Extubation Readiness and Variability Measurements in Extreme Preterm Infants

Presented by

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December 2011

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science

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References
Acknowledgements

There are many individuals whose support, guidance and collaboration have contributed to the successful completion of this thesis. My sincerest thanks go to my supervisor, Dr. Guilherme Sant’Anna. He provided me with the opportunity to pursue work in a field I am passionate about and fostered my academic and personal growth with many challenging and dynamic research activities. His expertise, responsiveness and support have greatly contributed to the completion of my Master’s degree. I am incredibly fortunate to have such a dedicated individual as a lifelong role model and mentor.

I would like to thank my thesis committee members, Dr. Louis Beaumier, Dr. Thérèse Perreault and Dr. Janusz Rak and physiology professors Dr. Jacopo Mortola and Dr. Charles Rholicek for their academic council, which undoubtedly improved the scope of my research.

My thesis studies would not have been completed without a solid research team. I would like to thank medical students Cinzia Marchica and Ionut Efanov, neonatal fellow Dr. Ali Al-Jabri and Barbara Jardin for their help with data collection and analysis. These individuals also provided a truly enjoyable working environment and I consider them all great friends. I was also provided with much needed support for study initiation and patient enrollment from Dr. Lajos Kovacs at the Jewish General Hospital, Dr. Nabeel Ali at the Royal Victoria Hospital, and all NICU and neonatal nursery directors. Furthermore, I would like to recognize all neonatal nursery and NICU staff for their cooperation through the data collection processes as well as all the infants and their respective families who agreed to participate in my research studies.

I would like to thank all of my study collaborators, Dr. Sanjay Chawla, Dr. Omar Kamlin, Dr. Colin Morley and Dr. Peter Davis, whose creativity and team work allowed my clinical research projects to be successfully developed and completed.

I acknowledge the Research Institute of the McGill University Health Centre for providing me with financial support throughout the completion of my Master’s degree.

Lastly, I express my utmost gratitude to my family, who has always fully supported all of my academic endeavours. My strong work ethic and commitment to integrity come from the way I was raised. To them I would like to dedicate this thesis.
Contribution of Authors

The contents of the manuscript entitled “Variability of Respiratory Parameters and Extubation Readiness in Ventilated Neonates”, submitted to Archives of Disease in Childhood, Fetal and Neonatal Edition on November 5th, 2011, comprises chapter two of this thesis. Authors of this manuscript are Jennifer Kaczmarek, Omar Kamlin, Peter G. Davis, Colin J. Morley and Guilherme M. Sant’Anna. Dr. Morley, Dr. Sant'Anna and I generated the concept for this study. Dr. Kamlin, Dr. Davis and Dr. Morley completed the original investigation that generated the data used for analysis. I completed all data analysis. I wrote the manuscript, with input from Dr. Sant'Anna, Dr. Kamlin, Dr. Davis and Dr. Morley.

Abstracts of the contents of chapters three, four and five of this thesis, entitled “Heart Rate Variability and Extubation Readiness in Extreme Preterm Infants: A Prospective, Observation Study”, “Respiratory Variability and Extubation Readiness in Extreme Preterm Infants: A Prospective, Observation Study” and “Heart Rate Variability and Respiratory Variability in Healthy Full-Term Newborns: Effect of Position and Feeding” have been submitted to the Pediatric Academic Societies Annual Meeting (2012). Authors of the manuscripts presented in chapters three and four are Jennifer Kaczmarek, Sanjay Chawla and Guilherme M. Sant’Anna. Dr. Sant’Anna and I generated the concept for these investigations. I obtained scientific and research ethics board approval for the conduction of these investigations at all hospital sites in Montreal. Dr. Chawla obtained scientific and research ethics board approval at the Detroit Medical Center in Detroit, USA. I completed data collection at all hospital sites in Montreal. Dr. Chawla completed data collection at the Detroit Medical Center. I performed all data analysis with guidance from Dr. Sant’Anna. I wrote the manuscripts, with input from Dr. Sant’Anna and Dr. Chawla. Authors of the manuscript presented in chapter five are Jennifer Kaczmarek and Guilherme M. Sant’Anna. Dr. Sant’Anna and I generated the concept for this investigation. I obtained scientific and research ethics board approval for the conduction of this investigation at the Royal Victoria Hospital in Montreal, Canada. I completed data collection and performed all data analysis with guidance from Dr. Sant’Anna. I wrote the manuscript, with input from Dr. Sant’Anna.
Abstract

Background
The ability to accurately determine extubation readiness in extreme preterm infants is important but difficult. Clinical decision making results in a 20-40% rate of extubation failure and strategies developed to predict successful extubation have shown limited success. Heart rate variability (HRV) and respiratory variability (RV) can distinguish weaning outcome in ventilated adults but have never been assessed in preterm infants undergoing disconnection from MV.

Objectives
Studies performed in extreme preterm neonates evaluated differences in HRV and RV prior to extubation between infants that would fail or succeed extubation. An additional study evaluated HRV and RV in healthy full-term newborns and determined the effect of position and feeding.

Methods
Mechanically ventilated infants with a birth weight $\leq 1250$g were included in studies evaluating preterm infants. HRV data was collected for 60 min prior to extubation during assist control or synchronized intermittent mandatory ventilation. RV data was collected for 3 min prior to extubation during endotracheal tube continuous positive airway pressure. Extubation failure was defined as the need for re-intubation within 72h of initial disconnection from MV.

HRV data was collected using electrocardiography and quantified using frequency analysis. RV data was collected using respiratory inductive plethysmography and quantified using time-domain analysis.

Similar methods of data collection and analysis were applied in healthy, full-term infants.

Results
A significant decrease in HRV prior to extubation was demonstrated in infants that failed extubation. An initial retrospective analysis revealed a significant decrease in mean inspiratory flow variability in infants that required re-intubation. However, a subsequent prospective evaluation showed no differences in RV prior to extubation between success and failure groups. In healthy full-term newborns, reduced HRV and RV were observed in the prone position. No feeding effect was described.

Conclusions
These studies provide a first assessment of HRV and RV in extreme preterm infants being extubated, with additional evaluation in a normative population using similar methodology. HRV and RV can function as biomarkers of extubation outcome and improve clinical decision making. The results described provide a solid basis for improved and refined investigations of both measurements as predictors of successful extubation in future.
Résumé

Contexte
La capacité de déterminer avec précision la facilité d’extubation parmi les nouveau-nés extrêmement prématurés, est importante mais difficile. La prise de décision clinique confère un taux d'échec d'extubation de 20 à 40% et les stratégies développées pour prédire une réussite à l’extubation ont démontré un succès limité. La variabilité du rythme cardiaque (VRC) et la variabilité respiratoire (VR) permettent de distinguer le sevrage de la ventilation mécanique (VM) chez les adultes, mais n'ont jamais été évalués chez les nouveau-nés extrêmement prématurés qui subissent une déconnexion de la VM.

Objectif
Les études réalisées chez les nouveau-nés extrêmement prématurés ont évalué les différences dans la VRC et RV avant l’extubation, entre les bébés qui seront extubé avec succès et les bébés qui échoueront l'extubation. Une étude additionnelle a évaluée la VRC et VR chez les nouveau-nés à terme et de bonne santé ainsi que l'effet de la position et de l'alimentation ces mesures susmentionnées.

Méthodes
Les bébés ventilés mécaniquement avec un poids de naissance ≤ 1250 g ont été inclus dans les études évaluant les nouveau-nés extrêmement prématurés. Les données de VRC ont été enregistrées pendant 60 min avant l’extubation lors d’un mode ventilatoire assisté contrôlé intermittent. Les données de VR ont été enregistrées pendant 3 min de pression expiratoire positive à travers le tube endotrachéale. Un échec d'extubation était défini par le besoin de réintubation avant 72h de la déconnexion initiale de VM.

Les données de VRC ont été recueillies en utilisant l’électrocardiographie et quantifiés dans le domaine fréquentiel. Les données de VR ont été recueillies par pléthysmographie et quantifiés dans le domaine temporel.

Des méthodes de collection de données et d'analyse similaires ont été appliquées pour les nouveau-nés à terme de bonne santé.

Résultats
Une diminution significative de VRC avant extubation a été démontrée chez les nouveau-nés qui ont échoué l'extubation. Une analyse rétrospective initiale a révélé une diminution significative de la variabilité du volume courant par durée du temps inspiratoire chez les nouveau-nés ré-intuber. Cependant, une évaluation prospective ultérieure, n’a démontré aucune différence de VR avant extubation entre les bébés qui ont été extubé avec succès et les bébés qui ont échoué l'extubation. Parmi les nouveau-nés à terme de bonne santé, une réduction de VRC et VR a été observée dans la position décubitus ventrale. Aucun effet d’alimentation n’a été décrit.

Conclusions
Ces études sont les premiers à évaluer les mesures de VRC et VR parmi les nouveau-nés extrêmement prématurés extubés, avec une évaluation supplémentaire dans une population normative utilisant une méthodologie similaire. La VRC et VR peuvent fonctionner comme des « biomarqueurs » du résultat d’extubation et par suite, améliorer la prise de décision clinique. Les résultats décrits dans cette étude fournis une base solide démontrant le rôle de ces deux mesures dans la prédiction d’extubation réussie et donc, des investigations complémentaires seraient d’un intérêt pour évaluer d’avantage l'utilisation de ces mesures dans le milieu clinique.
List of Abbreviations

MV – Mechanical Ventilation
BPD – Bronchopulmonary Dysplasia
VAP – Ventilator-Associated Pneumonia
ELBW – Extremely Low Birth Weight
ETT CPAP – Endotracheal Tube Continuous Positive Airway Pressure
SBT – Spontaneous Breathing Trial
PPV – Positive Predictive Value
NPV – Negative Predictive Value
HRV – Heart Rate Variability
MPIP – Multi-Centre Post-Infarction Program
NICU – Neonatal Intensive Care Unit
RV – Respiratory Variability
ECG – Electrocardiography
ACMV – Assist Control Mandatory Ventilation
PSV – Pressure Support Ventilation
\( V_T \) – Tidal Volume
RR – Respiratory Rate
\( T_{TOT} \) – Total Breath Duration
\( T_I \) – Inspiratory Time
\( T_E \) – Expiratory Time
\( V_T/T_I \) – Mean Inspiratory Flow
PEEP – Positive End Expiratory Pressure
SpO\(_2\) – Oxygen Saturation
FiO\(_2\) – Fraction of Inspired Oxygen
CPAP – Continuous Positive Airway Pressure
NIPPV – Nasal Intermittent Positive Pressure Ventilation
VI – Variability Index
SD – Standard Deviation
ROC – Receiver Operating Characteristic
MAP – Mean Airway Pressure
PaO₂ – Partial Pressure of Oxygen
PaCO₂ – Partial Pressure of Carbon Dioxide
AC – Assist Control
SIMV – Synchronized Intermittent Mandatory Ventilation
BW – Birth Weight
GA – Gestational Age
PCA – Post-Conceptual Age
PIP – Peak Inspiratory Pressure
IVH – Intraventricular Haemorrhage
PDA – Patent Ductus Arteriosus
ROP – Retinopathy of Prematurity
NEC – Necrotizing Enterocolitis
TP – Total Power
VLF – Very Low Frequency
LF – Low Frequency
HF – High Frequency
RIP – Respiratory Inductive Plethysmography
AUREA – Automated Unsupervised Respiratory Event Analysis
PMA – Post-Menstrual Age
Chapter 1 - Introduction

1.1 Extubation Readiness in Extreme Preterm Infants

The respiratory management of extreme preterm infants is challenging. Even with the increased use of non-invasive ventilatory support, fifty to eighty percent of these infants will still require endotracheal intubation and mechanical ventilation (MV) within the first days of life in order to survive\(^1,^2\).

Prolonged use of MV is invasive and can potentially injure the airways and lung parenchyma of premature newborns\(^3\). Ventilator-induced lung injury can include alveolar structural damage, pulmonary edema, inflammation and fibrosis\(^4\). In a baboon model of bronchopulmonary dysplasia (BPD), administering low tidal volume positive pressure MV for a five day period elicited detrimental pathophysiological effects, including cellular bronchiolitis, peribronchial alveolar wall thickening and elevated inflammatory cytokine and chemokine levels, when compared to ventilation for only twenty-four hours\(^5\).

Protracted MV is also associated with adverse clinical outcomes. An association between the duration of MV and ventilator-associated pneumonia (VAP) has been demonstrated in extremely preterm neonates. Each additional week spent on MV can increase the risk of VAP by eleven percent and the overall rate of VAP can increase almost five times if the duration of intubation is longer than five days\(^6,^7\). Additional outcomes in extremely low birth weight (ELBW) infants ventilated for more than thirty-nine days was outlined in a retrospective analysis performed through the National Institute of Child Health and Human Development Neonatal Research Network\(^8\). This particular sub-group of infants is at high risk for both mortality and impaired neurodevelopmental outcomes\(^8,^9\).

This evidence supports avoiding the use of prolonged MV. When caring for the most premature infants, clinicians now focus on removing MV as expeditiously as possible. Despite these efforts, twenty to forty percent of extreme preterm infants will fail an extubation attempt and require re-intubation\(^10,^11\). This extubation failure rate is almost double the prevalence reported in adults and older children, which ranges from two to twenty-five percent depending on the type of patient studied and time frame used to define failure\(^12\). Failure of extubation occurs because the most immature of infants demonstrate an inconsistent respiratory drive, weak
respiratory pump, upper airway instability, alveolar atelectasis or derecruitment and frequent lung injury. Re-intubation is also associated with increased risks of morbidity and mortality, often contributing to further airway and lung injury. In adults, extubation failure can prolong the overall duration of MV, length of hospital stay and can increase the risk for nosocomial pneumonia. When considering the high rate of extubation failure reported in preterm infants, it is conceivable that this particular population may be most vulnerable to the risks associated with re-intubation. Overall, it is important to identify when an extreme preterm infant is ready to be extubated with the highest chance of success, to not only avoid prolonged MV but to also prevent the risks associated with the re-institution of MV.

1.2 Strategies to Assess Extubation Readiness in Preterm Infants

Currently, the decision to extubate is based on clinical assessment, blood gas analysis and minimal ventilatory settings, with practices varying greatly by institutions and individuals. Given the high re-intubation rate that exists in extreme preterm infants when they are extubated based exclusively on clinical judgment, the development of any accurate and objective predictor of extubation readiness would be of great benefit.

Over the past decades, many strategies to determine extubation readiness in preterm infants have been investigated, including measurements of lung function such as dynamic compliance, resistance and tidal volumes, functional residual capacity and chest x-ray lung volume. None of these tools have been shown to provide any improvement in the ability to determine the outcome of extubation. Furthermore, the results of these older studies no longer apply to current clinical practice in neonatology. All of the infants in these trials were extubated to a headbox with humidified oxygen. Today, premature infants are routinely extubated to non-invasive ventilation, a post-extubation management approach which has significantly reduced overall re-intubation rates.

Tools to assess extubation readiness have also been investigated in more recent studies employing non-invasive ventilatory support during the immediate post-extubation phase, but with varying success. A randomized control trial reported a higher extubation failure rate with the use of a minute ventilation test to determine the time of extubation when compared to clinical decision making alone, demonstrating the low discriminatory ability of this prediction.
The application of a pressure-time index assessing respiratory muscle strength could predict successful extubation with high sensitivity and specificity, indicating a decreased diaphragmatic efficiency in neonates that fail extubation\textsuperscript{26}. However, this study was small and enrolled infants up to thirty-six weeks of gestation and weighing greater than three kilograms at birth\textsuperscript{26}. Whether the results of this study are applicable to the smallest and most immature infants who are at the greatest risk of failure remains indeterminate. The percentage of time an ELBW infant could breathe with a spontaneous expiratory minute ventilation below a pre-determined threshold during a two hour challenge of endotracheal tube continuous positive airway pressure (ETT CPAP) was shown to predict readiness for extubation with high sensitivity and specificity\textsuperscript{27}. The length of such a challenge has been questioned since ETT CPAP adds to the resistance of the respiratory system, increasing the work of breathing and decreasing both minute ventilation and lung volume over time\textsuperscript{15}. It is possible that a number of infants may have been successfully extubated if not exposed to such a challenge. Evidence suggests that extubation after several hours of ETT CPAP is less successful than extubation from low settings on MV\textsuperscript{28}. Therefore, the widespread clinical application of minute ventilation measurements during such a prolonged period of ETT CPAP to help predict extubation readiness may be limited.

