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CLINICAL RESEARCH ARTICLE

Autonomic markers of extubation readiness in premature infants

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BACKGROUND: In premature infants, extubation failure is common and difficult to predict. Heart rate variability (HRV) is a marker of autonomic tone. Our aim is to test the hypothesis that autonomic impairment is associated with extubation readiness.
METHODS: Retrospective study of 89 infants <28 weeks. HRV metrics 24 h prior to extubation were compared for those with and without extubation success within 72 h. Receiver-operating curve analysis was conducted to determine the predictive ability of each metric, and a predictive model was created.
RESULTS: Seventy-three percent were successfully extubated. The success group had significantly lower oxygen requirement, higher sympathetic HRV metrics, and a lower parasympathetic HRV metric. α_1 (measure of autocorrelation, related to sympathetic tone) was the best predictor of success—area under the curve (AUC) of .73 ($p = 0.001$), and incorporated into a predictive model had an AUC of 0.81 ($p < 0.0001$)—sensitivity of 81% and specificity of 78%.
CONCLUSIONS: Extubation success is associated with HRV. We show an autonomic imbalance with low sympathetic and elevated parasympathetic tone in those who failed. α_1, a marker of sympathetic tone, was noted to be the best predictor of extubation success especially when incorporated into a clinical model.

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IMPACT:

- This article depicts autonomic markers predictive of extubation success.
- We depict an autonomic imbalance in those who fail extubation with heightened parasympathetic and blunted sympathetic signal.
- We describe a predictive model for extubation success with a sensitivity of 81% and specificity of 78%.

Mechanical ventilation is a mainstay in the treatment of respiratory distress syndrome in extremely premature infants. Given the risks of ventilation induced lung injury,[1] avoiding intubation and early extubation when the need for ventilatory support is required has become integral in the care of this population.[2,3] Despite advances in care, most extremely low birth-weight infants will be supported on a ventilator,[4] and reintubation secondary to failed extubation attempts can cause atelectasis, airway trauma, and cardiorespiratory instability and worsening.[5–8]

The ability to predict which infants can be successfully maintained on non-invasive support is still lacking, and up to half of all patients will fail extubation despite having met unit specified extubation criteria.[9,10] Many studies have aimed to evaluate both demographic and clinical data to incorporate into predictive models. Proposed predictors have been factors such as gestational age, post-menstrual age and weight at extubation (markers of maturity) and pre-extubation ventilation parameters (FiO2, mean airway pressure, tidal volume, pH, pCO2, etc).[10–12] However, lack of agreement and variability between studies limits generalization.[13]

Respiratory maturity leading to extubation success is clearly multi-factorial. The autonomic nervous system plays a vital role in this regulation. Heart rate variability (HRV) has been used as a marker of autonomic tone,[14] and has been shown to be impaired prior to respiratory deterioration and extubation failure.[15–20] In premature infants, delayed and impaired maturation has been shown,[20,21] which may be exacerbated by increased morbidity.[22] In a study evaluating premature infants readmitted for apparent life-threatening events, it was shown that an elevated parasympathetic drive coupled with blunted sympathetic tone may play a role.[23]

This study aims to test the hypothesis that impaired autonomic tone development in premature infants less than 28 weeks gestation with a sympathetic/parasympathetic imbalance as assessed by HRV metrics is associated with extubation failure.

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METHODS

Study population

This was a retrospective cohort study of infants <28 weeks gestation admitted to the Children's National Hospital Neonatal Intensive Care Unit requiring mechanical ventilation for respiratory insufficiency between June 2017 and December of 2019. Patients were excluded if they were never extubated prior to discharge, were compassionately extubated, were mechanically intubated for a surgical procedure only, or had major congenital anomalies. The Children's National Health System Institutional Review Board approved the study and informed consent was waived.

Data collection

Clinical and demographic data were collected from the medical record. Ventilator parameters and blood gas data were collected just prior to each extubation attempt. For this study, only the first extubation attempt (regardless of intention) was considered. Based on previous studies,[18,19] extubations were considered successful if there was no reintubation within 72 h to minimize the effect of potential confounders on failure. Extubation readiness was determined by the care team and was not protocolized during the study period. Per unit protocol, all patients were maintained on caffeine citrate until 34 weeks corrected gestation with a general daily dose ranging from 5 to 10 mg/kg/day. Post-extubation respiratory support was recorded.

Continuous EKG recordings in the 24 h prior to extubation were obtained, if available, from the Philips Data Warehouse archive (PIIC iX Rev B, Phillips Healthcare, Andover, MA) at a sample rate of 250 Hz.

EKG processing

To attenuate the noise and to correct for the baseline shifts, the EKG was bandpass-filtered between 0.5 and 60 Hz using a Butterworth filter with zero-phase distortion. The R-wave (a wave with maximum amplitude of the cardiac cycle) was identified using a combination of Hilbert transform and the adaptive threshold detection approach,[24] and beat-to-beat interval (RRi) was calculated. The artifacts in the RRi were cleaned using a recently proposed data-driven approach.[25] The artifact-free RRi's were partitioned into 10-min epochs. The 10-min duration will contain sufficient cycles needed to characterize the frequency/periods used in our study. All analyses were performed offline using MATLAB (MathWorks, Natick, MA).

