# Factors associated with extubation success in premature infants submitted to the spontaneous breathing trial

Fatores associados ao sucesso na extubação de recém-nascidos prematuros submetidos ao teste de respiração espontânea

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# ABSTRACT

Many factors can influence the extubation of premature infants and it is not safe to use only the spontaneous breathing trial. **Objective:** To connect cardiac, neurological and pulmonary factors that influence the extubation success in premature infants submitted to the 5-minute Spontaneous Breathing Trial (SBT). **Methods:** The sample consisted of 27 premature infants that passed through the weaning protocol until eligibility for extubation. The premature infants were followed daily from birth to post-extubation. The extubation protocol/checklist was composed for clinical and neurological conditions, pulmonary and cardiac factors, medication, post-extubation ventilatory support, physiological variables, ventilatory parameters and SBT test with the Silverman Andersen Respiratory Severity Score (SA-RSS). Descriptive analyzes of quantitative variables and Mann-Whitney statistical tests were performed. **Results:** The ventilatory parameters that showed statistical differences between the groups were plateau pressure and tidal volume. The gestational age (GA) using Capurro method, GA corrected and birth weight were higher in the success group (0.02, 0.003 and 0.0). The use of caffeine may have contributed to successful extubation (p = 0.03). The post-extubation support that presents statistical significance was non-invasive intermittent positive pressure ventilation (NIPPV) (0.01). **Conclusion:** The study pointed out important variables that contributed to the extubation success, such as the ventilatory parameters, clinical stability and use of caffeine for the weaning process.

Keywords: preterm infant; respiratory function tests; artificial respiration; ventilation weaning; neonatal intensive care units.

# RESUMO

Muitos fatores podem influenciar na extubação de recém-nascidos prematuros, não sendo seguro utilizar apenas o teste de respiração espontânea como parâmetro para garantia de sucesso. **Objetivo:** conectar fatores cardíacos, neurológicos e pulmonares que influenciam no sucesso da extubação de recém-nascidos prematuros (RNPTs) submetidos ao Teste de Respiração Espontânea (TRE) de 5 minutos. **Métodos:** a amostra foi composta por 27 RNPTs que passaram pelo protocolo de desmame até a elegibilidade para extubação. Os RNPTs foram acompanhados diariamente desde o nascimento até o período de pós-extubação. O protocolo/*checklist* de extubação foi composto por condições clínicas e neurológicas, fatores pulmonares e cardíacos, medicação, suporte ventilatório pós-extubação, variáveis fisiológicas, parâmetros ventilatórios e TRE com Boletim de Silverman Andersen. Foram realizadas análises descritivas das variáveis quantitativas e testes estatísticos de Mann-Whitney. **Resultados:** os parâmetros ventilatórios que apresentaram diferenças estatísticas significativas entre os grupos sucesso e falha foram pressão de platô e volume corrente. A idade gestacional (IG) pelo método Capurro, a IG corrigida e o peso ao nascer foram maiores no grupo sucesso (0,02; 0,003; e 0,0). O uso da cafeína pode ter contribuído para o sucesso da extubação (p = 0,03). O suporte pósextubação que apresentou significância estatística foi a ventilação não invasiva, sendo essa a pressão positiva intermitente (VNIPP) (0,01). **Conclusão:** o estudo apontou variáveis importantes que contribuíram para o sucesso da extubação, como os parâmetros ventilatórios, a estabilidade clínica e o uso de cafeína para o processo de desmame.

Palavras-chave: recém-nascido prematuro; testes de função respiratória; respiração artificial; desmame do respirador; unidades de terapia intensiva neonatal.

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# INTRODUCTION

Invasive Mechanical Ventilation (IMV) is an advance in the Intensive Care Units area, being of fundamental importance in Neonatal Intensive Care Units (NICU).<sup>1</sup> IMV is necessary for survival and aims to optimize gas exchange and the newborn's clinical status, but it is not risk-free. Such support can cause a health threat, causing damage to the disease or immature lungs. The weaning process occurs at one of the crucial moments in the use of mechanical pulmonary ventilation that can directly influence the success of the process.<sup>2</sup>

Many premature infants require endotracheal intubation and mechanical ventilation soon after birth. Although MV is considered a breakthrough in neonatal medicine, especially in extremely premature infants, prolonged exposure is associated with morbidity and mortality.<sup>3</sup> Extubation attempt is often performed prematurely, so many newborns fail and need to return to mechanical ventilation. The weaning of premature infants from MV is a critical period, during which the health care team must be very careful to ensure effective extubation. Some studies present suggestions of clinical and ventilatory parameters considered predictors of successful extubation.<sup>4</sup>