Other ventilatory strategies have also been evaluated in the context of extubation readiness (Table 1.3). The implementation of a respiratory therapist driven neonatal ventilation protocol with specific guidelines for extubation in extreme preterm infants demonstrated a significant decrease in extubation failure rates\textsuperscript{29}. After implementation of the protocol, reintubation rates were halved but remained clinically significant at twenty percent\textsuperscript{29}. A randomized control trial evaluating a thirty-six hour delay of extubation in preterm infants once criteria were met showed no improvement in extubation failure rates when compared to immediate removal of the endotracheal tube\textsuperscript{30}.

For extreme preterm infants, the most compelling evidence to date concerning a potential prediction tool for successful extubation can be attributed to a spontaneous breathing trial (SBT) (Table 1.4). A SBT can be performed once an infant has reached minimal ventilatory settings and consists of observing changes in oxygen saturation and heart rate during three minutes of ETT CPAP immediately prior to extubation\textsuperscript{15}. This test was shown to guide suitability of extubation in very low birth weight infants with a high positive predictive value (PPV), negative
predictive value (NPV), sensitivity and specificity\textsuperscript{15}. After implementation of this prediction tool as part of clinical practice, however, an extubation failure rate of twenty-two percent was reported\textsuperscript{31}. The SBT was deemed only as effective as clinical decision making alone in determining extubation readiness\textsuperscript{31}.

In summary, no single approach applied prior to extubation investigated so far has significantly decreased the incidence of re-intubation in the extreme preterm population. Thus, the need to improve a clinician’s ability to correctly identify when an infant can be successfully extubated remains. Alternative means of predicting extubation readiness in extreme preterm infants warrants further investigation.
<table>
<thead>
<tr>
<th>Study Population</th>
<th>Predictive Strategy</th>
<th>Failure Rate</th>
<th>Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Veness-Mehan 1990</strong>&lt;sup&gt;17&lt;/sup&gt;</td>
<td><strong>Success (n = 36)</strong> BW 1563 ± 688 g, GA 30 ± 3.7 wks</td>
<td><strong>V&lt;sub&gt;T&lt;/sub&gt;, V&lt;sub&gt;E</strong></td>
<td>28%</td>
</tr>
<tr>
<td><strong>Failure (n = 14)</strong> BW 1251 ± 407 g, GA 29 ± 2.2 wks</td>
<td>C&lt;sub&gt;RS&lt;/sub&gt;, R&lt;sub&gt;RS&lt;/sub&gt;, WOB</td>
<td>Mean Inspiratory Flow</td>
<td>C&lt;sub&gt;RS&lt;/sub&gt; &lt; 0.9 ml/cmH&lt;sub&gt;2&lt;/sub&gt;O = Failure (100%)</td>
</tr>
<tr>
<td><strong>Balsan 1990</strong>&lt;sup&gt;18&lt;/sup&gt;</td>
<td><strong>Success (n = 33)</strong> Weight 1442 ± 57 g PCA 31.2 ± 0.3 wks</td>
<td><strong>C&lt;sub&gt;RS&lt;/sub&gt;, R&lt;sub&gt;RS&lt;/sub</strong></td>
<td>22%</td>
</tr>
<tr>
<td><strong>Failure (n = 16)</strong> BW 1229 ± 187 g, GA 29.5 ± 2.3 wks</td>
<td>V&lt;sub&gt;T&lt;/sub&gt;, C&lt;sub&gt;RS&lt;/sub&gt;, RR, T&lt;sub&gt;I&lt;/sub&gt;, T&lt;sub&gt;E**</td>
<td>Inspiratory flow</td>
<td>V&lt;sub&gt;T&lt;/sub&gt; &lt; 7 ml/kg: Sensitivity 69, Specificity 47</td>
</tr>
<tr>
<td><strong>Smith 1999</strong>&lt;sup&gt;20&lt;/sup&gt;</td>
<td><strong>Success (n = 33)</strong> BW 1235 ± 164 g, GA 30.6 ± 1.9 wks</td>
<td><strong>C&lt;sub&gt;RS&lt;/sub&gt;, R&lt;sub&gt;RS&lt;/sub</strong></td>
<td>33%</td>
</tr>
<tr>
<td><strong>Failure (n = 16)</strong> BW 1229 ± 187 g, GA 29.5 ± 2.3 wks</td>
<td>V&lt;sub&gt;T&lt;/sub&gt;, C&lt;sub&gt;RS&lt;/sub&gt;, RR, T&lt;sub&gt;I&lt;/sub&gt;, T&lt;sub&gt;E**</td>
<td>Inspiratory flow</td>
<td>C&lt;sub&gt;RS&lt;/sub&gt; &lt; 0.5 ml/cmH&lt;sub&gt;2&lt;/sub&gt;O: Sensitivity 81, Specificity 41</td>
</tr>
<tr>
<td><strong>Dimitriou 1996</strong>&lt;sup&gt;21&lt;/sup&gt;</td>
<td><strong>Success (n = 20)</strong> BW 1141 ± 602 g GA 29.8 ± 2.8 wks</td>
<td>FRC</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Kavvadia 2000</strong>&lt;sup&gt;22&lt;/sup&gt;</td>
<td><strong>Success (n = 20)</strong> BW 1092 (744-1500) g GA 30 (27-33) wks</td>
<td>FRC, V&lt;sub&gt;T&lt;/sub&gt;, C&lt;sub&gt;RS&lt;/sub**</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Failure (n = 10)</strong> BW 1107 (770-1462) g GA 27 (25-30) wks</td>
<td></td>
<td></td>
<td>C&lt;sub&gt;RS&lt;/sub&gt; &lt; 0.8 ml/cmH&lt;sub&gt;2&lt;/sub&gt;O/kg: Sensitivity 60, Specificity 55, PPV 40</td>
</tr>
<tr>
<td><strong>Dimitriou 2000</strong>&lt;sup&gt;23&lt;/sup&gt;</td>
<td><strong>Success (n = 20)</strong> BW 1096 (822-2004) g GA 28 (25-33) wks</td>
<td>Chest X-ray Lung Volume</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Dimitriou 2002</strong>&lt;sup&gt;24&lt;/sup&gt;</td>
<td><strong>Success (n = 36)</strong> BW 1569 (685-2856) g GA 31 (25-36) wks</td>
<td>Inspiratory Pressures</td>
<td>19.4%</td>
</tr>
</tbody>
</table>
Legend: BW = Birth Weight, GA = Gestational Age, $V_T$ = Tidal Volume, $V_E$ = Minute Ventilation, $C_{RS}$ = Dynamic Lung Compliance, $R_{RS}$ = Total Lung Resistance, WOB = Work of Breathing, PCA = Post-Conceptual Age, RR = Respiratory Rate, $T_I$ = Inspiratory Time, $T_E$ = Expiratory Time, FRC = Functional Residual Capacity, PPV = Positive Predictive Value, ROC = Receiver Operating Characteristic, IP = Inspiratory Pressure and MIP = Maximum Inspiratory Pressure
Table 1.2 Strategies assessing extubation readiness with the use of non-invasive ventilation post-extubation

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Predictive Strategy</th>
<th>Failure Rate</th>
<th>Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gillespie 2003&lt;sup&gt;23&lt;/sup&gt;</td>
<td>MVT</td>
<td>Clinical: 9%</td>
<td>MVT: PPV 76</td>
</tr>
<tr>
<td>n = 42</td>
<td></td>
<td>MVT: 24%</td>
<td></td>
</tr>
<tr>
<td>Clinical (n = 21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW 1440 (700-2700) g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA 30 (24-37) wks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVT (n = 21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW 1360 (600-3200) g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA 30 (23-37) wks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vento 2004&lt;sup&gt;27&lt;/sup&gt;</td>
<td>VE, CR, RS</td>
<td>Clinical: 26.8%</td>
<td>&gt; 8.1% of time VE &lt; 125 ml/min/kg: Sensitivity 100, Specificity 90</td>
</tr>
<tr>
<td>n = 41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success (n = 30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW 860 (590-1000) g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA 27.5 (25-30) wks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure (n = 11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW 825 (680-1000) g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA 27 (25-29) wks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimitriou 2011&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Respiratory Drive (P&lt;sub&gt;0.1&lt;/sub&gt;)</td>
<td>Derivation:</td>
<td>PTIdi ≤ 0.12: Sensitivity 100, Specificity 100</td>
</tr>
<tr>
<td>n = 56</td>
<td>Pdi&lt;sub&gt;max&lt;/sub&gt;, P&lt;sub&gt;max&lt;/sub&gt;, VT</td>
<td></td>
<td>PTImus ≤ 0.10: Sensitivity 100, Specificity 100</td>
</tr>
<tr>
<td>Derivation (n = 28)</td>
<td>Respiratory Frequency</td>
<td>Validation:</td>
<td>PTIdi ≤ 0.12: Sensitivity 100, Specificity 100</td>
</tr>
<tr>
<td>BW 1360 (630-3350) g</td>
<td>PTIdi, PTImus</td>
<td></td>
<td>PTImus ≤ 0.10: Sensitivity 83.3, Specificity 100</td>
</tr>
<tr>
<td>GA 30 (25-36) wks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Validation (n = 28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW 1410 (680-3220) g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA 30 (25-36) wks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend: BW = Birth Weight, GA = Gestational Age, MVT = Minute Ventilation Test, PPV = Positive Predictive Value, VE = Minute Ventilation, CR = Dynamic Lung Compliance, RS = Total Lung Resistance, Pdi<sub>max</sub> = Maximum Transdiaphragmatic Pressure, P<sub>max</sub> = Maximum Inspiratory Airway Pressure, VT = Tidal Volume, PTIdi = Diaphragmatic Pressure-time Index and PTImus = Pressure-time Index of Respiratory Muscles
Table 1.3 Impact of ventilatory strategies on extubation failure rates

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Ventilation Strategy</th>
<th>Failure Rate</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hermeto 2009</strong>&lt;sup&gt;29&lt;/sup&gt; 301</td>
<td>Before (n = 93) BW 872 ± 202 g GA 27 ± 2 wks</td>
<td>Ventilation protocol driven by respiratory therapists</td>
<td><strong>Before</strong>: 40% <strong>After 1</strong>: 26% <strong>After 2</strong>: 20%</td>
</tr>
<tr>
<td></td>
<td>After 1 (n = 109) BW 875 ± 209 g GA 27 ± 2 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 2 (n = 99) BW 871 ± 216 g GA 27 ± 2 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Danan 2008</strong>&lt;sup&gt;30&lt;/sup&gt; 86</td>
<td>IE (n = 44) BW 828 ± 185 g GA 26.2 ± 1.0 wks</td>
<td>Delayed Extubation: ETT removal 36 hrs after extubation criteria met</td>
<td>IE: 36% DE: 40%</td>
</tr>
<tr>
<td></td>
<td>DE (n = 42) BW 788 ± 146 g GA 26.2 ± 1.1 wks</td>
<td>Immediate Extubation: ETT removal as soon as extubation criteria met</td>
<td></td>
</tr>
</tbody>
</table>

Legend: BW = Birth Weight, GA = Gestational Age, IE = Immediate Extubation, DE = Delayed Extubation, ETT = Endotracheal Tube and MV = Mechanical Ventilation
Table 1.4 Spontaneous breathing trial to assess extubation readiness

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Predictive Strategy</th>
<th>Failure Rate</th>
<th>Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kamlin 2006</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Success (n = 39)</td>
<td>Expiratory $V_E$ Ratio SBT</td>
<td>Clinical: 22%</td>
</tr>
<tr>
<td></td>
<td>BW 957 ± 215 g</td>
<td>$V_E &gt; 220$ ml/kg/min:</td>
<td>SBT: PPV 93, NPV 89, Sensitivity 97, Specificity 73</td>
</tr>
<tr>
<td></td>
<td>GA 27 ± 1.7 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Failure (n = 11)</td>
<td>$V_E$ ratio ≥ 0.8:</td>
<td>SBT: PPV 87, NPV 50, Sensitivity 85, Specificity 45</td>
</tr>
<tr>
<td></td>
<td>BW 855 ± 232 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GA 26.3 ± 2.2 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controls (n = 90)</td>
<td>SBT: PPV 87, NPV 55, Sensitivity 87, Specificity 54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BW 914 ± 189 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GA 27 ± 2 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SBT (n = 90)</td>
<td>SBT: 22%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BW 861 ± 229 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GA 27 ± 2 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Kamlin 2008</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td>SBT</td>
<td>Clinical: 28%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SBT: 22%</td>
<td>SBT: Sensitivity 83</td>
<td></td>
</tr>
</tbody>
</table>

Legend: BW = Birth Weight, GA = Gestational Age, $V_E$ = Minute Ventilation, SBT = Spontaneous Breathing Trial, PPV = Positive Predictive Value and NPV = Negative Predictive Value
1.3 Measurements of Physiologic Variability

The application of physiological variability measurements as markers of well-being has a long tradition in medicine. Illness usually causes a loss of physiological variability and low variability can predict a worse outcome\textsuperscript{32,33}. The importance of variability measurements as prognostic indicators has been clearly proven in a variety of acute and chronic illnesses across the lifespan\textsuperscript{34}. For example, a robust literature links decreased heart rate variability (HRV) to cardiac events and mortality in adults. From the Multi-Center Post-Infarction Program (MPIP) reported in 1987, it was demonstrated that decreased HRV predicts a substantially higher mortality rate among survivors of myocardial infarction\textsuperscript{35} (Figure 1.1).

![Image](image.png)

\textbf{Figure 1.1.} Kaplan-Meier survival curves from the Multi-Center Post-Infarction Program Study, demonstrating a significantly decreased survival among patients with a standard deviation of all normal RR intervals recorded over a 24 hour period below 50 milliseconds\textsuperscript{35}.

Multiple investigations since the MPIP study was published have confirmed the power of HRV analysis in risk stratification post myocardial infarction\textsuperscript{35}. Furthermore, HRV has been used to quantify risk in a wide variety of other disorders, including stroke, multiple sclerosis, end stage renal disease and diabetes mellitus\textsuperscript{35}.

In neonates, early and accurate prediction of any clinical event that may increase the likelihood of morbidity is of particular importance because it can allow for customized medical management in patients at highest risk\textsuperscript{36}. Physiological variability measurements have been evaluated in this context. Reduced variability and transient decelerations in heart rate occur at increased frequency in the preclinical phases of sepsis and systemic inflammatory response.
syndrome in infants admitted to the neonatal intensive care unit (NICU)\textsuperscript{37}. Monitoring these changes in HRV over time can add independent information to conventional laboratory tests in detecting a higher-than-expected risk for the onset of neonatal sepsis\textsuperscript{38}. This can allow for diagnosis and treatment in infants who have never displayed signs of illness\textsuperscript{38}. Another risk assessment model called the “Physiscore”, which incorporates physiological signals including HRV and respiratory variability (RV) recorded during the first three hours of life, can accurately predict an increased risk of morbidity due to infections and cardiopulmonary complications, even when these events are not diagnosed until days or weeks later (Figure 1.2)\textsuperscript{36}.

![Signal for an infant in LM](image1.png) ![Signal for an infant in HM](image2.png)

**Figure 1.2.** HRV measured in two neonates. Differences in HRV can be appreciated between the neonate at low risk of morbidity (left) and the neonate at high risk (right)\textsuperscript{36}.

Most recently, a large randomized control trial demonstrated that the use of heart rate characteristics monitoring, which detects reduced variability and transient decelerations, could significantly reduce mortality in very low birth weight infants by 22\textsuperscript{39}.