Detrended fluctuation analysis

Detrended fluctuation analysis involves the following four steps: (i) removing the average value of the data and calculating the profile function, which is a cumulative sum of the data; (ii) dividing the profile function into time windows, each containing s-number of beats; (iii) fitting a polynomial function to the profile inside each window and calculating the local fluctuation as the root mean square (RMS) deviation of the profile from the best fit; (iv) averaging the local fluctuation function over all windows to get an overall fluctuation function. For power-law-correlated signals such as RRi, the fluctuation function varies with the window size s in a power-law fashion. The fluctuation exponent is calculated as the slope of the fluctuation function. In this work, we used a fourth-order polynomial to detrend the RRi and calculated the following metrics: α_1 (15–50 beats), RMS_1 (15–50 beats), and RMS_2 (100–150 beats).[26] The α metric characterizes the autocorrelations in the data, whereas the RMS metrics characterize the variability in the data. For less variable data, RMS and α_1 values will be low.

Spectral analysis

For spectral analysis, the RRis in each 10-min epoch were interpolated using cubic spline with a sample rate of 5 Hz and converted into evenly sampled data. To estimate the power spectrum of RRi in a 10-min window, we used a Welch periodogram approach with a frequency resolution of 0.016 Hz. In this approach, we partitioned the RRi into 1-min nonoverlapping epochs. For the RRi in each epoch, we subtracted the mean and normalized it by the standard deviation to mitigate the effects of non-stationarity as described previously.[27] In each window, we calculated the periodogram as the square of the magnitude of the Fourier transform of the RRi. To obtain an estimate of the power spectrum, we averaged the periodograms over all 1-min epochs. We multiplied the resulting spectrum by the median of the variance of the RRi from all the windows. The sum of powers in low frequency (0.05–0.25 Hz) and high frequency (0.3–1 Hz) bands were calculated. The normalized or relative powers (normalized low

Table 1. Demographic and clinical characteristics.

	Failed ($n = 24$)	Successful ($n = 65$)	p-value
Infant variables			
GA at birth[a]	25.1 ± 1.4	25.9 ± 1.8	0.05
Birth weight	726 ± 169	806 ± 235	0.13
Male sex, *n* (%)	14 (58)	34 (52)	0.61
Maternal Pre-eclampsia, *n* (%)	4 (16)	8 (13)	0.84
Small for GA, *n* (%)	4 (16)	10 (15)	0.88
No antenatal steroids, *n* (%)	3 (13)	10 (15)	0.1
5 min Apgar median(range)	7 (3, 9)	7 (1, 9)	0.36
Corrected GA at extubation	30.2 ± 4.7	31 ± 3.6	0.35
Ventilatory settings prior to extubation			
PIP, cm H_2O	16.8 ± 1.6	16.2 ± 1.4	0.09
PEEP, cm H_2O	5.7 ± .8	5.8 ± .8	0.7
TV (mL)	4.1 ± 3	4.6 ± 3	0.56
Fraction of inspired oxygen	.31 ± .1	.25 ± .05	0.01
Ventilator rate, breaths per minute	19.8 ± 5	18.7 ± 4	0.29
Blood gas prior to extubation			
pH	7.35 ± .07	7.37 ± .05	0.31
pCO_2	46.3 ± 8	44.6 ± 6	0.44
Bicarbonate	25.4 ± 4	25.5 ± 4	0.95
Base excess	−0.04 ± 4	0.14 ± 3.7	0.84
Clinical outcomes			
Post-extubation support *n* (%)			0.34
Room air	1 (4)	0 (0)	
Nasal cannula	0 (0)	1 (2)	
CPAP	3 (13)	11 (17)	
NIPPV	20 (83)	53 (82)	
Invasive ventilation days; median (range)	44 (5, 548)	30 (1, 135)	0.0013
Length of stay; median (range)	118 (43, 548)	99 (10, 274)	0.26
Bronchopulmonary dysplasia, *n* (%)	19 (79)	42 (67)	0.25
Patent ductus arteriosus, *n* (%)	13 (54)	47 (72)	0.1
Sepsis <7 days, *n* (%)	1 (4)	6 (9)	0.67
Retinopathy of prematurity, *n* (%)	20 (83)	52 (80)	0.68
Necrotizing enterocolitis, *n* (%)	4 (17)	21 (32)	0.27
Intraventricular hemorrhage Grade 3 or 4, *n* (%)	10 (42)	17 (26)	0.34

PIP peak inspiratory pressure, *PEEP* positive end expiratory pressure, *TV* tidal volume, *CPAP* continuous positive airway pressure, *NIPPV* non-invasive positive pressure ventilation.

