Assessment of Extubation Readiness in Extremely Preterm Infants

Presented by

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Abstract

In the modern era of Neonatology, an increasingly smaller and more immature population of extremely preterm infants (born ≤ 28 weeks gestational age) is exposed to mechanical ventilation (MV). Given the adverse outcomes associated with MV, every effort is made to extubate these infants as early as possible. However, the scientific basis for determining extubation readiness is imprecise. Currently, the decision to extubate is primarily guided by the physician's clinical judgment, which is highly subjective and variable. As an adjunct to clinical judgment, studies have turned towards assessments of clinical and physiological parameters during a period of spontaneous breathing without mechanical inflations. Amongst those assessments, the spontaneous breathing trial (SBT) has increasingly been adopted in neonatal units worldwide despite limited evidence to guide its use. In a systematic review and meta-analysis, we found that predictor tests had limited accuracies in the assessment of extubation readiness when compared to clinical judgment alone. In the absence of accurate tools to assess extubation readiness, many infants fail their extubation attempt and require reintubation. Unfortunately, the exact occurrence of reintubation, the patterns by which infants require reintubation and the clinical implications of a failed extubation on respiratory outcomes are incompletely understood. Thus, the following thesis aimed to comprehensively decipher the complexities associated with the assessment of extubation readiness and reintubation in extremely preterm infants. We conducted a prospective, multicenter observational study aiming to develop an Automated Predictor of Extubation readiness in extremely preterm infants (APEX, Clinicaltrials.gov-NCT01909947). Infants requiring MV, with birth weights ≤ 1250g and undergoing their first planned extubation were included. Immediately prior to extubation, detailed clinical and cardiorespiratory data was acquired during 60-min on conventional MV and

5-min of spontaneous breathing on endotracheal continuous positive airway pressure (ET-CPAP). Clinical data pertaining to patient demographics, pre-extubation and reintubation characteristics, and final outcomes at discharge was also prospectively collected. A total of 266 infants were recruited in APEX. Using the cohort's clinical database, three sub-analyses were conducted for this thesis. First, we longitudinally described the patterns of reintubation in our cohort. Overall, 47% of infants were reintubated at some point during neonatal hospitalization. Reintubation rates significantly varied as a function of the reason for reintubation and post-extubation observation window used. Reintubations occurring within 7 days post-extubation were primarily related to respiratory causes, while those beyond 14 days were caused by non-respiratory-related reasons. Second, we explored the impact of time interval between extubation and reintubation on the outcome of death or bronchopulmonary dysplasia (BPD), an important respiratory morbidity in this population. Reintubation within any time interval after extubation was associated with significantly increased risk of death/BPD, independent of known confounders. Notably, reintubation within 48h from extubation conferred the greatest odds of death/BPD compared to any other observation window. Lastly, we attempted to understand the safety and value of SBTs in the assessment of extubation readiness during ET-CPAP. We found that 57% of infants developed signs of clinical instability during the 5-min ET-CPAP recording. After evaluating 41,602 different combinations of clinical events to define SBT pass/fail, all definitions had low accuracies in predicting extubation success compared with clinical judgment alone. All in all, the thesis provides a more structured understanding of the major issues surrounding assessment of extubation readiness and reintubation in extremely preterm infants. It also lays the groundwork for better determining which specific populations and interventions should be targeted in future work on this complex subject.

Résumé

Dans l'ère moderne de la néonatologie, une population de plus en plus petite et extrêmement immature de grands prématurés (nés ≤ 28 semaines d'âge gestationnel) est exposée à la ventilation mécanique (VM). Compte tenu des résultats défavorables associés à la VM, tout est mis en œuvre pour extuber ces nourrissons le plus tôt possible. Cependant, le fondement scientifique permettant de déterminer l'état de préparation à l'extubation est imprécis. Actuellement, la décision d'extubation est principalement guidée par le jugement clinique du médecin, qui est hautement subjectif et variable. En complément au jugement clinique, les études se sont tournées vers l'évaluation des paramètres cliniques et physiologiques au cours d'une période de respiration spontanée sans inflations mécaniques. Parmi ces évaluations, l'essai de respiration spontanée (ERS) est de plus en plus adopté dans les unités de néonatologie du monde entier, malgré le peu de données probantes permettant d'en guider son usage. Dans une revue systématique et méta-analyse, nous avons constaté que les tests de prédicteurs avaient une précision limitée dans l'évaluation de l'état de préparation à l'extubation comparé au jugement clinique. En l'absence d'outils précis permettant d'évaluer l'état de préparation à l'extubation, de nombreux nourrissons échouent dans leur tentative d'extubation et nécessitent une réintubation. Malheureusement, la survenue exacte de la réintubation, les causes pour lesquelles les nourrissons doivent être réintubés, et les implications cliniques d'une extubation non réussie sur les résultats respiratoires sont mal comprises. Ainsi, la thèse suivante visait à déchiffrer de manière complète les complexités associées à l'évaluation de l'aptitude à l'extubation et à la réintubation chez le grand prématuré. Nous avons mené une étude observationnelle multicentrique prospective visant à développer un prédicteur automatisé de l'état de préparation à l'extubation chez les grands prématurés (APEX, Clinicaltrials.gov-NCT01909947). Les

nourrissons nécessitant une VM, avec un poids de naissance ≤ 1250g et subissant leur première extubation planifiée ont été inclus. Immédiatement avant l'extubation, des données cliniques et cardiorespiratoires détaillées ont été acquises pendant 60 minutes sous VM conventionnelle et pendant 5 minutes de respiration spontanée sous pression positive continue endotrachéale (PPC-ET). Les données cliniques relatives aux données démographiques des patients, caractéristiques pré-extubation et à la réintubation, et aux résultats finaux à la sortie ont également été collectées de manière prospective. Au total, 266 nourrissons ont été recrutés dans APEX. À l'aide de la base de données clinique de la cohorte, trois sous-analyses ont été réalisées pour cette thèse. Premièrement, nous avons décrit de manière longitudinale les schémas de réintubation dans notre cohorte. Dans l'ensemble, 47% des nourrissons ont été réintubés à un moment donné au cours de l'hospitalisation néonatale. Les taux de réintubation variaient de manière significative en fonction de la raison de la réintubation et de la fenêtre d'observation post-extubation utilisée. Les réintubations survenant dans les 7 jours suivant l'extubation étaient principalement liées à des causes respiratoires, tandis que celles au-delà de 14 jours étaient autres que respiratoires. Deuxièmement, nous avons étudié l'impact de l'intervalle de temps entre l'extubation et la réintubation sur l'issue du décès ou de la dysplasie bronchopulmonaire (DBP), une morbidité respiratoire importante dans cette population. La réintubation dans n'importe quel intervalle de temps après l'extubation était associée à une augmentation significative du risque de décès/DBP, indépendamment des variables confondantes connues. Notamment, la réintubation dans les 48h suivant l'extubation conférait la plus grande probabilité de décès/DBP comparé à toute autre fenêtre d'observation. Enfin, nous avons tenté de comprendre l'innocuité et la valeur des ERS dans l'évaluation de l'état de préparation à l'extubation au cours d'une PPC-ET. Nous avons constaté que 57% des nourrissons avaient développé des signes d'instabilité clinique au cours de

l'enregistrement de 5 minutes de PPC-ET. Après avoir évalué 41 602 combinaisons d'événements cliniques pour définir le succès/échec du ERS, toutes les définitions n'avaient que peu de précision dans la prédiction du succès d'extubation comparé au jugement clinique. Au total, la thèse fournit une compréhension plus structurée des principaux problèmes entourant l'évaluation de la préparation à l'extubation et de la réintubation chez les nouveau-nés grands prématurés. Elle permet également de mieux identifier les populations et les interventions qui devraient être ciblées dans les travaux futurs sur ce sujet complexe.

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List of Abbreviations

AC – Assist control

APEX – Automated prediction of extubation readiness

BPD – Bronchopulmonary dysplasia

CPAP – Continuous positive airway pressure

ELBW – Extremely low birth weight

ET-CPAP – Endotracheal continuous positive airway pressure

FiO_2 – Fraction of inspired oxygen

HFOV – High frequency oscillatory ventilation

HFJV – High frequency jet ventilation

HFNC – High flow nasal cannula

MAP – Mean airway pressure

MV – Mechanical ventilation

NAVA – Neurally adjusted ventilatory assist

NICU – Neonatal intensive care unit

NIPPV – Nasal intermittent positive pressure ventilation

PCO_2 – Partial pressure of carbon dioxide

PEEP – Positive end-expiratory pressure

PIE – Pulmonary interstitial emphysema

PIP – Peak inflation pressure

PS – Pressure support

RACE – Repeated alveolar collapse and expansion

RCT – Randomized controlled trial

SBT – Spontaneous breathing trial

SIMV – Synchronized intermittent mandatory ventilation

VALI – Ventilator-associated lung injury

VAP – Ventilator-associated pneumonia

VLBW – Very low birth weight

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Next, it is important to highlight that the work presented in this thesis was part of a larger collaborative initiative entitled the 'Automated Prediction of Extubation Readiness' (APEX) project. The APEX project was a multidisciplinary and multi-institutional initiative composed of biomedical engineers, computer scientists and clinicians from five neonatal intensive care units in North America. I am extremely grateful to have been part of this team, from whom I learnt

tremendously. From the group of biomedical engineers, I would like to specially thank Lara Kanbar (the PhD student working with Dr. Kearney) for her exceptional support and collaboration. She was instrumental for the realization of the project and became a great friend along the way. From the computer scientists, I would like to thank Dr. Doina Precup as well as Charles Onu (Dr. Precup's PhD student) for all their support and for having introduced me to some of the principles of machine learning. As for the clinicians working on the APEX project, there are many individuals to whom I am very grateful. I am very thankful to have worked with Dr. Karen Brown, Anesthesiologist and co-investigator on the APEX project. Through our numerous interactions at the weekly APEX meetings, I learnt a great deal from Dr. Brown, especially with regards to the analysis of respiratory patterns of breathing. In addition, I am grateful for the hard work and dedication of Smita Rao, the APEX research assistant, who spent countless hours enrolling patients, acquiring data and reviewing charts. I am also extremely thankful to Samantha Latremouille (PhD student of Dr. Sant'Anna) for her tremendous help at the bedside (enrolling or studying patients) and for her astute intellectual contributions. I am also very appreciative of the help I received from two students from McGill University, Monica Bhuller and Isabel Janmey, who volunteered a lot of their time to assist with data acquisition and data collection. Finally, the realization of the APEX project became possible and successful thanks to the incredible work of all collaborators, namely at the Jewish General Hospital (Dr. Lajos Kovacs), at Hutzel Women's Hospital in Detroit (Dr. Sanjay Chawla, Bogdan Panaitescu, Meghan Dwaihy), and at Women & Infants Hospital of Rhode Island (Dr. Martin Keszler, Dr. Khushbu Shukla, Alyse Laliberte).

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and generosity of all the families who participated in the research project, in the name of advancing science. Thank you!

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Original Scholarship and Contributions to Knowledge

This manuscript-based thesis consists of five papers published in peer-reviewed journals for which I was the first author:

Manuscript 1: Shalish W**,** Latremouille S, Papenburg J, Sant'Anna GM. Predictors of extubation readiness in preterm infants: A systematic review and meta-analysis. *Archives of Diseases in Childhood: Fetal & Neonatal Edition* 2019 Jan;104(1)F89-F97.

Manuscript 2: Shalish W, Kanbar LJ, Rao S, Robles-Rubio CA, Kovacs L, Chawla S, Keszler M, Precup D, Brown K, Kearney RE, Sant'Anna GM. Prediction of Extubation readiness in extremely preterm infants by the automated analysis of cardiorespiratory behavior: study protocol. *BMC Pediatrics* 2017;17(1):167.

Manuscript 3: Shalish W, Kanbar L, Keszler M, Chawla S, Kovacs L, Rao S, Panaitescu BA, Laliberte A, Precup D, Brown K, Kearney RE, Sant'Anna GM. Patterns of reintubation in extremely preterm infants: A longitudinal cohort study. *Pediatric Research* 2018 May;83(5):969-975.

Manuscript 4: Shalish W, Kanbar L, Kovacs L, Chawla S, Keszler M, Rao S, Panaitescu BA, Laliberte A, Precup D, Brown K, Kearney RE, Sant'Anna GM. The impact of time interval between extubation and reintubation on death or bronchopulmonary dysplasia in extremely preterm infants. *Journal of Pediatrics* 2019 Feb;205:70-76.e2.

Manuscript 5: Shalish W, Kanbar L, Kovacs L, Chawla S, Keszler M, Rao S, Latremouille S, Precup D, Brown K, Kearney RE, Sant'Anna GM. Assessment of extubation readiness using spontaneous breathing trials in extremely preterm neoantes. *JAMA Pediatrics* 2019 Dec (Epub ahead of print).

All five manuscripts in this thesis represent original work and provided the following novel contributions to the science of assessment of extubation readiness in extremely preterm infants:

(1) We used an original approach (meta-analysis of diagnostic accuracy studies) to systematically and analytically evaluate the accuracy of available predictors of extubation readiness in preterm infants.

(2) To our knowledge, this was the largest multicenter study to prospectively collect detailed information about peri-extubation practices and reintubation in extremely preterm infants, and longitudinally follow them throughout neonatal hospitalization. This allowed us to have a more thorough understanding of the patterns of extubation and reintubation in a contemporary cohort of infants.

(3) To our knowledge, this was also the largest study to evaluate the diagnostic accuracy of spontaneous breathing trials for the assessment of extubation readiness in preterm infants. Moreover, using a programing approach (with Matlab), we were able to comprehensively evaluate the accuracy of over 40,000 spontaneous breathing trial pass/fail definitions in a computationally efficient manner.

(4) All in all, the thesis provides a more evidence-based framework for designing future studies aiming to assess extubation readiness in preterm infants, or aiming to evaluate interventions to prevent/reduce extubation failure in this population.

Contribution of Authors

Manuscript 1

Concept and design of study: Shalish, Sant'Anna.

Systematic review of studies and data extraction: Shalish, Latremouille, Sant'Anna.

Risk of bias assessment: Shalish, Latremouille.

Data analysis and interpretation: Shalish, Papenburg, Sant'Anna.

Manuscript draft: Shalish.

Critical revision of manuscript for important intellectual contribution: all authors.

Manuscript 2

This manuscript represents the published study protocol for the Automated Prediction of Extubation Readiness (APEX) study.

Principal investigators for APEX: Sant'Anna, Kearney.

Design and development of original study protocol: Kanbar, Robles-Rubio, Kovacs, Chawla, Brown, Precup, Kearney, Sant'Anna.

Site investigators and supervisors: Sant'Anna (McGill University Health Center), Kovacs (Jewish General Hospital), Chawla (Detroit Medical Center, Detroit, Michigan, USA), Keszler (Women and Infants Hospital, Providence, Rhode Island, USA).

Preparation of cardiorespiratory data acquisition template and standardized data collection form: Shalish, Kanbar.

Training of facilitators across all sites and in-service trainings: Shalish.

Development of the data anonymization, validation and quality control algorithms: Shalish, Kanbar, Kearney, Sant'Anna.

Manual scoring of the respiratory data: Brown.

Data analysis plan: Shalish, Kanbar, Robles-Rubio, Brown, Precup, Kearney, Sant'Anna.

Manuscript draft: Shalish.

Critical revision of manuscript and final approval: all authors.

Manuscripts 3 and 4

Concept and design of study: Shalish, Kanbar, Kearney, Sant'Anna.

Data acquisition: Shalish, Rao, Panaitescu, Laliberte.

Statistical analysis: Shalish

Supervision: Kearney, Sant'Anna.