Measurements of HRV and RV are simple, non-invasive and can be performed in the fragile preterm infant population. These particular measures of physiologic variability have been chosen for evaluation in the investigations comprising this thesis.
1.3.1 Heart Rate Variability

Heart rate is the result of a variety of interactive influences, including intrinsic sinoatrial nodal rhythm, intracardiac conduction, sympathetic and parasympathetic autonomic interaction at the atrioventricular node and circulating catecholamine concentrations\textsuperscript{34}. Given these many influences, the beating of the heart, even under resting conditions, does not occur at perfectly constant time intervals\textsuperscript{40}. HRV is a measurement of the naturally occurring beat-to-beat changes in heart rate (Figure 1.3).

![Heart rate tracing from an extreme preterm infant under MV, recorded using electrocardiography. R-R interval lengths change on a beat-to-beat basis.](image)

\textit{Figure 1.3.} Heart rate tracing from an extreme preterm infant under MV, recorded using electrocardiography. R-R interval lengths change on a beat-to-beat basis.

1.3.2 Respiratory Variability

RV represents the naturally occurring variability in the timing and magnitude of sequential breaths on a breath-to-breath basis (Figure 1.4)\textsuperscript{41}.

![Breathing pattern of an extremely preterm infant undergoing a three minute SBT, recorded using respiratory inductive plethysmography. No individual breath is exactly identical to the one preceding or following it, in both timing and volume measurements of breathing.](image)

\textit{Figure 1.4.} Breathing pattern of an extremely preterm infant undergoing a three minute SBT, recorded using respiratory inductive plethysmography. No individual breath is exactly identical to the one preceding or following it, in both timing and volume measurements of breathing.

RV results from rapidly occurring changes in respiratory mechanics, blood gases, chemosensitivity and inputs from airway receptors\textsuperscript{41}.
Overall, the abundance of evidence demonstrating the accurate and specific use of variability measurements as predictors of overall morbidity and mortality in both adults and neonates provides a strong rationale for further exploration of these tools in other settings. More specifically, given the increased risk of morbidity and mortality associated with both prolonged MV and re-intubation, variability measurements may be able to provide further insight into the determination of extubation readiness in extreme preterm infants.

1.4 Variability Measurements and Weaning from Mechanical Ventilation

HRV and RV have been evaluated in the adult population in the context of ventilator weaning. Each of these measures of physiologic variability has been assessed individually and in combination with the potential to ameliorate clinical decision making when determining the optimal time to discontinue ventilatory support.

HRV measurements have been evaluated prospectively in mechanically ventilated intensive care unit adult patients recovering from respiratory failure. HRV was measured using stable five minute segments of electrocardiography (ECG) tracings during three weaning phases: 1) assist-control mandatory ventilation (ACMV), 2) pressure support ventilation (PSV) and 3) ETT CPAP and analyzed in the frequency domain\(^42\). All components of HRV were significantly reduced in patients that failed ETT CPAP or required re-intubation when shifting from PSV to ETT CPAP and when comparing ACMV with ETT CPAP\(^42\).

RV measurements have also been evaluated prospectively in various mechanically ventilated adult populations. In post-cardiac surgery patients undergoing weaning from MV, the regularity of tidal volume (\(V_T\)) and respirator rate (RR) was determined\(^43\). Each patient underwent a one to two hour trial of spontaneous ventilation, during which the RR and \(V_T\) of over 1000 consecutive breaths were recorded\(^43\). The variability of these respiratory parameters was quantified using approximate entropy\(^43\). \(V_T\) irregularity was associated with failure to wean from MV\(^43\). In post-operative patients recovering from systemic inflammatory response syndrome, the ability to predict weaning outcome using breathing pattern variability was investigated\(^44\). During a thirty minute weaning trial, expiratory \(V_T\), total breath duration (\(T_{TOT}\)), inspiratory time (\(T_I\)), expiratory time (\(T_E\)) and peak inspiratory flow were measured on a breath-to-breath basis\(^44\). The variability of each of these respiratory parameters was quantified by
calculating coefficients of variation and poincaré plots\textsuperscript{44}. Reduced breathing pattern variability was associated with an increased incidence of weaning failure\textsuperscript{44}. These results were recently confirmed while studying intensive care unit patients being extubated\textsuperscript{45}. Decreased RV was again associated with a high incidence of extubation failure\textsuperscript{45}.

In adults patients requiring MV due to respiratory failure, increased and decreased RV have both been associated with weaning failure. Coefficients of variation and advanced chaos theories were applied to quantify RV of peak flow and spontaneous $V_T$, comparing patterns in patients either successfully extubated or requiring re-intubation\textsuperscript{46}. A regular breathing pattern was associated with the ability to tolerate weaning from MV\textsuperscript{46}. In contrast, breath-to-breath variability of $V_T$, $T_i$, $T_E$, $T_{TOT}$, $T_i/T_{TOT}$ and mean inspiratory flow ($V_T/T_i$) was also quantified in another group of patients successfully or unsuccessfully separated from MV using coefficients of variation and autocorrelation analysis\textsuperscript{47}. Breathing variability during a sixty minute SBT was decreased in patients who failed separation from MV (Figure 1.5), which could have been due to an acute deterioration of the load-capacity balance of the respiratory system during the SBT or an unfavourable load-capacity balance before the SBT\textsuperscript{47}.

![Figure 1.5](image.png)

*Figure 1.5.* Time series of respiratory variables recorded in one patient successfully extubated (left) and one patient unsuccessfully separated from MV (right) following a sixty minute SBT\textsuperscript{47}.
The differences in RV measurements between groups of adult patients successfully or
unsuccessfully weaned from MV are variable, but this is most likely due to the heterogeneity of
the patient populations studied and the wide variety of methodologies applied to assess RV.

The combination of both HRV and RV measurements has also been investigated during
discontinuation from MV in adult intensive care unit patients recovering from respiratory failure.
A classification between patients who are considered ready for spontaneous breathing and
patients who are not was proposed based on respiratory frequency, instantaneous variability of
respiratory frequency, heart rate and the spectral components of HRV\(^48\). All parameters were
different between patients with a successful weaning trial and patients who failed to maintain
spontaneous breathing and were reconnected to MV\(^48\). A sequential discriminant analysis based
on these cardiac and respiratory variability parameters was able to correctly classify more than
eighty percent of the patients\(^48\).

Variability measurements show much promise as potential predictors of extubation
readiness and have never been assessed in extreme preterm infants, a population most vulnerable
to the risks associated with the decision to extubate.

1.5 Variability Measurements and Extubation Readiness in Extreme Preterm Infants

This thesis will assess whether measurements of HRV or RV can provide new
information that may benefit the ventilatory management of extreme preterm infants; more
specifically, the ability to accurately determine extubation readiness in this population. Four
studies have been completed and will be outlined in the chapters to follow:

1) Variability of Respiratory Parameters and Extubation Readiness in Ventilated
   Neonates.

   Kaczmarek J\(^1\), Kamlin O\(^2\), Davis PG\(^b\), Morley CJ\(^b\) and Sant’Anna GM\(^a\)

2) Hear Rate Variability and Extubation Readiness in Extreme Preterm Infants: A
   Prospective, Observation Study.

   Kaczmarek J, Chawla S\(^3\) and Sant’Anna GM

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\(^1\) Montreal Children’s Hospital, Montreal, Canada
\(^2\) Royal Women’s Hospital, Melbourne, Australia
3) Respiratory Variability and Extubation Readiness in Extreme Preterm Infants: A Prospective, Observational Study

Kaczmarek J, Chawla S and Sant’Anna GM

4) Heart Rate Variability and Respiratory Variability in Healthy Full-Term Newborns: Effect of Position and Feeding.

Kaczmarek J and Sant’Anna GM

Data collection for studies two and three were completed in the same prospectively studied population simultaneously. For the purpose of this thesis, each study will be introduced and described separately.
Chapter 2 – Variability of Respiratory Parameters and Extubation Readiness in Ventilated Neonates

Kaczmarek J, Kamlin O, Davis PG, Morley CJ and Sant’Anna GM

This study was accepted for oral presentation at the Perinatal Society of Australia and New Zealand Annual Congress (Hobart, Tasmania, 2011) and poster presentation at the Pediatric Academic Societies Annual Meeting (Denver, 2011).

This manuscript has been submitted to the Archives of Disease in Childhood, Fetal and Neonatal Edition (November 5, 2011).

2.1 Objective

The objective of this study was to evaluate the predictive value of respiratory variability alone and in combination with the spontaneous breathing trial for successful extubation.

2.2 Methods

Study Population

This study was a retrospective analysis, done in Montreal, Canada, of infant data previously collected in detail during a three minute SBT done in Melbourne, Australia15. The human research ethics committee of the institution approved the original study and written informed consent was obtained from parents.

Data Collection

Spontaneous Breathing Trial

The SBT has been previously described15. Briefly, when the clinical team decided an infant was ready for extubation, the ventilator was switched to ETT CPAP at the same pressure as the positive end expiratory pressure (PEEP) setting for three minutes. A SBT failure was recorded if the infant had either a bradycardia lasting longer than fifteen seconds and/or a fall in oxygen saturation (SpO2) below eighty-five percent despite a fifteen percent increase in the fraction of inspired oxygen (FiO2) during the three minute period of the trial. Methylxanthines were used before or after extubation at the clinician’s discretion and infants were extubated to
either nasal continuous positive airway pressure (CPAP) or nasal intermittent positive pressure ventilation (NIPPV) using bi-nasal Hudson prongs. Extubation failure was defined as the need for re-intubation within seventy-two hours of initial disconnection from MV.

**Respiratory Variables**

The following respiratory variables were recorded in all infants during each three minute SBT on a breath-to-breath basis: $T_I$, $T_E$ and $V_T$ from which $T_I/T_{TOT}$ and $V_T/T_I$ were calculated. Data were measured using the Dräger Babylog 8000 plus (Lubeck, Germany) with its hot wire anemometer just proximal to the endotracheal tube. Data was downloaded from the RS232 port of the ventilator for analysis.

**Data analysis**

The variability index (VI) of each respiratory variable was quantified using a time domain analysis previously described by Cameron et al.\textsuperscript{41}. This analysis was done blinded to patient outcome of extubation failure or success and included the maximum number of consecutive breath-to-breath values recorded during the SBT of each infant, regardless of SBT pass or fail. Five individual calculations of variability were performed for each respiratory variable: 1) *Coefficient of Variation*: the standard deviation (SD) divided by the mean for all sequential breaths, 2) *Triangular Index*: construction of a histogram with bins of 0.05 sec for $T_I$ and $T_E$, 0.25 ml/kg for $V_T$, 0.05 for $T_I/T_{TOT}$ and 2 ml/kg/sec for $V_T/T_I$, corresponding to the total number of breaths divided by the number occurring at the peak of the histogram, 3) $DIFF > 30\%$: percent of breaths differing from the mean value by more than thirty percent, 4) $B-B_{\text{absolute}}$: percent of breaths differing from the one immediately preceding it by more than the SD of all breaths and 5) $B-B_{\%\text{mean}}$: percent of breaths differing from the one immediately preceding it by more than thirty percent of the overall mean. For each of these calculations, higher values indicate greater variability.

Once this analysis was complete, values were stratified based on patient outcome of extubation failure or success. All five calculations of variability for each respiratory variable in each infant were then expressed as a percentage of the mean value of successfully extubated infants. Following this transformation, it was possible to average these newly calculated percentages into one overall VI for $T_I$, $T_E$, $V_T$, $T_I/T_{TOT}$ and $V_T/T_I$. 
Statistical analysis

Continuous variables are expressed as mean ± SD or median (interquartile range). The student t-test was used to compare continuous variables between infants that were successfully extubated or failed extubation. A p value < 0.05 was considered statistically significant.

The ability of each VI to accurately discriminate between successful and failed extubation was assessed using receiver operating characteristic (ROC) curves. The first inflection point of each curve was identified as a cut-off to discriminate success and failure of extubation for the VI of each respiratory variable. Standard formulae were used to calculate sensitivity, specificity, PPV and NPV for: 1) the SBT alone, 2) the VI of each respiratory variable and 3) the combination of the SBT and VI of each respiratory variable.

2.3 Results

Of the fifty preterm infants included in the original study, a subset of respiratory data from forty-four infants was included in the current analysis. Data from one patient could no longer be recovered and data from five patients were excluded because less than forty breaths were available for analysis. Of the forty-four patients included, thirty-six infants were successfully extubated while eight infants (18%) required re-intubation.

The population characteristics and absolute values for all respiratory variables, averaged over the three minute period of the SBT, were similar between success and failure patients (Table 2.1). A comparable number of breaths were analyzed in success and failure patients (84 [55-143] vs. 70 [56-112]; Table 2.1).

The VI of $V_T/T_I$ was significantly decreased in the failure group during the SBT prior to extubation when compared to the VI achieved in successfully extubated infants (76.5 ± 25.6% vs. 100 ± 29.8%, p < 0.05; Figure 2.1). The VIs of $T_I$, $T_I/T_{TOT}$ and $V_T$ were also decreased in the failure group when compared to successfully extubated infants, although this decrease did not reach statistical significance (76.8 ± 38.5% vs. 100 ± 35.3%, 78.9 ± 40.5% vs. 100 ± 36.3% and 83.1 ± 39.3% vs. 100 ± 28.9%, respectively; Figure 2.1). For $T_E$, the VI achieved by infants that required re-intubation and successfully extubated infants was similar (95.4 ± 44.2 vs. 100 ± 30.5; Figure 2.1).
The VIs of each respiratory variable individually had low specificity in predicting successful extubation (Table 2.2). The SBT alone correctly classified a large majority of infants. All infants that failed the SBT failed extubation, contributing to a sensitivity of 100% with no false negatives and a NPV of 100%. However, three infants that passed the SBT failed extubation representing false positives, which contributed to a specificity of 63% and a PPV of 92% (Table 2.2). In combination, the SBT and VI of T₁ or VT enhanced the predictive accuracy of the SBT alone, with increased specificity from 63% to 75% and PPV from 92% to 95% (Table 2.2). Overall, a combination of the SBT and VI of either T₁ or VT were the most accurate predictors of successful extubation.

2.4 Limitations

This investigation did have several limitations. Analysis was performed retrospectively in a small sample size of infants which included only eight failure patients. Also, a reduced number of breaths were available for analysis of RV in certain patients. During the SBT, the most common cause of bradycardia and hypoxia was poor respiratory drive and apnea. When this occurred, infants were switched back to prior MV settings before the three minute test was over, thus limiting the number of breaths available for analysis. Results should be interpreted as exploratory findings.

