King's Research Portal

DOI:

[10.1159/000477233](https://doi.org/10.1159/000477233)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Dassios, T., Kaltsogianni, O., & Greenough, A. (2017). Relaxation Rate of the Respiratory Muscles and Prediction of Extubation Outcome in Prematurely Born Infants. *Neonatology*, 112(3), 251-257.
<https://doi.org/10.1159/000477233>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Relaxation rate of the respiratory muscles and prediction of extubation outcome
in prematurely born infants

Theodore Dassios PhD¹, Ourania Kaltsogianni¹, Anne Greenough MD^{2,3}

¹ Neonatal Intensive Care Centre, King's College Hospital NHS Foundation Trust, London, UK;

² Division of Asthma, Allergy and Lung Biology, MRC-Asthma UK Centre in Allergic Mechanisms of Asthma, King's College London, UK;

³ National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London; UK

Short title: Prediction of extubation by respiratory muscle relaxation

Corresponding author: Anne Greenough, NICU, 4th Floor Golden Jubilee Wing, King's College Hospital, Denmark Hill, London, SE5 9RS, Tel: 0203 299 3037; fax: 0203 299 8284; email: anne.greenough@kcl.ac.uk

Key words: Extubation; respiratory muscles; mechanical ventilation; premature infant

ABSTRACT

Background: Accurate prediction of extubation outcome could result in a significant reduction of respiratory morbidity in premature neonates.

Objectives: To assess whether the respiratory muscle time constant of relaxation (τ) predicted extubation outcome in mechanically ventilated, premature infants.

Methods: Forty-six mechanically ventilated infants with a median gestational age of 26 [interquartile range (IQR) 25-29] weeks were prospectively studied. τ was calculated from the reciprocal of the slope of the airway pressure decline as a function of time. Measurements of τ were done during five to ten minutes of a spontaneous breathing test (SBT) prior to extubation. During the first and last minute of the SBT, τ_1 and τ_2 respectively were assessed and the difference between them was calculated ($\Delta\tau$).

Results: The median τ_2 was significantly higher in infants that failed extubation [20.7(IQR 12.9-34.7)sec/cmH₂O] compared to infants that succeeded extubation [8.2(IQR 6.2-17.8) sec/cmH₂O, p=0.002]. The median $\Delta\tau$ was significantly higher in infants that failed extubation [10.3(IQR 4.4-23.9)sec/cmH₂O] compared to infants that succeeded extubation [-1.63(IQR -5.7-0.3)sec/cmH₂O, p=0.001]. Extubation failure was associated with τ_2 (p=0.011) and $\Delta\tau$ (p=0.010) after correcting for postmenstrual age, patent ductus arteriosus and intraventricular haemorrhage. Receiver operator characteristic curve analysis demonstrated that $\Delta\tau$ predicted extubation failure with an area under the curve of 0.937. A $\Delta\tau$ of +1.02 sec/cmH₂O predicted extubation failure with 94% sensitivity and 83% specificity.

Conclusions: The respiratory muscle time constant of relaxation during a SBT was significantly greater in infants who failed extubation and could be used to predict extubation outcome in prematurely born infants.

INTRODUCTION

Mechanical ventilation (MV) is a lifesaving intervention for prematurely born infants. Prolonged MV, however, is associated with significant respiratory morbidity [1], but inappropriately early discontinuation of MV (extubation) might precipitate a sudden deterioration with adverse consequences and necessitate re-institution of MV (reintubation) [2]. Various factors have been evaluated in order to predict extubation outcome such as blood gases [3], minute ventilation [4, 5], lung volume and compliance measurements [5-7], assessment of cardiorespiratory variability [8, 9] and composite indices describing respiratory muscle efficiency [2, 3, 10]. Unfortunately, accurate prediction of extubation outcome remains evasive as the evaluated indices have been shown to demonstrate high sensitivity, but only moderate specificity.

The ability to sustain the work of breathing is dependent on the functional capacity of the respiratory muscles to cope with the imposed workload [11]. Previous studies investigating respiratory muscle function in prematurely born infants have shown that univariate indices such as the maximal inspiratory or expiratory pressures have not been useful, as differences according to extubation outcome were not statistically significant when the results were related to birth weight [12]. Furthermore, composite indices of respiratory muscle function such as the tension-time index of the respiratory muscles did not perform significantly better in predicting extubation outcome than gestational age or birth weight [10].