[a]Described as mean ± SD unless otherwise noted; bronchopulmonary dysplasia—defined as requiring oxygen at 36 weeks corrected gestation or discharge.

frequency (nLF), normalized high frequency (nHF)) were calculated by dividing the spectral powers by the total power in order to minimize the effect of changes in total power on the estimations of LF and HF components.[28] The total power was defined as the sum of powers in the frequency band of 0.05–2 Hz.[26,27,29]

α_1, RMS_1, RMS_2 have been demonstrated to characterize sympathetic tone while nHF characterizes parasympathetic tone. nLF reflects both sympathetic and parasympathetic tone.[14,30] For each HRV metric, the 10-min epochs were averaged for the 24 h prior to extubation to account for multiple sleep–wake cycles.[31]

Statistical analysis

Univariate analysis of baseline characteristics and clinical data was conducted. Continuous data were presented as mean (standard deviation) or median (range) depending on the distribution. Categorical data were presented as number (%). Clinical characteristics were compared for those with and without extubation failure using Student's *t*-test, Wilcoxon rank-sum, Chi-square, or Fisher's Exact test as appropriate.

HRV metrics medians were compared for those with and without extubation failure using Wilcoxon rank-sum, and *p*-values were adjusted using logistic regression for factors determined a-priori (corrected gestational age at extubation and tidal volume) and clinical factors noted to be significant between the groups. In addition, receiver-operating characteristic curves were constructed to determine the ability of each HRV metric at predicting extubation success. The metric that showed the best predictive ability was incorporated into a model controlling for potential confounders (gestational age (GA), corrected GA (CGA) at extubation, TV, and FiO_2 were explored) that yielded the lowest Akaike information criterion. Metric thresholds were determined by choosing the inflection point that was farthest from the diagonal. In this exploratory analysis, no adjustments were made for multiple comparisons, which might have inflated Type I error. Statistical analysis was performed using SAS 9.4 software (SAS Institute, Inc., Cary, NC).

RESULTS

Patient characteristics

One-hundred sixty-seven infants were eligible for the study during the study timeframe. Exclusions included: 41 infants never extubated, 19 were intubated for reasons other than respiratory failure, and 18 did not have HRV data available for analysis. Data from 89 infants was available for analysis. 65 (73%) had a successful extubation. Four (4%) subjects were reintubated between 72 h and 7 days. Extubation in 4 (4%) infants was unintended, and of these 3 were successful attempts. Differences in demographic and clinical variables between the two groups are depicted in Table 1. The 2 groups were largely similar with the exception of a trend towards lower mean GA at birth in those who failed (25.1 ± 1.4 vs. 25.9 ± 1.8, $p = 0.05$), a significantly higher fraction of inspired oxygen prior to extubation in those who failed ($0.31 \pm .1$ vs. $0.25 \pm .05$, $p = 0.01$), and longer median number of invasive mechanical ventilation (IMV) days in those who failed (44 (5, 548) vs. 30 (1, 135), $p = .0013$. We did not note any significant differences in the overall length of stay or the outcome of severe IVH or BPD.

HRV analysis

To account for potential covariates, *p*-values were adjusted for GA at birth and corrected GA, tidal volume, and FiO_2 at the time of extubation. Utilizing spectral analysis (Fig. 1a–c), we note

