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Analysis of Respiratory Behavior and Clinical Parameters for Successful Extubation in Premature Infants

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Abstract

Background
The weaning process is complex and needs to be done carefully. The success of extubation in premature babies is associated with brain maturity and adequate function of the lungs. We aimed to identify the ventilator parameters and clinical conditions related to extubation success and failure in premature infants.

Materials and Methods

This is an observational study, analytical and non-comparative cohort. We selected all premature infants, into inclusion criterion, admitted to the Neonatal Intensive Care Unit (NICU) of Hospital de Clínicas, Curitiba, Brazil in Invasive mechanical ventilation (IMV). The fifty-one premature infants were evaluated every day until tracheal extubation and the data of the day of extubation were used.

Results
Thirty-nine premature infants had extubation success and the majority of them 32(82.05%) were appropriated for gestational age (AGA). The parameters that showed a statistical difference between success and failure group were Positive end-expiratory pressure ($p = 0.03$), plate pressure ($p = 0.03$), Partial pressure oxygen ($p = 0.04$), pH ($p = 0.04$), end-tidal CO2 ($p = 0.01$) and heart rate ($p = 0.04$). The use of caffeine periextubation and the permanence in Continuous positive airway pressure (CPAP) during the post-extubation period was higher in the success group (46.15% and 87.18%, respectively). The presence of piratory distress syndrome (RDS) was high in both groups, success group, 82.05% and failure group 100%.

Conclusion
The pressure values, the arterial blood gas analyses, and capnometry are important parameters to evaluate in the weaning process, checking these values closer to reference values. Supports before and after endotracheal extubation, such as the use of caffeine and CPAP, are important to avoid the need for reintubation.

Key Words: Brazil, Endotracheal extubation, Infants, Neonatal Prematurity.

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1- INTRODUCTION

The mechanical ventilation (MV) is considered an advantage in neonatal medicine, especially in extremely preterm infants (1). However, there is progress in the non-invasive respiratory support to minimize the injuries caused by invasive mechanical ventilation (IMV). Most premature infants require endotracheal intubation for a long time, and the longer this time in the IMV the higher the morbidity and mortality, so that extubation is indicated as soon as possible (1, 2). In 2010 the World Health Organization (WHO) estimated 14.5 million babies were born preterm, it represented a preterm birth rate of 11.1% (3). The mortality rate increases with the decrease of gestational age, but medical innovations can decrease this rate (3, 4).

The weaning process is complex and needs to be done carefully. Before the endotracheal tube is removed, the ventilator is gradually weaned until spontaneous respiration commences. Some evaluation methods can help to monitor this transition from the ventilator to ambient air, as blood gas parameters, oxygen saturation, and ventilator settings. Extubation success is considered by many authors without reintubation within 24 to 72 hours (5–9). The decision to remove the MV is based on the clinical experience of the medical team, and there is no protocol that could guide clinicians during this weaning period, which is why it may sometimes be considered successful or failed by some researchers (1, 10).

In general, extubation process begins when the respiratory insufficiency that caused the indication to MV starts to improve and the premature infants are hemodynamically stable, with spontaneous breathing, good ventilation, and oxygenation (9, 11). The success of extubation in premature babies is associated with brain maturity and adequate function of the lungs, but some other factors may influence the success of extubation, such as weight, gestational age, length of MV, type of respiratory support used after endotracheal tube removal, medications used prior to extubation, for example, caffeine and surfactant administration (12, 13). There are recommendations and protocols in the weaning process for adults, but in pediatric and neonatal patients this information is still not clear. This study aimed to identify the ventilator parameters and clinical conditions related to extubation success and failure in premature infants and thus, prevent mortality and morbidity risk in these babies and reduce hospital costs.

2- MATERIALS AND METHODS

2-1. Method

This was an observational study, an analytical and non-comparative cohort, conducted to investigate the respiratory parameters and clinical conditions associated with extubation success in premature babies admitted in the neonatal intensive care unit (NICU) of Hospital de Clínicas, Curitiba, Brazil from July 2014 to November 2016. The study was approved by the Ethics Committee of the Federal University of Parana, Curitiba, Brazil. All parents were informed and formally agreed to have their infants included in the study.