IMV removal must be performed safely to avoid complications. One way to ensure successful extubation is to carry out extubation tests when the patient is deemed fit.<sup>5</sup>

According to Johnston *et al.*,<sup>6</sup> to define the ideal moment for weaning from IMV and extubation is a challenge in NICUs, because there is no evidence of effective weaning methods that can be considered reliable to determine the NB's readiness for extubation. Shalish *et al.*<sup>7</sup> state that the scientific basis for determining extubation readiness remains imprecise and guided primarily clinical judgment, which is variable and subjective. Therefore, this study aims to connect cardiac, neurological and pulmonary factors that influence the extubation success in premature infants submitted to the 5-minute Spontaneous Breathing Trial (SBT).

# METHODOLOGY

## Study design

This research was approved by the Human Research Ethics Committee with the number 5.360.742. This is an observational, descriptive and retrospective study, carried out between July 2021 and June 2022 at the Neonatal and Pediatric Intensive Care Unit of the Hospital do Trabalhador, Curitiba, Brazil. We correlated the possible factors that influence in the extubation success of premature infants guided by the unit's protocol/checklist using the eligibility criteria of extubation associated with SBT.

## Setting and participants

All premature infants admitted to the NICU, with gestational age up to 37 weeks, of both genders, regardless of birth weight, assisted by IMV for at least 24 hours, hemodynamically stable, in the weaning process with eligibility for the protocol/checklist and SBT were selected. The newborn (> 37 weeks), premature infants with congenital anomalies, genetic syndromes, transferred from other hospitalization units, premature infants with unplanned extubation and those who did not undergo the extubation protocol/checklist were excluded.

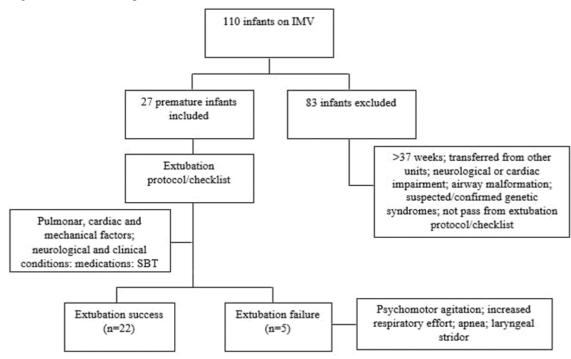
The calculation of gestational age was performed using the Capurro method. This method is a tool used by the medical team to estimate the gestational age of the newborn, through the observation of physical signs and neurological characteristics. This instrument is quick and relatively simple to apply, especially where there are no ultrasounds or reliable dates available for the mother's last menstrual period, helping to determine whether the newborn is premature, full-term or post-term.

The premature infants were divided according to the classification of the World Health Organization: extremely premature (< 28 weeks), very premature (28 - 31 weeks and six days), moderately premature (32 - 33 weeks and six days) or late premature (34 - 36 weeks and six days).

The sample was initially composed of 110 newborns on IMV. Following the pre-established criteria, 83 patients were excluded. Some newborns were > 37 weeks, others were transferred from other hospitalization units and in some premature infants the SBT was not performed because they had a neurological or cardiac impairment, airway malformation, or suspected/confirmed genetic syndromes. The extubated unplanned and premature infants who did not pass from protocol/checklist were excluded. The sample consisted of 27 premature infants from the obstetric surgical centre of the Hospital do Trabalhador and referred to its Neonatal and Pediatric ICU (Figure 1).



Figure 1. Flowchart of patients.



Legend: IMV = Invasive Mechanical Ventilation; SBT = Spontaneous Breathing Trial.

## Variables and procedures

All premature infants went through the weaning protocol until eligibility for extubation. After extubation, the procedure's possible success and failure factors were correlated via the "HOSPUB" electronic medical record, from the daily IMV records from birth to post-extubation and the extubation protocol/checklist. It was composed of the Capurro method, corrected gestational age, doses of pulmonary surfactant, weight, ventilatory data (dynamic compliance, pulmonary resistance, minute volume and tidal volume), pulmonary factors (data from blood gas analysis, X-ray, airway leak, drive/trigger present), cardiac factors (patent Arterial Duct, pulmonary hypertension), neurological conditions, clinical conditions, medications, postextubation ventilatory support and the SBT test with the Silverman Andersen Respiratory Severity Score (SA-RSS).