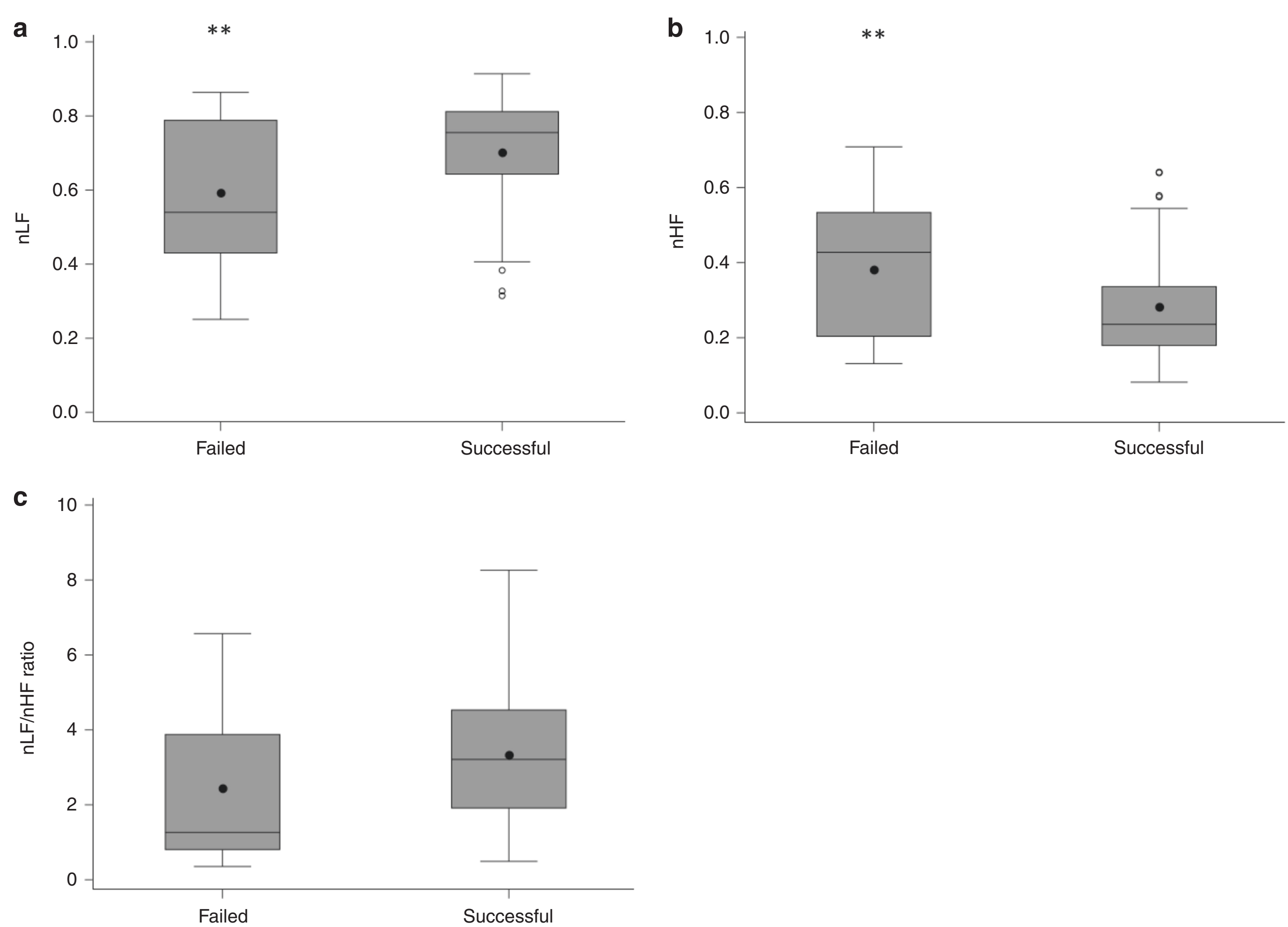

Fig. 1 Comparison of spectral HRV metrics. Boxplots of spectral HRV metrics (**a** nLF, **b** nHF, and **c** nLF/nHF ratio) depicting median, mean, IQR, and range (solid line, filled circle, shaded box, and whiskers) between those with failed and successful extubations. *p*-values adjusted for GA at birth and CGA, TV, and O2 at extubation. *denotes $p \leq 0.01$, **denotes $p \leq .005$.

significantly lower median nLF, a marker of combined sympathetic and parasympathetic tone (0.54 (0.25, 0.86) vs. 0.76 (0.31, 0.91), $p = 0.004$) and significantly higher nHF, a marker of parasympathetic tone (0.43 (0.13, 0.7) vs. 0.24 (0.08, 0.64), $p = 0.005$) in those with failed extubation attempts. The ratio of nLF/nHF demonstrated a trend towards being lower in the failure group (1.26 (0.35, 2.57) vs. 3.21 (0.49, 11.2), $p = 0.052$). Metrics obtained utilizing detrended fluctuation analysis (Fig. 2a–c), all of which are associated with sympathetic tone, similarly noted a significantly lower median in those who failed extubation: RMS_1 (−2.57 (−2.9, −1.8) vs. −2.33 (−2.8, −1.4), $p = 0.01$), RMS_2 (−1.69 (−2.3, −1.04) vs. −1.5 (−2.1, −1), $p = 0.01$), and α_1 (0.39 (0.19, 1.4) vs. 0.64 (0.2, 1.5), $p = 0.01$).

ROC analysis

Receiver-operating characteristic curve analysis for each metric is shown in Table 2. α_1 was noted to have the best discrimination between the 2 groups—an AUC of 0.73 (CI .59, 0.86, $p = 0.001$) with a cut-off value of 0.49 yielding a 71% sensitivity and a 75% specificity. When incorporated into a logistic regression model, α_1 with GA, and pre-extubation tidal volume and FiO_2 as covariables had the lowest Akaike information criterion of 85.8, $p < 0.0001$ with FiO_2 noted to be a statistically significant covariable (Table 3). ROC analysis of the model showed improved prediction of extubation success with an AUC of .81 (CI 0.7, 0.93, $p < 0.0001$). A cut-off predicted probability of 0.69 yields a sensitivity of 81% and a specificity of 78% (Fig. 3).

DISCUSSION

In this study of premature infants <28 weeks gestation, we show that the ability to predict extubation failure was improved utilizing a model incorporating α_1, a marker of sympathetic tone, along with other clinical parameters, which has the potential to aid in clinical decision making. In addition, metrics associated with sympathetic tone were noted to be significantly lower in infants with failed extubation attempts while the metric associated with parasympathetic tone was increased. This autonomic imbalance may be secondary to abnormal maturation of the autonomic nervous system in this population.