The premature infants were selected according to the gestational age (between 24 and 36 weeks + 6 days), and in the presence of invasive mechanical ventilation (IMV) on the first day in NICU. Premature infants with neurological impairment, airway malformation, accidentally extubated, transferred to other hospitals, early death, big instabilities and those who we could not obtain the consent from their parents were excluded from this study. A non-probabilistic sample was used, in the convenience and systematic form that includes all the premature newborns in IMV within the inclusion and exclusion criteria. The intubation criteria followed the routine practice manual of the NICU of the Clinical Hospital of the Federal University of Paraná in 2014 (14), and considered these criteria:

- Recurrent apnea associated with bradycardia (<80 to 100/min), requiring a ventilation mask more than once every 12 hours;
- Hypoventilation with pH < 7.25 and Partial pressure oxygen [$PaCO_2$] > 55-60 mmHg;
- Hypoxemia with PaO_2< 50 with an inspired fraction of oxygen (FiO_2) in 70%;
- The anticipation of imminent cardiovascular collapse (as in severe sepsis), or ventilatory instability (frequent unsaturation in Persistent Pulmonary Hypertension [PPH]);
- Frequent apneas, even without the need for Positive Pressure Ventilation (PPV), in a newborn with necrotizing enterocolitis and the need for ventilatory support, periventric Intraventricular hemorrhage; and
- Sepsis.

The criterion for extubation also followed those recommended by the manual of the routine practice of the NICU/ HC-UFPR (the neonatal intensive care unit / Hospital de Clínicas- Universidade Federal do Paraná) of 2014, except those with accidental extubation and the decision of the clinical team to maintain the extubation.

The criteria for extubation are: having a regular spontaneous breathing and cough reflex; $FiO_2 \leq 40\%$ to maintain saturation $\geq$ 90%; the peak inspiratory pressures (PIP) <15-18 cm H_2O and respiratory rate of 15-20/min; pH above 7.25 and $PaCO_2$ below 50 mmHg (14). The ventilator used was Puritan Bennett™ 840®, Carlsbad, California. Premature infants with severe hemodynamic instability, airway congenital malformation, neurological syndromes, irregular breathing frequency and accidentally extubated infants were excluded. For blood gas analysis, heparinized arterial blood samples from the radial artery were used and analyzed with the GEM Premier equipment 3000® (Instrumentation Laboratory, Lexington, MA), which was calibrated daily. The end-tidal of carbon dioxide ($EtCO_2$) in the exhaled air was measured by a mainstream portable Capnometer Monitor (EMMA Emergency Capnometer, Phase in AB, Danderyd, Sweden) placed between the endotracheal tube and the circuit of the mechanical ventilator.

The values of heart rate and oxygen saturation were used in the pulse oximetry monitor (OxiMax® N-560, Covidien, Mansfield, USA), and for the temperature values they were used from the medical records. The analyses started on the first day of the mechanical ventilation until the removal of the endotracheal tube and the data from the day of extubation were used and only the first attempt at extubation was included. Successful extubation was considered without reintubation within 72 hours.

2-2. Ethics Approval

This study was approved by Ethics Committee of the Federal University of Parana, Curitiba, Brazil.

2-3. Statistical Analysis

The data were analyzed using the SPSS Statistical package®, version 10.0. The premature Infants were divided into two groups, successful and failed extubation. Student’s paired *t*-test was used to analyze the differences between groups, for continuous variables. The Mann-Whitney test was used for the abnormally distributed variable. The data are presented as mean (± standard deviation) or median (range). A p-value < 0.05 was considered significant.

3- RESULTS

Between July 2014 and November 2016, 507 premature infants with gestational age between 24 to 36 weeks were born, 177 premature infants were in MV and 125 fitted in exclusion criteria. Fifty-one premature infants were into inclusion criteria and were selected for the research. Some reasons for the exclusion after the intubation were the transfer to others hospitals, malformation, babies with neurological disease, big hemodynamics instability, accidentally extubated, death in the first day in MV, researcher absence and the ones without parent`s authorization. The flowchart shows the infants selected (**Figure.1**).