#### **Statistical Analysis**

Data were reported as either mean (standard deviation) or median (IQR) for quantitative variables. Qualitative variables were summarized using frequencies and percentages. To assess the association of qualitative variables with successful extubation, Fisher's exact test was considered. By means of the nonparametric Mann-Whitney test, we had assessed the association between quantitative variables and extubation success. Differences were considered statistically significant if the p value < 0.05. Statistical analysis was performed using Stata/SE v.14.1 computer program. StataCorpLP, USA.

# RESULTS

#### **Characteristics of the premature infants**

Of the 22 patients who were successfully extubated, 13 were boys and 9 were girls. In terms of weight, 12 of them weighed up to 1,500 g, while 10 weighed more than 1,500 g. The premature infants were categorized as: extremely premature newborn (18.52%); very premature newborn (48.15%); moderately premature newborn (22.22%) and late premature newborn (11.11%).

#### **Extubation protocol/checklist**

In this case, the extubation protocol/checklist establishes criteria that increase the chances of successful extubation. Thus, the null hypothesis that the probability of reintubation is equal in cases with and without an extubation protocol/checklist (assessed during the SBT) was tested versus the alternative hypothesis of different probabilities. The results demonstrate that premature infants who were extubated after the 5-minute SBT are less likely to be reintubated (p = 0.003) (Table 1).

	Extubation sucess							
Reintubation	1	No	Yes					
	n	%	n	%				
No	0	0%	17	77.3%				
Yes	5	100%	5	22.7%				
Total	5	100%	22	100%				
				p = 0.003(*)				

Table 1. Probability of reintubation of premature infants who underwent to extubation protocol/checklist.

\* p < 0,05; Fisher's exact test.

# Analysis of Pulmonary, Cardiac, Neurological Factors, Clinical Conditions

Regarding the arterial blood gases, we had observed that of the 25 premature infants who had compensated arterial blood gases, 20 had gotten successful extubation. Regarding the radiographic image with signs of pulmonary pathology, airway without escape, infection and patent ductus arteriosus (PDA) with repercussions, we had verified a sample balance in relation to extubation success. Regarding PDA, 12 premature infants had presented this condition and 15 did not, and 14 of these had gotten successful extubation.

As for the radiographic image with signs of cardiac patho-

logy, of the 23 premature infants who had not presented the mentioned factor, 20 had obtained successful extubation. We had observed that pulmonary hypertension, motor activity and anaemia had not presented statistically significant differences.

## Medications

Eighteen premature infants had not use caffeine, and of these, 17 had gotten extubation success and of the 9 who had used this medication, 5 had gotten extubation success (p = 0.03) (Table 2).

Variable	Classification	No		Yes		Total	р
		n	%	n	%		
Caffeine	No	1	5.6	17	94.4	18	0.03*
Carrenne	Yes	4	44.4	5	55.6	9	
Corticosteroid	No	4	18.2	18	81.8	22	1
	Yes	1	25	3	75	4	
Diuretic	No	4	17.4	19	82.6	23	1
Diuretic	Yes	1	25	3	75	4	
Sedation	No	5	19.2	21	80.8	26	1
Sedation	Yes	0	0	1	100	1	
Analgesia	No	5	20	20	80	25	1
	Yes	0	0	2	100	2	

Table 2. Quantitative variables of the extubation protocolo/checklist in relation to medication. Curitiba (PR), Brazil, 2021 - 2022 (n = 27).

\* p < 0,05; Mann-Whitney test.



## **Post-Extubation Analysis**

We had observed that 14 premature infants who did not use the post-extubation nasal or non-invaisve intermittent positive pressure ventilation (NIPPV) modality had extubation success and that of the 13 who had used the post-extubation NIPPV modality, 8 had gotten extubation success, with a statistically significant difference (p = 0.01). As for the continuous positive airway pressure (CPAP) mode, of the 17 premature infants who used this support, 12 had obtained extubation success and 10 who did not use this support had gotten extubation success (Table 3).

Table 3. Quantitative variables of the extubation protocolo/checklist in relation to post-extubation ventilatory support. Curitiba (PR), Brazil, 2021 - 2022 (n = 27).