Interpretation of the data: all authors.

Drafting of the manuscript: Shalish

Critical revision of the manuscript for important intellectual content: all authors.

Manuscript 5

Concept and design of study: Shalish, Kanbar, Kearney, Sant'Anna.

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Drafting of the manuscript: Shalish

Critical revision of the manuscript for important intellectual content: all authors.

Chapter 1 – Literature Review

1.1 Context

An estimated 15 million infants worldwide are born prematurely (gestational age < 37 weeks) each year, of which nearly 800,000 infants are extremely preterm (gestational age ≤ 28 weeks).[1] Over the decades, major advances in perinatal and neonatal care, especially in developed countries, have led to marked improvements in survival of extremely preterm infants.[2-4] However, this progress has also been accompanied by persistently high rates of survival with long-lasting medical and social disabilities in this population.[5] Infants born extremely preterm carry significantly greater risks of motor and neurosensory impairments, cognitive deficits, lower academic performance and overall poorer social adaptive skills during childhood compared to their term counterparts.[6-8] Furthermore, those infants are more likely to have lower educational qualifications, higher rates of unemployment, and increased risk of chronic illnesses as adults (e.g. hypertension, type 2 diabetes and renal, cardiovascular or cerebrovascular diseases).[9, 10] Therefore, more than ever, extreme prematurity accounts for a disproportionately large proportion of healthcare-related adverse outcomes, resources and costs in our societies.

Many of the long-term challenges faced by extremely preterm infants take their origins during the initial hospitalization in the neonatal intensive care unit (NICU). As a result of early separation from their natural in-utero environment and consequent immaturity of the organ systems, infants born extremely preterm are highly susceptible to developing serious complications in the NICU. Based on contemporary reports from the Canadian Neonatal Network (Canada) and Neonatal Research Network (USA), less than one-third of all infants born below 28 weeks gestation survive to NICU discharge without any major morbidity.[2, 11] The

presence of three of these morbidities, namely severe retinopathy of prematurity, severe brain injury, and chronic lung disease (also known as bronchopulmonary dysplasia, BPD) can predict with high accuracy the infants' likelihood of death or childhood disability by the age of 5 years.[12] BPD is by far the most commonly encountered morbidity in survivors, affecting 40-60% of infants born between 25 and 27 completed weeks' gestation and up to 70-100% of infants born between 22 and 24 completed weeks' gestation.[2] In addition to increasing the risk of neurodevelopmental impairment, BPD is associated with long-lasting risks of airflow obstruction and decreased lung function into childhood and adulthood.[13] Thus, targeting strategies to prevent or reduce the occurrence of major neonatal morbidities, especially BPD, can have substantial benefits on long-term outcomes of these patients.

In its simplest form, BPD is defined and classified based on the degree of oxygen supplementation and respiratory support needed at 36 weeks postmenstrual age. However, the pathogenesis and clinical definitions of BPD are complex and have been subject to multiple revisions over the years, due to the ever evolving epidemiological, pharmaceutical and technological realities of the NICU (Figure 1.1).[14] When originally described by Northway in 1967, BPD depicted a constellation of clinical, radiological and histological lung changes amongst infants with severe hyaline membrane disease who had received prolonged positive pressure ventilation and excessive oxygen supplementation.[15] These were more mature infants (mean gestational age 34 weeks), with surfactant-deficient lungs, who would have otherwise not survived without the assistance of the ventilator. At that time, BPD was characterized by various lung pathologies (atelectasis, emphysema, and fibrosis) that were thought to result from oxygen toxicity and ventilator-induced lung injury following the 'healing phase' of hyaline membrane disease. Since then, several advancements in neonatal care (including mainstream adoption of

antenatal steroids and surfactant, more gentle ventilation, more judicious oxygen use and improved nutrition) have virtually eliminated the BPD phenotype previously described by Northway. In its place, a newer form of BPD emerged amongst the increasingly surviving cohort of extremely preterm infants. In that newer phenotype, BPD is primarily characterized by arrested development and impaired growth of the alveoli and pulmonary vascular bed, due to preterm birth during the late canalicular (22-26 weeks) and early saccular (26-30 weeks) stages of lung development. The risk of BPD is multifactorial, increasing proportionately with the degree of prematurity but also exacerbated by various antenatal (intrauterine growth restriction, lack of antenatal steroids, chorioamnionitis) and postnatal factors (including mechanical ventilation, oxidative stress, infection and inflammation).[16]

Mechanical ventilation (MV) is well recognized to increase the risk of mortality or BPD. Nonetheless, it remains a vital component of the initial respiratory management of most extremely preterm infants today. In an attempt to limit the duration of MV, clinicians strive to transition these infants to some form of non-invasive respiratory support as early as possible. Unfortunately, this transition process (known as extubation) has proven challenging and surprisingly devoid of strong evidence to guide practices. Currently, the decision to extubate is primarily determined from interpretation of the infant's ventilatory requirements, gas exchange and overall clinical stability. But such clinical judgment is subjective, which often leads to variable practices and suboptimal decisions. That is, some infants may be exposed to unnecessary harm from MV due to delayed recognition of their extubation potential, while many others require reintubation (and resumption of MV) if prematurely disconnected from the ventilator. Thus, it would be ideal to identify an accurate and objective predictor of extubation readiness that minimizes the duration of MV while maximizing the chances of a successful

extubation, as a means of standardizing practices and improving outcomes. Although several predictors of extubation readiness have already been developed and adopted in clinical practice, their accuracies at predicting successful extubation have not been systematically evaluated. This is further complicated by the fact that no consensus exists in the literature as to what constitutes a clinically meaningful definition of extubation success or failure in this population. In fact, there is presently no longitudinal data describing the timing and causes for which extremely preterm infants are reintubated during the course of their NICU hospitalization. Furthermore, the clinical implications of failing an extubation attempt at different time points and for different reasons are incompletely understood. All these key gaps in knowledge hinder our ability to determine the optimal strategy for extubation of this vulnerable population.

The following thesis will comprehensively review the complexities surrounding the extubation process in extremely preterm infants, and attempt to decipher some of the current gaps in knowledge around this subject. A framework for the thesis and literature review is displayed in Figure 1.2. First, section 1.2 will present the prevalence and complications associated with MV use in extremely preterm infants. Section 1.3 will review the various elements that constitute the extubation process in clinical practice today, with a particular focus on the consequences of practice variability on patient outcomes. Section 1.4 will critically appraise the currently available definitions of extubation success, and then provide an overview of the existing markers and predictors of extubation readiness in extremely preterm infants. Lastly, section 1.5 will review the prevalence, causes and adverse events associated with extubation failure in extremely preterm infants. Altogether, this literature review will provide the basis for identifying gaps in knowledge and framing the main objectives of this thesis.

Figure 1.1 Pathogenesis of bronchopulmonary dysplasia

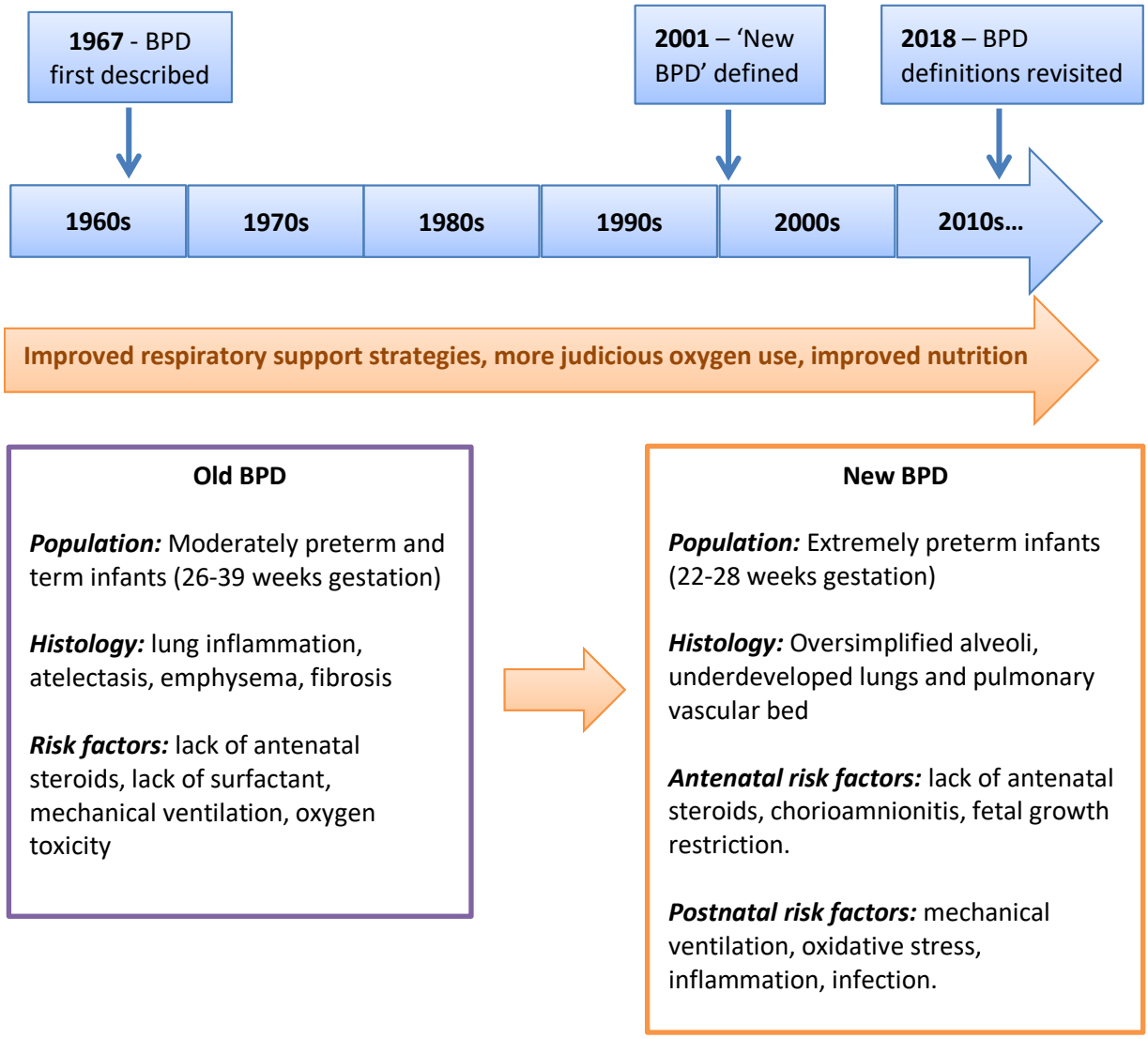
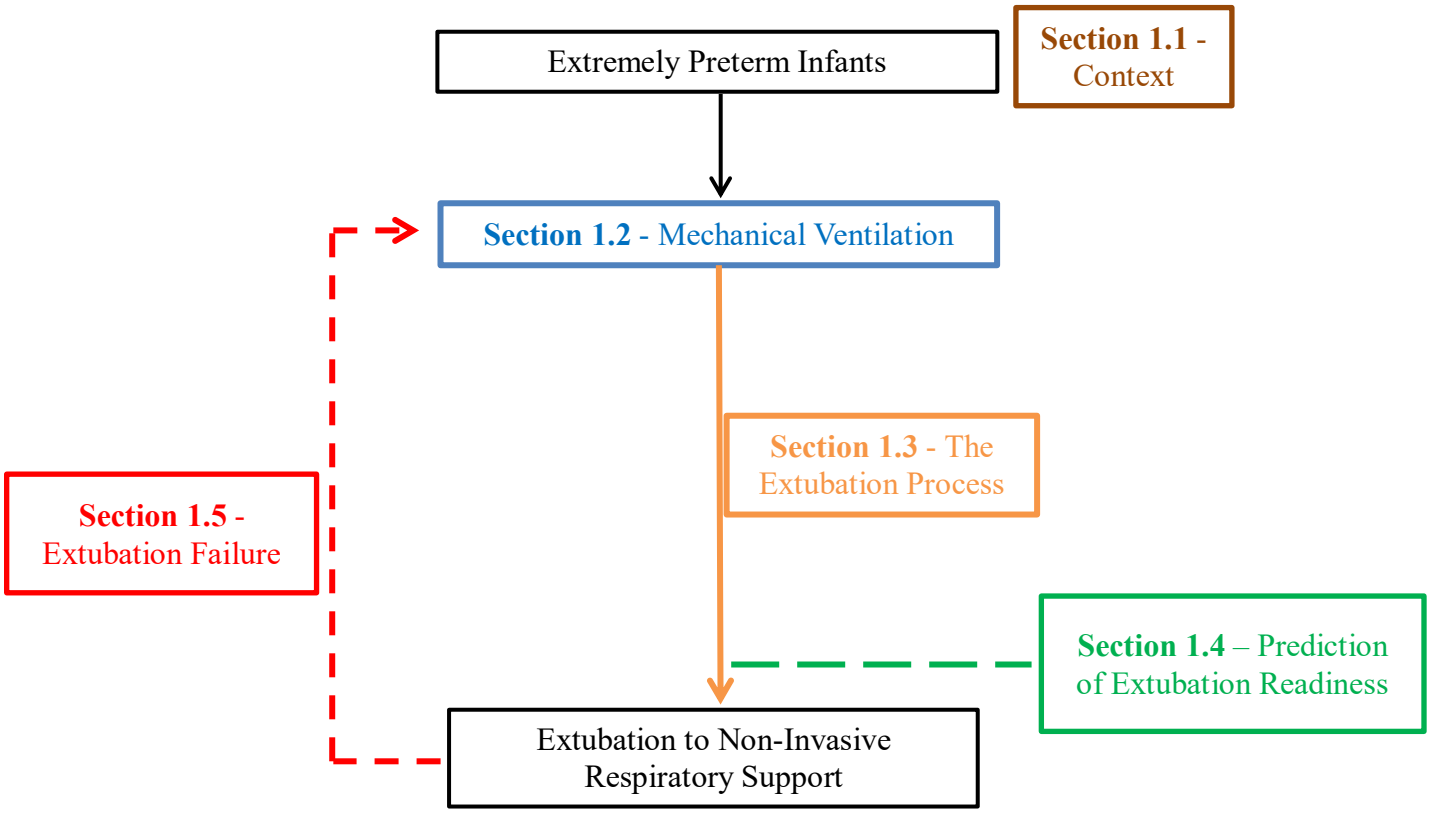


Figure 1.2 Framework for the thesis literature review



1.2 Mechanical Ventilation Use in Extremely Preterm Infants

1.2.1 Prevalence of Mechanical Ventilation Use

As a result of lung immaturity, weak respiratory drive and surfactant deficiency, the majority of extremely preterm infants require endotracheal intubation and MV shortly after birth. Based on the most recent Canadian Neonatal Network annual report (2017), 76% of infants ≤ 28 weeks' gestation required MV during hospitalization, and only 33% of infants had not received any MV in the first three days of life.[11] In another contemporary epidemiological study from the United States, 82% of extremely preterm infants born in 2012 received some type of MV during their hospital stay, and almost all infants below 25 weeks were mechanically ventilated within the first three days of life.[2] Similarly, in the most recent cohort study from Norway, more than 95% of infants born in 2013-2014 with gestational age ≤ 25 weeks' required MV.[17]

MV also appears necessary beyond the postnatal transition period amongst the smallest and most immature patients. Based on a recent cohort study from the United States evaluating more than 3000 extremely low birth weight (ELBW, birth weight ≤ 1000g) infants on MV, nearly 50% were ventilated for more than 3 cumulative weeks and 40% for more than 5 cumulative weeks.[18] In another equally large cohort study from South Korea, approximately 50%, 25% and 15% of very low birth weight (VLBW, birth weight ≤ 1250g) infants who required MV were ventilated for more than 1, 4 and 6 cumulative weeks, respectively.[19] Thus, a significant proportion of extremely preterm infants are exposed to prolonged periods of MV during the course of their hospitalization.

