¹² A *p*-value <0.05 was considered significant.

This study was approved by the Research Ethics Committee of Federal Fluminense University in November 06, 2017 (CAAE 76609917.2.0000.5243)

Results

During the study period, 239 subjects were submitted to ventilatory support in the PICU. ► **Figure 1** describes details of the number of excluded patients.

Data from 63 subjects were analyzed. Median age was 44 months (IQR: 3–108 months). Thirty-two patients were male (50.79%), median weight was 14.2 kg (IQR: 4.5–25.0 kg), median baseline hematocrit was 33% (IQR: 31.5–35%), and median PRISM score was 3 (IQR: 2–5). Admission diagnoses

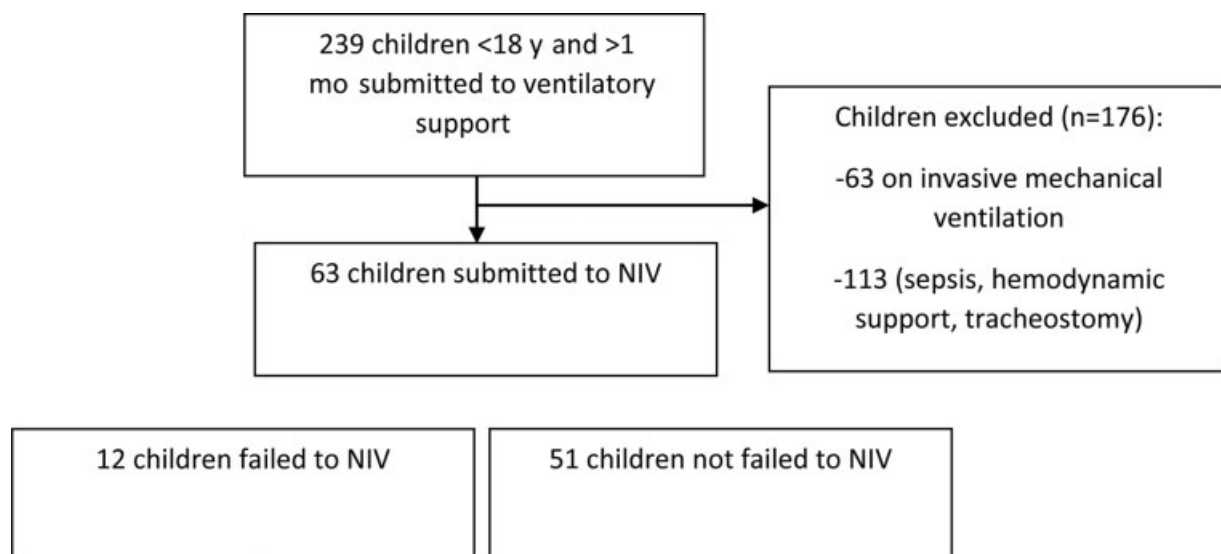


Fig. 1 Flow of patients through the study. NIV, noninvasive ventilation.

Table 1 Patients' characteristics ($n = 63$) comparisons

| | Failure to NIV | | p-Value |
|------------------------------|------------------------------|-----------------------------|-------------------|
| | No ($n = 51$) | Yes ($n = 12$) | |
| Male sex | 52.94% (95% CI: 30.99–56.74) | 41.67% (95% CI: 2.67–17.82) | 0.48 ^a |
| Age (months) | 46 (IQR: 3–123) | 14 (IQR: 2–58) | 0.13 ^b |
| Weight (kg) | 15.0 (IQR: 4.9–30.0) | 9.2 (IQR: 3.9–21.0) | 0.17 ^b |
| Hematocrit (%) | 33 (IQR: 31.6–35) | 33.75 (IQR: 30–34.65) | 0.79 ^b |
| PRISM III score | 3 (IQR: 2–3) | 5 (IQR: 4–7) | 0.02 ^b |
| Initial lactate | 20 (IQR: 15–24) | 20 (IQR: 18–29) | 0.27 ^b |
| Initial SpO ₂ (%) | 94 (IQR: 92–96) | 93 (IQR: 90–95) | 0.09 |

Abbreviations: CI, confidence interval; IQR, interquartile range; NIV, noninvasive ventilation; PRISM III, Pediatric Risk of Mortality; SpO₂, peripheral capillary oxygen saturation.

^aChi-squared test.

^bMann–Whitney U test.

were respiratory (95.3%) and orthopaedic surgery (4.7%). All patients were discharged from hospital successfully. The number of patients who had their lactate measured at baseline, 6h, 24h, and 48h were: 63, 22, 36, and 17.