			Extubatio	n Success			
Variable	Classification	No		Yes		Total	р
		n	%	n	%		
Nasal catheter	No	5	20.8	19	79.2	24	1
Inasai catheter	Yes	0	0	3	100	3	
HOOD	No	5	18.5	22	81.5	27	
HOOD	Yes	0		0		0	
01	No	5	19.2	21	80.8	26	1
O2	Yes	0	0	1	100	1	
СРАР	No	5	29.4	12	70.6	17	0.12
	Yes	0	0	10	100	10	
NIPPV	No	0	0	14	100	14	0.01*
	Yes	5	38.5	8	61.5	13	

p < 0.05; Mann-Whitney nonparametric test.

CPAP = continuous positive airway pressure; NIPPV = nasal intermittent positive pressure ventilation.

## Quantitative analysis of variables

We had observed that the gestational age at birth according to the Capurro method, corrected gestational age and birth weight had shown a statistically significant difference (p = 0.003). Regarding pre-extubation weight, we had found that there was no statistically significant difference, although the median pre-extubation weight of premature infants who were extubated successfully was higher than those who were not.

Regarding ventilatory parameters, plateau pressure and tidal volume, we had found a statistically significant difference. In relation to inspiration and expiration, peak pressure, inspiratory resistance, inspiratory resistance in the SBT, and heart rate, we had observed a trend of difference in p-value. Although the median of the inspiration-expiration ratio was lower in premature infants who were extubated successfully, the pulmonary resistance in the SBT and inspiratory resistance were higher in premature infants who were extubated successfully in relation to the median. The mean airway pressure, pre-extubation dynamic complacency, dynamic complacency, minute volume and tidal volume performing SBT had not shown statistically significant difference, but with higher median values in relation to premature infants with extubation success.

In the aspects of oxygen saturation, respiratory rate  $FiO_2$ , flow, Inspiratory Time, respiratory rate from the respirator, PEEP, mechanical ventilation time and sensitivity, we had found no statistically significant difference (Table 4).

Variable	Extubation Success	n	Mean	Minimum	1° Quartile	Median	3° Quartile	Maximum	SD	<b>p</b> *
Heart rate (bpm)	No	5	163.2	140	153	164	177	18	17.22	
	Yes	22	148	123	140.5	147.5	159.5	173	14.49	0.09
E'O	No	5	0.27	0.21	0.22	0.25	0.25	0.40	0.08	0.7
FiO <sub>2</sub>	Yes	22	0.26	0.21	0.21	0.25	0.30	0.45	0.07	0.08
Ventilatory Parameters										
P. plateau (cmH2O)	No	5	6	2	3	6	9	10	3.54	
	Yes	21	10.2	2	9	10	13	16	3.66	0.04*
VT (mL/kg)	No	5	6.6	4.8	5	6.1	7.5	10	2.14	
	Yes	22	10.5	3	8.88	11	11.78	16	2.84	0.01*
CAPURRO weeks	No	5	28.54	27.29	27.86	28,57	29	30	1.05	
	Yes	22	31.44	25	30.14	31.79	33	37	3.17	0.02*
Demographic data										
GA corrected weeks	No	5	29.49	28.86	29	29.57	30	30	0.54	
	Yes	21	32.76	29	31	33	34	38	2.32	0.003*
Birth weight (g)	No	5	1.01	854	978	1.01	1.07	1.18	121.47	0.0*
	Yes	22	1.60	750	1.08	1.42	2.04	3.39	56.94	

Table 4. Physiological variables, ventilatory parameters and demographic data. Curitiba (PR), Brazil, 2021 - 2022 (n = 27).

\* p < 0.05; Mann-Whitney nonparametric test.

SD = standard deviation; bpm = beats per minute; FiO<sub>2</sub> = fraction of inspired oxygen; P. platô = plateau pressure; VT = tidal volume; mL/kg = milliliters per kilogram; cmH<sub>2</sub>O = centimeters of water pressure

## DISCUSSION

In this study, we had investigated the correlation of ventilatory data, pulmonar, cardiac and neurological factors, clinical conditions, spontaneous breathing trial and post-extubation support, focused on success after the removal of the orotracheal tube cannula in premature infants. These results are in agreement with the literature, since neonatal extubation is complex and marked by the possibility of causing negative outcomes that can increase the risk of adverse outcomes such as bronchopulmonary dysplasia, neurological deficit, increased mechanical ventilation time and reintubations.<sup>8</sup> In this context Bacci *et al.*<sup>9</sup> and Shalish *et al.*<sup>10</sup> reinforce the need for predictive factors for extubation success, since IMV interruption is related to subjective criteria and conflicting evidence.