The demographic characteristic was separated into successful and failed groups and it is shown in **Table.1**. The gestational age, weight, and temperature were similar in both groups and the presence of RDS was high in groups, 82.05% in the successful group, and 100% in the failed group. The Apgar score was divided into 3 groups and the score obtained at 5 minutes was used in the analysis. Scores between 0 and 3 received punctuation 0, between 4 and 6 received 1 and above 6, were classified as 2.

The successful group had more babies in classification 2 (63.16%). These characteristics in **Table.1** did not show statistically significant differences between the groups. Six infants failed extubation and six others died before the first attempt of extubation. In total thirty-nine premature infants had extubation success and the majority of them were appropriate for gestational age (AGA). The infants, small for gestational age (SGA) were associated with extubation failure or died before the first attempt of extubation. Only one infant was large for gestational age (LGA) (**Figure.2**). The ventilatory threshold and arterial blood gas parameters that showed statistical differences between successful and failed groups were positive end-expiratory pressure [PEEP] ($p = 0.03$), plate pressure ($p = 0.03$), $PaCO_2$ ($p = 0.04$), pH ($p = 0.04$), and end-tidal carbon dioxide [EtCO2] ($p = 0.01$). Infants who failed extubation had lower pressure value and higher CO_2 values. The heart rate also showed statistically significant differences ($p = 0.04$), and it was higher in failed groups (**Table.2**).

There is a considerable difference between the failed and successful groups. One of them is the size of the sample, with only six infants in failed extubation group. It is important to consider the reason these infants failed even with some similar characteristics as gestational age, birth weight, and temperature.

The characteristics that showed difference in successful and failed groups were length in mechanical ventilation 3 (1–31)/ 1.5 (1–4), caffeine peri-extubation 18 (46.15%)/ 2 (33.33%), the permanence in continuous positive airway pressure (CPAP) during postextubation period 34 (87.18%)/ 2 (33.33%) and best score in Apgar 24 (63.16%)/ 3 (50%).

Another feature that could influence successful extubation was 100 percent of pulmonary disease (RDS, [respiratory distress syndrome]) in the failure group (**Table.1**).