Considering the first 48 hours, nine (14.28%) subjects failed to NIV and were intubated. Three patients were intubated after 48 hours. Three children were intubated in less than 6 hours and six were intubated from 6 to 24 hours. Not all subjects were equally informative. NIV was discontinued in one child before 6 hours, in 18 between 6 and 24 hours, in 18 between 24 and 48 hours. Censures and loss of information occurred over time. A comparison between patients' characteristics was made (► **Table 1**). Considering the OR for NIV failure and variables as independent factors, it was observed: male sex (OR: 0.63, $p = 0.48$; 95% CI: 0.17–2.26), age > 6 months (OR: 0.45, $p = 0.23$; 95% CI: 0.97–1.00), weight (OR: 0.99, $p = 0.26$; 95% CI: 0.99–1.00), hematocrit (OR: 0.96, $p = 0.78$; 95% CI: 0.75–1.23), PRISM score (OR: 1.24, $p = 0.08$; 95% CI: 0.97–1.58).

Overall median duration of NIV was 26.2 hours (IQR: 14.4–54). Median duration of NIV for the success group was 27.5 hours (IQR: 15.5–54) and those who failed was 10.3 hours (IQR: 6.45–47.9). There was a difference between groups ($p = 0.01$). Blood lactate medians, differences over time, and AUC–ROC at each time are shown in ► **Table 2**. The

AUC for repeated measures resulted on a time-dependent ROC curve (► **Fig. 2**).

► **Table 3** shows the performance of blood lactate indices on time 0, 6, 24, and 48 for predicting NIV failure considering lactate cutoff > 2.2 mmol/L.

Discussion

NIV was used as first-line mode of mechanical ventilation in PICU. Studies suggested predictive factors for NIV success, and this may help identify patients who probably will not benefit from NIV. In our study, groups differed on PRISM score, as those with higher scores failed to NIV. Bakalli et al studied 42 children, before NIV and after 2 hours. They suggested that some variables that were not predictive before NIV were predictive after 2 hours, as respiratory and heart rates. Those who failed had higher rates after 2 hours.¹³ James et al in 2011 investigated 83 children submitted to NIV; 36% failed and were intubated. They included oncologic and septic patients. Higher FiO₂, respiratory rates, and lower pH were associated with NIV failure.¹⁴ Identifying characteristics before NIV associated with a worse prognosis is important in the selection of the most appropriate mode of mechanical ventilation. Clinical parameters and laboratory follow-up after initiation of NIV

Table 2 Blood lactate indices during 48 hours in failure and nonfailure to NIV groups in critically ill children

| Lactate | Overall (IQR) | Failure to NIV (IQR) | | p-Value ^a | AUC–ROC |
|----------------------|------------------|----------------------|------------------|----------------------|---------|
| | | No ($n = 51$) | Yes ($n = 12$) | | |
| Time 0 | 2.2 (1.65–2.75) | 2.2 (1.65–2.64) | 2.2 (2.03–3.13) | 0.27 | 0.6021 |
| Time 6 | 2.53 (2.31–3.24) | 2.64 (2.47–3.19) | 2.31 (2.25–3.13) | 0.45 | 0.6000 |
| Time 24 | 1.98 (1.65–2.20) | 1.76 (1.37–1.98) | 1.98 (1.65–2.20) | 0.62 | 0.5859 |
| Time 48 | 1.65 (1.54–2.31) | 1.65 (1.54–2.22) | 2.53 (1.92–2.75) | 0.31 | 0.6905 |
| p-value ^b | | <0.001 | 0.4283 | | |

Abbreviations: AUC, area under the curve; IQR, interquartile range; NIV, noninvasive ventilation; ROC, receiver-operating characteristic.

^aFisher's exact test.

^bKruskal–Wallis (analysis of variance) test.

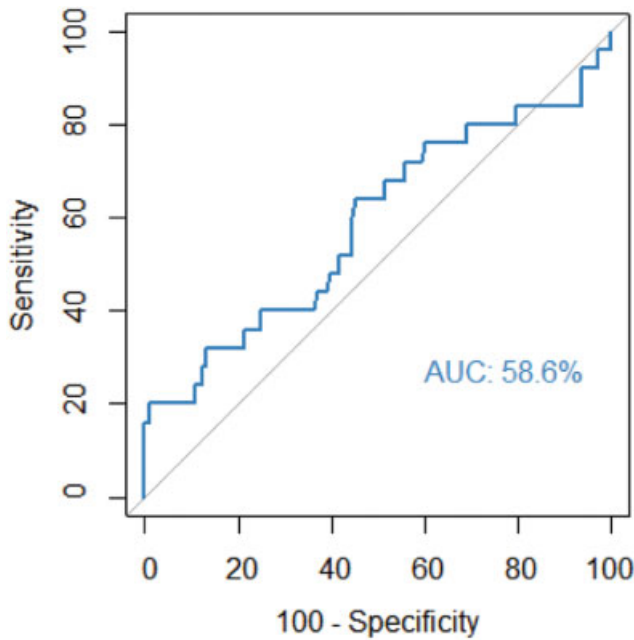


Fig. 2 Time-dependent receiver-operating characteristic curve for blood lactate indices on time 0, 6, 24, and 48 and failure to noninvasive ventilation in critically ill children. AUC, area under the curve.