1.2.2 Complications Associated with Mechanical Ventilation Use

MV serves many purposes in extremely preterm infants. Upon inflation it provides sufficient volume to allow for pulmonary gas exchange, and at the end of expiration it maintains a constant distending pressure to prevent the alveoli from completely or partially collapsing (also known as atelectasis). It is also a vehicle for the delivery of surfactant to the immature and poorly compliant lungs. Ultimately, it buys time for the preterm infant's lungs and brain to grow and mature before they are ready to breathe spontaneously without the assistance of the ventilator. Nevertheless, while MV can be a life-saving intervention in most preterm infants, it is often accompanied by several complications that exacerbate the degree of pulmonary disease. These include ventilator-associated lung injury, air leak syndromes, airway trauma, ventilator-associated pneumonia (VAP), ventilator-induced diaphragmatic dydfunction and other iatrogenic complications (Table 1.1).[20]

Ventilator-associated lung injury

Provision of optimal MV in extremely preterm infants is difficult. On one hand, lung mechanics vary dynamically as the infant's clinical condition improves (e.g. post-surfactant) or worsens (e.g. evolving inflammation or infection) over time. On the other hand, there are important regional variations in the distribution of ventilation and perfusion within the lung, which can further be affected by the infant's position (e.g. prone or supine), the placement of the endotracheal tube (e.g. too high or too deep) and the presence of secretions. Together, these complex variations in pulmonary mechanics over time and space make it very challenging for the ventilator to deliver the right amount of volume to the different parts of the lung. As a result, exposure to MV undoubtedly leads to either excessive or insufficient volume delivery to some alveolar lung units, which can trigger ventilator-associated lung injury (VALI). Indeed, VALI is

a well-recognized phenomenon not only affecting preterm infants, but also affecting mechanically ventilated adults and children.[21, 22] The three best understood mechanisms by which MV leads to VALI are volutrauma, atelectrauma and biotrauma.[16, 23, 24]

Volutrauma is characterized by overdistension and excessive stretching of the alveoli. Studies in preterm sheep and rabbits have consistently shown an association between high tidal volumes and lung injury. In fact, only a few inflations (or a few minutes of ventilation) with high tidal volumes are sufficient to damage the lungs.[25] Volutrauma exerts its injurious effects through various pathways. Overstretching of the lungs can cause structural damage through disruption of the alveolar epithelium, which leads to increased leakage of protein into the interstitium and alveoli thus causing pulmonary edema.[16] Volutrauma has also been shown to reduce lung compliance and limit the effectiveness of surfactant therapy in preterm lambs.[26] Furthermore, ventilation with excess tidal volumes can trigger an influx of inflammatory cells whilst also upregulating genes involved in the inflammatory response.[27]

Atelectrauma is thought to occur due to repeated alveolar collapse and expansion (RACE) of unstable alveoli with atelectasis (due to surfactant deficiency or insufficient positive end-expiratory pressure).[16, 23] RACE may cause structural damage and cellular necrosis through shear forces at the level of the affected epithelium, which ultimately trigger local and systemic inflammation.[28] Alternatively, atelectrauma may be the result of preferential ventilation of the stable alveoli over those with atelectasis, thereby leading to uneven tidal volume distribution and regional volutrauma.

Biotrauma refers to the inflammatory cascade caused by the processes of volutrauma and atelectrauma. That is, the injuries caused by the ventilator trigger the release of proteases and pro-inflammatory cytokines (such as interleukin 8, interleukin 1 beta and tumor necrosis factor

alpha) as well as neutrophils and activated macrophages into the alveolar space.[29] These cells and mediators aggravate the local lung injury and further disrupt the alveolar-capillary barrier, which leads to a loss of compartmentalization of bacteria and inflammatory cells within the lungs. As a result, both bacteria and inflammatory cells are released into the systemic circulation, thereby increasing the risks of systemic inflammation and end organ dysfunction.[21, 30]

Air leak syndromes

Overdistension of the lungs during MV may lead to air leakage into different extrapulmonary components, including the pleural space (pneumothorax), the mediastinum (pneumomediastinum), the interstitial space (pulmonary interstitial emphysema - PIE), the peritoneal cavity (pneumoperitoneum) and pericardial cavity (pneumopericardium). Infants with lower birth weights and higher ventilatory support are at greatest risk of air leaks syndromes, likely due to the severity of their lung disease. However, factors that increase exposure to excessive volumes either homogeneously (e.g. prolonged inspiratory time, high peak inflation pressure or mean airway pressure, high frequency oscillatory ventilation) [31, 32] or heterogeneously (e.g. endobronchial intubation) may further increase the risk. In clinical practice, pneumothorax and PIE are the two most commonly encountered forms of air leak. PIE is often a precursor to pneumothorax, occurring as a result of rupture of the terminal bronchioles or alveoli. Reported rates of PIE range from 14 to 24% in ELBW infants.[33-35] In contrast, pneumothorax has been reported in anywhere from 4 to 14% of extremely preterm infants,[31, 33, 36-38] with the highest rates amongst infants with birth weights below 750 grams.[37] Both pneumothorax and PIE have been associated with increased mortality and neurodevelopmental impairment.[33, 34, 38]

Airway trauma

Airway trauma occurs either as a result of direct injury (from intubation and endotracheal tube placement), or from protracted exposure to positive pressure ventilation.

Intubation may give rise to a number of complications to the upper airway, including superficial mucosal lacerations, vocal cord injuries, subglottic stenosis, subglottic cysts and, more rarely, perforation of the trachea or esophagus.[20] Subglottic stenosis is estimated to occur in approximately 0-2% of preterm infants,[39] but in as high as 9% of the most immature patients who survive to discharge.[40] Risk factors for subglottic stenosis include traumatic intubations, oversized endotracheal tubes and repeated intubation attempts.[40] Furthermore, prolonged presence of an oral endotracheal tube or nasotracheal tube may increase the risk of long-term palatal deformities (e.g. acquired palatal grooves) and naso-septal deformities, respectively.

Exposure of the immature airway to positive pressure ventilation leads to deformation and weakening of the muscle-cartilage structures of the trachea and bronchi via pressure-induced high-shear forces. This in turn makes the trachea and bronchi less compliant and more easily collapsible, a condition known as tracheobronchomalacia.[41, 42] Its incidence is unknown but estimated to occur in 16-50% of preterm infants with BPD.[41]

Ventilator-associated pneumonia

VAP typically occurs when exogenous microorganisms gain access into the patient's lungs and cause an infectious or inflammatory reaction, as characterized by worsening oxygenation and gas exchange, increased respiratory secretions, and sudden clinical, biochemical or radiographic changes.[43] The endotracheal tube and ventilator circuit act as ports of entry for the microorganisms to colonize the respiratory tract, thus increasing the infant's susceptibility to developing an infection. Making a diagnosis of VAP is extremely difficult and imprecise in

preterm infants, but is estimated to occur at a rate of 0.3 to 1.6 episodes per 1000 ventilator days.[43] Risk factors include duration of MV, need for reintubation and frequency of endotracheal suctioning.[44]

Ventilator-induced diaphragmatic dysfunction

In adults, prolonged exposure to mechanical ventilation has been well demonstrated to lead to diaphragmatic weakness and dysfunction. Based on animal studies, MV causes a decrease in the force-generating capacity and ultimately leads to atrophy of the diaphragmatic muscle fibers.[45] Similarly, clinical studies have shown that prolonged MV leads to disuse or inactivation of the diaphragm, which in turn results in skeletal muscle proteolysis (through autophagy) (Hussain et al AJRCCM 2010) and atrophy of the diaphragm myofibers (Levine et al NEJM 2008).[46, 47] In addition, MV exposure increases muscle fiber injury, oxidative stress and mitochondrial dysfunction, which all lead to impaired contractility of the diaphragm.[48, 49]

In critically ill children, the notion of ventilator-induced diaphragmatic dysfunction is also increasingly being recognized. In a longitudinal cohort study of critically ill children, the electrical activity of the diaphragm was commonly found to be very low or even absent during MV compared to after extubation, suggesting that over-assistance from the ventilator could blunt the natural work of the diaphragm.[50] In another two studies that primarily included infants, ultrasound measurements of diaphragm thickness significantly declined between the time of MV initiation and the time of MV discontinuation, thereby indicating some evidence of MV-induced diaphragmatic atrophy.[51, 52] Furthermore in another study of mechanically ventilated infants of children, nearly 35% of subjects had evidence of respiratory muscle weakness at the time of extubation, which was associated with a three-fold increased risk for reintubation.[53]

Contrary to adults and children, less is known about ventilator-induced diaphragmatic

dysfunction in the neonatal population. In a clinical study from 1988, neonates ventilated for 12 or more days before death were found to have evidence of decreased diaphragmatic muscle mass on autopsy compared to neonates ventilated for 7 days or less.[54] This suggested that prolonged mechanical ventilation might lead to disuse atrophy or blunted growth and maturation of the diaphragm muscle. More recently, a study in newborn lambs revealed that exposure to MV after birth led to early onset diaphragmatic dysfunction through rapid decline in force-generating capacity of the diaphragm muscle.[55] Therefore, based on the recent data in newborn lambs and extrapolation from the adult and pediatric literature, it is physiologically likely that MV exposure contributes to diaphragmatic dysfunction in neonates as well.

1.2.3 Consequences of Prolonged Mechanical Ventilation

Prolonged exposure to MV incrementally increases the risk of mortality as well as several short and long-term morbidities in extremely preterm infants (Table 1.2).[18, 19, 56-58] In an earlier cohort of ELBW infants born in the 1990s, Walsh et al. showed that each additional week of MV conferred significantly increased odds of neurodevelopmental impairment at 18-24 months corrected age. When infants were ventilated for more than 60 days, only 24% survived without impairment. Moreover, amongst infants ventilated for more than 90 days, 50% died and only 7% survived without impairment.[56] Since then, similar observations have been derived from more contemporary cohorts. In a cohort of VLBW infants from 2013-2014, Choi et al. demonstrated that mortality rates significantly increased once infants were exposed to more than 8 weeks of MV, reaching a 50-60% mortality rate when ventilated for greater than 90 days.[19] In another cohort of preterm infants born between 2010 and 2015, Vliegenthart et al. found that each additional day on MV significantly increased the risk of neurodevelopmental impairment at 24 months corrected age.[58]

In addition to increasing mortality and long-term neurodevelopmental impairment, prolonged exposure to MV has been linked to several in-hospital morbidities. For instance, the odds of having BPD, pulmonary hypertension, or require supplemental oxygen at discharge gradually rise with increasing exposure to MV.[18, 19] Furthermore, MV exposure for more than 2 weeks has been associated with increased risk of retinopathy of prematurity (requiring laser treatment) and periventricular leukomalacia, while MV exposure for greater than 4 weeks has been associated with increased risk of having an abnormal hearing screen result before discharge.[19] Lastly, the cumulative duration of MV has been shown to be positively correlated with increased length of hospitalization, increased duration of parental nutrition and lower z-scores for weight, height and head circumference at discharge.[19]

1.2.4 Avoidance of Mechanical Ventilation

Given the numerous complications and morbidities associated with MV, a major focus over the past two decades has been placed towards avoidance of MV altogether, using various non-invasive respiratory support strategies. These include different modalities, such as continuous positive airway pressure (CPAP) and nasal intermittent positive pressure ventilation (NIPPV), as well as various ways to deliver surfactant less-invasively (with little to no mechanical inflations). A list of the randomized controlled trials evaluating the different non-invasive respiratory support strategies in extremely preterm infants and their respective abilities to prevent MV is detailed in Appendix A1, and summarized in Figure 1.3. As highlighted in the Figure, non-invasive respiratory support strategies appear to be most successful at reducing the need for MV amongst infants with gestational ages greater than 27 weeks. In other words, infants of lower gestational ages are more likely to fail non-invasive strategies and eventually require

MV within 7 days after birth. In fact, in a trial enrolling only infants below 27 weeks' gestation who received less-invasive surfactant, over 90% of infants with gestational ages 23-24 weeks' and over 75% of infants born at 25 weeks' gestation required MV, respectively.[59] Thus, more than ever, MV has become reserved to an increasingly smaller, more immature, and sicker subset of the extremely preterm population.

Table 1.1 Complications associated with mechanical ventilation

Ventilator-induced lung injury
Volutrauma
Atelectrauma
Biotrauma – pulmonary and systemic inflammation

Air leak syndromes
Pneumothorax
Pneumomediastinum
Pulmonary interstitial emphysema
Pneumoperitoneum
Pneumopericardium

Airway trauma – related to intubation
Superficial mucosal lacerations
Vocal cord injuries
Subglottic stenosis
Subglottic cysts
Tracheal or esophageal perforation
Palatal deformities (prolonged endotracheal intubation)
Naso-septal deformities (prolonged nasotracheal intubation)

Airway trauma – related to positive pressure ventilation
Tracheomalacia
Bronchomalacia

Ventilator-induced diaphragmatic dysfunction
Diaphragm atrophy secondary to disuse
Decreased respiratory muscle strength

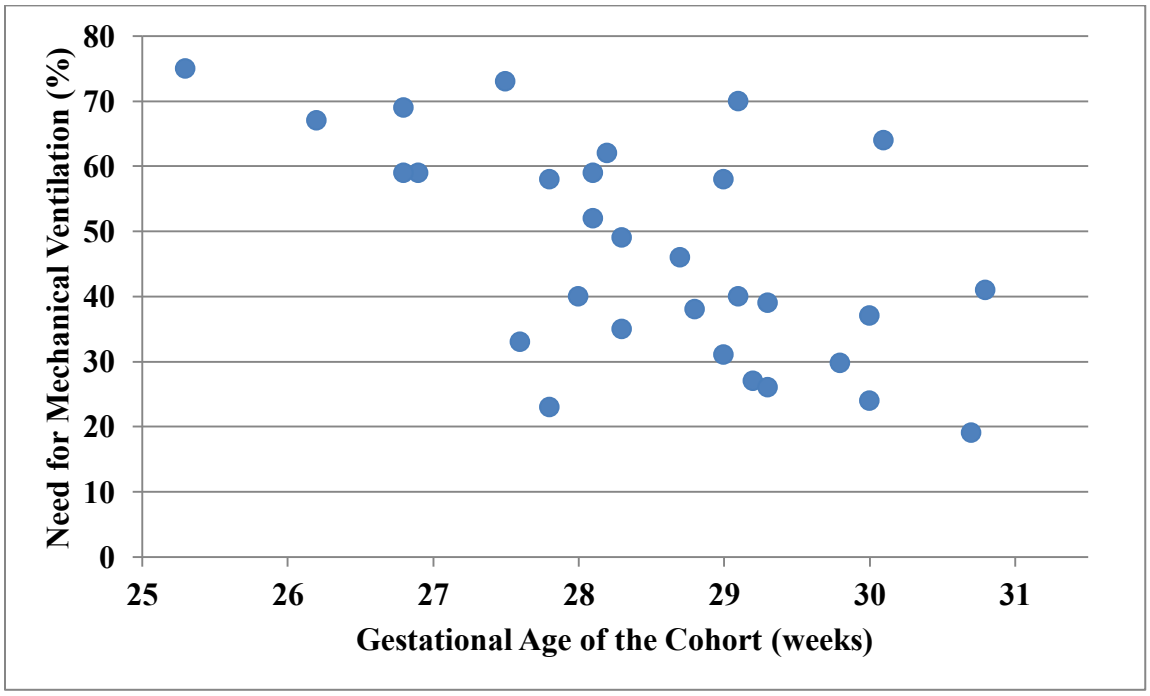
Iatrogenic complications
Endotracheal tube displacement
Endotracheal tube obstruction

Table 1.2 Morbidities associated with prolonged mechanical ventilation

Cumulative MV duration	Study	Associated Morbidities
> 7 days	Jensen 2015	Bronchopulmonary dysplasia Discharge home on oxygen
	Choi 2018	Bronchopulmonary dysplasia Pulmonary hypertension
> 14 days	Tsai 2014	Cerebral palsy Attention-deficit hyperactivity disorder
	Choi 2018	Retinopathy of prematurity needing laser Periventricular leukomalacia
> 28 days	Choi 2018	Abnormal auditory screening
Each additional day or week of MV	Walsh 2005 Vliegenthart 2019	Neurodevelopmental impairment (at 18-24 months corrected age)

Abbreviation: MV – mechanical ventilation.
Legend: The following table presents a summary of all studies that have evaluated associations between various cumulative durations of mechanical ventilation and morbidities in extremely preterm infants. Only those morbidities significantly associated with prolonged mechanical ventilation, after having adjusted for potential confounders, are presented.