Premature infants generally have been noted to have lower heart rate variability as compared to their term counterparts.[32] A previous study has suggested that premature infants may have a blunted maturation of autonomic control with neither LF nor HF signal showing the expected increase over time as compared to their full-term counterparts. Premature infants do demonstrate a significant increase in HF signal (parasympathetic tone) after birth, and perhaps abnormally so during quiet sleep.[20,33,34] However, when premature infants reach term correction, they have been found to have depressed autonomic tone in both sympathetic and parasympathetic indices as compared to infants born at term.[21] Premature infants corrected to 28–31 weeks gestation, often a key time for extubation trials, have been shown to lack an appropriate response to stressful stimuli.[35] These studies suggest that prematurity may be associated with sympathetic failure, and parasympathetic "catch-up" may lead to an autonomic imbalance that can leave

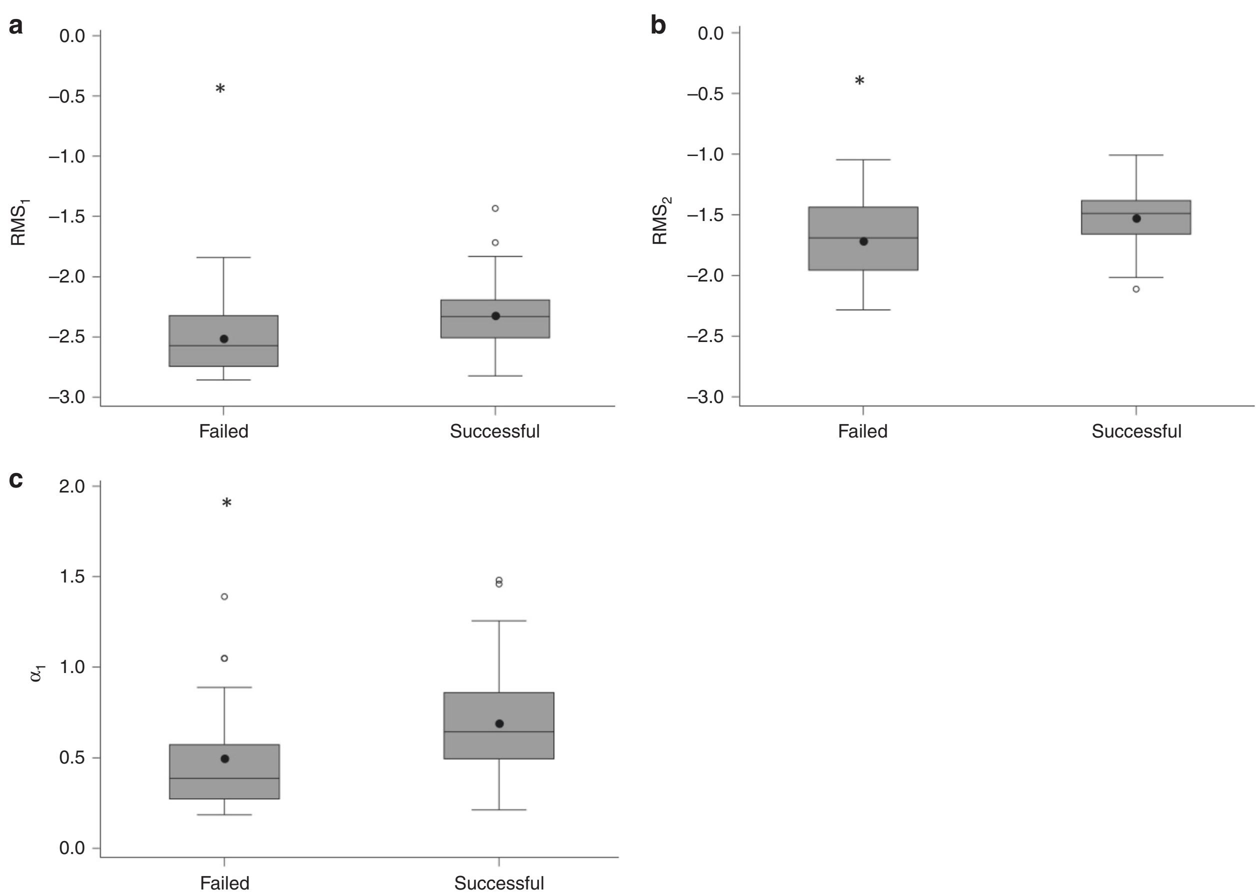

Fig. 2 Comparison for detrended fluctuation HRV metrics. Boxplots of detrended fluctuation HRV metrics (**a** RMS_1, **b** RMS_2, and **c** α_1) depicting median, mean, IQR, and range (solid line, filled circle, shaded box, and whiskers) between those with failed and successful extubations. p-values adjusted for GA at birth and CGA, TV, and O_2 at extubation. *denotes $p \leq 0.01$, **denotes $p \leq .005$.

