Predicting Extubation Outcomes – A Model Incorporating Heart Rate Characteristics Index

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Short Title: Heart Rate Characteristics and extubation outcomes in neonates

Abstract

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 analysed 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 post-extubation for successful extubations (SE) or at re-intubation for failed extubations (FE). Mean of 6-hourly epoch HRCi-scores (baseline) or fold-changes (post-extubation) were analysed. Results are expressed as medians (inter-quartile range) for continuous data and proportions for categorical data. Multi-variable logistic regression mixed model was used for statistical analysis.

Results: Sixty-six infants contributed to 96 episodes (18 FE, 78 SE) in the study. FE 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 SE. Baseline HRCi scores (1.68, 1.29-2.45 *vs.* 0.95, 0.54-1.86) and Post-Extubation Epoch-1 (PEE-1) fold changes (1.25, 0.94-1.55 *vs.* 0.94, 0.82-1.11) were higher in FE compared to SE. Multi-variable linear mixed-effects regression was used to create prediction models for success of extubation, using relevant variables.

Conclusion: The baseline and post-extubation HRCi were significantly higher in neonates with extubation failure compared to those who succeeded. Models using HRCi and clinical variables to predict extubation success may add to the confidence of clinicians considering extubation.

Abbreviations used frequently in the manuscript:

HRCi – Heart Rate Characteristics index

FE – Failed Extubation

SE – Successful Extubation

BE – Baseline Epoch

PEE – Post-Extubation Epoch

IQR – Inter-Quartile Range

GA – Gestational Age

Introduction:

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 non-invasive ventilation reduces such complications. (4) A challenge for clinicians is to optimise 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 parameters. Attempts to standardise this decision in the past using parameters such as gestational age, (9) respiratory mechanics, (10) and lung-function indices (11, 12) have met with variable success and acceptability amongst clinicians. Thus, extubation remains an inexact science. (13)

Heart rate is regulated by a balanced interplay of the sympathetic and parasympathetic nervous system on the sinus node. In health, our heart rate has subtle variations. Alterations of this physiological pattern or Heart Rate Characteristics (HRC) occur as part of the pathophysiologic response to infection and inflammation even before clinical symptoms are apparent. Reduced heart rate variability and transient decelerations have been reported in the sub-clinical stages of neonatal sepsis and sepsis-like illnesses. (14, 15) Heart Rate

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Characteristics index (HRCi) is a hourly numerical score derived from a mathematical model that analyses continuous electrocardiogram data from routine real time monitoring for heart rate variability, asymmetry and entropy. HRCi has been validated in neonates and represents the fold-increase in the risk of an acute adverse event in the subsequent 6-24 hours. (14, 16) In a large multicentre randomised controlled trial in North America, displaying the HRCi to clinicians reduced all-cause mortality in very low birth weight infants, primarily contributed by the reduction of late onset sepsis related deaths. (17-19) However, an acute rise in HRCi (spike) is not specific to sepsis and has also been reported with urinary tract infection, (20) necrotising enterocolitis, (21) abnormal neuro-imaging (22) and use of anticholinergic medications. (23) A common association of a HRCi spike is impending acute respiratory deterioration, accounting for 34% of the abnormal HRCi spikes. (23) 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. (23)

HRCi monitoring is now commercially available and routinely used in many neonatal units in North America and Europe. As HRCi is affected by respiratory and haemodynamic characteristics, it may well be a good predictive bio-marker of extubation readiness as well as subclinical respiratory instability in the post-extubation period. This information may be valuable to the clinician considering or managing extubation of ventilated infants. However, 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 individualised and physiological basis for extubation readiness in neonates, and combined with other clinical parameters, can contribute to predictive models of extubation success from mechanical ventilation either before or shortly after the extubation event.

Materials and methods

This retrospective observational cohort study was undertaken at Singleton Hospital, Swansea, UK, where HRCi monitoring (HeRO, MPSC, Charlottesville, Virginia) is routine. Analogue ECG data is digitised and analysed 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, UK). 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 necrotising enterocolitis were only included if they were present or actively being treated during each episode being analysed. These clinical parameters were included as dichotomous variables (yes/no) for each episode, thereby ensuring relevance to the episode in consideration. The data on the maximum white cell count and C - reactive protein (CRP) recorded during each episode was collected. However, major intraventricular haemorrhage (IVH) (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 six hours prior to the extubation event or at primary intubation if ventilation duration

was shorter than 6 hours. Each episode ended at 72 hours post-extubation or earlier if the infant was re-intubated. Infants who remained off mechanical ventilation following extubation for a 72-hour period were categorised as 'Successful Extubations' (SE) (a total of 12 epochs post-extubation) and those who required reintubation during this period as 'Failed Extubations' (FE) (variable numbers of post-extubation 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 due to 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 two 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 (BE) score. Mean HRCi scores from post-extubation epochs (PEE) for each infant were normalised to their own BE score, and expressed as fold-changes from the baseline. The first 6-hour epoch post-extubation was labelled as PEE-1, the second 6-hour epoch as PEE-2 and so on. The BE, 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 version 3.3.2 (R Core Team 2016 Vienna, Austria). Descriptive statistics are presented as medians and inter-quartile ranges (IQR) for continuous variables, and as numbers (percentages) for categorical variables. Continuous variables were compared between FE and SE using the Mann-Whitney U test, and categorical variables using the Fisher's exact test. Correlation between variables was calculated using Pearson's coefficient. A p-value of < 0.05 was considered statistically significant. A Multi-Variable Linear Mixed-Effects model with the logit link function and

with the intercepts as a random effect on infant ID 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.