Figure 1.3 Need for mechanical ventilation amongst infants exposed to different non-invasive respiratory support strategies after birth



Legend: Each blue circle represents a study evaluating some type of non-invasive respiratory strategy to avoid the need for mechanical ventilation in extremely preterm infants after birth. The x-axis represents the mean or median gestational age of the cohort exposed to the evaluated non-invasive respiratory support strategy. The y-axis represents the percentage of infants who required invasive mechanical ventilation within 7 days (or more) after birth. For the purposes of this review, only studies published after the year 2000, with >30 patients per intervention arm, with available data on the need for MV within at least 7 days after birth, and including extremely preterm infants (gestational age < 28 weeks or birth weight < 1250g), were evaluated. Details of the included studies as well as the types of non-invasive respiratory strategies evaluated are provided in Appendix A1.

1.3 The Extubation Process

Extubation is a complex, multi-step process that requires meticulous planning and the full collaboration of all team members caring for the infant. This peri-extubation process consists of three major steps: weaning from MV, assessment of extubation readiness, and provision of post-extubation respiratory support. Unfortunately, there is often limited or conflicting evidence to guide clinicians during this process, which often leads to variable practices. In an attempt to better understand peri-extubation practices in preterm infants, we conducted two surveys (one international and one Canadian survey) on the subject. For the international survey, we developed 13 questions related to extubation practices in extremely preterm infants, and sent them electronically to clinical directors of NICUs across Canada, USA, Ireland, Australia and New Zealand between October 2013 and February 2014.[60] The survey was circulated to 158 NICUs, of which 112 (71%) responded. For the Canadian survey, we sent out a postal survey of 40 questions related to MV practices in preterm infants (and respiratory care protocol usage) to the medical directors of all NICU's in Canada between December 2012 and March 2013.[61] A total of 24 NICUs responded to the survey (75% response rate). Results of both surveys have been published, and the preprints of each manuscript are available in Appendix A2 (International survey) and Appendix A3 (Canadian survey). In addition to the surveys, we conducted and published a review of the literature about the current variability in respiratory care practices across NICU's and its impact on patients, their families, and the NICU workplace.[62] A preprint of the published review is presented in Appendix A4. Thus, the following section will explore the current variations in respiratory care practices surrounding extubation of extremely preterm infants (Subsection 1.3.1) and their impact on the patients and on the NICU (Subsection 1.3.2).

1.3.1 Variability of Peri-Extubation Practices in Extremely Preterm Infants

Based on the results of the surveys and review of the literature, we observed significant variations in practices for all components of the peri-extubation process. Decisions were often dependent on the clinical team on duty, and were seldom driven by guidelines or protocols to streamline patient care. Moreover, many practices were either outdated or did not reflect the best-available clinical evidence. Below are included some examples illustrating these observations for each step of the extubation process.

Weaning

In many NICUs today, clinicians have at their disposal a wide array of modalities to choose from when providing MV. These include conventional modes such as assist control (AC) and synchronized intermittent mandatory ventilation (SIMV) with or without pressure support (PS), but also less conventional modes such as high frequency oscillatory ventilation (HFOV), high frequency jet ventilation (HFJV), and neurally adjusted ventilatory assist (NAVA). What's more, several MV modes have the option of being either pressure-limited or volume-controlled, which adds further complexity. All the above modes can readily be used during the acute, chronic or weaning phases of MV, and are generally selected on the basis of familiarity or preference of the NICU personnel. With regards to weaning from MV, we found in our Canadian survey that clinicians most commonly used SIMV as their preferred pre-extubation mode (74% of respondents), followed by AC and HFOV in 44% and 30% of respondents, respectively (Figure 1.4). This practice diverges from the available evidence suggesting that assist control ventilation provides more homogeneous tidal volume delivery, reduces work of breathing and may be associated with shorter weaning durations compared to SIMV.[63-66] Additionally, we noted that only 44% of respondents in the Canadian survey applied volume-targeted ventilation

during the weaning phase of MV.[61] Again, this contrasts with results obtained from randomized controlled trials suggesting that volume-targeted ventilation is associated with faster weaning and lower rates of death/BPD, pneumothorax and severe brain abnormalities compared to pressure-limited ventilation.[67] Our survey results echoed those of other surveys, whereby the uptake of volume-guaranteed ventilation has also been reportedly low (ranging anywhere from 5 to 60% across centers).[62]

One way of harmonizing practices related to weaning from MV is through the development and implementation of weaning protocols. Protocols are a set of instructions (or guidelines) to follow for a certain patient population, disease or treatment. Weaning protocols are often driven by nurses and/or respiratory therapists, hence allowing for more standardized and timely sampling of blood gases and titration of ventilator settings. In adult intensive care patients, weaning protocols have been demonstrated to improve outcomes, reduce costs and decrease MV duration and length of stay.[68] In fact, they have been incorporated as evidence-based recommendations by a collective task force facilitated by the American College of Chest Physicians, the American Association of Respiratory Care and the American College of Critical Care Medicine since 2001.[69] In contrast to adults, the evidence for recommending MV weaning protocols in pediatric and neonatal patients is less conclusive, due to a paucity of trials on the subject. In the only neonatal study of its kind, implementation of a weaning protocol in ventilated preterm infants with birth weight $\leq$ 1250g led to significant reductions in weaning duration, total MV duration and extubation failure rates.[70] As a result of the limited evidence, most NICUs have not yet adopted MV weaning protocols in their unit. In our international survey, only 36% reported having a guideline or written protocol for ventilator weaning.[60] Similarly in our Canadian survey only 7 out of 24 units (29%) had a protocol for weaning from

MV.[61] Interestingly, we observed in the Canadian survey that units with MV protocols were significantly more likely to use AC as a weaning mode of ventilation compared to units with no protocol (75% vs. 27%), and were more likely to use volume-targeted ventilation (63% vs. 33%) although this did not reach statistical significance.[61] These findings raise the hypothesis that institutions developing MV weaning protocols are more prone to adopt evidence-based practices.

Assessment of extubation readiness

Following weaning, an assessment is generally required to determine whether the infant is ready for a trial of extubation. According to a recent international survey distributed to representatives of NICUs from 10 different neonatal networks, the majority relied on clinical judgment of the attending team to determine readiness for extubation, with less than 25% of units using a protocol or guideline for that process.[71] Similarly in our international survey, most respondents also stated relying on clinical judgment, based on evaluation of the patient's ventilatory settings, blood gases and overall clinical/hemodynamic stability (Figure 1.5).[60] Unfortunately, there is significant variability between assessors as to what constitutes "clinical stability" and what ventilator parameters or blood gases are considered low enough for extubation. The usefulness and predictive ability of clinical judgment in the assessment of extubation readiness is further explored in section 1.4.1 of this chapter.

Another interesting trend has been the use of predictor tests or trials to determine readiness for extubation. Of all predictor tests, the most commonly used in clinical practice is the spontaneous breathing trial (SBT), a brief challenge on endotracheal CPAP during which the infant is monitored for signs of clinical instability prior to extubation (apneas, bradycardias, desaturations and/or increased O_2 needs). In one international survey spanning 10 different neonatal networks, SBTs were reportedly used by 10% of NICUs.[71] In the other international

survey performed by our group, we found that 16% of NICUs extubated extremely preterm infants on the premise of passing a SBT (Figure 1.5).[60] Moreover, 38% of respondents stated using SBTs in their respective units at least sometimes to decide whether to extubate or not. Unfortunately, SBTs are performed in highly variable ways, lasting anywhere from less than 3 minutes to more than 10 minutes in duration and using various combinations of clinical criteria to define pass/fail. An in-depth discussion about SBTs and the various types of predictor tests evaluated in preterm infants, how they are performed, and their accuracies in predicting extubation success are provided in section 1.4.3 of this chapter as well as chapter 2 of the thesis.

Lastly, it's important to note that some clinicians don't necessarily use formal assessment tools of extubation readiness (such as clinical judgment or SBTs), but rather rely on other inbuilt philosophies about the optimal timing of extubation. For instance, in our international survey, 18% of respondents stated that infants in their unit were generally extubated immediately following surfactant administration.[60] Another 22%, 36% and 15% stated that infants were extubated within 24h, between 24h-3d and between 3d-7d of life, respectively. As such, most clinicians have an inherent tendency towards early extubation irrespective of assessments of extubation readiness. However, there are some clinicians who still favor delaying extubation until the infant gains more maturity or reaches a higher weight threshold. Also, some clinicians have recently questioned the idea of extubation within the first 72h of life, under the premise that a failed attempt may cause clinical instability and therefore increase the risk of intraventricular hemorrhage during this fragile postnatal transition period.

Post-extubation

There is ample evidence in the literature to suggest that extremely preterm infants should be extubated to some form of respiratory support that provides positive end-expiratory pressure

(PEEP), such as CPAP or NIPPV.[72] The addition of PEEP allows for stenting of the upper airway and maintenance of functional residual capacity, which increases cardiorespiratory stability during the fragile post-extubation period and therefore increases chances of successful disconnection from MV.[73] Indeed, our international survey reflects this practice as 84% and 55% of respondents reported using nasal CPAP and NIPPV post-extubation in their units, respectively (Figure 1.6).[60] However, there remain some important sources of heterogeneity in practices related to both CPAP and NIPPV. For instance, nasal CPAP can be delivered using many different devices (ex: bubble CPAP, ventilator-derived CPAP or variable-flow CPAP) and interfaces (ex: single or binasal prongs, nasal mask, nasopharyngeal tube), while NIPPV devices can deliver inflations that are either non-synchronized or synchronized (flow-triggered, or neurally-triggered using non-invasive NAVA).[62] Each of these combinations of devices and interfaces confer highly variable physiological and clinical effects. Moreover, their respective applications can greatly depend on the expertise and familiarity of the bedside caregivers. As a result, CPAP and NIPPV use doesn't always translate into optimal benefits in everyday practice. In our international survey, although most respondents reported using CPAP or NIPPV during the immediate post-extubation period, a minority also used low flow nasal cannula (8%), oxyhood (2%) or no respiratory support (1%).[60] These results are concerning, since the lack of PEEP increases odds of lung derecruitment, respiratory fatigue and reintubation.[72]

Another emerging trend has been the use of heated and humidified high flow nasal cannula (HFNC) in preterm infants. HFNC is thought to exert its actions via washout of the nasopharyngeal dead space (which improves gas exchange), gas conditioning (through heating and humidification), and to a lesser and more variable extent via provision of continuous distending pressure.[73] In our international survey, 33% of respondents reported using HFNC in

their units as a post-extubation modality in extremely preterm infants.[60] HFNC has particularly gained traction in the recent years due to its simple interface and the increased patient comfort and nurse satisfaction associated with its use. In the most recent meta-analysis of randomized controlled trials on the subject, HFNC was demonstrated to be non-inferior to other non-invasive modalities during the post-extubation period (i.e. similar rates of treatment failure, death and BPD), with the added benefits of reducing the risks of nasal trauma and pneumothorax.[74] However, very few extremely preterm infants were included or enrolled in those trials. As such, the safety and efficacy of HFNC in the most immature patients (at highest risk of reintubation) during the immediate post-extubation period is unclear. In fact, recent clinical and physiological studies have raised concerns regarding the use of HFNC in this subpopulation. Kanbar et al. showed that HFNC was associated with longer respiratory pauses and higher oxygen requirements compared to CPAP following extubation.[75] Liew et al. demonstrated significant variations in transmitted PEEP levels across ELBW infants receiving HFNC, with sometimes dangerously high PEEP levels when flow rates exceed 6L/min.[76] Finally, in a large cohort study of ELBW infants, HFNC use was associated with significantly increased risk of death/BPD, prolonged MV duration, delayed attainment of oral feeding and prolonged hospitalization.[77] Thus, the increasing practice of HFNC use in extremely preterm infants, particularly during the unstable post-extubation period, is unsupported by the available evidence.

1.3.2 Impact of Practice Variability on Outcomes

Excess variations in extubation practices have potentially negative effects on patients, their families, the allied health care team members and the overall NICU workplace as a whole (Table 1.3).[62] Firstly, preterm infants are exposed to a multitude of clinical practice styles due to

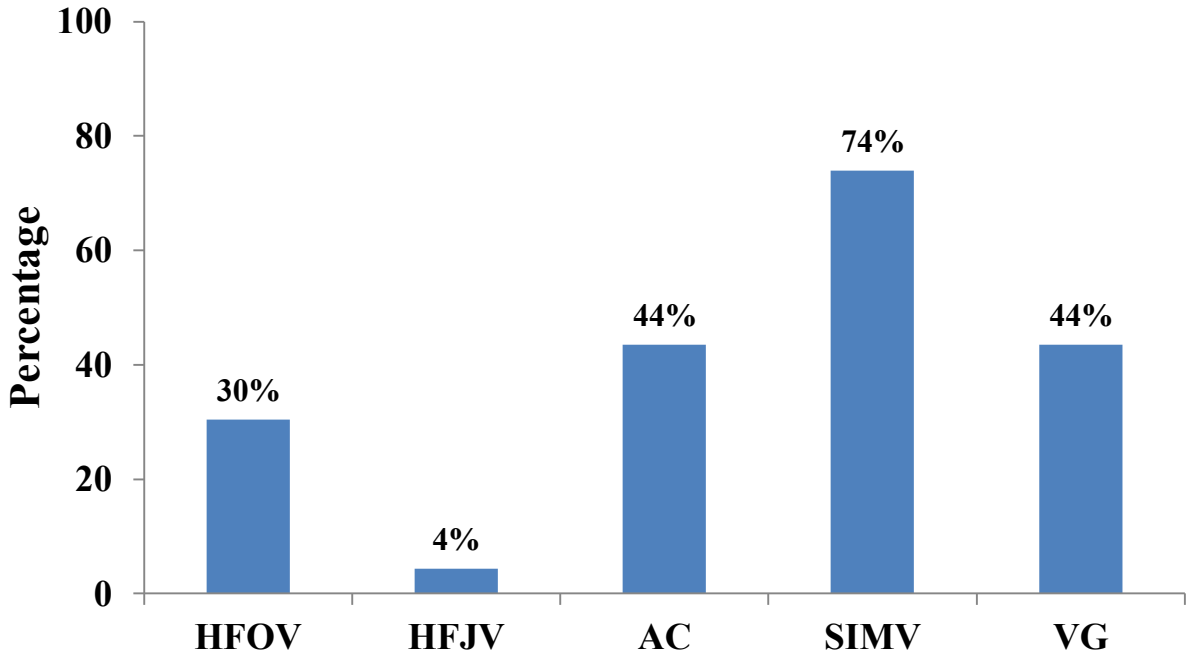
the high turnover of doctors, nurses and respiratory therapists caring for them throughout hospitalization. Given the absence of clinical evidence for many practices surrounding the extubation process, most decisions tend to be based on clinicians' personal experiences and preferences. In cases where evidence is available, there is often delayed uptake of study recommendations, primarily due to the increasing difficulties of staying up-to-date with scientific advances in this information-saturated world. Besides, the available evidence is often weak or shows conflicting results between studies, which renders its interpretation even more variable from one provider to the next. Putting all these factors together, it becomes inevitable for the patient to incur some negative consequences from this practice variability. Indeed, a number of studies have demonstrated that center variations for many outcomes (including mortality/BPD) cannot be simply explained by markers of illness severity, thus suggesting that unmeasured practice variations play a contributory role. Moreover, this fact is further enforced by the solid evidence in adults,[68] and to a lesser extent in neonates,[70] that standardization of weaning and extubation via protocols leads to improved patient outcomes by significantly reducing the total duration of MV and length of hospitalization. As such, streamlining the extubation process has the potential to weed out non-evidence based practices and therefore reduce the chances of unnecessary complications.