Table 2. HRV metric predictive ability.

	AUC (CI)	*p*-value	cut-off	Sensitivity	Specificity
GA	0.62 (0.49, 0.74)	0.05	--	--	--
FiO_2	0.68 (0.54, 0.81)	0.009	0.24	58%	71%
nLF	0.65 (0.51, 0.79)	0.04	0.66	72%	63%
nHF	0.65 (0.5, 0.79)	0.05	--	--	--
nLF/HF ratio	0.65 (0.5, 0.79)	0.05	--	--	--
RMS-1	0.7 (0.57, 0.84)	0.003	−2.48	74%	63%
RMS-2	0.68 (0.54, 0.82)	0.01	−1.63	72%	63%
α_1	0.73 (0.59, 0.86)	0.001	0.49	75%	71%

Table 3. Predictive model of extubation success.

	Estimate ± SE	OR (CI)	*p*-value
Intercept	−5.59 ± 5.3	---	---
α_1	3.76 ± 1.3	42.9 (3.2, 575)	0.005
GA	0.28 ± 0.19	1.33 (0.92, 1.9)	0.13
TV	0.15 ± 0.1	1.16 (0.96, 1.4)	0.12
Fraction of inspired oxygen	−0.13 ± 0.05	0.88 (0.81, 0.97)	0.006

these infant vulnerable to clinical decompensation, especially in the setting of stressful events such as a planned extubation. The ability to correctly identify this physiologic maturation can aid the clinician in proactive decision making by adding more objective longitudinal data, especially in light of the variability noted in perceptions of extubation readiness using more standard clinical parameters.[13]

Autonomic imbalance has been described previously in premature infants readmitted for apparent life-threatening events.[23] They showed that this subset of preterm infants had a distinct autonomic developmental trajectory, reduced sympathetic and elevated parasympathetic tone, with differences noted starting at 33 weeks corrected gestation. Prematurity related co-morbidities have been noted to further contribute to sympathetic failure as noted by blunted α_1 metric similar to our extubation failure group.[22] Sympathetic activation leading to hyperpnea and gasping is a crucial response to apnea and hypoxia,[36,37] while parasympathetic predominance may further dampen auto-resuscitative efforts. It is likely that a subset of infants is at elevated risk of poor auto-resuscitation response, which can contribute to extubation failure.

Autonomic maturation is multi-factorial cannot be assumed from post-menstrual age alone. Like other studies, we note no difference in the corrected gestational age at extubation.[11,18,19,38,39] Despite similar age-related maturity and background characteristics, infants with extubation failure display stunted autonomic maturity.[18,19,39] Kaczmarek et al.[19] demonstrated a decrease in all indices in the failure group, including HF (parasympathetic marker) while Silva and colleagues[39] only noted a difference in the non-linear variables in their infants less than 1000 g. These differences may be attributed to smaller sample size, shorter monitoring time, and the lack of normalization for the total power when evaluating frequency domain metrics. The use of normalized indices may better tamper the effect of the ventilator artifact on these signals that cause power spikes.[27] Elevations in the Heart Rate Characteristics Index, a commercially available tool that measures variability, entropy, and asymmetry, has also been noted to be associated with extubation failure, and improved prediction when incorporated into a model.[17,18]

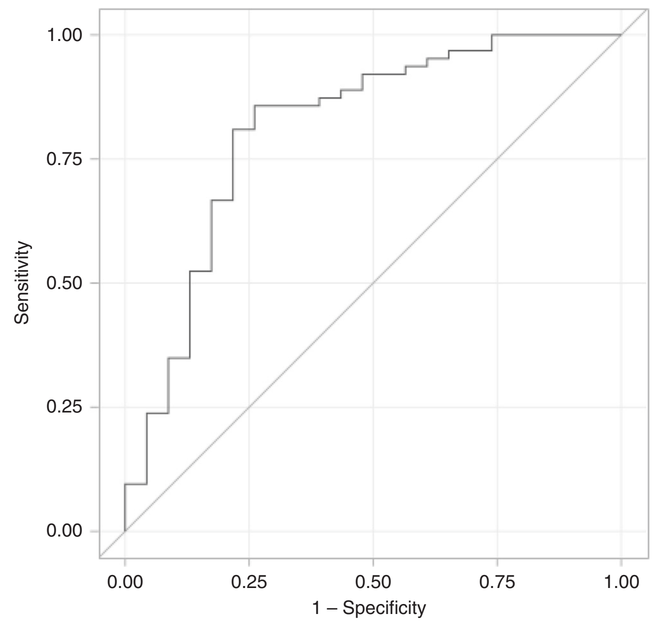

Fig. 3 Predictive ability of a multivariable model. Receiver-operating characteristic curve for the regression model predicting extubation success. Area under the curve of 0.81 (CI 0.7, 0.93; $p < 0.0001$) giving a sensitivity of 81% and specificity of 78% using predicted probability of 0.69.