The functional state of the respiratory muscles and the risk for muscle fatigue can be assessed by measuring the rate of relaxation of the respiratory muscles [13]. The rate of decline in airway pressure during a spontaneous breathing test when an infant is switched from MV to endotracheal continuous positive airway pressure (CPAP) can be used as a surrogate for the measurement of the rate of relaxation. Healthy skeletal muscles relax rapidly, but when

skeletal muscles operate against an increased load, their rate of contraction and relaxation slows [14]. The rate of relaxation can be quantified by the time constant of respiratory muscle relaxation – τ (tau) which is calculated as the reciprocal of the absolute value of the slope of the pressure decline as a function of time at the lower 60% part of the curve. Higher values of τ indicate slower relaxation and increased risk for respiratory muscle fatigue, while lower values of τ indicate rapid relaxation and healthy muscle function [15]. τ has not been studied in prematurely born infants undergoing MV.

We hypothesized that τ will be increased in premature infants who fail extubation. The aim of this study was to test that hypothesis and determine whether τ predicted extubation outcome in mechanically ventilated premature infants.

MATERIALS AND METHODS

Subjects

Infants born at less than 34 completed weeks of gestation without congenital anomalies ventilated at King's College Hospital NHS Foundation Trust were eligible for study. The infants were ventilated with a Cole's shouldered endotracheal tube (size 2.5 or 3.0) on volume-targeted or pressure-controlled time-cycled ventilation with the SLE5000 neonatal ventilator or the SLE2000 infant ventilator (SLE, Croydon, UK). The study was approved by the London – Surrey Borders Research Ethics Committee (REC Reference 15/LO/2111). Written, informed parental consent was obtained.

The infants were studied when they were clinically stable and ready for extubation. Extubation was considered, as per unit policy, if the fraction of inspired oxygen (FiO_2) was less than 0.4, the infant had acceptable blood gases, that is a $\text{pH} > 7.25$ and a $\text{PaCO}_2 < 8.5$

kPa, and their breathing rate was above the set ventilator rate. Sedation was discontinued at least 12 hours before extubation and all infants were receiving caffeine at a standard maintenance dose.

Study protocol

When the clinical team decided that an infant was ready for extubation, the infant underwent a SBT which consisted of switching the infant from MV to endotracheal (ET)-CPAP for a period of 5 to 10 minutes during which time the oxygen saturation (SpO_2) and heart rate were monitored [16]. During the SBT, the ET-CPAP level was the same pressure as the positive end expiratory pressure during mechanical ventilation. A failed SBT was recorded if the infant had either a bradycardia with a heart rate of less than 100 per minute for more than 15 seconds and/or a fall in SpO_2 below 85% despite a 15% increase in the fraction of inspired oxygen (FiO_2). The study was then stopped and MV resumed. The clinical team caring for the infant was not present during the SBT and not made aware of the results. Regardless of the result of the SBT, all infants were extubated. Infants were extubated on to either heated, humidified, high-flow nasal cannula or nasal CPAP at the discretion of the clinical team. Reintubation within 72 hours of extubation was the primary outcome of the study [16]. The indications for reintubation were development of respiratory acidosis ($pH < 7.25$ and $PaCO_2 > 8.5$ kPa), a significant apnoea requiring bag and mask ventilation or frequent episodes of apnoea requiring stimulation or a $FiO_2 > 0.6$ to maintain an oxygen saturation in the range of 90–95% [16].

Monitoring equipment

A respiratory function monitor (NM3 respiratory profile monitor (RPM) (Philips Respironics, Connecticut, USA [17, 18] was used. The monitor was connected to a Laptop (Dell Latitude, Dell, Bracknell, UK) with customised Spectra software (3.0.1.4) (Grove Medical, London, UK). The NM3 RPM had a combined pressure and flow sensor which was placed between the endotracheal tube and the ventilator circuit. Flow was measured using a fixed orifice pneumotachograph. One of the tubes from the pneumotachograph was connected to a pressure transducer which measured airway pressure.