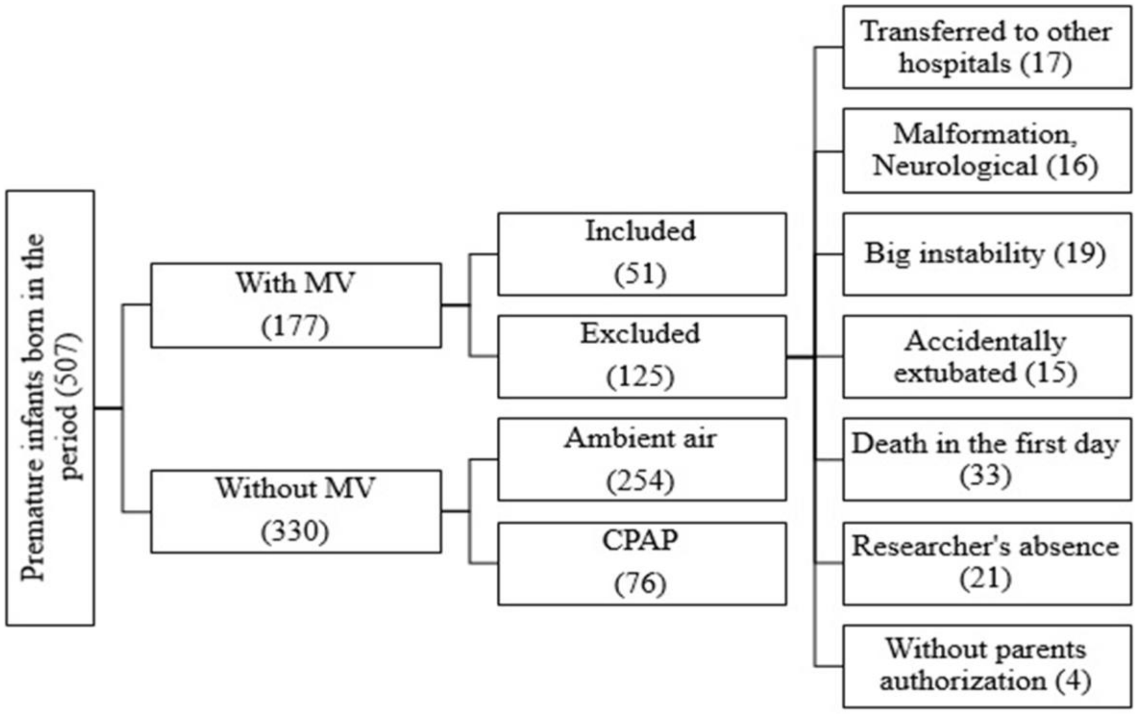

Fig.1: The flow chart of all the babies that were born between July 2014 and November 2016.

Table 1: Demographic characteristics of premature infants (n = 45).

Characteristics	Successful group (n=39)	Failed group (n = 6)
	Number (%), Median (IQR) or Mean ± SD	
Gender		
Boys	19 (48.72)	5 (83.3)
Girls	20 (51.28)	1 (16.7)
Gestational age (weeks)	28 ± 3.2	28.83 ± 3.06
Birth weigth (g)	1102.2 (485 – 3.230)	1064.2 (610 – 1.790)
Apgar (5º minute)	38 (100)	6 (100)
<3 = 0	4 (10.52)	0 (0)
3-6 = 1	10 (26.32)	3 (50)
>6 = 2	24 (63.16)	3 (50)
Temperature (˚C)		
Incubator	34.65 ± 1.58	34.45 ± 2.11
Body	36.39 ± 1.13	36.67 ± 0.48
Pulmonary Disease (RDS)	32 (82.05)	6 (100)
Days in MV	3 (1 – 31)	1.5 (1 – 4)
Periextubation caffeine	18 (46.15)	2 (33.33)
CPAP ostextubation	34 (87.18)	2 (33.33)

IQR: interquartile range; SD: standard deviation; RDS: respiratory distress syndrome; MV: mechanical ventilation.

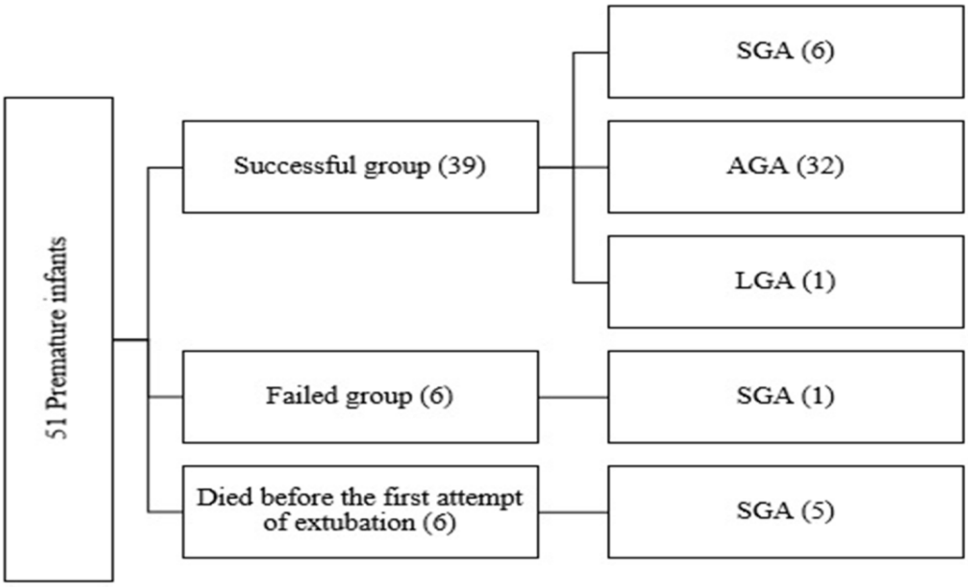

Fig.2: The characteristics of preterm infants selected.

Table-2: Extubation parameters premature infants (n = 45).