However, the AUC of our model utilizing α_1 was higher and may be due to the isolation of sympathetic tone as the key autonomic driver in extubation failure.

This study is not without limitations. The single center nature and lack of uniform extubation/reintubation guidelines limit generalizability. In a retrospective study, it is difficult to decipher the nuanced rational and cause for reintubation in each case. In addition, there may have been additional confounders affecting heart rate variability and contributed to extubation failure that were unable to be accounted for such as clinical status, caffeine dosing, steroid use, sedation, positioning, etc in the 24 h prior to extubation. We also did not evaluate and correct specifically for sleep–wake cycles, which have been associated with HRV,[20,40,41] rather we averaged the recordings over a longer period to account for multiple cycles. We also acknowledge that the definition of extubation failure varies in the literature and 72 h may not capture all events.

In conclusion, we demonstrate that extubation failure is associated with abnormal HRV. Specifically, we show an autonomic imbalance with low sympathetic and elevated parasympathetic tone. α_1, a marker of sympathetic tone, was noted to be the best predictor of extubation failure especially when incorporated into a clinical model. Future studies should focus on prospectively incorporating this prediction model into clinical decision making to determine the ability to predict extubation readiness and potentially minimize time on invasive ventilation in real-time practice.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Miller, J. D. & Carlo, W. A. Pulmonary complications of mechanical ventilation in neonates. *Clin. Perinatol.* **35**, 273–281 (2008).
2. Network, S. S. G. Early Cpap versus surfactant in extremely preterm infants. *N. Engl. J. Med*. **362**, 1970–1979 (2010).
3. Subramaniam, P., Ho, J. J. & Davis, P. G. Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants. *Cochrane Database Syst. Rev.* CD001243 (2016).
4. Stoll, B. J. et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA* **314**, 1039–1051 (2015).
5. Venkatesh, V. et al. Endotracheal intubation in a neonatal population remains associated with a high risk of adverse events. *Eur. J. Pediatr.* **170**, 223–227 (2011).
6. Gupta, D. et al. Respiratory setback associated with extubation failure in extremely preterm infants. *Pediatr. Pulmonol.* **56**, 2081–2086 (2021).
7. Odita, J. C., Kayyali, M. & Ammari, A. Post-extubation atelectasis in ventilated newborn infants. *Pediatr. Radio.* **23**, 183–185 (1993).
8. Schuman, T. A., Jacobs, B., Walsh, W. & Goudy, S. L. Iatrogenic perinatal pharyngoesophageal injury: a disease of prematurity. *Int. J. Pediatr. Otorhinolaryngol.* **74**, 393–397 (2010).
9. Chawla, S. et al. Markers of successful extubation in extremely preterm infants, and morbidity after failed extubation. *J. Pediatr.* **189**, 113–119 (2017). e112.
10. Gupta, D. et al. A predictive model for extubation readiness in extremely preterm infants. *J. Perinatol.* **39**, 1663–1669 (2019).
11. Kidman, A. M., Manley, B. J., Boland, R. A., Davis, P. G. & Bhatia, R. Predictors and outcomes of extubation failure in extremely preterm infants. *J. Paediatr. Child Health* **57**, 913–919 (2021).
12. Mhanna, M. J., Iyer, N. P., Piraino, S. & Jain, M. Respiratory severity score and extubation readiness in very low birth weight infants. *Pediatr. Neonatol.* **58**, 523–528 (2017).
13. Shalish, W., Latremouille, S., Papenburg, J. & Sant'Anna, G. M. Predictors of extubation readiness in preterm infants: a systematic review and meta-analysis. *Arch. Dis. Child Fetal Neonatal Ed.* **104**, F89–F97 (2019).
14. Shaffer, F. & Ginsberg, J. P. An overview of heart rate variability metrics and norms. *Front. Public Health* **5**, 258 (2017).
15. Sullivan, B. A., Grice, S. M., Lake, D. E., Moorman, J. R. & Fairchild, K. D. Infection and other clinical correlates of abnormal heart rate characteristics in preterm infants. *J. Pediatr.* **164**, 775–780 (2014).
16. Shen, H. N. et al. Changes of heart rate variability during ventilator weaning. *Chest* **123**, 1222–1228 (2003).
17. Goel, N., Chakraborty, M., Watkins, W. J. & Banerjee, S. Predicting extubation outcomes-a model incorporating heart rate characteristics index. *J. Pediatr.* **195**, 53–58 (2018). e51.
18. Chakraborty, M., Watkins, W. J., Tansey, K., King, W. E. & Banerjee, S. Predicting extubation outcomes using the heart rate characteristics index in preterm infants: a cohort study. *Eur. Respir. J.* **56**, 1901755 (2020).
19. Kaczmarek, J. et al. Heart rate variability and extubation readiness in extremely preterm infants. *Neonatology* **104**, 42–48 (2013).