Calculation of the time constant of relaxation

The time constant of respiratory muscle relaxation (τ) was calculated as the reciprocal of the absolute value of the slope of the pressure decline as a function of time at the lower 60% of the curve (figure 1) [15]. The part of the trace with a smooth pressure decay was hand selected and analysed. Breaths whose waveforms exhibited evidence of expiratory diaphragmatic braking were excluded from the analysis. For each subject, the mean τ value of at least five consistent breaths was recorded. τ was calculated during the first minute (τ_1) and the last minute of the SBT (τ_2). The difference between these values ($\tau_2 - \tau_1$) was calculated ($\Delta\tau$) (delta tau).

Information from the medical records

Gender, gestation age at birth, birth weight, postmenstrual age, postnatal age and weight at the time of SBT were recorded. The FiO_2 , mean airway pressure and backup rate during MV and the arterial pressure of CO_2 (P_aCO_2) and pH within two hours prior to the SBT were also recorded. The inspiratory pressures that were spontaneously generated during the SBT and the PEEP during the SBT were recorded from a mean of ten spontaneous breaths during the last minute of the SBT. Endotracheal tube leak was estimated as the difference of inspiratory minus expiratory tidal volume, expressed as a percentage of the inspiratory tidal volume.

Information recorded from the infant's medical notes included whether the infant had a patent ductus arteriosus (PDA), had been exposed to antenatal steroids or had had an intraventricular haemorrhage (IVH). A PDA was diagnosed clinically and confirmed by echocardiography. Administration of antenatal corticosteroids was recorded as a positive if at least two doses were given. The cranial ultrasound was recorded as normal if there was no intraventricular haemorrhage or intracranial pathology.

Sample size calculation

The sample size calculation was based on the assumption that a difference in τ of 26 between infants that failed and infants that succeeded extubation was clinically significant based on values of τ that were observed before and after induced diaphragmatic fatigue in healthy young men [19]. The standard deviation of τ was obtained from pilot data and was equal to 22. The required sample size to detect an increase in τ of 26 with 90% power at the 5% level of statistical significance was 15 subjects in each group.

Statistical analysis

Data were tested for normality with the Kolmogorov–Smirnov test and found not to be normally distributed. Hence, differences between those who did and did not fail extubation were assessed for statistical significance using the Mann-Whitney rank sum test or Chi-squared test, as appropriate. The factors that were statistically different (p value <0.05) were inserted into a multivariate logistic regression model with extubation failure as the outcome. Variables without normal distribution were logarithmically transformed. Multi-collinearity among the independent variables in the regression analysis was assessed by calculation of the tolerance for the independent variables.

The performance of the factors that were identified from the multivariate regression model in predicting extubation failure was assessed by receiver operator characteristic (ROC) curve analysis and estimation of the corresponding area under the curve (AUC). The relationship of the duration of the SBT with τ was assessed with the Spearman-rho correlation coefficient (r). Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago IL).

RESULTS

Between 1 February 2016 and 1 August 2016, 113 infants were ventilated on the Neonatal Unit. Sixty-seven infants were excluded from the study as they had congenital anomalies, they were born at more than 34 weeks of gestational age or were extubated before the SBT could be performed. Forty-six infants underwent the SBT. Five infants failed the SBT and all of them failed extubation. Forty-one infants passed the SBT, twenty three were subsequently successfully extubated and eighteen failed extubation. τ was not assessed in the infants that failed the SBT, as they had apnoeas and hence there was no airway pressure waveform for

analysis. The infants that failed extubation had significantly lower postmenstrual age and weight at the time of the SBT and significantly higher τ_2 and $\Delta\tau$ compared to the premature infants that succeeded extubation (Table 1). Premature infants that failed extubation had a significantly higher incidence of abnormal cranial ultrasound examinations and PDA (Table 1). Multivariate regression analysis revealed that τ_2 and $\Delta\tau$ were significantly related to extubation failure independently of PMA, PDA and cranial ultrasound abnormalities (Table 2). Weight was excluded from the multivariate regression model because of collinearity with postmenstrual age. The median (IQR) respiratory rate during the first minute of the SBT was 67 (59 - 78) and during the last minute of the SBT was 72 (60 - 87), $p=0.292$. ROC curve analysis demonstrated in predicting extubation success PMA had an AUC of 0.688, τ_2 an AUC of 0.790 (figure 2a) and $\Delta\tau$ an AUC of 0.937 (figure 2b). A $\Delta\tau$ equal to +1.02 sec/cm H₂O predicted extubation failure with 94% sensitivity and 83% specificity.