2.5 Conclusions

To conclude, infants that required re-intubation had a significantly lower VI of VT/T₁ prior to extubation. A combination of SBT failure and decreased VI of T₁ or VT maintained a high NPV and sensitivity and increased the PPV and specificity in predicting successful extubation. This combination of prediction tools is promising but requires further evaluation in a larger, prospectively studied population.
Table 2.1 Population characteristics and mean respiratory variables

<table>
<thead>
<tr>
<th></th>
<th>Success (n = 36)</th>
<th>Failure (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (g)</td>
<td>946 ± 220</td>
<td>901 ± 250</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>26.9 ± 1.7</td>
<td>26.8 ± 2.3</td>
</tr>
<tr>
<td>Weight at Study (g)</td>
<td>989 ± 199</td>
<td>897 ± 210</td>
</tr>
<tr>
<td>Age at Study (days)</td>
<td>4 (2-10)</td>
<td>5 (3-10)</td>
</tr>
<tr>
<td>PEEP during SBT (cmH$_2$O)</td>
<td>5.3 ± 0.5</td>
<td>5.1 ± 0.4</td>
</tr>
<tr>
<td>Number of breaths analyzed during SBT</td>
<td>84 (55-143)</td>
<td>70 (56-112)</td>
</tr>
<tr>
<td>Inspiratory Time (sec)</td>
<td>0.43 ± 0.20</td>
<td>0.39 ± 0.12</td>
</tr>
<tr>
<td>Expiratory Time (sec)</td>
<td>0.58 ± 0.22</td>
<td>0.53 ± 0.13</td>
</tr>
<tr>
<td>Inspiratory Time/Total Breath Time</td>
<td>0.44 ± 0.08</td>
<td>0.46 ± 0.08</td>
</tr>
<tr>
<td>Tidal Volume (ml/kg)</td>
<td>4.5 ± 1.8</td>
<td>4.21 ± 1.2</td>
</tr>
<tr>
<td>Mean Inspiratory Flow (ml/kg/sec)</td>
<td>14.2 ± 8.0</td>
<td>11.2 ± 4.1</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD or median (interquartile range).
Legend: PEEP = Positive End-Expiratory Pressure and SBT = Spontaneous Breathing Trial
Table 2.2 Predictive value of the spontaneous breathing trial, variability index of each respiratory variable and the combination of the spontaneous breathing trial and variability index of each respiratory variable for successful extubation

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBT</td>
<td>100</td>
<td>63</td>
<td>92</td>
<td>100</td>
</tr>
<tr>
<td>Inspiratory Time</td>
<td>100</td>
<td>13</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>Expiratory Time</td>
<td>100</td>
<td>13</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>T&lt;sub&gt;i&lt;/sub&gt;/T&lt;sub&gt;TOT&lt;/sub&gt;</td>
<td>97</td>
<td>50</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>Tidal Volume</td>
<td>100</td>
<td>13</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>Mean Inspiratory Flow</td>
<td>100</td>
<td>13</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>SBT + Inspiratory Time</td>
<td>100</td>
<td>75</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>SBT + Tidal Volume</td>
<td>100</td>
<td>75</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>SBT + Mean Inspiratory Flow</td>
<td>100</td>
<td>63</td>
<td>92</td>
<td>100</td>
</tr>
<tr>
<td>SBT + T&lt;sub&gt;i&lt;/sub&gt;/T&lt;sub&gt;TOT&lt;/sub&gt;</td>
<td>100</td>
<td>63</td>
<td>92</td>
<td>100</td>
</tr>
<tr>
<td>SBT + Expiratory Time</td>
<td>97</td>
<td>87</td>
<td>97</td>
<td>88</td>
</tr>
</tbody>
</table>

Legend: PPV = Positive Predictive Value, NPV = Negative Predictive Value, SBT = Spontaneous Breathing Trial, T<sub>i</sub> = Inspiratory Time and T<sub>TOT</sub> = Total Breath Duration
Figure 2.1 Variability index of respiratory variables during the spontaneous breathing trial prior to extubation

*\( p < 0.05 \)

Legend: \( T_I \) = Inspiratory Time, \( T_E \) = Expiratory Time, \( T_{TOT} \) = Total Breath Time and \( V_T \) = Tidal Volume
Chapter 3 - Heart Rate Variability and Extubation Readiness in Extreme Preterm Infants: A Prospective, Observational Study

Kaczmarek J, Chawla S and Sant’Anna GM

Abstract submitted to the Pediatric Academic Societies Annual Meeting (Boston, 2012).

3.1 Objectives

The primary objective of this study was:

1. To assess differences in heart rate variability prior to extubation between extreme preterm infants who fail or succeed a first extubation attempt.

The secondary objectives of this study were:

1. To determine the predictive value of heart rate variability for successful extubation.

2. To assess differences in heart rate variability during the early post-extubation period between extreme preterm infants who fail or succeed a first extubation attempt.

3.2 Methods

Study Population

All infants admitted to the NICU at the Royal Victorian Hospital (Montreal, Canada), Jewish General Hospital (Montreal, Canada), Montreal Children’s Hospital (Montreal, Canada) and Detroit Medical Centre (Detroit, USA) with a birth weight ≤ 1250g and requiring MV were eligible for inclusion. The human research ethics committee of each institution approved the study and written informed consent was obtained from parents.

The decision to extubate was made by the most responsible physician according to the following guidelines: 1) infants below 1000g were extubated with a mean airway pressure (MAP) ≤ 7 cmH₂O and FiO₂ ≤ 0.3 and 2) infants ≥ 1000g were extubated with a MAP ≤ 8 cmH₂O and FiO₂ ≤ 0.3. All infants were studied at the time of their first extubation from MV. Infants were excluded if they had any major congenital anomalies, congenital heart disease, cardiac arrhythmias, been administered vasopressor or sedative drugs at the time of extubation or were being extubated directly from high frequency oscillatory ventilation. Post-extubation
management involved the application of nasal CPAP or NIPPV using either bi-nasal prongs or a single nasopharyngeal tube at the medical team’s discretion.

Infants were re-intubated if they met at least one of the following four criteria: 1) FiO$_2$ > 0.5 in order to maintain SpO$_2$ > 88% or partial pressure of oxygen (PaO$_2$) > 45 mmHg, 2) partial pressure of carbon dioxide (PaCO$_2$) > 55-60 mmHg with a pH < 7.25, 3) apnea requiring positive pressure ventilation with bag and mask or 4) significant evidence of increased respiratory distress including frequent retractions, grunting and chest wall distortion. Extubation failure was defined as the need for re-intubation within seventy-two hours of initial disconnection from MV.

Data Collection

Data collection began immediately prior to extubation for sixty minutes while the infant was receiving either assist control (AC) or synchronized intermittent mandatory ventilation (SIMV) and continued for another three minutes while the mode of ventilation was switched to ETT CPAP at the same PEEP setting. An additional sixty to ninety minutes of data collection took place twelve to twenty-four hours post-extubation.

HRV data was collected using electrocardiography. Three ECG leads were placed on the infant’s chest or limbs for heart rate detection and monitoring. The leads were connected to a bioamplifier and Powerlab® data acquisition system, allowing real-time recordings directly downloaded to a research laptop at the patient’s bedside (Figure 3.1).

Figure 3.1 A snapshot demonstrating the ECG signal being collected from each infant enrolled in the study in real time.

The following clinical outcomes were also collected: 1) antenatal and maternal variables: mode of delivery, multiple birth, use of antenatal steroids, use of antibiotics during labour and histologic chorioamnionitis, 2) infant characteristics: sex, birth weight (BW),
gestational age (GA), Apgar scores (at one and five minutes), weight at extubation, age at extubation and post-conceptual age (PCA) at extubation, 3) ventilatory settings prior to extubation: peak inspiratory pressure (PIP), PEEP, MAP, FiO2, set T1, ventilatory rate and SpO2, 4) blood gases: pH, pCO2, pO2, bicarbonate and base excess (prior to extubation and twelve to twenty-four hours post-extubation), 5) ventilatory management post-extubation: use of NIPPV, CPAP, high flow nasal cannula or low flow oxygen, 6) reason and timing of extubation failure and 7) infant outcomes: use of surfactant, caffeine administration prior to extubation, intraventricular haemorrhage (IVH), patent ductus arteriosus (PDA) (treated medically or with ligation surgery), oxygen supplementation at twenty-eight days of life, BPD at 36 weeks PCA (mild, moderate or severe), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), use of antibiotics, use of post-natal steroids, total duration of MV and death during NICU stay.

Data Analysis

HRV was calculated from the ECG tracing recorded during AC/SIMV and twelve to twenty-four hours post-extubation in each infant by selecting a five minute steady, artifact-free segment from each of the data collection periods. Five minute segments were chosen for analysis as recommended by the Task Force guidelines of the European Society of Cardiology and North American Society of Pacing and Electrophysiology for short term analysis of HRV. Given the short three minute length of the switch to ETT CPAP, it was not possible to assess HRV during this mode of ventilation prior to extubation. Analysis of respiratory data collected simultaneously during ETT CPAP will be described in chapter 4.

HRV was quantified in the frequency domain by power spectrum analysis (Labchart® software), also according to the guidelines established by the Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology. The following spectral components of HRV were quantified: 1) total power (TP), 2) very low frequency (VLF; < 0.04 Hz), 3) low frequency (LF; 0.04 - 0.15 Hz), 4) high frequency (HF; > 0.15 Hz) and 5) LF/HF ratio.

Statistical Analysis

Continuous variables are expressed as mean ± SD or median (interquartile range) and categorical variables as counts and percentages. The Fisher's exact test was used for categorical
variables and the student \textit{t-test} for continuous variables to compare outcomes between infants that were successfully extubated or that failed extubation. A \textit{p} value \textless{} 0.05 was considered statistically significant.

The ability of each spectral component of HRV to accurately discriminate between successful and failed extubation was assessed using ROC curves. The first inflection point of each curve was identified as a cut-off to discriminate success and failure of extubation for each spectral component of HRV. Standard formulae were used to calculate sensitivity, specificity, PPV and NPV for the spectral components of HRV prior to extubation.

\textit{Sample Size}

Sample size calculations were performed for this study and the prospective evaluation of RV and extubation readiness in extreme preterm infants (chapter 4) simultaneously, in collaboration with the biostatistician of the institution. Assuming HRV or RV would achieve an area under the ROC curve equal to 0.85, with a 95\% lower limit of 0.75, the sample size required would be 39 given a failure rate of forty percent and 47 given a failure rate of thirty percent. Using the lower rate for extubation failure (30\%) and allowing for a ten percent rate of missing data and refusal to consent, a sample size of fifty-six infants was required.

3.3 Results

\textit{Study Enrollment}

Study enrollment took place between March 2010 and June 2011. During this period, 164 extreme preterm infants met the inclusion criteria at participating hospital centers. Of these, fifty-six infants were enrolled.

\textit{Heart Rate Variability Prior to Extubation}

A subset of data from forty-seven infants was analyzed to evaluate differences in HRV during AC/SIMV between infants successfully extubated and infants that failed extubation (Figure 3.2). Data from nine infants was lost due to lack of quality. Thirty-six neonates were successfully extubated while eleven (23.4\%) required re-intubation.
The main reason for extubation failure was multiple apneas and bradycardias (Table 3.1). The remaining infants that required re-intubation failed extubation because of respiratory acidosis, a FiO\textsubscript{2} requirement greater than 0.5 to maintain SpO\textsubscript{2} above 88% or significant evidence of increased respiratory distress (Table 3.1). The majority of infants that required re-intubation failed extubation within the first twenty-four hours of initial disconnection from MV (54%; Table 3.2).

Population characteristics between success and failure patients were similar, including maternal, antenatal and infant variables (Table 3.3). Ventilatory settings and blood gases prior to extubation were also comparable between both groups. Only the set T\textsubscript{I} was significantly lower in infants that failed extubation when compared to infants successfully extubated (0.37 ± 0.03 sec vs. 0.39 ± 0.04 sec, \( p < 0.05 \); Table 3.4). Infants successfully extubated and infants that required re-intubation were managed similarly in the post-extubation period (Table 3.5). Blood gases post-extubation were also comparable between groups, except for the pCO\textsubscript{2} level, which was significantly increased in the failure group (46.7 ± 7.7 mmHg vs. 40.7 ± 7.0 mmHg, \( p < 0.05 \); Table 3.5). Successfully extubated infants and those that failed extubation had similar final outcomes. However, the percentage of infants with ROP was significantly higher in the failure group (56% vs. 3.1%, \( p < 0.05 \); Table 3.6).

HRV was significantly decreased in extreme preterm infants that failed extubation when compared to infants that were successfully extubated, as quantified by all components of the power spectrum analysis: TP (35.9 ± 24.8 ms\textsuperscript{2} vs. 135.9 ± 161.5 ms\textsuperscript{2}, \( p < 0.05 \); Figure 3.3), VLF (27.2 ± 24.4 ms\textsuperscript{2} vs. 98.2 ± 125.9 ms\textsuperscript{2}, \( p < 0.05 \); Figure 3.3), LF (3.6 ± 3.5 ms\textsuperscript{2} vs. 27.0 ± 38.6 ms\textsuperscript{2}, \( p < 0.05 \); Figure 3.3) and HF (0.7 ± 0.7 ms\textsuperscript{2} vs. 5.5 ± 8.6 ms\textsuperscript{2}, \( p < 0.05 \); Figure 3.3). The LF/HF ratio was also significantly decreased in infants that required re-intubation when compared to successfully extubated infants (5.3 ± 2.6 vs. 9.2 ± 7.0, \( p < 0.05 \); Figure 3.3).

When evaluated as predictors of extubation readiness in extreme preterm infants, spectral components of HRV and the LF/HF ratio generated high areas under the ROC curve, with specificities and PPVs of 100 (Table 3.7). Sensitivities and NPVs were lower (Table 3.7).

*Heart Rate Variability Post-Extubation*
Of the fifty-six infants enrolled, a subset of data from forty-three infants was available for a secondary analysis of differences in HRV twelve to twenty-four hours post-extubation. Data from thirteen infants was lost either due to lack of quality or because a majority of infants requiring re-intubation failed extubation within the first twenty-four hours of initial disconnection from MV, thus making it impossible to complete the post-extubation period of data collection. Of the forty-three infants included in this analysis, thirty-eight were successfully extubated while five required re-intubation.

There were no significant differences in HRV between infants that were successfully extubated and infants that failed extubation, as quantified by all components of the power spectrum analysis: TP ($113.3 \pm 171.0$ ms$^2$ vs. $75.6 \pm 69.3$ ms$^2$; Figure 3.4), VLF ($79.5 \pm 119.5$ ms$^2$ vs. $49.2 \pm 33.5$ ms$^2$; Figure 3.4), LF ($25.7 \pm 48.6$ ms$^2$ vs. $21.4 \pm 32.3$ ms$^2$; Figure 3.4) and HF ($3.7 \pm 6.3$ ms$^2$ vs. $3.1 \pm 3.9$ ms$^2$; Figure 3.4). The LF/HF ratio was also similar between infants successfully extubated and infants that failed extubation ($11.4 \pm 7.9$ vs. $6.3 \pm 2.3$; Figure 3.4).

3.4 Limitations

This investigation did have several limitations. All HRV measurements within both success and failure groups had large standard deviations. This finding is discussed in further detail in section 6.1. To appropriately assess the predictive value of HRV for successful extubation, a much larger sample size of infants would be required. Furthermore, mechanically ventilated extreme preterm infants are cared for in complex clinical environments. It would be impossible to control for every variable that may affect measurements of HRV. For example, electromagnetic fields produced by incubators can influence HRV in newborns\(^49\). In this study, the types of incubators used at each hospital site differed and could not be standardized.