Practice variability can also be an important source of distress for the patient's parents and caregivers. In the face of high turnover of medical personnel and lack of predictability in respiratory management, parents can become very anxious and may even lose trust in their providers. In addition to parents, allied health care workers (such as nurses or respiratory therapists) and trainees rotating in the NICU may also become confused by the shifting care plans and inconsistent teachings. This has the potential to weaken the educational experience and

learning potential of all members of the health care team. Finally, at the institutional level, practice variability can be very costly, resource-intensive, and unsuitable for quality improvement initiatives. For example, in a unit where multiple invasive or non-invasive modalities are available, undue expenses are needed to pay for all the equipment, its maintenance, its storage, and all the training of personnel that goes with its implementation. Moreover, the existence of variability makes it extremely difficult to audit clinical practices as a means to identify factors associated with improved or worsened respiratory outcomes.

All in all, variability in respiratory care provision is a common problem in extremely preterm infants that is associated with potentially suboptimal practices and increased morbidities. To circumvent this issue, more clinical evidence is needed to better understand the extubation process, especially with regards to weaning and the assessment of extubation readiness in this fragile population.

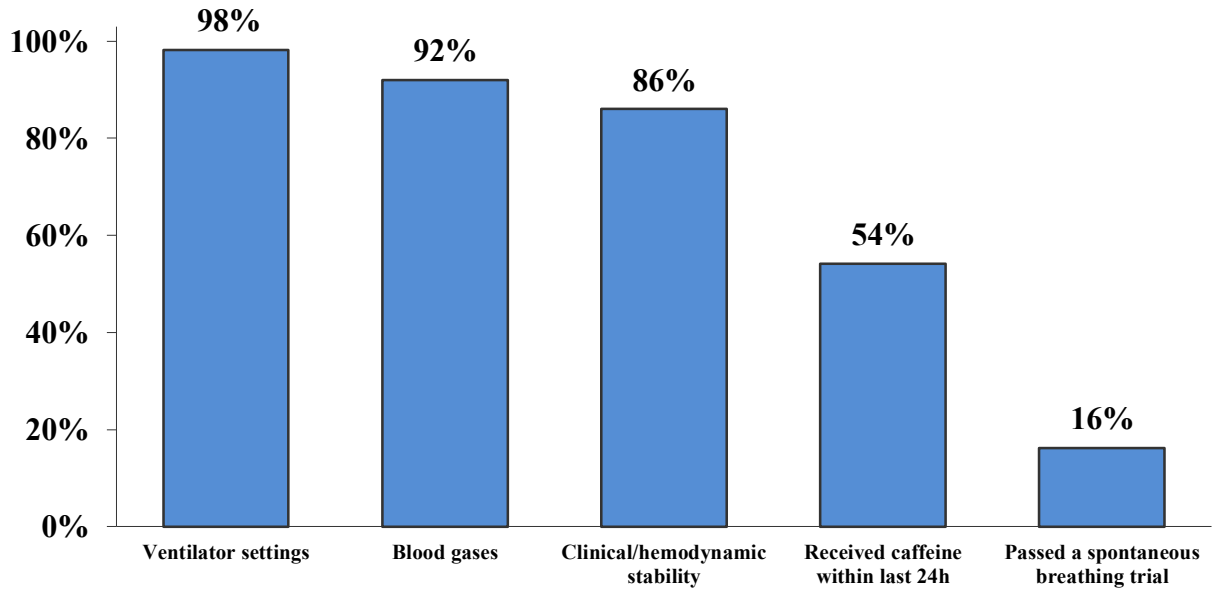
Figure 1.4 Mechanical ventilation modes used for weaning in Canadian NICUs



Abbreviations: HFOV – high frequency oscillatory ventilation, HFJV – high frequency jet ventilation, AC – assist control ventilation, SIMV – synchronized intermittent mandatory ventilation, VG – volume-guaranteed ventilation

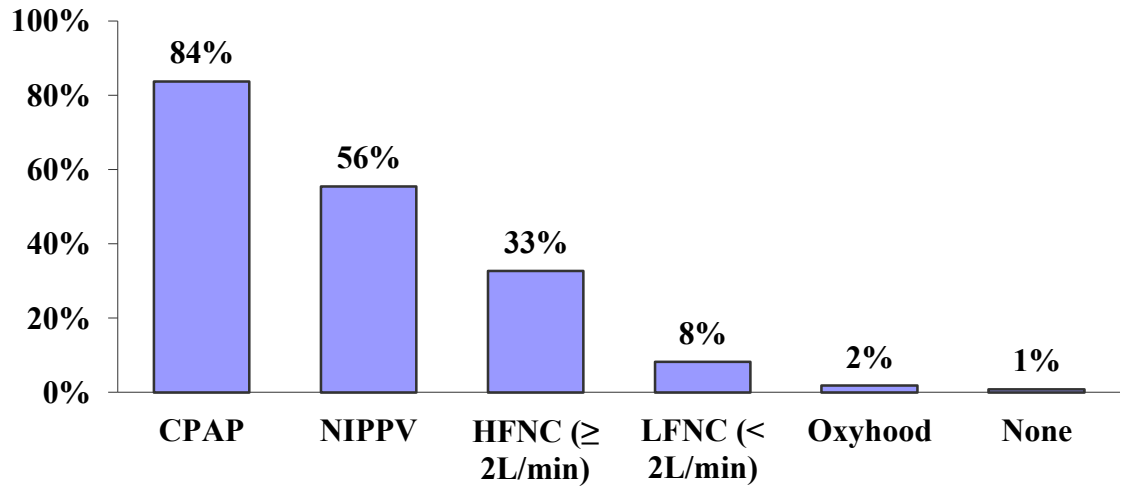
Legend: The figure presents the proportion of Canadian NICUs using each mode of mechanical ventilation for weaning prior to extubation. Data was derived from a Canadian survey in which representatives from 24 out of 32 NICUs responded.[61] Of note, respondents could check more than one answer.

Figure 1.5 Criteria used to assess extubation readiness in extremely preterm infants



Legend: The figure presents the proportion of clinicians using each criterion as part of the assessment of extubation readiness in extremely preterm infants. Data was derived from an international survey on peri-extubation practices in which representatives from 112 out of 158 NICUs responded.[60] Of note, respondents could check more than one answer.

Figure 1.6 Types of post-extubation respiratory support used in extremely preterm infants



Abbreviations: CPAP – continuous positive airway pressure, NIPPV – nasal intermittent positive pressure ventilation, HFNC – high flow nasal cannula, LFNC – low flow nasal cannula.
Legend: The figure presents the proportion of clinicians using each mode of post-extubation respiratory support. Data was derived from an international survey on peri-extubation practices in which representatives from 112 out of 158 NICUs responded.[60] Of note, respondents could check more than one answer.

Table 1.3 Consequences of respiratory practice variability

On patients
Increased potential for using non-evidence based practices
Increased risk of errors
Increased risk of morbidities
Lack of consistency in respiratory management
On parents
Anxiety in the face of changing care plans
Weakening of therapeutic alliance with health care team
On the allied health care team
Increased confusion
Weakening of the learning potential for trainees
On the NICU workplace
Higher costs
More resource-intensive
Unsuitable for quality improvement initiatives

Legend: The table presents the consequences of respiratory practice variability on patients, their parents, the allied health care team and the NICU workplace. The table was adapted from a previously published book chapter done by our group.[62]

1.4 Assessment of Extubation Readiness in Extremely Preterm Infants

As highlighted in the previous section, the ability to assess extubation readiness in extremely preterm infants has proven to be challenging, with decisions often being highly variable, subjective and devoid of strong evidence to guide practices. These challenges have led to a wide display of trends across NICU's, from units with high rates of reintubation to units where infants are exposed to MV much longer than necessary. The following section will review in more depth the current tools commonly used by clinicians to assess extubation readiness in these infants. First, Subsection 1.4.1 will critically appraise the limitations associated with clinical judgment for the assessment of extubation readiness. Subsection 1.4.2 will review the clinical markers of extubation readiness, and Subsection 1.4.3 will provide an overview of currently evaluated predictor tests of extubation readiness.

1.4.1 Clinical Judgment

In practice, the decision to extubate is made once the responsible physician deems that the infant appears clinically stable, is maintaining adequate gas exchange and has reached "low" or "minimal" ventilatory settings.[60] Indeed, the terms 'minimal ventilatory settings' or "minimal respiratory support" have become a familiar part of the neonatal vocabulary and are commonly used to imply that an infant has reached suitable criteria for extubation. It is also often quoted in the literature by neonatal textbooks, consensus guidelines, reviews and original articles. For instance, in 2001 a Cochrane review concluded that preterm infants should be extubated from low ventilatory settings as opposed to prolonged trials of endotracheal continuous positive airway pressure.[78] In a more recent article, authors advocated for "routinely trialing extubation when low ventilator settings are reached".[18] Unfortunately, most recommendations do not

provide a definition of what actually constitutes "low" or "minimal", and when definitions are provided they are only based on expert opinion. Over the past decades, a large number of randomized control trials (RCTs) have investigated several respiratory care strategies and therapies aimed at shortening length of MV, improving extubation outcomes and reducing rates of BPD in preterm infants. Given the rigorous methodological design associated with RCTs, we sought to determine whether a definition of "minimal" ventilatory settings in very preterm infants could be ascertained from these high quality studies.

We conducted a systematic review of the literature to identify the proposed minimal ventilatory settings at which preterm infants are considered ready for extubation. We searched MEDLINE and EMBASE using the search terms "neonate OR preterm", "ventilation", "weaning" and "extubation". We limited the search to RCTs published in English between October 2003 and September 2013. All studies pertaining to a ventilation strategy in preterm infants (< 32 weeks gestation or < 1500 grams) and reporting either "BPD", "need or duration of MV" or "reintubation" as an outcome were included. All RCTs that provided "minimal" ventilator settings were identified. Data pertaining to the ventilatory parameters at which preterm infants should be extubated were extracted, including: peak inflation pressure (PIP), PEEP, mean airway pressure (MAP), ventilator rate and fraction of inspired oxygen (FiO_2) during conventional and HFOV. Information on the partial pressure of carbon dioxide (PCO_2) and pH required on pre-extubation gases was also collected if available.

A total of 285 RCTs were assessed for eligibility, of which 100 RCTs met inclusion criteria (see Appendix A5 for flow diagram and study characteristics). Only 38 of the included studies reported "minimal" ventilatory settings, with wide variations in the proposed extubation parameters (Table 1.3). To illustrate, an infant on one extreme could be extubated from a PEEP

of 2 cmH_2O, MAP of 5 cm H_2O, ventilator rate of 6 inflations/min and FiO2 of 0.25. An infant on the other extreme could be extubated from a PEEP of 5 cmH_2O, MAP of 10 cmH_2O, ventilator rate of 30 inflations/min and FiO2 of 0.5.

Thus, based on this systematic review of the literature, we conclude that there are currently wide variations and lack of consensus on what constitutes "minimal ventilatory settings" for extubation. These results consolidate the notion that clinical judgment, when used to determine extubation readiness, is highly inconsistent from one practitioner to the next and generally unfounded on solid grounds to justify each decision.

1.4.2 Clinical Markers of Extubation Readiness

When assessing extubation readiness, clinicians intuitively weigh in various factors relating to the patient's clinical history and comorbidities to make their decisions. For example, a clinician may be more cautious to extubate an infant who is still very immature and small, who has high oxygen requirements, or had a previous failed extubation attempt. Actually, many studies have attempted to identify clinical markers of extubation readiness in extremely preterm infants. Upon reviewing the literature, a total of 10 studies (published after the year 2000) evaluated markers of extubation success/failure in a cohort of preterm infants with gestational age < 29 weeks and/or birth weight ≤ 1250g (Table 1.4).[79-88] Overall, infants with successful extubation tended to have significantly higher gestational age and weight (at birth and at extubation), had less severe lung disease in the first 24h of life, and had lower oxygen requirements compared to infants who failed extubation. However, as highlighted in Table 1.4, the results were not consistent between studies. For instance, only 4 out of 10 studies showed significant differences in gestational ages and birth weights between infants with extubation

success or failure. Moreover, when there were statistically significant differences, there remained a lot of overlap between groups. As a result, it is very difficult to determine thresholds for each clinical variable at which the extubation outcome can be accurately predicted. Indeed, a few studies have attempted to develop prediction models of extubation readiness using clinical variables.[88-92] Prediction models were developed using traditional methods (such as multivariate logistic regression) but also using more sophisticated machine-learning methodologies (including artificial neural networks, Bayesian classifiers, decision trees and support vector machines). In a few select studies, prediction models had good accuracies but were either not validated or could not be replicated in a second cohort. In most other studies, all prediction models had low-to-modest accuracies in classifying extubation outcomes when compared to clinical judgment alone. Therefore, these results confirm that using a handful of clinical variables to determine extubation readiness is unlikely to mimic the complex decision-making process that goes into expert clinical judgment. At the same time, the findings imply that the use of clinical variables alone (whether through clinical judgment or prediction modeling) is likely insufficient in accurately capturing all the intrinsic reasons why infants have a successful or failed extubation. For that reason, the use of physiological and/or clinical predictor tests, as adjuncts to clinical judgment, are justifiable when assessing extubation readiness.

1.4.3 Predictor Tests of Extubation Readiness

For many years, clinicians have attempted to identify objective predictors of extubation readiness in preterm infants as adjuncts to clinical judgment. Predictor tests are generally performed during a brief period on endotracheal CPAP (ET-CPAP), or more rarely during temporary disconnection from the ventilator, while the patient is spontaneously breathing via the

endotracheal tube without the assistance of mechanical inflations (Figure 1.7). During this imposed challenge, various physiological and/or clinical parameters are measured or monitored to assess whether the infant can successfully sustain breathing after extubation without the help of the ventilator. Examples of clinical and physiological parameters evaluated in the literature as potential predictors of extubation readiness are shown in Table 1.5. Physiological parameters include various measurements of lung mechanics, respiratory muscle strength and breathing patterns, while clinical parameters involve assessments of the patient at the bedside for signs of clinical instability (e.g. apneas, desaturations, bradycardias, increased work of breathing or increased oxygen needs). In clinical practice, one of the most commonly used assessments is the spontaneous breathing trial (SBT), a 3-30 minute challenge on ET-CPAP during which the patient is monitored for various thresholds of clinical instability. The use of a 30-minute SBT has been standard of care for assessing extubation readiness in mechanically ventilated adults,[69, 93] but the applicability of SBT's in the neonatal population is still unclear. In fact, there is limited data on the optimal SBT duration, the amount of PEEP to provide and the definitions of SBT pass/fail that best differentiate infants with extubation success from those with failure. Nonetheless, recent surveys suggest that SBTs are increasingly applied in preterm infants worldwide.[60, 71] In our international survey on peri-extubation practices, 16% of NICUs extubated infants on the basis of passing a SBT and 38% of neonatologists at least occasionally used SBTs prior to extubation.[60] Thus, in order to thoroughly understand the role of predictor tests (including SBTs) in practice, we performed a systematic review and meta-analysis of all published diagnostic accuracy studies. The aims were to (1) describe the predictor tests of extubation readiness in preterm infants, and (2) determine their accuracies compared to clinical

judgment alone. The systematic review has been published and will be presented in its manuscript format in Chapter 2.