The duration of the SBT was not significantly related to τ_2 ($r=0.044$, $p=0.733$) or $\Delta\tau$ ($r=0.021$, $p=0.869$).

DISCUSSION

We have demonstrated that prematurely born infants who failed extubation exhibited significantly slower respiratory muscle relaxation compared to those who were successfully extubated. In addition, we have highlighted that the change in τ during a spontaneous breathing test had a high sensitivity and specificity in predicting extubation failure. The SBT has been reported to have a sensitivity of 97% in predicting extubation outcome [16], which is enhanced to 100% by incorporating measurements of respiratory variability [8]. Unfortunately, the specificity of the SBT is only moderate (73%) [3] which increases only to

202 75% by incorporating respiratory variability information [18]. In our cohort, the SBT had a
203 sensitivity of 100% in predicting extubation failure, but the specificity of the test was low (22
204 %).

205 Previous studies have evaluated the relaxation rate as an index of respiratory muscle fatigue
206 in healthy adults [14, 19, 20]. Goldstone et al [21] reported that the relaxation rate in
207 intubated adults being weaned from mechanical ventilation was slower in patients that failed
208 to wean from MV. Furthermore, they also reported that measurements from the endotracheal
209 tube, as used in this study, reflected the relaxation of the diaphragm as assessed by
210 oesophageal and transdiaphragmatic catheters [21].

211 The importance of our study is that it is the first neonatal study to report that the relaxation
212 rate of the respiratory muscles can be used to accurately predict extubation outcome in
213 premature infants. Our study also highlights a potential pathophysiological mechanism that
214 might be implicated in respiratory failure in prematurely born infants. While it is known that
215 prematurely born infants generate lower inspiratory pressures [22], we now describe that they
216 also exhibit a relaxation pattern that might put them at a higher risk of muscle fatigue. A
217 number of anatomical features render the infantile respiratory muscles more prone to
218 dysfunction. Unlike the adult dome-shaped diaphragm, the newborn diaphragm is
219 morphologically flattened and inserted to the chest wall with a larger angle, resulting in
220 smaller zone of apposition and decreased range of displacement [23]. Structurally, the
221 newborn diaphragm consists of fewer fatigue-resistant slow twitch fibres, decreased oxidative
222 capacity and a low total cross sectional area of all fibre types [24]. Furthermore, the
223 premature infants in our cohort had been ventilated for long periods (interquartile range 3-32
224 days) and prolonged mechanical ventilation can lead to ventilator-induced diaphragmatic
225 dysfunction [25]. Even brief mechanical ventilation has been shown to result in diaphragm

atrophy and contractile dysfunction as a result of oxidation, diaphragmatic proteolysis and reduced protein synthesis [25].

Interestingly, the infants that were successfully extubated had a lower median τ at the end of the SBT compared to the median τ at the beginning of the SBT (negative $\Delta\tau$). This might represent the functional sufficiency of the respiratory muscles to undertake the work of breathing as they transition to lower levels of support

Theoretically, as the duration of the SBT in our study ranged from 5 to 10 minutes, the duration of the test could have influenced our results. The infants who underwent a longer test might have had a longer period for muscle fatigue to be induced by breathing against the resistance of the endotracheal tube. The duration of the test, however, was not related to τ in our cohort. In our study we report a median endotracheal tube leak of 6-7%. It is standard practice in our unit to use shouldered endotracheal tubes which are associated with a low level of leak (26). Further studies in units that routinely use straight tubes could elucidate whether higher leaks might render the relaxation pattern unsuitable as a predictor of extubation outcome.

The strengths of our study include that the clinical team was not informed of the SBT result and hence were not biased with regard to the time of extubation. By measuring the rate of relaxation in intubated subjects we bypassed the upper airway and the possible contribution of upper airway dysfunction in extubation failure. Our study has some potential limitations. Measuring the rate of relaxation through the endotracheal tube in a ventilated subject might theoretically not accurately reflect respiratory muscle function as the measurements might be skewed by the resistance of the ventilator circuit and of the upper and lower airways. Increased resistance of the airways or the endotracheal tube would impose an additional workload on the respiratory muscles and slow their relaxation, especially in the face of