3.5 Conclusions

To conclude, infants that required re-intubation had significantly decreased heart rate variability during assist control or synchronized intermittent mandatory ventilation prior to extubation. As a predictor of successful extubation, all spectral components of HRV produced perfect specificities and positive predictive values but much lower sensitivities and negative predictive values. This prediction tool is promising but requires further evaluation and validation in a larger, prospectively studied population.
Table 3.1 Analysis of heart rate variability prior to extubation: reasons for extubation failure

<table>
<thead>
<tr>
<th>Reason</th>
<th>Extubation Failure (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Apneas and Bradycardias</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Respiratory Acidosis</td>
<td>3 (27)</td>
</tr>
<tr>
<td>$\text{FiO}_2 &gt; 0.5$ in order to maintain $\text{SpO}_2 &gt; 88%$</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Significant Evidence of Increased Respiratory Distress</td>
<td>1 (9)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%).
Legend: $\text{FiO}_2$ = Fraction of Inspired Oxygen and $\text{SpO}_2$ = Oxygen Saturation
Table 3.2 Analysis of heart rate variability prior to extubation: timing of extubation failure

<table>
<thead>
<tr>
<th>Extubation Failure (n = 11)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 hours</td>
<td>3 (27)</td>
<td></td>
</tr>
<tr>
<td>12-24 hours</td>
<td>3 (27)</td>
<td></td>
</tr>
<tr>
<td>24-48 hours</td>
<td>4 (36)</td>
<td></td>
</tr>
<tr>
<td>&gt; 48 hours</td>
<td>1 (9)</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as n (%).
Table 3.3 Analysis of heart rate variability prior to extubation: population characteristics

<table>
<thead>
<tr>
<th></th>
<th>Success (n = 36)</th>
<th>Failure (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal and Antenatal Variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of Antenatal Steroids (1 or 2 doses)</td>
<td>32/34 (88)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>C-Section</td>
<td>23 (64)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Multiple Birth</td>
<td>12 (33)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Antibiotics during Labour</td>
<td>19/34 (56)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>11/33 (33)</td>
<td>2/9 (22)</td>
</tr>
<tr>
<td><strong>Infant Variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth Weight (g)</td>
<td>923 ± 191</td>
<td>876 ± 197</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>26.9 ± 1.6</td>
<td>26.4 ± 1.4</td>
</tr>
<tr>
<td>Male</td>
<td>16 (44)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Apgar Scores (1 and 5 minutes)</td>
<td>5 (3-6), 7 (5-8)</td>
<td>4 (3-6), 7 (6-8)</td>
</tr>
<tr>
<td>Weight at Study (g)</td>
<td>997 ± 281</td>
<td>882 ± 225</td>
</tr>
<tr>
<td>Age at Extubation (days)</td>
<td>4 (2-10)</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>Post-conceptual Age at Extubation (weeks)</td>
<td>28.6 ± 2.5</td>
<td>27.4 ± 1.8</td>
</tr>
<tr>
<td>Surfactant Administration</td>
<td>35 (97)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Caffeine Administration prior to Extubation</td>
<td>30 (83)</td>
<td>10 (91)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD, median (interquartile range), n (%) or n/N (%).
Table 3.4 Analysis of heart rate variability prior to extubation: ventilatory settings and blood gases prior to extubation

<table>
<thead>
<tr>
<th></th>
<th>Success (n = 36)</th>
<th>Failure (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilatory Settings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Inspiratory Pressure (cmH₂O)</td>
<td>12.9 ± 2.2</td>
<td>13.1 ± 1.8</td>
</tr>
<tr>
<td>Positive End-Expiratory Pressure (cmH₂O)</td>
<td>4.4 ± 0.6</td>
<td>4.5 ± 0.8</td>
</tr>
<tr>
<td>Mean Airway Pressure (cmH₂O)</td>
<td>5.8 ± 0.9</td>
<td>6.3 ± 1.2</td>
</tr>
<tr>
<td>Fraction of Inspired Oxygen</td>
<td>0.26 ± 0.06</td>
<td>0.26 ± 0.06</td>
</tr>
<tr>
<td>Set Inspiratory Time (seconds)</td>
<td>0.39 ± 0.04</td>
<td>0.37 ± 0.03*</td>
</tr>
<tr>
<td>Ventilator Rate (breaths per minute)</td>
<td>21 ± 8</td>
<td>25 ± 11</td>
</tr>
<tr>
<td>Oxygen Saturation (%)</td>
<td>95 ± 3</td>
<td>94 ± 2</td>
</tr>
<tr>
<td>Blood Gases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH (n)</td>
<td>7.3 ± 0.1 (30)</td>
<td>7.3 ± 0.05 (10)</td>
</tr>
<tr>
<td>pCO₂ (mmHg, n)</td>
<td>40.0 ± 7.4 (30)</td>
<td>44.4 ± 9.3 (10)</td>
</tr>
<tr>
<td>pO₂ (mmHg, n)</td>
<td>47.4 ± 12.8 (30)</td>
<td>46.1 ± 6.9 (10)</td>
</tr>
<tr>
<td>HCO₃ (n)</td>
<td>21.4 ± 2.9 (30)</td>
<td>21.8 ± 3.0 (10)</td>
</tr>
<tr>
<td>Base Excess (n)</td>
<td>-3.6 ± 2.9 (30)</td>
<td>-1.8 ± 4.1 (10)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

*p < 0.05
Table 3.5 Analysis of heart rate variability prior to extubation: post-extubation management and blood gases

<table>
<thead>
<tr>
<th></th>
<th>Success (n = 36)</th>
<th>Failure (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Invasive Ventilation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal Intermittent Positive Pressure Ventilation</td>
<td>17 (47)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Continuous Positive Airway Pressure</td>
<td>16 (44)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Synchronized Inspiratory Positive Airway Pressure</td>
<td>0 (0)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>High Flow Nasal Cannula</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Low Flow Oxygen</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Room Air</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Blood Gases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH (n)</td>
<td>7.3 ± 0.1 (28)</td>
<td>7.3 ± 0.1 (9)</td>
</tr>
<tr>
<td>pCO₂ (mmHg, n)</td>
<td>40.7 ± 7.0 (28)</td>
<td>46.7 ± 7.7 (9)*</td>
</tr>
<tr>
<td>pO₂ (mmHg, n)</td>
<td>43.5 ± 13.6 (28)</td>
<td>45.8 ± 14.2 (9)</td>
</tr>
<tr>
<td>HCO₃ (n)</td>
<td>20.7 ± 3.2 (28)</td>
<td>21.4 ± 2.4 (9)</td>
</tr>
<tr>
<td>Base Excess (n)</td>
<td>-4.4 ± 3.4 (28)</td>
<td>-3.8 ± 3.0 (9)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD, or n (%).

*p < 0.05
Table 3.6 Analysis of heart rate variability prior to extubation: final infant outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Success (n = 36)</th>
<th>Failure (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraventricular Hemorrhage (Grades III or IV)</td>
<td>1 (2.7)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Patent Ductus Arteriosus – Medical Management</td>
<td>16 (44)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Patient Ductus Arteriosus Ligation</td>
<td>4 (11)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Bronchopulmonary Dysplasia (28 days)</td>
<td>17/33 (52)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Mild Bronchopulmonary Dysplasia (36 weeks PCA)</td>
<td>10/33 (30)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Moderate or Severe Bronchopulmonary Dysplasia (36 weeks PCA)</td>
<td>7/33 (21)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Retinopathy of Prematurity</td>
<td>1/32 (3.1)</td>
<td>5/10 (56)*</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis</td>
<td>3/35 (8.6)</td>
<td>1/9 (10)</td>
</tr>
<tr>
<td>Total Duration of Mechanical Ventilation</td>
<td>5 (3-24)</td>
<td>36 (21-51)</td>
</tr>
<tr>
<td>Use of Antibiotics</td>
<td>36 (100)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Antibiotic Use at Time of Extubation</td>
<td>20 (56)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Post-Natal Steroids (Dexamethasone or Hydrocortisone)</td>
<td>9 (25)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Post-Natal Steroids at Time of Extubation</td>
<td>7 (19.4)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (2.8)</td>
<td>1 (9)</td>
</tr>
</tbody>
</table>

Values are expressed as median (interquartile range), n (%) or n/N (%).

*p < 0.05

Legend: PCA = Post-Conceptual Age
### Table 3.7 Predictive values for heart rate variability prior to extubation

<table>
<thead>
<tr>
<th></th>
<th>ROC Curve Area</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Power</strong></td>
<td>0.79</td>
<td>53</td>
<td>100</td>
<td>100</td>
<td>39</td>
</tr>
<tr>
<td><strong>Very Low Frequency</strong></td>
<td>0.79</td>
<td>42</td>
<td>100</td>
<td>100</td>
<td>34</td>
</tr>
<tr>
<td><strong>Low Frequency</strong></td>
<td>0.84</td>
<td>44</td>
<td>100</td>
<td>100</td>
<td>35</td>
</tr>
<tr>
<td><strong>High Frequency</strong></td>
<td>0.77</td>
<td>39</td>
<td>100</td>
<td>100</td>
<td>33</td>
</tr>
<tr>
<td><strong>LF/HF ratio</strong></td>
<td>0.63</td>
<td>39</td>
<td>100</td>
<td>100</td>
<td>33</td>
</tr>
</tbody>
</table>

Legend: ROC = receiver operating characteristic, PPV = positive predictive value, NPV = negative predictive value, LF = Low Frequency and HF = High Frequency
Figure 3.2 Study enrollment: March 2010 to June 2011

Legend: BW = Birth Weight
Figure 3.3 Spectral components of heart rate variability during assist control or synchronized intermittent mandatory ventilation prior to extubation

*\( p < 0.05 \)

Legend: LF = Low Frequency, HF = High Frequency
Figure 3.4 Spectral components of heart rate variability post-extubation

Legend: LF = Low Frequency, HF = High Frequency
Chapter 4 - Respiratory Variability and Extubation Readiness in Extreme Preterm Infants: A Prospective, Observational Study

Kaczmarek J, Chawla S and Sant’Anna GM

Abstract submitted to the Pediatric Academic Societies Annual Meeting (Boston, 2012).

4.1 Objectives

The primary objective of this study was:

1. To assess differences in respiratory variability prior to extubation between extreme preterm infants who fail or succeed a first extubation attempt.

The secondary objectives of this study were:

1. To determine the predictive value of respiratory variability for successful extubation.

2. To assess differences in respiratory variability during the early post-extubation period between extreme preterm infants who fail or succeed a first extubation attempt.

4.2 Methods

Study Population

Infants were enrolled in this study and the study described in chapter 3 simultaneously. Therefore, criteria outlining the study population of this investigation are identical to those described in section 3.2.

Data Collection

Data collection began immediately prior to extubation for sixty minutes while the infant was receiving either AC or SIMV and continued for another three minutes while the mode of ventilation was switched to ETT CPAP at the same PEEP setting. An additional sixty to ninety minutes of data collection took place twelve to twenty-four hours post-extubation.

RV data was collected using respiratory inductive plethysmography (RIP) with the Respitrace QDC system®. This system generates respiratory waveforms using two transducers called respibands. One respiband was placed around the infant’s chest at the level of the nipple
line. The other respiband was placed around the infant’s abdomen, half a centimeter above the umbilicus. The respibands are designed to measure the rib cage and abdominal components of respiration as well as the sum of these two signals. These bands were also connected to the PowerLab® data acquisition system, allowing real-time recordings directly downloaded to a research laptop at the patient’s bedside (Figure 4.1).

Figure 4.1 A snapshot demonstrating three channels of data being collected from each infant in real time. Each channel represents the following: 1) the rib cage component of respiration, 2) the abdominal component of respiration and 3) the sum of rib cage and abdominal components of respiration.

Additional clinical outcomes collected in each infant were identical to those described in section 3.2.

Data Analysis

RV was calculated from the RIP sum signal recorded in each infant during ETT CPAP and twelve to twenty-four hours post-extubation. The maximum number of consecutive breaths (minimum of 100) free of movement artifacts was manually selected from each of these data collection periods. During AC/SIMV, the infant’s spontaneous respiratory efforts cannot be distinguished from respiratory efforts influenced by the peak pressures generated from the mechanical ventilator. This can affect both timing and volume measurements of specific respiratory parameters. Therefore, RV was not assessed during this mode of ventilation prior to extubation. Analysis of heart rate data collected simultaneously during AC/SIMV was described in chapter 3.
A peak analysis (LabChart® software) was utilized to determine the following respiratory variables from each segment selected for analysis on a breath-to-breath basis: \(T_I\), \(T_E\), Height and Height-to-Height, from which \(T_I/T_{TOT}\) and \(\text{Height}/T_1\) were calculated. The baseline of each breath was defined by the software as the average signal level in a flat region before the start of each peak. The height of each breath was defined by the software as the signal level at the peak minus the baseline. The start of each breath was defined by the software as five percent of the height away from baseline. Applying these basic definitions, \(T_I\) was calculated as the time interval between the start and peak of each breath. \(T_{TOT}\) was calculated by subtracting the start time of one breath from the start time of the previous breath. \(T_E\) was calculated by subtracting \(T_I\) from \(T_{TOT}\). Height-to-height was calculated as the time interval from the peak of one breath to the peak of the following breath.

\[\text{RV of } T_I, T_E, \text{Height, Height-to-Height, } T_I/T_{TOT} \text{ and } \text{Height}/T_1\] was quantified using the time domain analysis previously described in section 2.2.

**Statistical Analysis**

Continuous variables are expressed as mean ± SD or median (interquartile range) and categorical variables as counts and percentages. The Fisher's exact test was used for categorical variables and the student t-test for continuous variables to compare outcomes between infants that were successfully extubated or that failed extubation. A \(p\) value < 0.05 was considered statistically significant.

The ability of the VI of each respiratory variable to accurately discriminate between successful and failed extubation was assessed using ROC curves. The first inflection point of each curve was identified as a cut-off to discriminate success and failure of extubation for the VI of each respiratory variable. Standard formulae were used to calculate sensitivity, specificity, PPV and NPV for the VI of each respiratory variable prior to extubation.

**4.3 Results**

**Study Enrollment**

Overall study enrollment has been previously described in section 3.3.
Respiratory Variability Prior to Extubation

Of the fifty-six infants enrolled, a subset of data from thirty-six infants was manually analyzed to evaluate differences in RV during ETT CPAP between infants successfully extubated and infants that failed extubation (Figure 4.2). Data from twenty infants was lost due to lack of quality. Of the thirty-six infants included in this analysis, thirty were successfully extubated while six (16.7%) required reintubation.

The main reason for extubation failure was multiple apneas and bradycardias (Table 4.1). The remaining infants that required reintubation failed extubation because of respiratory acidosis or a FiO₂ requirement greater than 0.5 to maintain SpO₂ above 88% (Table 4.1). The majority of infants that required reintubation failed extubation within the first twenty-four hours of disconnection from MV (66%; Table 4.2).

Population characteristics between success and failure patients were similar, including maternal, antenatal and infant variables (Table 4.3). However, infants that failed extubation were significantly more immature than infants successfully extubated (25.8 ± 1.5 weeks vs. 27.0 ± 1.5 weeks, p < 0.05; Table 4.3). Significant differences in ventilatory settings and blood gases prior to extubation were present between the groups. MAP (6.6 ± 1.6 cmH₂O vs. 5.7 ± 0.9 cmH₂O, p < 0.05; Table 4.4) and the ventilator rate (29 ± 14 breaths per minute vs. 21 ± 8 breaths per minute, p < 0.05; Table 4.4) were significantly increased, while set T₁ was significantly decreased in the failure group (0.37 ± 0.03 seconds vs. 0.40 ± 0.03 seconds, p < 0.05; Table 4.4). Furthermore, pH was significantly decreased while the pCO₂ level was significantly increased in infants that failed extubation (7.30 ± 0.05 vs. 7.35 ± 0.05 and 49.4 ± 10.6 mmHg vs. 39.7 ± 8.1 mmHg, respectively, p < 0.05; Table 4.4). Both infants successfully extubated and infants that required reintubation were managed similarly in the post-extubation period. Blood gases post-extubation were also comparable between groups, except for the pCO₂ level, which was significantly increased in the failure group (49.3 ± 8.3 mmHg vs. 41.6 ± 9.5 mmHg, p < 0.05; Table 4.5). Successfully extubated infants and those that failed extubation had similar final outcomes. However, the percentage of infants with ROP was significantly higher in the failure group (83% vs. 7.1%, p < 0.05; Table 4.6).
The time domain analysis of RV during ETT CPAP included a mean of 145 ± 73 breaths in the success group and a mean of 143 ± 33 breaths in the failure group. RV was similar between infants successfully extubated and infants requiring re-intubation, as quantified by the VI of each respiratory variable investigated: Height (100 ± 26.3 vs. 110 ± 30.6; Figure 4.3), $T_1$ (100 ± 29.9 vs. 97.7 ± 35.9; Figure 4.3), $T_E$ (100 ± 24.3 vs. 99.8 ± 35.3; Figure 4.3), Height-to-Height (100 ± 35.6 vs. 107.5 ± 48.8; Figure 4.3), Height/$T_1$ (100 ± 23.8 vs. 114.3 ± 32.6; Figure 4.3) and $T_f$/TOTAL (100 ± 28.6 vs. 99.6 ± 29.0; Figure 4.3).

As predictors of extubation readiness in extreme preterm infants, the VIs of each respiratory variable investigated generated low areas under the ROC curve (Table 4.7). Specificities and PPVs were high, however, sensitivities and NPVs were low (Table 4.7).

**Respiratory Variability Post-Extubation**

Of the fifty-six infants enrolled, a subset of data from forty-two infants was available for a secondary analysis of differences in RV twelve to twenty four hours post-extubation. Data from fourteen infants was lost due to lack of quality or because a majority of infants requiring re-intubation failed extubation within the first twenty-four hours of initial disconnection from MV, thus making it impossible to complete the post-extubation period of data collection. Of the forty-two infants included in this analysis, thirty-six were successfully extubated while six required re-intubation.