Another promising and relatively more novel avenue has been the use of cardiorespiratory signal analyses to help improve our ability to predict extubation readiness in preterm infants. Clinicians caring for infants in the NICU often rely on a wide range of monitoring devices, that capture various biomedical signals (e.g. heart rate, respiration, oxygen saturation), to obtain invaluable information about their patients' well-being. However, due to limited familiarity and time constraints, clinicians only rely on a small percentage of the data provided by these signals. With increasing multidisciplinary collaboration between the fields of medicine, biomedical engineering and computer science, there has been a rising interest in expanding our knowledge and exploring the full potential of these signals. Indeed, automated analyses of cardiorespiratory signals have the potential to be more objective, to be more inclusive of the entire available data, and allow for the detection of more subtle changes that are biologically important yet imperceptible to the human eye. For example, subtle variations in heart rate and respiration (also known as heart rate variability and respiratory variability) provide essential information about the integrity of the patient's cardiovascular system. In fact, several studies in adults and neonates have demonstrated the abilities of heart rate and respiratory variability to act as accurate predictors of health and disease for various conditions.[94-97] With regards to the use cardiorespiratory signal analyses for the prediction of extubation readiness in preterm infants, a thorough review of the literature has been published and will be provided in its manuscript format in Chapter 3.

Table 1.3 Ventilatory settings and blood gas thresholds for extubation.

	Mode (range)	**Median (Interquartile range)**
Conventional Ventilation		
Mean airway pressure, cmH_2O	6 (5-10)	6.5 (6-7)
Peak inflation pressure, cmH_2O	15 (12-18)	15 (14-16)
Positive end-expiratory pressure, cmH_2O	5 (2-5)	4 (4-5)
Ventilator rate, inflations per min	20 (6-30)	15 (14-20)
Fraction of inspired oxygen	0.3 (0.25-0.5)	0.35 (0.3-0.4)
High Frequency Ventilation		
Mean airway pressure (cmH_2O)	8 (6-8)	7 (7-8)
Blood Gas	**Limits**	
pH	≥ 7.20	
PCO_2 (mmHg)	≤ 70	

Legend: The table presents the ventilatory settings and blood gas thresholds proposed in randomized controlled trials for extubation of preterm infants. Results were obtained from a systematic review of the literature, as detailed in Chapter 1.4.1 and Appendix A5.

Table 1.4 Clinical markers of extubation success or failure

Author, year	Extubation Success	Extubation Failure
Birth Demographics		
Gestational Age, weeks		
Lee, 2002	26.1 (1.2)	25.8 (1.2)
Vento, 2004	27.5 (25-30)	27 (25-29)
Kamlin, 2006	27 (1.7)	26.3 (2.2)
Hermeto, 2009	29.5 (2.1)	26.4 (1)*
Dani, 2013	25.1 (1.5)	25.4 (1.9)
Kaczmarek, 2013	26.9 (1.6)	26.4 (1.4)
Robles, 2015	26.7 (1.6)	26.3 (1.4)
Manley, 2016	26.5 (1)	25.4 (1.2)*
Chawla, 2017	26.5 (1.04)	25.8 (1.04)*
Gupta, 2019	27 [26-28]	26 [25-27]*
Birth weight, grams		
Lee, 2002	849 (74)	808 (140)
Vento, 2004	860 (590-1000)	825 (680-1000)
Kamlin, 2006	957 (215)	825 (232)
Hermeto, 2009	994 (171)	846 (156)*
Dani, 2013	730 (230)	720 (150)
Kaczmarek, 2013	923 (191)	876 (197)
Robles, 2015	903 (186)	847 (227)
Manley, 2016	879 (179)	757 (161)*
Chawla, 2017	882 (180)	764 (177)*
Gupta, 2019	931 [790-1090]	815 [690-914]*
Male sex, %		
Lee, 2002	34	83*
Kamlin, 2006	54	91*
Hermeto, 2009	53	78
Dani, 2013	48	47
Kaczmarek, 2013	44	36
Robles, 2015	48	73
Manley, 2016	51	58
Chawla, 2017	55	61
Gupta, 2019	50	51
Small for gestational age, %		
Hermeto, 2009	47	33
Chawla, 2017	4	10*

Author, year	Extubation Success	Extubation Failure
Antenatal steroids, %		
Lee, 2002	76	72
Hermeto, 2009	93	78
Dani, 2013	81	83
Kaczmarek, 2013	88	82
Robles, 2015	90	73
Manley, 2016	94	90
Chawla, 2017	95	97*
Gupta, 2019	63	65
Chorioamnionitis, %		
Kaczmarek, 2013	33	22
Robles, 2015	37	25
Manley, 2016	34	29
Gupta, 2019	47	61*
Delivery characteristics		
Apgar 5 min		
Hermeto, 2009	8 [7-9]	7 [5-8]*
Dani, 2013	7 (5-9)	7 (4-9)
Kaczmarek, 2013	7 [5-8]	7 [6-8]
Robles, 2015	7 [5-8]	7 [5-8]
Manley, 2016	7 [6-8]	7 [5-8]
Chawla, 2017	7 [6-8]	7 [5-8]
Cord pH		
Lee, 2002	7.24 (0.13)	7.25 (0.12)
Intubation in delivery room, %		
Manley, 2016	66	85*
Pre-Extubation characteristics		
Max FiO_2 first 6-24h of life		
Chawla, 2017	0.29 (0.14)	0.36 (0.18)*
Peak RSS first 6-24h of life		
Gupta, 2019	3.6 [2.5-4.6]	3.8 [2.7-6.3]*
Max FiO_2		
Lee, 2002	0.66 (0.19)	0.77 (0.21)

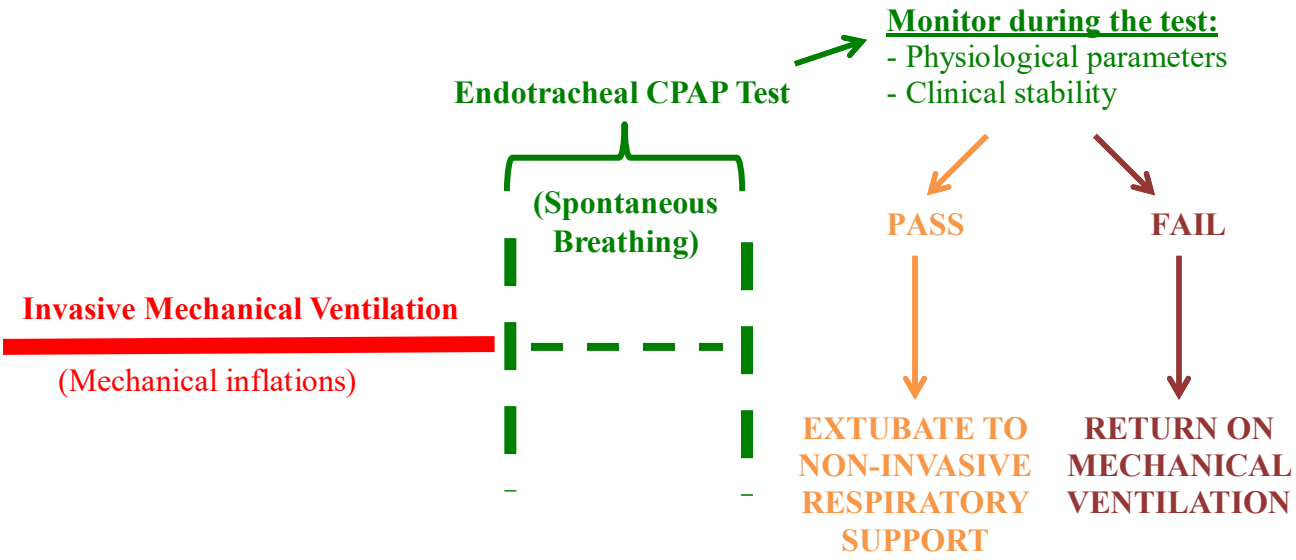
Author, year	Extubation Success	Extubation Failure
Patent ductus arteriosus, %		
Lee, 2002	76	83
Postnatal Steroids use, %		
Kaczmarek, 2013	19	18
Robles, 2015	23	27
Characteristics at extubation		
Postmenstrual age, weeks		
Kaczmarek, 2013	28.6 (2.5)	27.4 (1.8)
Chawla, 2017	27.5 (1.8)	27 (2)*
Gupta, 2019	28 [27-29]	27 [26-28]*
Postnatal age, days		
Vento, 2004	10 (6-55)	15 (5-59)
Kamlin, 2006	4 (1-45)	5 (1-21)
Hermeto, 2009	1 [0-17]	5 [1-20]
Kaczmarek, 2013	4 [2-10]	2 [1-4]
Robles, 2015	4 [2-17]	2 [1-5]
Manley, 2016	2 [1-5]	5 [2-11]*
Chawla, 2017	2 [2-6]	3 [2-9]*
Gupta, 2019	3 [2-9]	4 [2-9]
Weight, grams		
Vento, 2004	900 (560-1700)	850 (700-1720)
Kamlin, 2006	1043 (490-1270)	864 (560-1145)
Kaczmarek, 2013	997 (281)	882 (225)
Robles, 2015	1022 (292)	911 (231)
Gupta, 2019	970 [810-1100]	810 [700-980]*
FiO_2		
Vento, 2004	0.23 (0.21-0.28)	0.25 (0.22-0.3)*
Kamlin, 2006	0.24 (0.05)	0.26 (0.06)
Hermeto, 2009	0.27 (0.15)	0.25 (0.08)
Dani, 2013	0.25 (0.03)	0.28 (0.07)
Kaczmarek, 2013	0.26 (0.06)	0.26 (0.06)
Robles, 2015	0.26 (0.06)	0.26 (0.06)
Manley, 2016	0.23	0.25*
Chawla, 2017	0.26 (0.11)	0.38 (0.22)*
Gupta, 2019	0.23 [0.21-0.28]	0.25 [0.21-0.3]*
Mean airway pressure, cm H_2O		

Author, year	Extubation Success	Extubation Failure
Lee, 2002	8.1 (2.9)	8.4 (3.9)
Kamlin, 2006	7.1 (1.1)	7.3 (1.1)
Hermeto, 2009	5.3 (1.5)	5.1 (0.8)
Dani, 2013	7.5 (1.6)	7.3 (1.2)
Kaczmarek, 2013	5.8 (0.9)	6.3 (1.2)
Robles, 2015	5.9 (0.9)	6.4 (1.2)
Gupta, 2019	6 [5.6-6.7]	6.1 [5.5-6.6]
Peak inflation pressure, cm H_2O		
Lee, 2002	19 (6)	22 (7.4)
Kaczmarek, 2013	13 (2)	13 (2)
Robles, 2015	13 (2)	14 (2)
Gupta, 2019	15 [14-16]	14 [14-16]
Inspiratory time, sec		
Kaczmarek, 2013	0.39 (0.04)	0.37 (0.03)*
PEEP, cm H_2O		
Kaczmarek, 2013	4.4 (0.6)	4.5 (0.8)
Ventilator Rate, inflations/min		
Lee, 2002	26 (11)	27.5 (13)
Kamlin, 2006	29 (7)	32 (5)
Kaczmarek, 2013	21 (8)	25 (11)
Robles, 2015	21 (8)	24 (11)
Gupta, 2019	15 [14-16]	14 [14-16]
RSS		
Gupta, 2019	1.4 [1.2-1.8]	1.6 [1.4-1.8]*
pH		
Lee, 2002	7.41 (0.21)	7.37 (0.07)
Hermeto, 2009	7.38 (0.08)	7.29 (0.07)*
Dani, 2013	7.32 (0.08)	7.32 (0.07)
Kaczmarek, 2013	7.3 (0.1)	7.3 (0.05)
Robles, 2015	7.35 (0.05)	7.31 (0.04)*
Manley, 2016	7.32 (0.1)	7.28 (0.1)*
Chawla, 2017	7.37 (0.07)	7.29 (0.13)*
Gupta, 2019	7.36 [7.31-7.41]	7.33 [7.29-7.38]*
PO_2 or $TcPO_2$, mmHg		
Lee, 2012	76 (22)	80 (30)
Vento, 2004	72 (59-95)	60 (55-85)*

Author, year	Extubation Success	Extubation Failure
Dani, 2013	65 (15)	61 (16)
PCO_2 or $TcPCO_2$, mmHg		
Lee, 2002	39 (9)	42 (10)
Vento, 2004	44 (37-52)	52 (46-55)*
Hermeto, 2009	36 (12)	43 (7)*
Dani, 2013	43 (12)	39 (13)
Kaczmarek, 2013	40 (7)	44 (9)
Robles, 2015	47 (12)	45 (9)
Manley, 2016	44 (9)	50 (8)*
Chawla, 2017	40 (9)	50 (17)*
Gupta, 2019	36 [30-42]	38 [31-43]

Abbreviations: FiO_2 – fraction of inspired oxygen, RSS – respiratory severity score, PEEP – positive end-expiratory pressure, PO_2 – partial pressure of oxygen, $TcPO_2$ – transcutaneous oxygen pressure, PCO_2 – partial pressure of carbon dioxide, $TcPCO_2$ – transcutaneous carbon dioxide pressure.
Legend: The following table was derived from reviewing articles published since the year 2000 on the subject of extubation success/failure. It is limited to studies that only included extremely preterm infants, with gestational age <29 weeks and/or birth weight ≤ 1250g. Comparisons marked by an asterisk (*) were statistically significant (P value ≤ 0.05).

Figure 1.7 Procedure for performing predictor tests of extubation readiness in preterm infants



Abbreviations: CPAP – continuous positive airway pressure
Legend: The figure illustrates the process for performing predictor tests of extubation readiness in preterm infants, during a brief period on endotracheal continuous positive airway pressure.

Table 1.5 Clinical and physiological parameters evaluated during extubation readiness tests in preterm infants

Clinical Parameters

Heart rate
Respiratory rate
Work of breathing
Apneas
Oxygen saturation
Oxygen needs

Physiological Parameters

Pulmonary function
Tidal volume
Minute ventilation
Compliance
Resistance
Functional residual capacity

Respiratory muscle strength
Maximum inspiratory pressure
Diaphragmatic pressure
Tension-time index of the diaphragm and respiratory muscles

Breathing patterns
Respiratory rate
Inspiratory time
Expiratory time
Total respiratory cycle time

Cardiorespiratory behaviour
Heart rate variability
Respiratory variability

1.5 Extubation Failure

Considering that the assessment of extubation readiness remains highly subjective and inaccurate, it is not surprising that many extremely preterm infants fail their extubation attempt and require reintubation. Some studies have reported that nearly 70% of ELBW infants are reintubated during the course of their NICU hospitalization.[98, 99] That being said, when assessing whether an infant is ready for extubation (or developing a predictor of extubation readiness), it is important to first establish what exactly is considered a clinically meaningful definition of success/failure. Thus, this section reviews the definition (Subsection 1.5.1), causes (Subsection 1.5.2), and consequences of extubation failure (Subsection 1.5.3) in extremely preterm infants.