impeding muscle fatigue [13]. To overcome that problem, we measured the difference in τ when there were no changes in the level of respiratory support or use of an endotracheal tube during the SBT, hence the difference could be selectively attributed to respiratory muscle changes. We did not measure the relaxation time in infants who failed the SBT, but a failed SBT is already known to be highly predictive of extubation failure [16]. Our results highlight that a successful SBT can only accurately predict extubation failure when the rate of relaxation is taken into account. We also acknowledge that the airway pressure waveform has not been proven to reflect diaphragmatic activity in ventilated prematurely born newborns. It is plausible that these infants might have active expiration via activation of the abdominal muscles as accessory respiratory muscles, thus we have called our index “rate of relaxation of the respiratory muscles” rather than “diaphragmatic rate of relaxation”.

Our results have an obvious potential application. Modern neonatal ventilators incorporate a proximal pressure sensor and display the relevant pressure-time waveforms. Thus, the information on the rate of relaxation can be processed in real time by a customised ventilator software and inform the clinician as to the likelihood of extubation success.

In conclusion, we have demonstrated that the respiratory muscle time constant of relaxation is significantly higher in premature infants that fail extubation compared to premature infants that succeed extubation. We highlight that $\Delta\tau$ can be used to predict extubation outcome in premature infants with high sensitivity and specificity.

ACKNOWLEDGEMENTS

We thank Dr Gerrard Rafferty, Reader in Human Physiology, King's College London for his comments on the design of the study.

Funding source: The research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Financial disclosure: None to declare.

Conflict of interest statement: AG has held grants from various ventilator manufacturers; AG has received honoraria for giving lectures and advising various ventilator manufacturers .

Contributors' statement:

TD conceived the study, participated in the analysis of the data and drafted the first version of the article. OK collected the data and participated in the analysis of the data. AG supervised the project, contributed to the study design and interpretation of the results and critically revised the manuscript. All authors were involved in the preparation of the manuscript and approved the final manuscript as submitted.

REFERENCES

1. Clark RH, Gerstmann DR, Jobe AH, Moffitt ST, Slutsky AS, Yoder BA: Lung injury in neonates: causes, strategies for prevention, and long-term consequences. *J Pediatr* 2001;139:478-486.
2. Currie A, Patel DS, Rafferty GF, Greenough A: Prediction of extubation outcome in infants using the tension time index. *Arch Dis Child Fetal Neonatal Ed* 2011;96:F265-F269.
3. Dimitriou G, Fouzas S, Verveniotti A, Tzifas S, Mantagos S: Prediction of extubation outcome in preterm infants by composite extubation indices. *Pediatr Crit Care Med* 2011;12:e242-e249.
4. Gillespie LM, White SD, Sinha SK, Donn SM: Usefulness of the minute ventilation test in predicting successful extubation in newborn infants: a randomized controlled trial. *J Perinatol* 2003;23:205-207.
5. Vento G, Tortorolo L, Zecca E, Rosano A, Matassa PG, Papacci P, Romagnoli C: Spontaneous minute ventilation is a predictor of extubation failure in extremely-low-birth-weight infants. *J Matern Fetal Neonatal Med* 2004;15:147-154.
6. Veness-Meehan KA, Richter S, Davis JM: Pulmonary function testing prior to extubation in infants with respiratory distress syndrome. *Pediatr Pulmonol* 1990;9:2-6.
7. Balsan MJ, Jones JG, Watchko JF, Guthrie RD: Measurements of pulmonary mechanics prior to the elective extubation of neonates. *Pediatr Pulmonol* 1990;9:238-243.
8. Kaczmarek J, Kamlin CO, Morley CJ, Davis PG, Sant'anna GM: Variability of respiratory parameters and extubation readiness in ventilated neonates. *Arch Dis Child Fetal Neonatal Ed* 2013;98:F70-F73.
9. Patzak A: Short-term rhythms of the cardiorespiratory system and their significance in neonatology. *Chronobiol Int* 1999;16:249-268.
10. Bhat P, Peacock JL, Rafferty GF, Hannam S, Greenough A: Prediction of infant extubation outcomes using the tension-time index. *Arch Dis Child Fetal Neonatal Ed* 2016;101:F444-F447.
11. Vassilakopoulos T RC: Physiology and Testing of Respiratory Muscles. In: Albert R SS, Jett J, editor. *Clinical Respiratory Medicine*. III ed. Philadelphia PA: Mosby Elsevier; 2008. p. 135-46.