Knowing the subcategorization of preterm, their different clinical manifestations and impact on the different systems and maturity stages are essential for safety and strategies of specific treatment techniques. Prematurity is a complex syndrome with an outcome of multiple determinants, which may influence gestational age and birth weight.<sup>11</sup>

According to Moura *et al.*<sup>12</sup> and Kidman *et al.*,<sup>13</sup> in their multicentric analysis to investigate predictors of weaning failure in premature infants, they had showen that inadequate prenatal care, prematurity or low gestational age and birth weight are risk factors for the process of hospitalization and neonatal mortality.

In our study, we had considered birth weight as a descriptive variable only for the categorization of prematurity (premature infants below 1,500 g and above it).

When we had correlated birth weight, pre-extubation weight, gestational age and corrected gestational age, we had found that these factors corroborate the literature regarding the results found in relation to extubation success, even observing a great variability between weight and minimum gestational age and weight with maximum gestational age. Birth weight is an important factor for successful extubation; however, signs of respiratory distress cannot be underestimated considering that these are the main cause of failure and reintubation.

Hermeto *et al.*<sup>14</sup> had showed that the higher the birth weight, gestational age, 5-minute APGAR (between 7 - 9), pH and PaCO<sub>2</sub> closer to the reference values are factors associated with successful extubation.

Nakato *et al.*<sup>15</sup> had shown that pressure parameters, arterial blood gases and capnometry are important parameters to be evaluated in the weaning process and that support before and after endotracheal extubation, such as the use of caffeine and CPAP, are important to avoid need for reintubation.

Soares *et al.*<sup>16</sup> and Ferguson *et al.*<sup>17</sup> mention that the particularities of premature infants as well as the characteristics of their respiratory system, including greater instability of the upper airways and rib cage as well as cardiac and neurological factors, can make successful extubation difficult.

However, efforts have been made to define and establish objective criteria that can help with safe weaning and extubation through protocols and readiness tests. On the other hand, Shalish *et al.*<sup>10</sup> and Ferguson *et al.*<sup>17</sup> report disagree-



ment regarding the real effectiveness of SBT in neonatology, even so, in an attempt to produce concrete evidence for its use. In this perspective, SBT was correlated with possible success factors for extubation, since effective criteria can indicate the moment to start the weaning and extubation process, avoiding reintubations.

Nakato *et al.*<sup>18</sup> had shown that performing the 3-minute SBT was associated with increased respiratory instability, although it still led to a 10% drop in extubation failure rate, suggesting that the use of SBT to assess readiness for extubation in this population is not yet recommended.

In our study, we aimed not only to use SBT to determine readiness for extubation, but the association of SBT with pulmonary, cardiac, neurological and clinical status.

Studies indicate that precise parameters and clinical laboratory criteria identified by respiratory functions are important to determine the most appropriate time for effective extubation. Therefore, minimizing the risks of comorbidities such as bronchopulmonary dysplasia, neurological deficit and prolonged mechanical ventilation time.<sup>15,19</sup>

According to Lanetzki *et al.*,<sup>20</sup> clinical and ventilatory parameters based on laboratory tests, stabilization of the underlying disease that led to the need for mechanical ventilation, as well as hemodynamic stability, are predictors of spontaneous ventilatory capacity without using of invasive support, that are factors related to success.

Other relevant factors related to successful weaning, according to Dimitriou *et al.*<sup>12</sup> and Kidman *et al.*<sup>13</sup> include ventilatory parameters and mechanics. Jurkevicz *et al.*<sup>22</sup> agree with the importance of considering the respiratory and ventilatory parameters, asserting that they must present respiratory drive with the presence of regular spontaneous breathing and cough reflex.

Evidence suggests values of mean airway pressure between 6 and 8 cmH<sub>2</sub>O, a fraction of inspired oxygen less than 40% to maintain saturation above 90%, inspiratory pressure between 12 and 15 cmH<sub>2</sub>O and hydrogen potential (pH) between 7.30 and 7.40 showing favourable results for the weaning and extubation process.

In our study, those measures are consistent and those parameters are part of the neonatal and paediatric ICU protocol.

Bacci *et al.*<sup>9</sup> report that the applied mechanical ventilation weaning protocols differ from one unit to another, indicating that there are no standardized weaning protocols in neonatology.