1.5.1 Definition of Extubation Failure

The definition of extubation failure is generally divided into two components: (1) a set of criteria that need to be fulfilled, and (2) a pre-set observation window.

Criteria to define extubation failure

In the literature, most studies define extubation failure as the need for reintubation (and resumption of MV) within a certain window of observation. However, there are some limitations to using reintubation as the outcome of interest. Typically, the decision to reintubate extremely preterm infants is made by the medical team based on evaluation of the frequency/severity of various symptoms (including apneas & bradycardias, increased work of breathing, respiratory acidosis and increased oxygen needs). But this decision is highly subjective, since tolerance of respiratory events and thresholds for reintubation may differ between clinicians and may depend on the environmental realities of the unit (e.g. staffing ratios, presence of in-house trained personnel and unit culture). Based on our international survey on peri-extubation practices, less

than 10% of respondents reported having standardized criteria for reintubation in their respective units.[60] Thus, while reintubation represents a simple and pragmatic definition of extubation failure, results may not be reproducible or generalizable to all units.

To circumvent the concerns about variability in reintubation practices, many clinical studies either propose (or mandate) criteria for reintubation, or define extubation failure as fulfillment of these criteria (irrespective of reintubation). A list of criteria proposed for reintubation or used to define extubation failure in clinical trials is presented in Table 1.6. The latter trials were identified using a recent systematic review of the literature evaluating interventions to improve extubation success rates in preterm infants.[72] As highlighted in the Table, significant variations exist in the criteria proposed to define failure, especially with regards to the frequency and severity of respiratory events (apneas, bradycardias and/or desaturations). This is not surprising, as relatively little is understood about how respiratory events of different frequencies, durations and severities (e.g. the depth of bradycardias or desaturations) can negatively impact the preterm lung and brain in the long-term. Besides, monitoring and documentation of respiratory events in practice is extremely challenging. As it stands, nurses and/or respiratory therapists are first warned about respiratory events via integrated bedside alarms on the patient's monitor. So they often cannot witness the triggers or sequence of events in real-time. As a result, their documentation typically underestimates the true occurrence of respiratory events.[100]

In sum, defining extubation failure as either the need for reintubation or as a set of clinical criteria is currently associated with important limitations. For that reason, further work is needed to better understand the best way to define extubation failure. Moreover, a more

evidence-based and standardized approach to reintubation is desirable. In the meantime, this thesis will mainly focus on reintubation when defining extubation failure.

Observation window

If an infant is reintubated 5 days after extubation, does this count as an extubation failure? Based on our international survey on peri-extubation practices, only 3% of respondents would have considered this infant to fail extubation.[60] In fact, extubation failure was defined as the need for reintubation within 24h, 48h, or 72h by 30%, 22% and 41% of respondents respectively. There are two plausible reasons why clinicians and researchers alike tend to limit observation windows to the first 72h after extubation. First, clinicians commonly believe that reintubations occurring beyond 72h from extubation are unlikely to be related to the patient's condition at the time of extubation. As an example, some have reasoned that a longer observation window may capture reintubations caused by new clinical diagnoses (such as sepsis or necrotizing enterocolitis), thereby leading to falsely elevated or misleading extubation failure rates.[87] However, there is currently no available longitudinal data (prior to this thesis) describing the timing and specific causes for which extremely preterm infants are reintubated in the NICU (see Subsection 1.5.2). Second, while clinicians are generally unanimous about the harms of prolonged MV exposure, there is less agreement about the independent effects of reintubation on morbidities and mortality. As a result, many clinicians consider that remaining extubated beyond 72h equates with reduced exposure to MV and hence better outcomes (even if later reintubation is required). However, the clinical implications of reintubations (for different causes and at different time intervals after extubation) are incompletely understood (see Subsection 1.5.3).

In the face of uncertainty regarding the optimal observation window, a recent systematic review of the literature was conducted to critically appraise the currently published definitions of

extubation failure.[101] The authors found significant variations in the observation windows used across studies to define extubation failure, ranging anywhere from 12h to 7 days. Interestingly, amongst studies limited to ELBW infants, the chosen observation window significantly affected the reported extubation failure rates. That is, failure rates increased from 13% when using an observation window of 24h, to 35% when extending the window to 7 days. The authors rightfully suggested that any observation window shorter than 72h (and potentially even shorter than 7 days) underestimated the true extubation failure rate amongst the smallest preterm infants.

All in all, given our incomplete understanding of the patterns and clinical implications of reintubations in extremely preterm infants, it is difficult to know which observation window to choose when evaluating extubation readiness in this population.

1.5.2 Causes of Extubation Failure

The decision to reintubate extremely preterm infant is generally prompted by various manifestations that tend to either cause clinical compromise to the patient, or cause distress to the patient's caregivers and allied health care professionals. The most common reason for reintubation is related to frequent and profound apneas, bradycardias and desaturations. Less common reasons (yet equally distressful) include increased oxygen needs, significant work of breathing, and severe respiratory acidosis. While the above symptoms represent direct reasons that trigger reintubation, they are highly non-specific and provide little information about the underlying causes for actually failing extubation. As highlighted in Table 1.7, infants can fail extubation for a multitude of complex and often co-existing causes. These different causes can be grouped around four main categories, including decreased respiratory drive, upper airway obstruction, lung disease (e.g. decreased functional residual capacity, atelectasis, inflammation),

and suboptimal delivery of non-invasive respiratory support. Some of these causes are physiological in nature (ex: immaturity of the respiratory control centers and lung parenchyma), some are pathological (ex: sepsis or necrotizing enterocolitis), and some are iatrogenic (ex: inadequate prong size, large interface leak or suboptimal suctioning of airway secretions). Altogether, these causes manifest themselves as respiratory events, higher oxygen needs, respiratory acidosis and increased work of breathing. However, with the current surveillance technology at our disposal, it is impossible to accurately know the exact causes behind each reintubation and their timing with respect to extubation (i.e. hours or days after extubation). As a consequence, current assessments of extubation readiness (and the chosen definitions of extubation failure) are not tailored towards the prediction of specific etiologies of reintubation.

1.5.3 Consequences of Extubation Failure

As alluded to in Subsection 1.5.1, little is concretely known about the unintended consequences of failing extubation in extremely preterm infants. In our international survey, when clinicians were asked whether they believed that reintubation was independently associated with increased mortality/morbidity, 43% said yes, 35% said no and 23% were unsure.[60] Most of the uncertainty stems from the fact that it is unclear whether the reintubation in itself directly causes harm, or whether the harm is indirectly incurred from re-exposure to MV (and its known complications). This doubt contrasts with adults, where a number of studies have consistently shown an independent association between extubation failure and increased mortality.[93]

Theoretically, there are two plausible mechanisms by which extubation failure could independently increase mortality/morbidities. First, the process of reintubation in itself is technically challenging and can thus lead to complications. In a large prospective study of 162

neonates, 107 out of 273 (39%) endotracheal intubations were associated with adverse events, and 24 intubations (9% overall) were associated with severe adverse events including hypotension (n=10), chest compressions (n=8), pneumothorax (n=1) and death (n=1).[102] Interestingly, adverse events were significantly more likely to occur with increasing number of intubation attempts, but also in cases where intubation was immediately needed for stabilization (with no time for premedication). From this study, one can infer that reintubations may technically be associated with more complications, since they are often more urgent in nature, with less time for preparation of equipment or premedication, and a more stressful environment (which could lead to a greater number of intubation attempts). Second, the clinical instability of the patient prior to reintubation (while still on non-invasive respiratory support) combined with the stress during the reintubation process (e.g. bag mask ventilation or clinical instability due to difficult intubation) may lead to additional ventilator-induced lung injury.

A total of 3 studies have attempted to evaluate the independent associations between reintubation and respiratory morbidities/mortality in extremely preterm infants, but with variable methodologies and results (Table 1.8).[18, 86, 87] In 2014, Jensen et al performed a retrospective study aiming to evaluate whether the number of MV courses (i.e. reintubations) during NICU hospitalization increased the risk of BPD, supplemental O_2 at discharge, tracheostomy and death amongst 3343 ELBW infants.[18] Prior to adjusting for the cumulative duration of MV, the authors observed a progressive increase in the risks of BPD and supplemental O_2 at discharge with each additional reintubation. However after adjusting for the cumulative MV duration, only exposure to 3 or more reintubations remained significantly associated with increased risk of BPD. Of note, 42% of all reintubated infants actually required ≥ 3 reintubations, suggesting that this scenario was fairly common. Moreover, the study did not take into account the time interval between

extubation and reintubation since all MV courses were included. Next, in 2016, Manley et al performed a secondary analysis of a RCT comparing post-extubation HFNC vs. CPAP, aiming to evaluate the outcomes associated with extubation failure (defined as reintubation within 7 days from extubation).[86] Out of 174 extremely preterm infants, 56 (32%) had a failed extubation. After adjusting for confounders (but not including cumulative MV duration), these infants had significantly greater risk of death prior to discharge, more prolonged respiratory support and more prolonged hospitalization compared to infants with successfully extubation. However, extubation failure did not increase the risk-adjusted odds of BPD or death/BPD in this cohort. Last, in 2017, Chawla et al performed a secondary analysis of the Surfactant, Positive Pressure and Oxygenation Randomized Trial (SUPPORT), aiming to investigate the effects of a failed extubation (defined as reintubation within 5 days from extubation) on morbidities/mortality in a cohort of extremely preterm infants.[87] After adjusting for confounders (but not including cumulative MV duration), the authors found that extubation failure was associated with significantly increased risk of mortality, BPD, duration of oxygen therapy, duration of MV, and length of hospitalization. Summarizing from these three available studies, although the need for reintubation appears to increase the risk of mortality and respiratory morbidities in extremely preterm infants, it may be partly (or mostly) mediated by the extension of MV exposure that accompanies reintubation. That being said, the differential impacts of reintubation at different time intervals from extubation on respiratory outcomes are unclear. Such information would be particularly crucial when trying to determine which reintubations should be targeted when developing a clinically useful predictor of extubation readiness.

Table 1.6 Criteria proposed for reintubation or to define extubation failure

Author, Year	FiO_2	pH	pCO_2	# Major Events [a]	# Respiratory Events [b]
Engelke, 1982	> +15%	> 7.2	> 60		
Higgins, 1991	> 0.6	< 7.23	> 60	1	≥ 3 apneas/h
Chan, 1993	> 0.6	< 7.25	> 50	1	Frequent minor
Annibale ,1994	> 0.8	< 7.2		1	≥ 6/h requiring stim
So, 1995	> 0.7	< 7.25	> 60	1	≥ 3/h
Davis, 1998	> +15%	< 7.25	> 50	1	> 6 in 6 h requiring stim
Friedlich ,1999	> 0.6	< 7.25	> 25%	1	
Dimitriou, 2000	> 0.6	< 7.25		1	Frequent minor
Barrington, 2001	> 0.7		> 70	> 2	> 6/day
Davis, 2001	> +15%	< 7.25	> 50	1	> 1/h in 6h
Khalaf , 2001		< 7.25	> 60	1	> 2–3/h
Stefanescu, 2003	> 0.5	< 7.25	> 65	> 1	Recurrent
Campbell, 2006	> 0.6	< 7.25		1	≥ 3/h any severity
Moretti, 2008	> 0.7	< 7.2	> 70		Severe recurrent
Gupta, 2009		< 7.2	> 60	> 1	
Yadav, 2012	> 0.7	> 7.2	> 60		Repeated episodes
Miller, 2010	> 0.7	< 7.25	> 65	2	>3 moderate events in 12h
Kumar, 2011	> 0.6			1	> 3/h
Obrien, 2012	> 0.6	< 7.25		1	≥ 4/h requiring mod stim
Collins, 2013	> +15%	< 7.25	> 66	1	> 6 in 6h
Kahramaner, 2013	> 0.6	< 7.25	> 60	1	Frequent apneas
Kirpalani, 2013				> 1	> 6 in 6h requiring stim
Manley, 2013	≥ +20%	> 7.2	> 60	> 1	≥ 6 in 6h requiring stim
Yoder, 2013	> 0.6		> 65	≥ 1	Frequent
Buzzella, 2014	> 0.6 and > +20%		> 65 or > +15		Repeated episodes
Peake, 2015	> 0.7	< 7.25	> 55	1	≥ 3 requiring stim

The table presents the criteria proposed to define extubation failure in randomized controlled trials. The trials were identified using a recent systematic review of the literature evaluating interventions to improve extubation success rates in preterm infants.

[a] Major events are apneas, bradycardias or desaturations requiring either bag mask ventilation, vigorous stimulation or significant resuscitation.

[b] Respiratory events are any apneas, bradycardias or desaturations requiring some form of intervention (e.g. stimulation or oxygen supplementation).

Abbreviations: FiO_2 – fraction of inspired oxygen, stim – stimulation, BMV – bag-mask ventilation

Table 1.7 Causes of reintubation in extremely preterm infants

Decreased respiratory drive / Central apneas
Immature respiratory control centers
Infection/necrotizing enterocolitis
Decreased O_2 delivery (hypoxia, shock, anemia)
Intraventricular hemorrhage (during the acute process)
Thermal instability
Metabolic derangements (ex: hypoglycemia)
Upper airway obstruction / Obstructive apneas
Airway edema (especially post-extubation)
Airway inflammation (e.g. from gastroesophageal reflux)
Airway secretions / mucus plugs
Vocal cord injuries
Subglottic stenosis
Pulmonary causes
Immature lung parenchyma
Atelectasis/Lung collapse
Low functional residual capacity (e.g. from abdominal distension)
Pulmonary overcirculation/hemorrhage (e.g. from large PDA)
Lung inflammation
Surfactant deficiency or dysfunction
New onset air leak syndrome (e.g. pneumothorax)
Diaphragmatic weakness/fatigue
Suboptimal provision of non-invasive respiratory support
Inadequate nasal prongs or mask size
Excessive interface leak
Inadequate clearance of airway secretions
Suboptimal positioning (e.g. excessive neck flexion or extension)

Abbreviation: PDA – patent ductus arteriosus.

Table 1.8 Independent associations between reintubation and respiratory morbidities/mortality in extremely preterm infants

Author, Year	N	Observation Window	Adjusted for MV	Findings (after adjusting for confounders)
Jensen, 2015	3343	Anytime	No	- Increased BPD and supplemental O_2 at discharge - No increase in death or tracheostomy
			Yes	- Increased BPD (only when ≥ 3 reintubations) - No increase in death, supplemental O_2 at discharge, or tracheostomy
Manley, 2016	174	7 days	No	- Increased death, prolonged respiratory support and prolonged hospitalization. - No increase in BPD or death/BPD
Chawla, 2017	926	5 days	No	- Increased death, BPD, death/BPD, days on O_2, length of MV and length of hospitalization

Abbreviation: BPD – bronchopulmonary dysplasia, MV – mechanical ventilation.