The time domain analysis of RV post-extubation included a mean of 232 ± 126 breaths in the success group and a mean of 295 ± 130 breaths in the failure group. The VI of Height/$T_1$ was significantly decreased in the failure group when compared to the value achieved in the success group (82.0 ± 20.3 vs. 100 ± 22.3, $p < 0.05$; Figure 4.4). For all other respiratory variables investigated, there were no significant differences between the VI of infants successfully extubated and infants requiring re-intubation (Figure 4.4).

**4.4 Limitations**

This investigation did have several limitations. Analysis was performed in a small sample size of infants which included only six failure patients. The small number of infants enrolled in this study could be attributed to a loss of data due to lack of quality, which was underestimated
in the sample size calculation. The short three minute duration of ETT CPAP limited the number of breaths available for analysis. A larger number of breaths analyzed allows for a more robust measurement of RV. Furthermore, the quantification of RV included the maximum number of consecutive breaths free of movement artifacts selected from data collected in each infant. This selection was made from any segment of the overall three minute ETT CPAP trial. Ideally, the first minute of this data collection period would have been excluded from analysis because it represents infant adaptation to a new ventilatory mode. However, given the short duration of the ETT CPAP phase, this was not possible. Lastly, the time domain analysis applied to assess RV was operator-dependant and time consuming. Ultimately, an objective and automated means of analyzing RV would be required if this tool were to be applied clinically as a means of assessing extubation readiness. Investigators from the biomedical engineering department at McGill University have developed an automated unsupervised respiratory event analysis (AUREA) programme which can quantify RV from data collected using RIP. This software is currently being applied to the data collected in this study as a preliminary investigation of differences in RV between infants successfully and unsuccessfully extubated.

4.5 Conclusions

There were no differences in respiratory variability between infants successfully extubated and those that required re-intubation during a three minute trial of endotracheal tube continuous positive airway pressure prior to extubation. Specific population differences and methodological issues limited this analysis. This prediction tool requires further evaluation in a larger, prospectively studied population with improved methodology.
Table 4.1 Analysis of respiratory variability prior to extubation: reasons for extubation failure

<table>
<thead>
<tr>
<th>Reason</th>
<th>Extubation Failure (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Apneas and Bradycardias</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Respiratory Acidosis</td>
<td>2 (33)</td>
</tr>
<tr>
<td>FiO₂ &gt; 0.5 in order to maintain SpO₂ &gt; 88%</td>
<td>1 (17)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%).
Legend: FiO₂ = Fraction of Inspired Oxygen and SpO₂ = Oxygen Saturation
Table 4.2 Analysis of respiratory variability prior to extubation: timing of extubation failure

<table>
<thead>
<tr>
<th>Extubation Failure (n = 6)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 hours</td>
<td>2 (33)</td>
</tr>
<tr>
<td>12-24 hours</td>
<td>2 (33)</td>
</tr>
<tr>
<td>24-48 hours</td>
<td>2 (33)</td>
</tr>
<tr>
<td>&gt; 48 hours</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%).
Table 4.3 Analysis of respiratory variability prior to extubation: population characteristics

<table>
<thead>
<tr>
<th>Maternal and Antenatal Variables</th>
<th>Success (n = 30)</th>
<th>Failure (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of Antenatal Steroids (1 or 2 doses)</td>
<td>25/28 (89)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>C-Section</td>
<td>20 (67)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Multiple Birth</td>
<td>11 (37)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Antibiotics during Labour</td>
<td>17/28 (61)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>8/28 (27)</td>
<td>2 (33)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infant Variables</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (g)</td>
<td>947 ± 184</td>
<td>805 ± 229</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>27.0 ± 1.5</td>
<td>25.8 ± 1.5*</td>
</tr>
<tr>
<td>Male</td>
<td>16 (53)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Apgar Scores (1 and 5 minutes)</td>
<td>5 (2-7), 7 (5-8)</td>
<td>4 (2-6), 7 (5-7)</td>
</tr>
<tr>
<td>Weight at Study (g)</td>
<td>1058 ± 330</td>
<td>874 ± 266</td>
</tr>
<tr>
<td>Age at Extubation (days)</td>
<td>3 (2-5)</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td>Post-conceptual Age at Extubation (weeks)</td>
<td>28.7 ± 2.9</td>
<td>27.5 ± 2.4</td>
</tr>
<tr>
<td>Surfactant Administration</td>
<td>28 (93)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Caffeine Administration prior to Extubation</td>
<td>25 (83)</td>
<td>5 (83)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD, median (interquartile range), n (%) or n/N (%).

*p < 0.05
Table 4.4 Analysis of respiratory variability prior to extubation: ventilatory settings and blood gases prior to extubation

<table>
<thead>
<tr>
<th></th>
<th>Success (n = 30)</th>
<th>Failure (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventilatory Settings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Inspiratory Pressure (cmH₂O)</td>
<td>13.0 ± 2.5</td>
<td>13.0 ± 1.7</td>
</tr>
<tr>
<td>Positive End-Expiratory Pressure (cmH₂O)</td>
<td>4.3 ± 0.5</td>
<td>4.7 ± 1.0</td>
</tr>
<tr>
<td>Mean Airway Pressure (cmH₂O)</td>
<td>5.7 ± 0.9</td>
<td>6.6 ± 1.6*</td>
</tr>
<tr>
<td>Fraction of Inspired Oxygen</td>
<td>0.25 ± 0.07</td>
<td>0.29 ± 0.07</td>
</tr>
<tr>
<td>Set Inspiratory Time (seconds)</td>
<td>0.40 ± 0.03</td>
<td>0.37 ± 0.03*</td>
</tr>
<tr>
<td>Ventilator Rate (breaths per minute)</td>
<td>21 ± 8</td>
<td>29 ± 14*</td>
</tr>
<tr>
<td>Oxygen Saturation (%)</td>
<td>95 ± 3</td>
<td>94 ± 2</td>
</tr>
<tr>
<td>PEEP level during ETT CPAP (cmH₂O)</td>
<td>4.5 ± 0.6</td>
<td>4.7 ± 1.0</td>
</tr>
<tr>
<td>FiO₂ during ETT CPAP</td>
<td>0.26 ± 0.08</td>
<td>0.27 ± 0.07</td>
</tr>
<tr>
<td>Oxygen Saturation during ETT CPAP (%)</td>
<td>94 ± 3</td>
<td>94 ± 3</td>
</tr>
<tr>
<td><strong>Blood Gases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH (n)</td>
<td>7.35 ± 0.05 (23)</td>
<td>7.30 ± 0.05 (5)*</td>
</tr>
<tr>
<td>pCO₂ (mmHg, n)</td>
<td>39.7 ± 8.1 (23)</td>
<td>49.4 ± 10.6 (5)*</td>
</tr>
<tr>
<td>pO₂ (mmHg, n)</td>
<td>48.9 ± 12.2 (23)</td>
<td>45.8 ± 8.2 (5)</td>
</tr>
<tr>
<td>HCO₃ (n)</td>
<td>21.4 ± 3.4 (23)</td>
<td>22.9 ± 3.1 (5)</td>
</tr>
<tr>
<td>Base Excess (n)</td>
<td>-3.7 ± 3.3(23)</td>
<td>-2.5 ± 2.6 (5)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

* p < 0.05

Legend: PEEP = Positive End-Expiratory Pressure, ETT CPAP = Endotracheal Tube Continuous Positive Airway Pressure and FiO₂ = Fraction of Inspired Oxygen
Table 4.5 Analysis of respiratory variability prior to extubation: post-extubation management and blood gases

<table>
<thead>
<tr>
<th></th>
<th>Success (n = 30)</th>
<th>Failure (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Invasive Ventilation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal Intermittent Positive Pressure Ventilation</td>
<td>10 (33)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Continuous Positive Airway Pressure</td>
<td>17 (57)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>High Flow Nasal Cannula</td>
<td>2 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Room Air</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**Blood Gases**

<table>
<thead>
<tr>
<th></th>
<th>Success (n = 30)</th>
<th>Failure (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (n)</td>
<td>7.3 ± 0.1 (23)</td>
<td>7.28 ± 0.1</td>
</tr>
<tr>
<td>pCO₂ (mmHg, n)</td>
<td>41.6 ± 9.5 (23)</td>
<td>49.3 ± 8.3*</td>
</tr>
<tr>
<td>pO₂ (mmHg, n)</td>
<td>44.0 ± 13.9 (23)</td>
<td>46.5 ± 17.7</td>
</tr>
<tr>
<td>HCO₃ (n)</td>
<td>20.6 ± 4.3 (23)</td>
<td>21.9 ± 2.7</td>
</tr>
<tr>
<td>Base Excess (n)</td>
<td>-4.9 ± 4.2 (23)</td>
<td>-3.2 ± 3.6</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD, or n (%).

*p < 0.05
Table 4.6 Analysis of respiratory variability prior to extubation: final outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Success (n = 30)</th>
<th>Failure (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraventricular Hemorrhage (Grades III or IV)</td>
<td>2 (6.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Patent Ductus Arteriosus – Medical Management</td>
<td>12 (40)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Patient Ductus Arteriosus Ligation</td>
<td>5 (17)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Bronchopulmonary Dysplasia (28 days)</td>
<td>14/29 (48)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>Mild Bronchopulmonary Dysplasia (36 weeks PCA)</td>
<td>4/29 (14)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Moderate or Severe Bronchopulmonary Dysplasia (36 weeks PCA)</td>
<td>5/29 (17)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Retinopathy of Prematurity</td>
<td>2/28 (7.1)</td>
<td>5 (83)*</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis</td>
<td>3/29 (10)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>Total Duration of Mechanical Ventilation</td>
<td>5 (3-25)</td>
<td>40 (19-55)</td>
</tr>
<tr>
<td>Use of Antibiotics</td>
<td>30 (100)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Antibiotic Use at Time of Extubation</td>
<td>17 (57)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Post-Natal Steroids (Dexamethasone or Hydrocortisone)</td>
<td>9 (30)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Post-Natal Steroids at Time of Extubation</td>
<td>6 (20)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (3.3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are expressed as median (interquartile range), n (%) or n/N (%).

*p < 0.05
Table 4.7 Predictive values for respiratory variability prior to extubation

<table>
<thead>
<tr>
<th>VI</th>
<th>ROC Curve Area</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>0.4</td>
<td>3</td>
<td>100</td>
<td>100</td>
<td>17</td>
</tr>
<tr>
<td>Inspiratory Time</td>
<td>0.57</td>
<td>3</td>
<td>100</td>
<td>100</td>
<td>17</td>
</tr>
<tr>
<td>Expiratory Time</td>
<td>0.56</td>
<td>30</td>
<td>83</td>
<td>90</td>
<td>19</td>
</tr>
<tr>
<td>Height-to-Height</td>
<td>0.46</td>
<td>10</td>
<td>100</td>
<td>100</td>
<td>18</td>
</tr>
<tr>
<td>Height/T₁</td>
<td>0.38</td>
<td>7</td>
<td>100</td>
<td>100</td>
<td>18</td>
</tr>
<tr>
<td>T₁/TTOT</td>
<td>0.51</td>
<td>3</td>
<td>100</td>
<td>100</td>
<td>17</td>
</tr>
</tbody>
</table>

Legend: VI = Variability Index, ROC = receiver operating characteristic, PPV = positive predictive value, NPV = negative predictive value, T₁ = Inspiratory Time, TTOT = Total Breath Time
Figure 4.2 Study enrollment: March 2010 to June 2011

n = 164
Infants BW ≤ 1250g and intubated

n = 56
Infants Enrolled in the study

Infants not enrolled in the study:
- n = 34 Refusal to Consent
- n = 18 Self-Extubation
- n = 23 Baby Died
- n = 33 Planned extubation without study

n = 20
Infant data excluded from analysis due to lack of quality

n = 30
Successful Extubation

n = 6
Extubation Failure

Legend: BW = Birth Weight
Figure 4.3 Variability index of respiratory variables during ETT CPAP prior to extubation

Legend: \( T_I \) = Inspiratory Time, \( T_E \) = Expiratory Time and \( T_{TOT} \) = Total Breath Time
Figure 4.4 Variability index of respiratory variables post-extubation

*\( p < 0.05 \)

Legend: \( T_I \) = Inspiratory Time, \( T_E \) = Expiratory Time and \( T_{TOT} \) = Total Breath Time
Chapter 5 - Heart Rate Variability and Respiratory Variability in Healthy Full-Term Newborns: Effect of Position and Feeding

Kaczmarek J and Sant’Anna GM

Abstract submitted to the Pediatric Academic Societies Annual Meeting (Boston, 2012).

5.1 Background

The evaluation of HRV and RV measurements in extreme preterm infants immediately prior to extubation has provided new information that can potentially enhance clinical decision making. However, the data generated from the studies described in this thesis are unique. Available data assessing HRV and RV in the preterm infants have applied varying methodologies and have studied different population groups. Therefore, comparison with a normative data-set using an equivalent methodology to improve our understanding and interpretation of these new results was not possible.

Identifying an appropriate normative population for comparison with extreme preterm infants is difficult. The challenge lies in defining a “healthy” preterm infant. Preterm infants constitute a category of neonates that span a wide range of gestational ages, anywhere from twenty-three to thirty-seven weeks. This group of infants faces an increased risk of various complications affecting multiple organ systems. Given the scope of ages and outcomes, the “healthy” preterm infant can be defined in many ways, on the basis of recovery from or absence of illness. To avoid the challenges that exist in comparing appropriate preterm infant populations, full-term newborns can be used as a reference group. Although full-term infants face the risk of clinical complications as well, defining a healthy population is much easier and criteria are more widely acceptable.

Previous studies have demonstrated that HRV measurements can be affected by sleep state, maturity, postnatal age and position, among other variables. Therefore, to maximize a comparison with extreme preterm infants, experimental conditions must be carefully evaluated. Measurements in preterm infants were performed immediately prior to extubation at a median age of two days, while feeds were being withheld and infants were lying supine. Therefore, data being compared in a healthy population must be derived from the early postnatal period, while
controlling for feeding and infant position. Furthermore, the importance of managing specific variables when interpreting measurements of HRV and RV in neonates can be evaluated in a stable population. In healthy full-term infants, conditions can be manipulated that must otherwise remain unchanged in preterm infants due to established protocols for the management of this more vulnerable population.

5.2 Objectives

The primary objective of this study was:

1. To evaluate heart rate variability and respiratory variability in healthy full-term newborns during the early postnatal period in order to obtain normative data using the same methodology as studies in extreme preterm infants.

The secondary objective of this study was:

2. To determine whether heart rate variability or respiratory variability measurements in this population are affected by infant position or feeding.

5.3 Methods

Study Population

Healthy, full-term newborns admitted to the neonatal nursery at the Royal Victoria Hospital (Montreal, Canada) were enrolled in this study. An infant was considered full-term if the GA at birth was between thirty-seven and forty-two weeks. If infants were small for GA (birth weight below the fifth percentile), had any major congenital anomaly, required resuscitation at time of delivery or had an Apgar score less than eight at five minutes of life, they were excluded from the study. Babies of mothers with pre-eclampsia, cardiometabolic co-morbidities or a history of maternal smoking were also excluded. The human research ethics committee of the institution approved the study and written informed consent was obtained from parents.

Data Collection
Data collection took place during each infant’s second day of life in four phases: 1) prone position pre-feeding, 2) supine position pre-feeding, 3) prone position post-feeding and 4) supine position post-feeding. Each data collection period lasted twenty minutes. The infant’s initial position was randomly assigned prior to each study. Post-feeding measurements took place within the first thirty minutes following breast or bottle feeding. Pre-feeding measurements took place a minimum of one hour after the infant had been fed.

HRV data was collected using electrocardiography as previously described in section 3.2. RV data was collected using respiratory inductive plethysmography as previously described in section 4.2.