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

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.

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

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 due to 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 FE (reintubated within 72 hours) and 78 SE (remained extubated for 72 hours). Of the FE, 8 were reintubated in the first 6-hours, 5 in the following 6-hours and only 3 beyond the first 24-hours (Figure 1; online only).

Table 1A shows the demographics of the 66 infants at birth and comparative parameters between FE and SE for all episodes. Table 1B compares these parameters between FE and SE at first extubation only. Figure 2 shows the HRCi BE scores and PEE fold-changes plotted against time for both FE and SE groups. Both the HRCi BE and the PEE-1 scores were

significantly higher in FE infants compared to SE infants. Univariate analysis comparing FE with SE is presented in Table 2. In addition to differences in HRCi, infants who were reintubated (FE) were born earlier, extubated at a lower corrected gestational age (GA), ventilated for a longer period before extubation and had significantly more positive blood cultures than SE. FE infants also had a lower birth weight, although this was of borderline statistical significance.

To prevent overfitting in the final multivariate model, correlations were calculated between all the variables. As expected, birth weight and GA were strongly correlated with each other (Figure 3A; online only), as were the HRCi BE score and PEE-1 score (Figure 3B; online only). Multivariate mixed models using all combinations of these correlated variables showed that, along with other variables, the combination of birth weight (instead of GA) and PEE-1 score (instead of BE score) resulted in the best-fit model (Table 3; online only). Gestational age was excluded from all subsequent models and birth weight was included as an independent variable instead. However, both HRCi BE and PEE-1 scores were considered valuable for two distinct clinical situations i.e. one before and the other after extubation. Accordingly, two separate models were run to predict the probability of extubation success incorporating the HRCi BE and PEE-1 score in each.

Results of the regression model using the HRCi BE score, birth weight, blood culture results, duration of ventilation and corrected GA at extubation are shown in Table 4A. All the variables, except BE score and positive blood-culture (which were of borderline significance), included in the model were statistically significant independent predictors of reintubation, and could be used to calculate the probability of extubation success. A similar model including all variables after extubation (replacing the HRCi BE score with the PEE -1 score) showed that, apart from positive blood cultures, all the included variables were statistically significant independent predictors of success of extubation (Table 4B).

Results of the regression models were used to create a probability calculator (Appendix; online only) for extubation success using all the variables in the model.

Discussion

Our study is unique in undertaking a detailed analysis of HRCi in the pre and post-extubation period. It demonstrates that infants who failed extubation had significantly higher baseline and post-extubation HRCi scores. We have created prediction models for extubation success, both before extubation and in the early hours following extubation incorporating HRCi and other clinical variables that remained independent predictors on multivariate regression analysis. The post-extubation model may influence the choice and level of non-invasive respiratory support and its subsequent escalation to minimise the risk of extubation failure. To our knowledge, this is the first time that routinely available clinical variables have been combined with HRCi to predict extubation outcomes in newborn infants, and demonstrates potential value of this new tool to the clinicians.

Clark et al have shown that the HRCi scores had strong association with upcoming unplanned intubations with ROC of 0.81 in univariate analysis. (24) This prospective study in a cohort of preterm infants showed that HRCi rises four-fold over the day preceding an unplanned intubation. However, the association of HRCi with extubation was not studied; data from the 12 hours after extubation was excluded from the analysis. In addition, more than 10% of the infants needing unplanned intubations had concomitant sepsis that may have explained the rise in HRCi. In a prospective cohort of preterm ventilated infants, a decrease in heart rate variability prior to extubation was shown in infants who failed the attempt. (25) However, the authors analysed a short 60-minute period of data before the extubation and data on post extubation variability was not collected. Of note, both were pragmatic studies with no defined protocol for respiratory management. Our study is possibly the first of its kind to assess the

changes in heart rate variability and HRCi before and up to 72 hours after an extubation event.

A number of clinical variables and medications can affect the HRCi score and we have carefully collected such data for each variable and directly related this information to individual intubation-extubation episodes. Readers will appreciate that birth weight was the only demographic factor which remained in the model; all other significant factors were episode-related, and add extra value to the model.