Characteristics	Successful group (n = 39)	Failed group (n = 6)	P-value
Breath rate (bpm)	30.55 ± 9.78	30.66 ± 7.53	0.98
Heart rate (bpm)	149.79 ± 17.96	167.8 ± 7.85	0.04
Body Temperature ºC	36.38 ± 1.18	36.9 ± 0.62	0.29
Incubator Temperature ºC	33.31 ± 1.32	33.48 ± 2.66	0.82
$SatO_2$ (%)	94.84 ± 2.85	95.17 ± 4.02	0.81
PEEP (cmH_2O)	5.37 ± 0.54	4.8 ± 0.44	0.03
PIP (cmH_2O)	17.55 ± 3.8	16 ± 3.28	0.35
P plateau (cmH_2O)	15.68 ± 3.3	12.4 ± 2.88	0.03
VT (ml/kg)	10 (4.9 – 29)	7.55 (4 – 25)	0.39
Cst (ml/cmH_2O)	1.07 (0.61 – 3)	1 (0.4–3.57)	0.55
Cdyn (ml/cmH_2O)	0.92 (0.54 – 2.2)	0.7 (0.37 – 2.08)	0.57
Tinp (s)	0.39 ± 0.03	0.36 ± 0.04	0.16
FiO_2	32.5 (21 – 90)	37.66 ± 11.43	0.92
PaO_2/FiO_2	182.54 (54.44 – 623.80)	153.42 (108 – 304.77)	0.36
Vol min (l/m)	0.55 (0.07 – 1.35)	0.41 (0.05 – 0.49)	0.08
PaO_2 (mmHg)	66.5 (31 – 150)	65.33 ± 16.46	0.47
$PaCO_2$ (mmHg)	38 ± 12.2	50.6 ± 10.62	0.04
pH	7.36 ± 0.09	7.24 ± 0.23	0.04
HCO_3 (mEq/L)	20.69 ± 6.08	21.63 ± 3.35	0.71
BE	-3.4 (-22.10 – 8.7)	-5.95 (-10.6 – 4.10)	0.73
$EtCO_2$ (mmHg)	39.54 ± 10.21	51.8 ± 8.07	0.01

Abbreviations: VT - tidal volume; Vol min – minute volume; bpm – breaths per minute and beats per minute; ºC: degree celsius; PIP – peak inspiratory pressure; Pplateau - plateau pressure; PEEP – positive end-expiratory pressure; Cdyn - dynamic compliance; Cst - static compliance; pH - potential of ionic hydrogen; $PaCO_2$ – partial pressure of arterial carbon dioxide; PaO_2 – partial pressure of arterial oxygen; HCO_3^- – bicarbonate; BE - base excess; SpO_2 – oxygen saturation; $EtCO_2$ - end-tidal of carbon dioxide; mmHg - millimeters of mercury ; ml - milliliter; mL/kg- milliliter per kilogram; s - seconds; cmH_2O – water centimeter; l/min - liters per minute; ml/cmH_2O – milliliter per water centimeter; cm_2 - square centimeter; mEq/L -milliequivalents per liter. Significant difference at a significance level of $p < 0.05$.

4- DISCUSSION

In a cohort study, we were able to show during nearly two-year studies with 51 mechanically ventilated premature babies that the majority of them were successfully extubated. The group showed similar features in gestational age, birth weight, Apgar score, temperature, length in mechanical ventilation and appropriate for gestational age. Six infants died before the first attempt at extubation and five of them were small for gestational age. The extubation parameters, which showed statistically significant differences, were heart rate, plateau pressure, PEEP, $PaCO_2$, pH, and $EtCO_2$, and the successful group had the values closer to reference values.