20. Yiallourou, S. R., Witcombe, N. B., Sands, S. A., Walker, A. M. & Horne, R. S. The development of autonomic cardiovascular control is altered by preterm birth. *Early Hum. Dev.* **89**, 145–152 (2013).
21. Mulkey, S. B. et al. Autonomic nervous system depression at term in neurologically normal premature infants. *Early Hum. Dev.* **123**, 11–16 (2018).
22. Schlatterer, S. D. et al. Autonomic development in preterm infants is associated with morbidity of prematurity. *Pediatr. Res.* **91**, 171–177 (2022).
23. Nino, G. et al. Premature infants rehospitalized because of an apparent life-threatening event had distinctive autonomic developmental trajectories. *Am. J. Respir. Crit. Care Med.* **194**, 379–381 (2016).
24. Ulusar, U. D. et al. Adaptive rule based fetal Qrs complex detection using hilbert transform. *Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.* **2009**, 4666–4669 (2009).
25. Govindan, R. et al. A spike correction approach for variability analysis of heart rate sick infants. *Phys. A: Stat. Mech. Appl.* **444**, 35–42 (2016).
26. Govindan, R. B. et al. Detrended fluctuation analysis of non-stationary cardiac beat-to-beat interval of sick infants. *EPL (Europhys. Lett.)* **108**, 40005 (2014).
27. Govindan, R. B., Massaro, A. N., Niforatos, N. & du Plessis, A. Mitigating the effect of non-stationarity in spectral analysis-an application to neonate heart rate analysis. *Comput. Biol. Med.* **43**, 2001–2006 (2013).
28. Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology Heart Rate Variability. Standards of measurement, physiological interpretation, and clinical use. task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur. Heart J.* **17**, 354–381 (1996).
29. Massaro, A. N. et al. Heart rate variability in encephalopathic newborns during and after therapeutic hypothermia. *J. Perinatol.* **34**, 836–841 (2014).
30. Metzler, M. et al. Pattern of brain injury and depressed heart rate variability in newborns with hypoxic ischemic encephalopathy. *Pediatr. Res*. **82**, 438–443 (2017).
31. de Groot, E. R. et al. The value of cardiorespiratory parameters for sleep state classification in preterm infants: a systematic review. *Sleep. Med. Rev.* **58**, 101462 (2021).
32. Cardoso, S., Silva, M. J. & Guimaraes, H. Autonomic nervous system in newborns: a review based on heart rate variability. *Childs Nerv. Syst.* **33**, 1053–1063 (2017).
33. Patural, H. et al. Birth prematurity determines prolonged autonomic nervous system immaturity. *Clin. Auton. Res.* **14**, 391–395 (2004).
34. Longin, E., Gerstner, T., Schaible, T., Lenz, T. & Konig, S. Maturation of the autonomic nervous system: differences in heart rate variability in premature vs. term infants. *J. Perinat. Med*. **34**, 303–308 (2006).
35. Mazursky, J. E., Birkett, C. L., Bedell, K. A., Ben-Haim, S. A. & Segar, J. L. Development of baroreflex influences on heart rate variability in preterm infants. *Early Hum. Dev.* **53**, 37–52 (1998).
36. Fewell, J. E. Protective responses of the newborn to hypoxia. *Respir. Physiol. Neurobiol.* **149**, 243–255 (2005).
37. Gershan, W. M., Jacobi, M. S. & Thach, B. T. Maturation of cardiorespiratory interactions in spontaneous recovery from hypoxic apnea (autoresuscitation). *Pediatr. Res*. **28**, 87–93 (1990).
38. Teixeira, R. F. et al. Factors associated with extubation failure in very low birth weight infants: a cohort study in the northeast Brazil. *J. Perinat. Med*. **49**, 506–513 (2021).
39. Silva, M. G. F., Gregorio, M. L. & de Godoy, M. F. Does heart rate variability improve prediction of failed extubation in preterm infants? *J. Perinat. Med.* **47**, 252–257 (2019).
40. Filtchev, S. I. et al. Heart rate variability during sleep in infants with bronchopulmonary dysplasia. effects of mild decrease in oxygen saturation. *Chest* **106**, 1711–1716 (1994).
41. Spassov, L. et al. Heart rate and heart rate variability during sleep in small-for-gestational age newborns. *Pediatr. Res*. **35**, 500–505 (1994).

AUTHOR CONTRIBUTIONS

S.B.H. was responsible for the concept, original draft, collection, analysis and interpretation of data, and drafting and revising the manuscript. E.K.J. and J.W. were responsible for data collection and interpretation. and revising the manuscript. S.D.S. was responsible for data interpretation and revising the manuscript. R.G. and A.J.d.P. were responsible for the concept, analysis and interpretation of data, and revising the manuscript. All authors have approved the manuscript as submitted.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Children's National Institutional Review Board, and informed parental consent was waived per IRB guidelines.

ADDITIONAL INFORMATION

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