Assessment of extubation readiness can be subjective and various tools with objective validity have been studied, yet one with sufficient high specificity and sensitivity is yet to be established. In a prospective study on 50 ventilated preterm infants, spontaneous breathing test (SBT) on CPAP through the endotracheal tube (ETT) was a better predictor than expired minute ventilation (V_E) analysis. (26) However, an earlier Cochrane review found no evidence in support of this practice. (27) Measuring extubation success is equally difficult, with no uniform criteria being followed by researchers. (28) A combination of demographic, clinical and intrinsic physiological parameters such as oxygen saturations, heart rate variability and respiratory pattern parameters (29) may be more useful in predicting outcomes. Our model is an attempt to incorporate such principle using HRCi.

A large volume of physiological and clinical data is generated routinely from patients in the health-care system. Traditionally, this data has been used by human observers to monitor changes; and subtle but important trends in the data have remained "hidden". More recently, computer algorithms capable of analysing trends in such "hidden" data have been developed. While HRCi is a relatively simple form of this analysis using a single physiological variable, trials incorporating multiple physiologic variable in automated models and complex "big data" are already recruiting and discussed at policy forming level. (30-32) Such complex

data analyses present new challenges but offers prospects for better predictive monitoring capabilities for future patients.

The conclusions from our study need to be applied in the context it has been undertaken. We only examined HRCi and clinical parameters as it relates to extubation outcome when clinicians considered extubation and felt strongly about their decision to proceed with the intervention. Outside the context of this prior clinical decision, our conclusions may not be applicable as a continuum throughout the duration of mechanical ventilation. The attrition of the number of babies remaining extubated in the early hours following extubation routinely happens in clinical practice. The infants who get reintubated are a clinically important group to try and predict the event. We had carefully considered this and in our methods, we have used HRCi data only up to the point of reintubation, calculating a mean of as many hourly scores available for the analysis. Thus, all scores in the PEE are "pre-reintubation", and can be used for predicting the impending event (reintubation). We did not include the PEE-2 and subsequent PEE HRCi scores in the model as the numbers were very small.

We acknowledge that there is a possibility that outcomes of the first extubation may affect that of subsequent episodes in the same infant. However, restricting the analysis to first extubations only will also exclude very important new and independent clinical variables that may have significant influence on the outcomes of subsequent extubation. We feel this is important information for clinicians in practice managing high risk infants at risk of multiple extubation failures.

We are unaware of a method that can completely do justice to both arguments. To address this we have carefully chosen factors for our model which are expected to vary between episodes, even in the same infant, including the corrected GA. In addition, we have used a hierarchical mixed model, where the infant ID was included to define the second level as

there are multiple episodes from the same infant. This allows for variation in the model both within and between infants.

Our study has several limitations. It is a retrospective, single centre study with a limited number of study subjects and included infants from a wide range of gestations with relatively high extubation success. Unfortunately, the limited numbers of infants did not allow us to consider stratified analysis by gestation band and instead we used statistical methods to adjust for the variables. The actual reason for extubation failure, leading to reintubation, was not recorded uniformly. The data on the mode, level and quality of non-invasive respiratory mode was difficult to extract and may be important contributors to extubation outcomes. Although broad guidance on ventilation was available, standardised extubation protocol was not used during the study period and may have contributed to practice variance. The clinicians were not blinded and although HRCi was not specifically known to predict extubation outcomes, it may have influenced the overall clinical judgment to extubate or intervene. The time required to compute the first HRCi score may be a limiting factor in infants where early extubation within the first 3 hours is being considered. This is a retrospective analysis in pragmatic settings and the limitations may be addressed by a well-designed prospective randomised study. Future studies or 'big data' capture from routine clinical practice may be able to validate or even refine this model further incorporating additional physiologic parameters.

Conclusion

The baseline and post-extubation HRCi were significantly different in infants who failed extubation, compared to those who succeeded, possibly due to a difference in their respiratory characteristics. We have developed prediction models for extubation success incorporating peri-extubation HRCi for the first time along with traditional clinical

parameters such as birth weight, gestational age at extubation and risk factors such as culture positive sepsis. This may assist clinicians in optimising the time of extubation and post-extubation monitoring and support. Further studies are required to confirm our preliminary findings in different gestation groups with different levels of inflammatory burden to predict extubation success.

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Figure Legends

Figure 1, online only: Survival analysis of failed and successful-extubations. Time (hours) is represented on the x-axis, and the proportion of episodes still remaining extubated at each time-point is represented on the y-axis. The x-axis is terminated at 40 hours as all failed-extubations got re-intubated by then.

Figure 2: Pattern of (a) HRCi scores and (b) HRCi fold-changes from baseline, over the study period in FE (open circles) and SE (closed squares). 6-hour epochs are represented on the x-axis, and HRCi (a) mean 6-hour scores and (b) fold-changes from baseline are represented on the y-axis. Each point represents mean ± SEM, and groups were compared at each epoch by Mann Whitney U test (** $p = < 0.01$). Number of episodes contributing to each epoch are stated next to the points plotted.

Figure 3, online only: Correlation between (a) baseline epoch scores and post extubation epoch-1 scores, and (b) birth weight and gestation, of all episodes. (Ln_Ep1_Score = log of post-extubation epoch-1 score, Ln_Pre = log of pre-extubation epoch score, BW_KG = birth weight in kg, GA = gestation age at birth)