- 316 12. Dimitriou G, Greenough A, Endo A, Cherian S, Rafferty GF: Prediction of extubation failure
317 in preterm infants. Arch Dis Child Fetal Neonatal Ed 2002;86:F32-F35.
- 318 13. ATS/ERS: ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med
319 2002;166:518-624.
- 320 14. Coirault C, Chemla D, Lecarpentier Y: Relaxation of diaphragm muscle. J Appl Physiol
321 1999;87:1243-1252.
- 322 15. Dassios T, Kaditis A, Katelari A, Chrousos G, Doudounakis S, Dimitriou G: Time constant of
323 inspiratory muscle relaxation in cystic fibrosis. Pediatr Res 2015;77:541-545.
- 324 16. Kamlin CO, Davis PG, Morley CJ: Predicting successful extubation of very low birthweight
325 infants. Arch Dis Child Fetal Neonatal Ed 2006;91:F180-F183.
- 326 17. Murthy V, Dattani N, Peacock JL, Fox GF, Campbell ME, Milner AD, Greenough A: The
327 first five inflations during resuscitation of prematurely born infants. Arch Dis Child Fetal Neonatal Ed
328 2012;97:F249-F253.
- 329 18. Murthy V, D'Costa W, Shah R, Fox GF, Campbell ME, Milner AD, Greenough A:
330 Prematurely born infants' response to resuscitation via an endotracheal tube or a face mask. Early
331 Hum Dev 2015;91:235-238.
- 332 19. Esau SA, Bye PT, Pardy RL: Changes in rate of relaxation of sniffs with diaphragmatic
333 fatigue in humans. J Appl Physiol 1983;55:731-735.
- 334 20. Mador MJ, Kufel TJ: Effect of inspiratory muscle fatigue on inspiratory muscle relaxation
335 rates in healthy subjects. Chest 1992;102:1767-1773.
- 336 21. Goldstone JC, Green M, Moxham J: Maximum relaxation rate of the diaphragm during
337 weaning from mechanical ventilation. Thorax 1994;49:54-60.
- 338 22. Dimitriou G, Greenough A, Rafferty GF, Moxham J: Effect of maturity on maximal
339 transdiaphragmatic pressure in infants during crying. Am J Respir Crit Care Med 2001;164:433-436.
- 340 23. Devlieger H, Daniels H, Marchal G, Moerman P, Casaer P, Eggermont E: The diaphragm of
341 the newborn infant: anatomical and ultrasonographic studies. J Dev Physiol 1991;16:321-329.

- 342 24. Sieck GC, Fournier M, Blanco CE: Diaphragm muscle fatigue resistance during postnatal
343 development. J Appl Physiol 1991;71:458-464.
- 344 25. Vassilakopoulos T, Petrof BJ: Ventilator-induced diaphragmatic dysfunction. Am J Respir
345 Crit Care Med 2004;169:336-341.
- 346 26. Hird M, Greenough A, Gamsu H: Gas trapping during high frequency positive
347 pressure ventilation using conventional ventilators. Early Hum Dev 1990;22:51-56.
- 348

349 **FIGURE LEGENDS**

350 **Figure 1:** Patterns of respiratory muscle relaxation: slower rate of relaxation and
351 increasing values of τ describe increasing respiratory muscle
352 dysfunction and risk for muscle fatigue.

353 **Figure 2:** ROC curves for τ_2 (a) and delta $\Delta\tau$ (b) to predict extubation failure.

354

355

Table 1: Demographics and mechanical ventilation settings at the start of the SBT and inspiratory muscle time constant of relaxation according to successful and failed extubation

Data are presented as median (IQR) or n (%)