may add important information regarding NIV failure and avoid delays on intubation.

In our study, although PRISM scores were different between groups, OR for NIV failure and PRISM was not significant suggesting that in this setting, only PRISM score did not explain NIV failure. Previous studies showed that higher severity scores are associated to NIV failure regardless the NIV indication.¹⁵⁻¹⁸ It is important to emphasize that PRISM score combines variables such as blood pressure, respiratory rate, PaO₂/FiO₂, heart rate, PCO₂, and others. This combination of variables is stronger than each variable alone as a determinant factor. Maybe the combination of PRISM score and other variable (s) explain better NIV failure.

Dynamic changes in lactate indices in the critically ill patient may predict outcome. It was suggested in adults that those indices may improve severity-score based predictions of mortality.⁴ Lactate clearance rather than lactate concentration has been correlated to anaerobic metabolism and adequacy of perfusion during cardiopulmonary by-pass.¹¹

This behavior raised the question if lactate over time could help explain NIV failure. We investigated blood lactate indices at different times. We did not find differences on lactate indices between groups, but we observed differences on lactate indices over time in the success group (lactate decreased over time), suggesting a better clearance. We did not find studies about lactate and NIV to compare our results.

As lactate decreased over time in the success group, we conducted longitudinal comparisons between groups. The AUC each time was 0.6021, 0.6000, 0.5859, and 0.6905; this implies that 69% of the subjects who failed to NIV at 48 hours had greater lactate indices, suggesting that this marker becomes better with increasing prediction time. We observed better accuracy to blood lactate indices (>2.2 mmol/L) at 48 hours (88.2%). The relevance of this finding on clinical basis must be better examined. Lactate indices alone may not help us to monitor the evolution in NIV. A multiple-center survey on NIV failure as first-line ventilatory support revealed respiratory rate after 1 hour as the best AUC (0.67) followed by basal and after 1-hour PaO₂/FiO₂ relation (0.61), reinforcing the importance of clinical examination.¹⁶

We suggest that lactate indices trend over time could be explored in a larger and prospective study and with the combination of variables. Also, we did not find other study that explored predictors using a longitudinal ROC curve, for comparison. Application of this statistical methodology in clinical studies is still lacking and should be encouraged, as not all individuals are equally informative and individual trends over time are very important.¹²

The present study has limitations. First, it was a single-center study and so, it reflects local population. Second, as a retrospective study, loss of data was not controlled. Third, as sample was small, censures over time resulted in few comparisons at 48 hours; a larger sample could be better. At last, few literature backups about lactate and NIV failure in children impaired extensive comparisons.

Conclusion

This study added to the body of literature supporting the investigation of parameters to predict NIV failure. Given the results of our analysis, we suggest that a higher PRISM score may predict NIV failure. Lactate indices decreased in the success group. Future prospective and larger studies combining variables would be important to validate the findings.

Table 3 Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and accuracy of blood lactate indices for predicting NIV failure (lactate cutoff > 2.2 mmol/L)

| | Sensitivity | Specificity | PPV | NPV | +LR | -LR | Accuracy |
|---------|-------------|-------------|------|------|------|------|----------|
| Time 0 | 75.0 | 47.0 | 25.0 | 88.8 | 1.41 | 0.53 | 52.3 |
| Time 6 | 57.1 | 80.0 | 57.1 | 80.0 | 2.8 | 0.53 | 72.7 |
| Time 24 | 60.6 | 66.6 | 13.3 | 95.2 | 1.69 | 0.55 | 61.1 |
| Time 48 | 66.6 | 92.8 | 66.6 | 92.8 | 9.3 | 0.36 | 88.2 |

Abbreviation: NIV, noninvasive.

Authors' Contributions

C.O.S.V. was involved in analyzing data and writing the original research, and agreed to the final manuscript. L.S. M.L. and A.R.A.S. were involved in data collection, critical review, obtained ethical approval, and approved the final manuscript.

Conflict of Interest

None.

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