Predicting Extubation Outcomes—A Model Incorporating Heart Rate Characteristics Index

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Objective To test the hypothesis that in neonates on mechanical ventilation, heart rate characteristics index (HRCi) can be combined with a clinical model for predicting extubation outcomes in neonates.

Study design HRCi and clinical data for all intended intubation-extubation events (episodes) were retrospectively analyzed between June 2014 and January 2015. Each episode started 6 hours pre-extubation or at the time of primary intubation if ventilation duration was shorter than 6 hours (baseline). The episodes ended at 72 hours postextubation for successful extubations or at reintubation for failed extubations. Mean of 6 hourly epoch HRCi-scores (baseline) or fold-changes (postextubation) were analyzed. Results are expressed as medians (IQR) for continuous data and proportions for categorical data. Multivariable logistic regression mixed model was used for statistical analysis.

Results Sixty-six infants contributed to 96 episodes (18 failed extubations, 78 successful extubations) in the study. Failed extubations had significantly longer duration of ventilation (65.3 hours, 19.94-158.2 vs 38.4, 16.5-71.3) and more culture positive sepsis (33.3% vs 3.8%) than successful extubations. Baseline HRCi scores (1.68, 1.29-2.45 vs 0.95, 0.54-1.86) and postextubation epoch-1 fold changes (1.25, 0.94-1.55 vs 0.94, 0.82-1.11) were higher in failed extubations compared with successful extubations. Multivariable linear mixed-effects regression was used to create prediction models for success of extubation, using relevant variables.

Conclusions The baseline and postextubation HRCi were significantly higher in neonates with extubation failure compared with those who succeeded. Models using HRCi and clinical variables to predict extubation success may add to the confidence of clinicians considering extubation. *(J Pediatr 2017;■■:■■-■■).*

Respiratory failure is a common neonatal morbidity, particularly in preterm infants, often requiring mechanical ventilation. Adverse effects of mechanical ventilation are well established including ventilator-associated pneumonia, airway trauma, bronchopulmonary dysplasia, and its consequent effect on adverse neurodevelopmental outcomes.[1-3] In contrast, avoidance of mechanical ventilation and greater reliance on noninvasive ventilation reduces such complications.[4] A challenge for clinicians is to optimize the time of extubation to reduce the time on mechanical ventilation and avoid complications of premature extubation, extubation failure, and reintubation. As much as 40% of intubations are associated with adverse events including cardiorespiratory instability, upper airway trauma, lung atelectasis and infection, 9% with serious sequelae such as hypotension, chest compressions, pneumothorax, and death.[3,5-8]

Traditionally, weaning and the assessment of extubation readiness of ventilated infants has been subjective and based on clinician's judgment of a combination of ventilator settings, blood gas trends, and other clinical variables. Attempts to standardize this decision in the past using variables such as gestational age (GA),[9] respiratory mechanics,[10] and lung-function indices[11,12] have met with variable success and acceptability among clinicians. Thus, extubation remains an inexact science.[13]

Heart rate characteristics index (HRCi) is an hourly numerical score derived from a mathematical model that analyzes continuous electrocardiogram data from routine real-time monitoring for heart rate variability, asymmetry, and entropy. HRCi has been validated in neonates and represents an increase in the risk of an acute adverse event in the subsequent 6-24 hours.[14,15] A common association of a HRCi spike is impending acute respiratory deterioration, accounting for 34% of the abnormal HRCi spikes.[16] The HRCi spikes in impending respiratory deterioration are probably secondary to the combined effect of breathing pattern alterations, lung inflammation, hypoxia, and hypercapnia on heart rate variability and decelerations.[16]

HRCi monitoring is now commercially available and routinely used in many neonatal units in North America and Europe. The value of HRCi in predicting the outcome of a clinical decision to extubate a neonate from ventilation has not been properly studied. This study examines the hypothesis that HRCi provides an individualized and physiological basis for extubation readiness in neonates, and

GA	Gestational age
HRCi	Heart rate characteristics index
PEE	Postextubation epoch

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combined with clinical variables, can contribute to predictive models of extubation success from mechanical ventilation either before or shortly after the extubation event.

Methods

This retrospective observational cohort study was undertaken at Singleton Hospital, Swansea, United Kingdom, where HRCi monitoring (HeRO; MPSC, Charlottesville, Virginia) is routine. Analogue Electro Cardio Gram (ECG) data are digitized and analyzed by the HeRO software. HRCi scores are computed and displayed hourly. The first HRCi score is usually computed within 3-4 hours of commencing ECG monitoring.