All measurements took place while the infant was lying in their crib. The behavioural state of the infant was recorded throughout the study period according to Prechtl’s state classification system of the newborn\textsuperscript{51}. Behavioural state one (eyes closed, regular respiration, no movements) was labelled “quiet sleep”. State two (eyes closed, irregular respiration, small movements) was labelled “active sleep”. States three and four (eyes open, no or gross movements) were labelled “awake” and state five (vocalization) was labelled “crying”. A descriptive classification of behavioural state was chosen because of the short duration of data collection and to avoid disrupting the infant with the more invasive instrumentation required for sleep state classification based on electroencephalogram and electrooculogram.

The following clinical variables were also collected for each infant: 1) antenatal and maternal variables: mode of delivery, multiple birth, complications during pregnancy, use of medications during pregnancy and 2) infants variables: sex, BW, GA, Apgar scores (at one and five minutes), age at study and use of medications.

Data Analysis

HRV was calculated from the ECG tracings recorded in each infant by selecting a five minute steady, artifact-free segment from each data collection period: 1) prone position pre-feeding, 2) supine position pre-feeding, 3) prone position post-feeding and 4) supine position post-feeding. HRV was quantified in the frequency domain by power spectrum analysis (Labchart® software) as previously described in section 3.2.
RV was calculated from the RIP sum signal recorded in each infant. The maximum number of consecutive breaths (minimum of 100) free of movement artifacts was manually selected from each data collection period: 1) prone position pre-feeding, 2) supine position pre-feeding, 3) prone position post-feeding and 4) supine position post-feeding. A peak analysis (LabChart® software) was employed to determine the following respiratory variables from each segment selected for analysis on a breath-to-breath basis: T1, T_E, Height and Height-to-Height, from which T1/T_TOT and Height/T1 could be calculated. The formulae used to quantify these respiratory variables have been previously described in section 4.2. RV of T1, T_E, Height, Height-to-Height, T1/T_TOT and Height/T1 was quantified using a time domain analysis previously described in section 2.3.

Statistical Analysis

Continuous variables are expressed as mean ± SD or median (interquartile range) and categorical variables as counts and percentages. Intra-group comparisons by infant position (prone vs. supine) and feeding (pre-feeding vs. post-feeding) were made using a paired Student’s t-test. A p value < 0.05 was considered statistically significant.

Sample Size

A convenience sample of 18 infants was chosen for this study.

5.4 Results

Study Population

Eighteen healthy, full-term newborns with a mean BW of 3459 ± 485 g and GA of 39.1 ± 0.9 weeks were included in this study. The majority of these infants were delivered by Caesarean section (78%) and studied at a mean age of 26.6 ± 6.2 hours of life. Population characteristics are summarized in Table 5.1.

I. Heart Rate Variability

a. Normative Data: pre-feeding in the supine position
Mean HRV values measured pre-feeding in the supine position in twelve healthy, full-term newborns are summarized in Table 5.2. Data from six infants was lost due to lack of quality.

b. Positional Effect Pre-feeding: supine vs. prone

Of the eighteen infants enrolled, a subset of data from eleven infants was analyzed to evaluate differences in HRV pre-feeding between the supine and prone positions. Data from seven infants was lost due to lack of quality.

HRV prior to feeding was significantly decreased when infants lay in the prone position when compared to the supine position, as quantified by the LF and HF components of the power spectrum analysis (40.4 ± 35.4 ms$^2$ vs. 99.9 ± 79.6 ms$^2$, 9.5 ± 8.4 ms$^2$ vs. 17.1 ± 12.9 ms$^2$, respectively, $p < 0.05$; Figure 5.1). TP, VLF and the LF/HF ratio were not significantly different between positions prior to feeding (Figure 5.1).

c. Positional Effect Post-feeding: supine vs. prone

Of the eighteen infants enrolled, another subset of data from eleven infants was analyzed to evaluate differences in HRV post-feeding between the supine and prone positions. Data from seven infants was also lost due to lack of quality.

There were no significant differences in HRV post-feeding when comparing the supine and prone positions, as quantified by all components of the power spectrum analysis: TP (392.0 ± 344.3 ms$^2$ vs. 214.1 ± 216.7 ms$^2$; Figure 5.2), VLF (299.2 ± 310.1 ms$^2$ vs. 137.3 ± 173.5 ms$^2$; Figure 5.2), LF (70.9 ± 42.1 ms$^2$ vs. 54.1 ± 60.2 ms$^2$; Figure 5.2) and HF (12.2 ± 7.5 ms$^2$ vs. 13.8 ± 12.0 ms$^2$; Figure 5.2). The LF/HF ratio was also similar between infants pre-feeding lying either supine or prone (6.6 ± 5.8 vs. 4.9 ± 3.5; Figure 5.2).

d. Feeding Effect Supine: pre-feeding vs. post-feeding

Of the eighteen infants enrolled, a subset of data from ten infants was analyzed to evaluate differences in HRV in the supine position pre-feeding and post-feeding. Data from eight infants was lost due to lack of quality.
There were no significant differences in HRV in the supine position when comparing the pre-feeding and post-feeding time periods, as quantified by all components of the power spectrum analysis: TP (487.4 ± 491.6 ms² vs. 405.3 ± 402.8 ms²; Figure 5.3), VLF (355.3 ± 444.2 ms² vs. 311.6 ± 365.5 ms²; Figure 5.3), LF (104.8 ± 82.1 ms² vs. 72.4 ± 44.6 ms²; Figure 5.3) and HF (18.2 ± 13.1 ms² vs. 11.6 ± 5.9 ms²; Figure 5.3). The LF/HF ratio was also similar between infants pre-feeding and post-feeding while lying in the supine position (5.8 ± 3.3 vs. 6.7 ± 6.0; Figure 5.3).

e. Feeding Effect Prone: pre-feeding vs. post-feeding

Of the eighteen infants enrolled, another subset of data from fourteen infants was analyzed to evaluate differences in HRV in the prone position pre-feeding and post-feeding. Data from four infants was also lost due to lack of quality.

There were no significant differences in HRV in the prone position when comparing pre-feeding and post-feeding time periods, as quantified by all components of the power spectrum analysis: TP (238.2 ± 262.1 ms² vs. 202.8 ± 193.3 ms²; Figure 5.4), VLF (162.5 ± 236.5 ms² vs. 130.4 ± 154.9 ms²; Figure 5.4), LF (52.2 ± 44.1 ms² vs. 51.9 ± 53.7 ms²; Figure 5.4) and HF (10.1 ± 8.1 ms² vs. 12.0 ± 11.1 ms²; Figure 5.4). The LF/HF ratio was also similar between infants pre-feeding and post-feeding while lying in the prone position (5.7 ± 4.1 vs. 5.6 ± 3.6; Figure 5.4).

II. Respiratory Variability

a. Positional Effect Pre-feeding: supine vs. prone

Of the eighteen infants enrolled, a subset of data from fifteen infants was analyzed to evaluate differences in RV pre-feeding between the supine and prone positions. Data from three infants was lost due to lack of quality.

The time domain analysis of RV pre-feeding included a mean of 166 ± 80 breaths in the supine position and a mean of 178 ± 52 breaths in the prone position. The VI of Height-to-Height and T/TTOT were significantly decreased in the prone position when compared to the supine position (73.7 ± 30.5 vs. 100 ± 43.1 and 80.9 ± 30.5 vs. 100 ± 28.7, respectively, p < 0.05; Figure...
5.5). For all other respiratory variables investigated, there were no significant differences between VIs when comparing supine and prone positions (Figure 5.5).

b. Positional Effect Post-feeding: supine vs. prone

Of the eighteen infants enrolled, another subset of data from fifteen infants was analyzed to evaluate differences in RV post-feeding between the supine and prone positions. Data from three infants was lost due to lack of quality.

The time domain analysis of RV post-feeding included a mean of 173 ± 46 breaths in the supine position and a mean of 199 ± 67 breaths in the prone position. The VIs of all respiratory variables investigated, except Height-to-Height, were significantly decreased in the prone position when compared to the supine position: Height (81.9 ± 24.3 vs. 100 ± 30.5, p < 0.05; Figure 5.6), T₁ (82.3 ± 24.2 vs. 100 ± 32.3, p < 0.05; Figure 5.6), Tₑ (83.4 ± 23.7 vs. 100 ± 24.3, p < 0.01; Figure 5.6), Height/T₁ (83.9 ± 30.4 vs. 100 ± 38.9, p < 0.01; Figure 5.6) and Tₑ/TₑTOT (83.0 ± 26.5 vs. 100 ± 26.2, p < 0.01; Figure 5.6).

c. Feeding Effect Supine: pre-feeding vs. post-feeding

Of the eighteen infants enrolled, a subset of data from fourteen infants was analyzed to evaluate differences in RV in the supine position pre-feeding and post-feeding. Data from four infants was lost due to lack of quality.

The time domain analysis of RV in the supine position included a mean of 169 ± 82 breaths in the pre-feeding period and a mean of 172 ± 48 breaths in the post-feeding period. RV was similar between pre-feeding and post-feeding periods, as quantified by the VI of each respiratory variable investigated: Height (100 ± 39.0 vs. 121.2 ± 40.7; Figure 5.7), T₁ (100 ± 31.4 vs. 110 ± 37.6; Figure 5.7), Tₑ (100 ± 34.0 vs. 109.2 ± 28.2; Figure 5.7), Height-to-Height (100 ± 40.3 vs. 100.9 ± 41.2; Figure 5.7), Height/T₁ (100 ± 34.8 vs. 114.7 ± 37.6; Figure 5.7) and Tₑ/TₑTOT (100 ± 26.9 vs. 104.6 ± 28.7; Figure 5.7).

d. Feeding Effect Prone: pre-feeding vs. post-feeding

Data from all eighteen infants enrolled was evaluated to assess differences in RV in the prone position pre-feeding and post-feeding, which included a mean of 170 ± 52 breaths
analyzed in the pre-feeding period and a mean of 194 ± 71 breaths analyzed in the post-feeding period. RV was similar between pre-feeding and post-feeding periods, as quantified by the VI of each respiratory variable investigated: Height (100 ± 53.0 vs. 108.9 ± 40.0; Figure 5.8), T₁ (100 ± 44.1 vs. 101.2 ± 40.2; Figure 5.8), Tₑ (100 ± 43.0 vs. 102.7 ± 36.6; Figure 5.8), Height-to-Height (100 ± 46.5 vs. 109.8 ± 49.4; Figure 5.8), Height/T₁ (100 ± 44.6 vs. 94.7 ± 34.0; Figure 5.8) and T₁/T₉OT (100 ± 44.4 vs. 99.1 ± 34.7; Figure 5.8).

5.5 Limitations

The primary limitation of this analysis was loss of data due to lack of quality, which could not have been anticipated while data collection was taking place. The evaluation of HRV and RV in full-term infants did not include data from all eighteen infants originally enrolled, including the assessment of positional and feeding effects on these measurements.

5.6 Conclusions

HRV and RV were evaluated during the early postnatal period in healthy, full-term newborns. A normative data-set describing HRV in a healthy population of full-term infants prior to feeding in the supine position was defined. Measurements of both HRV and RV were affected by infant position, with reduced variability described while lying prone. It is important to control for infant position when assessing HRV or RV in neonates during early life. Measurements of both HRV and RV were not affected by feeding. Controlling for this variable may not be necessary in the early postnatal period.
Table 5.1 Healthy full-term newborns: population characteristics

<table>
<thead>
<tr>
<th>Maternal and Antenatal Variables</th>
<th>n  = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Section</td>
<td>14 (78)</td>
</tr>
<tr>
<td>Multiple Birth</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Gravida</td>
<td>3 (2-3)</td>
</tr>
<tr>
<td>Para</td>
<td>1 (1-2)</td>
</tr>
<tr>
<td>Abortus</td>
<td>0 (0-1)</td>
</tr>
</tbody>
</table>

**Infant Variables**

<table>
<thead>
<tr>
<th>Birth Weight (g)</th>
<th>3459 ± 485</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age (weeks)</td>
<td>39.1 ± 0.9</td>
</tr>
<tr>
<td>Male</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Apgar Score at 1 minute</td>
<td>9 (8-9)</td>
</tr>
<tr>
<td>Apgar Score at 5 minutes</td>
<td>9 (9-9)</td>
</tr>
<tr>
<td>Age at Beginning of Study (hours)</td>
<td>26.6 ± 6.2</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD, median (interquartile range), n (%).
Table 5.2 Spectral components of heart rate variability in healthy, full-term newborns measured pre-feeding in the supine position

<table>
<thead>
<tr>
<th>Healthy Full-Term Newborns (n = 12)</th>
<th>TP (ms²)</th>
<th>VLF (ms²)</th>
<th>LF (ms²)</th>
<th>HF (ms²)</th>
<th>LF/HF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>420.6 ± 472.2</td>
<td>305.1 ± 419.0</td>
<td>91.7 ± 81.0</td>
<td>15.8 ± 13.1</td>
<td>5.7 ± 3.3</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD.
Legend: TP = Total Power, VLF = Very Low Frequency, LF = Low Frequency and HF = High Frequency
Figure 5.1 Spectral components of heart rate variability: positional effect pre-feeding

*\(p < 0.05\)

Legend: LF = Low Frequency, HF = High Frequency
Figure 5.2 Spectral components of heart rate variability: positional effect post-feeding

Legend: LF = Low Frequency, HF = High Frequency
Figure 5.3 Spectral components of heart rate variability: feeding effect in the supine position

Legend: LF = Low Frequency, HF = High Frequency
Figure 5.4 Spectral components of heart rate variability: feeding effect in the prone position

Legend: LF = Low Frequency, HF = High Frequency
Figure 5.5 Variability index of respiratory variables: positional effect pre-feeding

Legend: $T_I =$ Inspiratory Time, $T_E =$ Expiratory Time and $T_{TOT} =$ Total Breath Time

*p < 0.05
Figure 5.6 Variability index of respiratory variables: positional effect post-feeding

* indicates p < 0.05

Legend: 
- $T_I$ = Inspiratory Time
- $T_E$ = Expiratory Time
- $T_{TOT}$ = Total Breath Time
Figure 5.7 Variability index of respiratory variables: feeding effect in the supine position

Legend: $T_I$ = Inspiratory Time, $T_E$ = Expiratory Time and $T_{TOT}$ = Total Breath Time
Figure 5.8 Variability index of respiratory variables: feeding effect in the prone position

Legend: $T_I$ = Inspiratory Time, $T_E$ = Expiratory Time and $T_{TOT}$ = Total Breath Time
Chapter 6: Discussion

Determining extubation readiness is a difficult but necessary aspect of respiratory management of extreme preterm infants. The ability to identify when an infant can be extubated with the highest chance of success is important when considering the increased morbidity and mortality associated with both prolonged MV and re-intubation. Clinical decision making alone results in a 20-40% rate of extubation failure. Strategies developed to reduce extubation failure rates or predict successful extubation investigated so far have shown limited success. New objective methods that can accurately determine extubation readiness in extreme preterm infants are necessary, can enhance clinical decision making and may improve overall outcomes in this fragile population.

6.1 Heart Rate Variability and Extubation Readiness in Extreme Preterm Infants

The prospective, observational study presented in chapter three was the first to assess HRV prior to extubation in extreme preterm infants and quantify differences between infants successfully extubated and infants requiring re-intubation.