Mhanna *et al.*,<sup>23</sup> Knake *et al.*<sup>24</sup> and Dimitriou *et al.*<sup>21</sup> had found correlation between extubation success in relation to Mean Airway Pressure (MAP < 8 cmH<sub>2</sub>O), Peak Pressure (< 16 cmH<sub>2</sub>O), with the variables being used along with PEEP for MAP calculation. Another reported variable was the initial tidal volume of 5.0 mL/kg for infants. Fioretto *et al.*<sup>25</sup> recommend limiting tidal volume to values  $\leq$  6 mL/kg, plateau pressure to 30 cmH<sub>2</sub>O, and using adequate PEEP. In our study, we had observed that these parameters had reached statistically significant tendency when correlated with extubation success.

The extubation success rate was 81.4%, similar to Mhanna's *et al.*<sup>23</sup> study, and Spaggiari *et al.* 26 who had found rates of 69 and 63.8%, in windows of extubation failure of 48 h and 72 h,

respectively. We had used an observation window to consider extubation success or failure of 48h, respectively, described by Giaccone *et al.*,<sup>27</sup> as the second most used by the authors, the first being 168h (7 days).

Regarding the correlated medications in this study, the administration of caffeine and corticosteroids had been associated with successful extubation.<sup>23</sup>

A study carried out by Wan *et al.*<sup>28</sup> had showen that higher maintenance doses of caffeine citrate reduce the incidence of extubation failure and apnoea of prematurity without increasing the occurrence of adverse reactions. However, we had found statistically significant differences in the use of caffeine.

The premature infants who did not use this medication had a 94.4% extubation success and the premature infants who used it had a 55.6% success rate, not agreeing with the study by Mhanna *et al.*<sup>23</sup> in relation to corticosteroids, because we had found percentage difference, with a higher success degree for premature infants who did not use this medication.

Excessive sedation at the time of extubation has been associated with extubation failure in children. Although the administered medication dose was not an outcome investigated in our study, it is relevant to mention that the literature shows a significant difference regarding the number of sedatives and narcotics used between premature infants who succeeded or failed in extubation.

Most premature infants are submitted to oxygen therapy and/or CPAP/NIPPV after extubation. The patients evaluated in our study were extubated and followed the evidence in the literature, being submitted to NIPPV and/or CPAP support, according to the unit's protocol.

CPAP has been associated to higher extubation success rate. Studies describe that NIPPV can be used when premature infants fail to use nasal CPAP, to prevent reintubation. Although the most used initial post-extubation respiratory support is CPAP, we had obtained higher percentage of NIPPV modality, followed by CPAP and nasal catheter, with statistically significant difference in premature infants using NIPPV with extubation success.<sup>4,10,13</sup>

In our study, the NIPPV was used as initial respiratory support and not because of CPAP failure.

Kidman *et al.*<sup>13</sup> state that the reasons for failure in the extubation and reintubation process are multifactorial and include apnoea, reduced lung expansion verified by radiographic imaging, increased supplemental oxygen; being the failure described as a consequence of persistent immaturity of the newborn pulmonary and neural system, and loss of functional residual capacity due to obstruction of the upper airways. Even if the neonate is submitted to non-invasive ventilation after extubation, the respiratory stress resulting from the suspension of invasive pulmonary support can exceed its adaptive capacity and generate systemic disorders responsible for inducing reintubation.<sup>10</sup>

The limitation of our study was the sample size. Therefore, we intend to expand the sample, since many of these variables tended towards statistical significance. We believe that these correlations are essential for a better neurobehavioral and systemic prognosis, resulting in a high level of excellence in care, always prioritizing premature infants.



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# CONCLUSION

We can observe that factors such as weight, Parkin, GA, respiratory mechanics (P. Plato and VT) and the use of noninvasive support after extubation were factors associated to extubation success in premature infants submitted to the SBT. Thus, these data can contribute to the decision of the best moment for the tube removal and the favorable conditions to the extubation success, favoring the reduction of the need for reintubation and provide more security at the time of extubation.

Our study points out important variables in relation to the ventilatory parameters that indicate efficient ventilatory mechanics and clinical stability at the time of the weaning process, contributing to the extubation success. Although most preterm infants are successfully extubated, the failure rate was 18.5%.

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## **Conflict of interest**

The authors declare that there is no conflict of interest.

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