All ventilated infants between June 2014 and January 2015 were identified through the electronic patient data management system (Badgernet; CleverMed, Edinburgh, United Kingdom). A sequence of intubation-extubation event was treated as single "episode"; some infants had multiple episodes recorded. Basic demographics and clinical data were recorded for each infant at first extubation and then by all intubation-extubation episodes. The hourly HRCi scores were recorded for each of these episodes. Data on clinical variables that affect the HRCi such as blood culture positive sepsis (defined as active treatment for the condition during the episode), clinically suspected sepsis (pragmatic definition of any part of a 5-day antibiotic treatment course for suspected but blood culture negative sepsis during the episode), use of postnatal steroids, inotropes, muscle relaxants, and necrotizing enterocolitis were only included if they were present or actively being treated during each episode being analyzed. These clinical variables were included as dichotomous variables (yes/no) for each episode, thereby ensuring relevance to the episode in consideration. The maximum white cell count and C-reactive protein recorded during each episode were collected. However, major intraventricular hemorrhage (grade 3 or 4) were included if they were present at any time as they are known to affect HRCi score for a longer duration.

The hourly HRCi scores from each episode were grouped into 6-hour epochs. The first epoch started 6 hours before the extubation event or at primary intubation if ventilation duration was shorter than 6 hours. Each episode ended at 72 hours postextubation or earlier if the infant was reintubated. Infants who remained off mechanical ventilation following extubation for a 72-hour period were categorized as successful extubations (a total of 12 epochs postextubation) and those who required reintubation during this period as failed extubations (variable numbers of postextubation epochs until reintubation). Being a retrospective study, the definition of extubation failure and need for reintubation were pragmatic and determined by the attending clinician. Infants were excluded if they died because of planned withdrawal of care, transferred out before extubation, or extubated at another unit following transfer. Exclusion also applied if HRCi data was unavailable or insufficient to compute at least 2 hourly HRCi scores.

Mean HRCi scores were calculated for each epoch (6-hour period) and used for all subsequent analysis. Any missing hourly scores were not included in the mean score. Mean HRCi from the pre-extubation epoch of each episode served as the baseline epoch score. Mean HRCi scores from postextubation epochs (PEEs) for each infant were normalized to their own baseline epoch score, and expressed as changes from the baseline. The first 6-hour epoch postextubation was labeled as PEE-1, the second 6-hour epoch as PEE-2 and so on. The baseline epoch, PEE-1 score and duration of ventilation were not normally distributed and were log-transformed before analysis.

Statistical analysis was conducted using R for Windows v 3.3.2 (R Core Team 2016, Vienna, Austria). Descriptive statistics are presented as medians and IQRs for continuous variables, and as numbers (percentages) for categorical variables. Continuous variables were compared between failed extubations and successful extubations using the Mann-Whitney U test, and categorical variables using the Fisher exact test. Correlation between variables was calculated using the Pearson coefficient. A P value of <.05 was considered statistically significant. A multivariable linear mixed-effects model with the logit link function and with the intercepts as a random effect on infant identification was employed. The model assessed the probability of reintubation from clinical and physiological variables including HRCi. The final fitted model was of the form below with p being the probability of reintubation, and with α, and β_i as the fixed effects coefficients for the intercept and the explanatory variables respectively.

$$\text{logit}(p) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \cdots + \beta_n x_n = \alpha + \sum_{i=1}^{n} \beta_i x_i \quad (1)$$

With $\text{logit}(p) = log_e\left(\frac{p}{1-p}\right)$ the above could be rearranged to give the expression below for the predicted probability for each set of explanatory variables.

$$p = \frac{1}{1 + e^{-\left(\alpha + \sum_{i=1}^{n} \beta_i x_i\right)}} \quad (2)$$

Results

During the study period, 102 infants on mechanical ventilation were identified. Of these, 36 were excluded: 14 were not extubated on the unit (died/transferred out), 4 had no available data, and 18 had insufficient HRCi because of a very short period of ventilation. The remaining 66 infants contributed to 96 episodes and were included in the final analysis. Of the 96 episodes, 18 were failed extubation (reintubated within 72 hours) and 78 successful extubations (remained extubated for 72 hours). Of the failed extubations, 8 were reintubated in the first 6 hours, 5 in the following 6 hours, and only 3 beyond the first 24 hours (**Figure 1**; available at www.jpeds.com).

Table I shows the demographics of the 66 infants at birth and comparative variables between failed extubations and successful extubations for all episodes. **Table II** compares these variables between failed extubations and successful extubations

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