	Successful Extubation <i>N</i> =23	Failed Extubation <i>N</i> =18	p-value
GA (weeks)	28 (25 – 30)	26 (25 – 27)	0.208
PMA (weeks)	31 (29 - 33)	27 (26 - 32)	0.037
BW (kg)	0.88 (0.70 – 1.36)	0.88 (0.77 - 0.95)	0.368
Male gender	12 (52)	8 (44)	0.792
Weight (kg)	1.36 (1.06 – 1.69)	1.00 (0.83 - 1.21)	0.023
Postnatal age (days)	16 (2 – 47)	9 (4 - 43)	0.731
Antenatal Steroids	19 (82)	11 (61)	0.540
Abnormal Cranial US	3 (13)	7 (39)	0.047
Patent Ductus Arteriosus	2 (9)	6 (33)	0.025
ETT size 2.5 mm	4 (17)	4 (22)	0.538
ETT Leak (%)	6 (2 - 13)	7 (4 - 14)	0.494
No surfactant	1 (4)	0 (0)	0.152
FiO ₂	0.27 (0.22 – 0.37)	0.26 (0.22 - 0.31)	0.939
MAP (cm H ₂ O)	8 (7 – 9)	8 (7 - 9)	0.627
RR ₁	71 (56 – 89)	76 (63 – 81)	0.486
RR ₂	67 (59 – 79)	68 (60 -78)	0.674
Delta RR	-8 (-14 – 12)	-5 (-8 – 1)	0.511
Ti ₁ (sec)	0.41 (0.31 – 0.45)	0.32 (0.31 – 0.37)	0.069
Ti ₂ (sec)	0.37 (0.29 – 0.46)	0.36 (0.31 – 0.44)	0.674

Delta Ti	0.01 (-0.06 – 0.07)	0.01 (-0.01 – 0.06)	0.415
Backup rate	40 (40 – 45)	40 (30 - 40)	0.117
PaCO ₂ (kPa)	6.26 (5.39 – 6.62)	6.89 (5.37 - 7.86)	0.162
pH	7.36 (7.33 – 7.40)	7.36 (7.32 - 7.41)	0.937
Days of ventilation	8 (2 – 38)	9 (4 – 37)	0.838
PEEP (cm H ₂ O)	5.6 (4.2 – 6.3)	5.6 (4.8 – 6.0)	0.916
P _{insp} (cm H ₂ O)	7.0 (6.5 – 7.8)	6.8 (5.9 – 7.2)	0.236
Duration of SBT (min)	6 (5-8)	6 (5 – 8)	0.644
τ_1 (sec/cm H ₂ O)	11.3 (7.1 – 23.8)	10.7 (7.9 – 17.0)	0.608
τ_2 (sec/cm H ₂ O)	8.2 (6.2 – 17.8)	20.7 (12.9 – 34.7)	0.002
$\Delta\tau$ (sec/cm H ₂ O)	-1.63 (-5.7 – 0.3)	10.3 (4.4 – 23.9)	0.001
Extubated to CPAP	11 (48)	7 (39)	0.752

360

361 SBT: spontaneous breathing trial, GA: gestational age, PMA: postmenstrual age, ETT: Endotracheal tube, BW:
362 birth weight, FiO₂: fraction of inspired oxygen, MAP: mean airway pressure, RR₁: respiratory rate at during the
363 first minute of the SBT, RR₂: respiratory rate during the last minute of the SBT, Delta RR= RR₂ – RR₁, Ti₁:
364 inspiratory time during the first minute of the SBT, Ti₂: inspiratory time during the last minute of the SBT, Delta
365 Ti=Ti₂ – Ti₁, PaCO₂: Arterial partial pressure of CO₂, P_{insp}: peak inspiratory pressure generated during
366 spontaneous breathing, PEEP positive end expiratory pressure, τ_1 : time constant of respiratory muscle relaxation
367 during the first minute of the SBT, τ_2 : time constant of respiratory muscle relaxation during the last minute of
368 the SBT, $\Delta\tau = \tau_2 - \tau_1$, CPAP: continuous positive airway pressure.

369

Table 2: Multivariate logistic regression analysis including τ_2 (a) or $\Delta\tau$ (b) for extubation outcome

a

	Odds Ratio	Confidence intervals	P-value
Postmenstrual age	1.097	0.841-1.429	0.495
Patent Ductus Arteriosus	0.259	0.025-2.737	0.262
Normal cranial ultrasound	6.924	0.905-52.955	0.062
τ_2	0.875	0.789-0.969	0.011

b

	Odds Ratio	Confidence intervals	P-value
Postmenstrual age	1.264	0.655-2.439	0.485
Patent Ductus Arteriosus	0.537	0.018-16.218	0.721
Normal cranial ultrasound	12.323	0.298-509.672	0.186
$\Delta\tau$	0.573	0.374-0.877	0.010

a

b