Currently, the decision of extubation is based on clinical conditions, blood gas variables, oxygen support and the level of ventilator support needed, but there is no parameter that can show the extubation success, and it continues to be based on subjective assessments of premature babies (15,16). Some weaning concepts have failed to show superiority over doctors' experience and clinical judgment, but researchers showed that the combination of these variables, like respiratory mechanics, gas exchange, ability to maintain the work of breathing and clinical experience, is a good combination for a weaning success (17). Parameters that showed statistically significant differences between the groups were related to pressure and arterial blood gas. A study by Wang et al. (2017) showed the similar result in pH ($p = 0.05$), and bicarbonate level ($p = 0.03$), and in this case, arterial blood gas analyze might be associated with extubation outcomes (15). In our study, the arterial blood gas parameters, pH, and $PaCO_2$ ($p = 0.04$), can also be used as an indicator for a successful extubation. The $EtCO_2$ showed statistically significant differences ($p = 0.01$), this parameter is an alternative noninvasive method to monitor CO_2 values and has been showing a good estimate of the $PaCO_2$ (18), so the $EtCO_2$ can be used as an indicator for a successful extubation, too. In the periextubation period, the pH and $PaCO_2$ also showed statistically significant differences ($p = 0.01$) in the study done by Chawla et al. in 2017 (16). This results agree with the present study and shows the importance of the arterial blood gas analysis, that is considered the gold-standard test and might be used to predict extubation outcomes (19). Autonomic nervous system through sympathetic and parasympathetic innervation work in balance to adapt to different situations, but premature infants don’t have their systems balance well established, so some changes in intrathoracic pressure and lung volume during weaning may induce changes in heart rate, because the autonomic nervous system can induce alterations to maintain cardiac output (20, 21). The heart rate showed statistically significant differences between the groups ($p = 0.04$), and in the failed group the heart rate was higher than the successful groups, that could suggest the attempt of the autonomic nervous system to adapt the changes in the respiratory mechanics.

Another factor that may be associated with successful extubation is the administration of caffeine during the pre-extubation period. Caffeine is usually used in neonatal intensive care units because it can reduce the apnea, intermittent hypoxemia, avoid extubation failure of the mechanical ventilation, reduces the incidence of bronchopulmonary and patent ductus arteriosus in preterm infants (22). In the present study, with 39 preterm infants that had successful extubation, 18 used caffeine (46.15%), and only 2 (33.33%) premature infants used caffeine in the failed group. Caffeine dosage has not been reported in our study, but other research shows that the use of high dose of caffeine, in comparison to low doses, may decrease the chance of extubation failure in premature infants mechanically ventilated (23). One factor affecting successful extubation is post-extubation respiratory support and the most used is the continuous positive airway pressure (CPAP). CPAP is a type of flow used to generate the positive pressure and it is associated with lower incidence of intubation and reintubation because it prevents apnea and atelectasis (24, 25). In our study, the majority of premature infants in the successful group used CPAP in the post-extubation period (87.18%), and only 2 babies used in the failed group (33,33%). In this study, comparing two type of CPAP, bi-level nasal CPAP (NCPAP), and nasal intermittent positive pressure ventilation (NIPPV) showed that both have high extubation successful rates in the post-extubation period (24).

With these results, we assume that the gradual reduction of respiratory support can provide a better adaptation of the lung and avoid reintubation. Though the gestational age, weight, and temperature were similar in both groups, the Apgar score was better in successful groups, with 24 (63.16%) premature infants with classification 2, but did not show statistically significant differences between the failed group and the classifications. Research comparing risk factors associated with extubation failure in newborns with birth weight < 1,250 grams showed statistically significant differences between groups in the 5-minute Apgar score (p= 0.01), which showed that higher Apgar score can increase the chances of extubation success (26).

4-1. Limitations of the study

This is an observational study to evaluate the parameters associated with extubation success and these results match others researches already published. During the study period, we had some limitations, as a strike at the hospital and reform in NICU, which made it impossible to obtain a larger sample. It is important to conduct more research on the comparison between successful and failed extubation for future prospective studies.

5- CONCLUSION

The decision of extubation involves many factors, such as the clinical conditions of premature babies, arterial blood gas, oxygen support, ventilator support level and the experience of the clinical team; but in this study, we can consider the pressure values, the analyzes of arterial blood gases and capnometry as important parameters to evaluate in the weaning process, verifying these values closer to the reference values. Supports before and after endotracheal extubation, such as caffeine and CPAP, are important to avoid the need for reintubation.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENTS

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