The population of neonates studied was highly representative of preterm infants who most often require MV at birth and who face the highest risk of re-intubation. The extubation failure rate of 23.4% was similar to previously reported rates in the literature. Almost all infants received caffeine prior to extubation, a treatment commonly used to facilitate disconnection from MV in extremely preterm infants. Caffeine does affect cardiac rhythms but the specific effect on HRV is still unknown. Only one small observational study has measured the response of HRV to caffeine dosing in premature infants twenty-four to thirty-six weeks of gestation. A significant increase in HRV immediately following caffeine administration was reported. Given that eighty to ninety percent of the infants enrolled in this prospective study, both successfully and unsuccessfully extubated, were administered caffeine prior to extubation, it is highly unlikely that this variable could account for the significant differences in HRV outlined between groups. All antenatal, maternal and infant characteristics were similar between infants that would go on to be successfully extubated and infants that would require re-intubation. Prior to extubation, no differences in ventilatory settings or blood gases were present between groups. The significant decrease in set inspiratory time prior to extubation in infants requiring re-
intubation was not clinically significant and would not have influenced the outcome of extubation. Post-extubation management was similar between groups and the significantly higher pCO₂ level measured in the failure group twelve to twenty-four hours post-extubation was expected, indicating imminent respiratory failure in a group of infants that would eventually meet re-intubation criteria. The higher incidence of ROP in infants requiring re-intubation may point towards an increased risk of adverse outcomes associated with extubation failure. This study was not powered to assess long-term outcomes associated with re-intubation in extreme preterm infants; however, this finding certainly suggests that the outcome of extubation failure should be avoided.

In two groups of extreme preterm infants that were otherwise clinically identical immediately prior to extubation, a significantly reduced HRV was demonstrated during AC/SIMV in infants that failed extubation. This finding corresponds with results from the adult literature. A prospective evaluation of mechanically ventilated intensive care unit adult patients recovering from respiratory failure revealed a significantly reduced HRV during weaning in patients that failed a spontaneous breathing trial or required re-intubation⁴².

HRV has been measured in preterm infants. However, the majority of reports have evaluated spontaneously breathing convalescent preterm infants nearing corrected full-term post-conceptual age or hospital discharge. Only a few studies have assessed HRV in intubated preterm infants at birth. Overall, these studies identify important conditions that can affect HRV, which include sleep state, position of the infant and maturation. Active sleep, the supine position and increasing postnatal age have all been associated with increased HRV⁵⁴-⁶³. In the present study, extreme preterm infants were evaluated in the supine position at a median age of two days after birth. Sleep or behavioural states were not recorded. In very immature infants, behavioural states are not completely developed and are not easily identifiable⁵⁴. Furthermore, data evaluating the influence of sleep state upon HRV measurements in extreme preterm infants under MV and during the early postnatal period is not available. Nonetheless, data chosen to quantify HRV were selected while infants were quiet and stable, as stationary signals were required for appropriate analysis. Having controlled for important experimental conditions, differences in HRV between infants successfully and unsuccessfully extubated could be attributed to extubation readiness.
A particular mechanism of action explaining the differences in HRV between infants successfully and unsuccessfully extubated cannot be directly discerned from the current investigation. The normal control of heart rate is complex. Oscillations in both parasympathetic and sympathetic impulses arise in the brainstem and pass to the sinoatrial node. This cardioregulatory centre is also controlled by higher central nervous system centres, influenced by information obtained at central and peripheral levels. There is a high likelihood that multiple pathophysiological mechanisms, which may include an intrinsic immaturity of the autonomic nervous system, operate simultaneously to reduce beat-to-beat variability in heart rate in intubated infants who are unsuccessfully disconnected from MV but that otherwise meet all clinical criteria for extubation. HRV may be a biomarker for impending failure of extubation and could potentially be applied as an objective means to enhance clinical decision making.

In the immediate post-extubation period, HRV was not different between successfully extubated infants and infants that would go on to fail extubation. This time period was evaluated because any delay in re-intubating an infant who will ultimately fail extubation results in unnecessary deterioration before adequate ventilatory support is restored and can potentially contribute to increased morbidity. This has been illustrated in the adult literature. A lower incidence of pneumonia was documented in patients immediately re-intubated compared to patients with delayed re-intubation. Delayed time to re-intubation has also been associated with increased mortality in patients with extubation failure. Based on our evaluation of HRV in extreme preterm infants before and after extubation, differences were only demonstrated between success and failure groups prior to extubation.

Interestingly, HRV measured in successfully extubated infants was similar when comparing pre-extubation and post-extubation periods of data collection. However, HRV increased in infant that failed extubation in the post-extubation phase when compared to measurements done prior to extubation. Evidently, the failure group measured post-extubation did not include those infants that were re-intubated within twenty-four hours of initial disconnection from MV. Whether a similar increase in HRV occurred in infants that failed earliest is unknown.

This study also assessed the predictive value of HRV for extubation readiness in the extreme preterm infant population as a secondary objective. As a predictor of successful
extubation, all spectral components of HRV produced perfect specificities and PPVs but much lower sensitivities and NPVs. Any infant meeting the pre-determined threshold of HRV for any individual spectral component evaluated could be extubated with absolute certainty of a successful outcome. However, the outcome of extubation for any infant with a HRV value below the pre-determined threshold would be uncertain. The large standard deviations in HRV values reported most likely account for the level of uncertainty in outcome prediction generated from low sensitivities and NPVs. Such a wide range of variability among individual infants in both success and failure groups make it difficult to establish a threshold that can accurately categorize the extubation outcome of all infants.

Ultimately, extubation failure reflects a complex pathophysiological process. It is always possible that certain infant characteristics that are not apparent clinically and that are not picked up by HRV measurements may also influence failure, such as undiagnosed subglottic stenosis.

6.2 Respiratory Variability and Extubation Readiness in Extreme Preterm Infants

The retrospective analysis presented in chapter two was the first study to investigate variability of respiratory parameters of extreme preterm infants undergoing a trial of ETT CPAP prior to extubation. Calculations of RV evaluating both timing and volume measures of breathing could be performed during a SBT and add useful information.

The population of neonates studied was highly representative of preterm infants who most often require MV at birth and who face the highest risk of re-intubation. Infant characteristics and mean values for all respiratory parameters investigated immediately prior to extubation were similar between infants successfully and unsuccessfully extubated. Infants that required re-intubation had a significantly lower VI of mean inspiratory flow prior to extubation and overall, a combination of the SBT and VI of either T₁ or V_T were the most accurate predictors of successful extubation. These findings correspond with results from the adult literature. RV measurements have been evaluated prospectively in mechanically ventilated adults, with reduced breath-to-breath variability of both T₁ and V_T associated with an increased incidence of weaning failure^{44, 45}. Furthermore, during a sixty minute SBT, RV was significantly decreased in adult patients who failed extubation from MV^{47}. As may have been the case with the group of extreme preterm infants requiring re-intubation, this decrease in breath-to-breath
variability could have been due to an acute deterioration of the load-capacity balance of the respiratory system during the SBT or an unfavorable load-capacity balance before the SBT.\(^{47}\)

In preterm infants, very little data about RV is available. The effect of sleep state and positioning on RV was evaluated in a cohort of convalescent preterm infants studied at postmenstrual ages (PMA) between thirty-two and thirty-seven weeks. Reduced RV during quiet sleep was observed but no positioning effect was noted.\(^{64}\) Recently, the effect of weight and age on respiratory complexity has been investigated in preterm neonates at an earlier median PMA of twenty-nine weeks. The complexity of the \(V_T\) and RR time series increased with increasing age and weight.\(^{65}\) In the present study, extreme preterm infants were evaluated at similar weights and at a median age of four days after birth. Sleep or behavioural states were not recorded, given the short three minute length of ETT CPAP. In very immature infants, behavioural states are not completely developed and are not easily identifiable.\(^{54}\) Furthermore, data evaluating the influence of sleep state upon RV measurements in extreme preterm infants under MV and during the early postnatal period is not available. Nonetheless, data chosen to quantify RV were selected while infants were quiet and stable, as stationary signals were required for appropriate analysis. Having controlled for important experimental conditions, differences in RV between infants successfully and unsuccessfully extubated could be attributed to extubation readiness.

The findings presented in chapter two were then evaluated in a prospectively studied population of extreme preterm infants, as described in chapter four. For the most part, all clinical variables and aspects of patient management were similar between successfully and unsuccessfully extubated infants. However, key population differences were noted. The failure group was significantly more immature, was extubated from a higher level of ventilator support (higher MAPs and ventilator rates) and had inferior blood gases prior to extubation, representative of worse residual lung disease (as would be expected in more immature infants) when compared to the success group. These differences could have certainly influenced the outcome of extubation and therefore make it difficult to interpret measurements of RV quantified in both success and failure groups as exclusively attributable to extubation readiness. The higher incidence of ROP in infants requiring re-intubation may point towards an increased risk of
adverse outcomes associated with extubation failure but may also simply reflect the higher level of immaturity in the failure group.

Each study evaluating RV applied a different methodology to measure respiratory parameters. A hot wire anemometer was used for the retrospective analysis while RIP was used for the prospective evaluation. RIP was chosen for the prospective study for several reasons: 1) respiband placement is less invasive than positioning an anemometer proximal to the endotracheal tube which adds to the overall dead space of the ventilatory circuit, 2) respiratory measurements are unaffected by endotracheal tube leak which occurs frequently in preterm neonates ventilated with uncuffed tubes and 3) this methodology provides specific information about the rib cage and abdominal components of breathing, movement artifacts, distortion and asynchrony which cannot be obtained using the hot wire anemometer. Despite these important advantages, uncalibrated RIP data can only provide volume measurements of breathing in arbitrary units.

Results of the prospective evaluation of RV in extreme preterm infants yielded no significant differences in the VI of any respiratory parameter investigated when comparing infant successfully and unsuccessfully extubated. Given the lack of difference between outcome groups, each VI was unable to accurately predict successful extubation, as reflected by areas under the ROC curve less than 0.5.

In the immediate post-extubation period, the VI of Height/ T1 was significantly decreased in the group of infants that would end up requiring re-intubation. The advantage of assessing impending re-intubation once extubation has already occurred was explained in section 6.1. The result of this secondary study objective requires further investigation.

The prospective findings from chapter four did not replicate those from the initial retrospective analysis of chapter two. However, important population differences described above and several methodological limitations described in section 4.4, limit the validity of this prospective study. Overall, RV warrants further investigation as a potential predictor of successfully extubation in extreme preterm infants. This can easily be evaluated in a larger, prospectively studied population with improved methodology, given the developed expertise in
techniques of data collection in this fragile population and new prospects for automated, operator-independent analysis.

6.3 Heart Rate Variability and Respiratory Variability in Healthy Full-Term Newborns

This thesis provides a first evaluation of HRV and RV in extreme preterm infants immediately prior to extubation. To improve our understanding and interpretation of these unique results, comparison with a similarly derived normative data set applying matching experimental conditions was necessary. By means of a prospective observational study, HRV and RV were evaluated during the early postnatal period in healthy, full-term newborns.

Normative values of HRV in term infants lying supine prior to feeding during the second day of life were generated. The supine position, pre-feeding time period and second day of life as the age of study were chosen because measurements of HRV performed in extreme preterm infants were completed under similar experimental conditions and at a median postnatal age of two days. HRV has been previously quantified in healthy full-term newborns in the frequency domain\textsuperscript{60, 66-77}. These reports are extremely heterogeneous. Infants were studied at diverse postnatal ages, from the first day of life up to two years of age. Varying lengths of heart rate data were chosen for analysis of HRV and frequency bands used to differentiate spectral components of HRV were not defined consistently between studies. Furthermore, measurements of HRV were reported in many different units while sleep state classifications were based on assorted criteria. Altogether, the immense variation among previous studies makes it extremely difficult to draw comparisons with our results in extreme preterm infants. Therefore, having generated a completely new data set describing HRV in healthy full-term newborns was justified and necessary.

New prospectively collected data revealed increased values of HRV in healthy full-term newborns when compared to extreme preterm infants prior to extubation. This finding was expected. Previous studies have demonstrated an increase in HRV with increasing postnatal weeks of life in preterm infants as they reach theoretical term age\textsuperscript{54, 59-63}. Furthermore, HRV is influenced by artificial ventilation. In intubated preterm infants, a higher ventilation rate was correlated with a significant decrease in the HF component of HRV\textsuperscript{78}. In another prospective cohort of VLBW infants followed from twenty-three to thirty-eight weeks PMA, the LF
component of HRV was significantly reduced in infants that were intubated\textsuperscript{64}. Taken together, maturational and ventilatory effects explain and support the higher values of HRV described in healthy full-term newborns when compared to intubated extreme preterm infants.

Position of the infant was found to affect HRV prior to feeding. Significantly reduced HRV was measured in the prone position when compared to the supine position. This finding is consistent with previous reports similarly conducted during the early postnatal period in full-term infants\textsuperscript{56, 79, 80}. Both sympathetic and parasympathetic activities of the autonomic nervous system are affected by a postural change to the prone position, with documented increases in baseline heart rate and a decreased heart rate response to arousal\textsuperscript{78}. Given that HRV measurements provide an overall assessment of autonomic nervous system activity, differences in HRV between the supine and prone positions would be expected.

Measurements of HRV in newborns during early life were not affected by feeding in either the supine or prone positions. Given the physiological changes that occur during feeding, including an increase in metabolic rate, parasympathetic withdrawal, elevated heart rate and reduction in blood pressure, changes in HRV accompanying feeding may be expected. Only one previous study has evaluated the effect of feeding on HRV in healthy full-term infants studied at twelve to ninety-six hours of age and demonstrated reduced HRV post-feeding\textsuperscript{81}. Infants were studied within the first ten minutes following feeding. In contrast, infants enrolled in the study described in chapter five were measured within thirty minutes of feeding. Periods of data chosen for analysis were most likely selected from the latter portions of this data collection period, given that infants needed to be placed back in their cribs after breast or bottle feeding and required several minutes to fall asleep. Whether the physiological changes associated with feeding that may affect HRV measurements have a lasting effect beyond the immediate post-feeding phase is uncertain. Furthermore, the time taken to establish a fixed feeding pattern is highly variable amongst newborns. Varying intake of feeds resulting from individually established feeding patterns amongst the infants enrolled in this study may also explain why a feeding effect on measurements of HRV was not seen in the early postnatal period.

The time domains analysis applied to evaluate RV in healthy full-term infants allows for a comparison between experimental conditions (supine \textit{vs.} prone position, pre-feeding \textit{vs.} post-feeding). Thus, values for healthy full-term newborns pre-feeding in the supine position were not
generated. Several studies have evaluated RV in full-term newborns, however, differences in the number of breaths analyzed and classifications of sleep state varied greatly\textsuperscript{64, 82-84}. Further quantification of RV in term newborns during the early postnatal period is warranted.

Significantly reduced RV was also measured in the prone position when compared to the supine position both prior to and after feeding. The prone position affects breathing by decreasing chest wall movement asynchrony and diaphragmatic work, increasing tidal volume and improving oxygenation\textsuperscript{85}. The stability of the respiratory system and improvements in ventilation generated by a prone posture may produce a more constant breathing pattern resulting from fewer inputs to respiratory controllers. Only one previous study has evaluated the influence of position on RV in healthy full-term infants and no positional effect was described\textsuperscript{63}. Differences between the results of this preceding investigation and those presented in chapter five may be attributable to the age range of infants studied, the respiratory variables evaluated or the methodologies applied to assess RV.

Measurements of RV in newborns during early life were not affected by feeding in either the supine or prone positions. The lack of effect may be attributed to reasons described above.

6.4 Overall Conclusions

Determining extubation readiness in preterm infants is important but difficult. This thesis provides a scientific review of the literature pertaining to this topic and the use of physiological variability measurements as overall markers of system well-being and weaning outcome in ventilated adult patients. Several studies were performed to assess differences in heart rate variability and respiratory variability prior to extubation between extreme preterm infants who fail or succeed a first extubation attempt. An additional study performed in healthy full-term newborns demonstrated the influence of infant position on HRV and RV measurements, which was appropriately controlled for when studying extreme preterm infants. A significant decrease in HRV prior to extubation was demonstrated in infants that required re-intubation. No differences in RV prior to extubation were present between success and failure groups. Both HRV and RV were evaluated as predictors of successful extubation but limitations discussed in each section prevent definite conclusions. Measurements of variability described in this thesis have never been investigated before in the extreme preterm infant population undergoing...
disconnection from mechanical ventilation. Both HRV and RV can function as biomarkers of extubation outcome and can easily be applied in the clinical setting to improve clinical decision making. The results described provide a solid basis for improved and refined investigations of both measurements as predictors of successful extubation in future.
References


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