1.6 Gaps in Knowledge and Thesis Objectives

As portrayed in this literature review, the science of assessing extubation readiness in extremely preterm infants is highly imprecise and devoid of strong evidence to guide practices. On one hand, many predictor tests of extubation readiness have been evaluated over the years but their accuracy in predicting extubation success (over clinical judgment alone) has not been comprehensively evaluated. One of those predictors, the spontaneous breathing trial, has been adopted in many NICUs around the world despite the limited knowledge regarding its safety and efficacy. On the other hand, attempting to predict extubation readiness requires a solid understanding of what is considered a clinically representative and meaningful definition of extubation failure. Based on those gaps in knowledge, the thesis aims to comprehensively decipher the complexities associated with the assessment of extubation readiness and reintubation in extremely preterm infants. The thesis will be divided into five manuscript-based chapters. Chapter 2 will present a systematic review and meta-analysis about predictors of extubation readiness in preterm infants and their accuracies in predicting extubation success compared to clinical judgment. Chapter 3 will present the protocol for the prospective, multicenter observational study aiming to develop an Automated Predictor of Extubation readiness in extremely preterm infants (the APEX study). As part of APEX, a detailed clinical database was generated and served as the basis for three secondary studies (Chapters 4 through 6). Chapter 4 describes the longitudinal patterns of reintubation (i.e. the timing and causes of reintubation) amongst infants enrolled in APEX. Chapter 5 explores the impact of time interval between extubation and reintubation on death/BPD in the APEX cohort. Lastly, Chapter 6 describes the clinical safety of a 5-minute ET-CPAP trial and comprehensively evaluates its accuracy in predicting extubation success.

Bridging Text 1

As highlighted in Chapter 1, there has been ongoing interest in the literature to identify objective assessment tools that could improve our ability to predict a preterm infant's readiness for extubation in a timely and accurate fashion. Indeed, a number of studies have evaluated the accuracies of various different clinical and/or physiological parameters during a brief period of spontaneous breathing immediately prior to extubation. The most notable of these assessments, the spontaneous breathing trial, has even been increasingly adopted in clinical practice amongst the most immature patients. Nevertheless, the diagnostic accuracy of these different predictor tests and their usefulness in practice has not been carefully or systematically evaluated. Under that premise, we performed a systematic review and meta-analysis of published diagnostic accuracy studies to describe all evaluated predictor tests of extubation readiness in preterm infants and determine their accuracies in predicting successful extubation compared to clinical judgment alone. This review was published in *Archives of Diseases in Childhood: Fetal & Neonatal Edition* and the preprint of the article is presented in Chapter 2.[103]

Chapter 2 – Predictors of Extubation Readiness in Preterm Infants – A Systematic Review and Meta-Analysis

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2.1 Abstract

Context: A variety of extubation readiness tests have already been incorporated into clinical practice in preterm infants.

Objective: To identify predictor tests of successful extubation and determine their accuracy compared to clinical judgment alone.

Methods: MEDLINE, EMBASE, PubMed, Cochrane Library and Web of Science were searched between 1984 and June 2016. Studies evaluating predictors of extubation success during a period free of mechanical inflations in infants less than 37 weeks gestation were included. Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. After identifying and describing all predictor tests, pooled sensitivity and specificity estimates for the different test categories were generated using a bivariate random-effects model.

Results: Thirty-five studies were included, showing wide heterogeneities in population characteristics, methodologies and definitions of extubation success. Assessments ranged from a few seconds to 24h, provided 0-6 cmH_2O positive end-expiratory pressure and measured several clinical and/or physiological parameters. Thirty-one predictor tests were identified, showing good sensitivities but low and variable specificities. Given the high variation in test definitions across studies, pooling could only be performed on a subset. The commonly performed spontaneous breathing trials had pooled sensitivity 95% (95% CI 87-99%) and specificity 62% (95% CI 38-82%), while composite tests offered the best performance characteristics.

Conclusions: There is a lack of strong evidence to support the use of extubation readiness tests in preterm infants. Although spontaneous breathing trials are attractive assessment tools, higher quality studies are needed for determining the optimal strategies for improving their accuracy.

2.2 Introduction

Preterm infants commonly require intubation and mechanical ventilation (MV) after birth.[1] Due to complications associated with MV, early extubation is generally recommended.[2, 3] However, premature extubation increases the risk of respiratory failure and reintubation, which also carries hazards.[4] Therefore, both an early and successful extubation are desirable.

Currently, the decision to extubate relies primarily on clinical judgment, i.e. the physician's experience and interpretation of infants' overall clinical stability.[5] This subjective assessment has resulted in widely variable peri-extubation practices across neonatal intensive care units.[5] For those reasons, clinicians have attempted to identify objective predictors of extubation readiness. Assessments done while patients receive invasive ventilatory support have been rather disappointing; mechanical inflations likely mask the infant's ability to sustain breathing once disconnected from the ventilator.[6] Instead, investigators have turned towards assessments of clinical and physiological parameters during a pre-determined period free of mechanical inflations, either via endotracheal continuous positive airway pressure (ETT-CPAP) or through temporary disconnection from the ventilator. A variety of extubation readiness tests, particularly spontaneous breathing trials (SBT), have already been incorporated in clinical practice worldwide,[5] but the evidence supporting their use has not been established. Thus, we performed a systematic review of the literature to identify predictor tests of successful extubation in preterm infants and determine their accuracy compared to clinical judgment alone.

2.3 Methods

A protocol was developed in conformity with standard guidelines on systematic reviews of diagnostic studies [7] and reported using recommended PRISMA guidelines.[8]

Search strategy

A pre-specified written protocol was designed with the help of medical librarians (online supplementary appendix S2.1). Articles in all languages between 1984 and June 2016 were searched within Ovid MEDLINE, Ovid EMBASE, PubMed, Cochrane Library and Web of Science. References of articles assessed for eligibility were hand-searched for additional relevant studies.

Study selection

After removing duplicates, the title and abstract of all articles were screened by one investigator (WS). Studies were eligible for full-text review if they met the following pre-determined criteria: (1) study population included preterm infants < 37 weeks gestation; (2) topic was about extubation readiness and/or extubation success/failure; (3) full text was available. Animal or in-vitro studies, review articles, conference proceedings, case reports and commentaries were excluded. Once abstracts were identified, two independent investigators (WS and SL) reviewed the articles for eligibility. Only studies that specifically evaluated potential predictors or tests of extubation readiness during a period free of mechanical inflations were included. Any discrepancies regarding final inclusions were resolved through discussion with a third reviewer (GMS).

Data extraction

Two investigators (WS and SL) independently extracted all information using a standardized piloted data collection form.

Population characteristics – the study inclusion criteria and the cohort's birth weight and gestational age (GA) were recorded. In cases where weight and GA were reported in subgroups, weighted averages were calculated to deduce the cohort's mean values.

Reference standard – Extubation was defined as the reference standard, and was based on the treating physician's clinical judgment, routine institutional practices or study-specific criteria. A note was made of the ventilator mode, settings and blood gas ranges when infants were deemed 'ready' for extubation, as well as type of post-extubation respiratory support provided.

Index test – The index test referred to the extubation readiness assessment under evaluation. The duration, level of endotracheal positive end-expiratory pressure (PEEP) and types of physiologic measurements and/or clinical observations performed during the assessment were recorded. The results of all predictors of extubation success evaluated during that assessment were also abstracted; some studies reported the means or medians in patients who were successfully and unsuccessfully extubated. Others defined a diagnostic test (using thresholds or composite definitions) and reported its sensitivity, specificity, predictive values, accuracy or area under the receiver operating characteristic (ROC) curve.

Target condition: The primary definition and time frame used to classify infants into extubation success or failure were recorded. The proportion of infants that were successfully extubated was also noted for all definitions and time frames provided.

Assessment of risk of bias

Two reviewers (WS and SL) assessed the methodological quality of included studies using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool.[9] A narrative summary was produced outlining whether the studies had low, high or unclear risk of bias and any applicability concerns.

Data synthesis and analysis

A descriptive analysis was first conducted on all identified predictors of extubation readiness. Distinction was made between predictor tests that were incorporated into clinical

practice (i.e. extubation on the premise of passing the test) vs. those evaluated by cross-sectional design (i.e. tests were performed but did not guide extubation). Meta-analysis was only possible for studies in which one or more predictor test was defined and evaluated by cross-sectional design. From the available data, 2 x 2 tables were constructed to derive sensitivity/specificity and generate coupled forest plots (Review Manager 5.3). A 'cross-hairs' plot was also produced (R version 3.1.0) to better display the variability in ROC space between sensitivity/specificity estimates.[10] Wherever appropriate, pooled estimates of sensitivity and specificity were computed for the different types of predictor tests. Subgroups with ≥ 5 evaluations of the test were analyzed using the bivariate random-effects model ('metandi' module, Stata, version 10) while those with 2-4 evaluations could only be analyzed using a univariate model (Meta-DiSc software, version 1.4). A hierarchical summary ROC curve was planned to be constructed whenever more than five evaluations of the predictor test could be pooled.

2.4 Results

Our search strategy yielded 3052 abstracts, out of which 207 full-text articles were reviewed and 35 included for analysis (Figure 2.1).[11-44] A detailed outline of the quality of each included study is available in supplementary appendix S2.2. Of note, all but 3 studies had at least 2 or more domains from the QUADAS-2 evaluation with unclear or high risk of bias and applicability concerns.

The overall characteristics of the included articles are shown on Table 2.1 and expanded in supplementary appendix S2.3. There were 12 randomized controlled trials (RCTs), 22 prospective observational and 1 retrospective studies. Sample sizes were small (median 49 patients, interquartile range 35-59) and mostly single-center. All assessments of extubation

readiness were performed once the patient was deemed 'ready' for extubation, ranged anywhere from a few seconds to 24h and used PEEP levels between 0-6 cmH_2O. Infants were exposed to different peri-extubation practices, weaning strategies and post-extubation respiratory support modalities. Extubation success was described using varying definitions and time frames ranging from 24-120h of observation after extubation.

Eighteen studies evaluated at least one index test by cross-sectional design (Table 2.2). The most commonly investigated parameters related to tidal volume, spontaneous minute ventilation and respiratory muscle function. The majority of variables failed to classify infants into their respective extubation outcomes, except for some measures of minute ventilation and diaphragmatic function. From these variables, a large number of predictor tests were derived (supplementary appendix S2.4). Test definitions were highly variable across studies, and were divided into 3 categories: physiological, clinical and composite tests. Clinical tests defined extubation success/failure based on a combination of clinical events (apneas, bradycardias, desaturations) and/or blood gases. The assessment periods were either short (≤ 30min), intermediate (1h) or prolonged (4-24h). Composite tests combined 2 or more predictors instead of evaluating each component separately. These included tests combining SBT with variability indices of breathing, assessments of the load/capacity ratio of inspiratory muscles or cardiorespiratory signal analysis.

Thirteen studies had at least one diagnostic test for which 2x2 tables could be constructed, resulting in 31 predictor tests included in the meta-analysis. As illustrated on the forest plots (Figure 2.2) and 'cross hairs' plot (supplementary appendix S2.5), predictor tests had high sensitivity but low and variable specificity. Pooled sensitivities and specificities of the different tests are shown on Table 2.3. Minute ventilation-related tests had pooled sensitivity and

specificity of 84% (95% CI 77-90%) and 71% (95% CI 57-83%), while SBTs had pooled sensitivity and specificity of 95% (95% CI 87-99%) and 62% (95% CI 38-82%), respectively. Compared to individual tests, composite tests had higher sensitivities and specificities, with more balanced tradeoffs between the two values. Given the limited number of studies evaluating each type of predictor test, no hierarchical summary ROC could be generated.

Finally, 20 studies extubated infants on the basis of passing a predictor test; only 5 were evaluated using a RCT.[11, 12, 21, 23, 29] Four RCTs examined the usefulness of prolonged ETT-CPAP trials (4-24h) compared to direct extubation from low ventilatory settings, showing no added benefits and possible harm when ETT-CPAP was used for several hours. In the most recent RCT, outcomes were compared between infants extubated after passing a minute ventilation test compared to clinical judgment alone.[29] Although infants receiving the test were extubated significantly sooner, there were no statistically significant differences in extubation success rates between both groups. As for SBTs, 4 studies have reported using the test as part of routine practice, reporting extubation success rates between 67-78%.[33, 35, 39, 42] In the largest study, the performance of daily 3-min SBT's was compared with a historical cohort of infants extubated based on clinical judgment alone.[33] Although infants in the SBT group were extubated from significantly higher ventilator settings, they had similar weaning durations and extubation success rates compared to controls.

2.5 Discussion

To our knowledge, this is the first systematic review appraising the evidence for using extubation readiness tests in preterm infants. The majority of identified studies were small, single-center and with significant risks of bias and applicability concerns. Assessments were

done using heterogeneous methodologies and different definitions of extubation success, making it very difficult to infer any strong recommendation. From the meta-analysis, predictor tests had high sensitivity but low and variable specificity. For clinicians, this means that at the time a patient is deemed 'ready' for extubation, passing a test correctly identifies almost all patients that will have a successful extubation, but a significant proportion of infants that fail extubation would be misclassified by the test. In other words, predictors are great at reinforcing the clinician's intent to extubate, but add little to no value in detecting failures.

The fact that infants were only evaluated when deemed 'ready' for extubation by the clinicians introduces test-referral bias, whereby physicians' own judgments of extubation readiness influenced which patients actually underwent the test. As such, systematically fewer patients with negative results and relatively more patients with positive results were tested, thereby overestimating sensitivity and underestimating specificity.[45, 46] Moreover, given that perceptions of extubation readiness can highly vary within and between studies, there is considerable heterogeneity in the pre-test probability of extubation success, which in turn affects the results of diagnostic tests. Both phenomena can potentially impair internal validity and compromise generalizability of the predictor tests, as previously demonstrated.[47]

Despite the aforementioned limitations, some units have already incorporated predictors (especially SBTs) into daily practice as a way to promptly recognize an infant's potential for extubation.[5, 28, 33] Unfortunately, these tests are often interpreted differently and applied outside unit-specific guidelines.[5] Although SBTs are attractive, their diagnostic accuracy has only been evaluated in 2 small single-center studies, showing pooled sensitivity and specificity of 95% and 62%, respectively.[31, 40] Moreover, evidence from only 2 studies demonstrated that serial readiness tests did not affect extubation success rates.[29, 33] Contrary to neonates, the

incorporation of extubation readiness tests into MV weaning protocols in adult and pediatric patients has been extensively studied,[48, 49] showing improved outcomes, reduced costs and decreased MV duration.[50, 51] Such level of evidence is still lacking in preterm infants, but with the rising number of neonatal units developing weaning protocols,[52] understanding the role of those tests during that process is critical.

As demonstrated by our review, designing a predictor of extubation readiness in preterm infants is challenging. These infants are highly vulnerable and can fail extubation due to many reasons, including underdeveloped lungs, low lung compliance, high airway resistance and immature central respiratory drive. Ideally, the perfect test would accurately predict an infant's ability to tolerate extubation by integrating all these factors and mimic their post-extubation physiological conditions. As such, the choice of duration, level of support used and measurements performed during the test could considerably influence its accuracy.

Duration. A wide range of durations (few seconds to 24h) were noted in all studies. Original investigations performed ETT-CPAP trials of 6-24 hours, but this practice went out of style after mounting concerns of high airway resistance when breathing through an endotracheal tube.[53] For this reason, more recent studies curtailed the time frame to 3-5 minutes. Nonetheless, short trials could potentially be misleading, as they may not provide sufficient time to ensure that the highest-risk patients can sustain spontaneous breathing.

Level of support. An interesting change has occurred in the amount of PEEP provided during the assessment, from 0-3 cm H_2O to the currently adopted 5-6 cm H_2O. This stems from observations that infants submitted to low ETT-CPAP levels were at higher risk of derecruitment and extubation failure.[53] However, these same infants were kept at 2-3 cm H_2O for 12-24h, a significantly prolonged duration that may have potentiated the loss of functional residual

capacity. Evidence from adult and pediatric critical care patients suggests that PEEP can reduce patient efforts by 30-60%, significantly decreasing the respiratory load in comparison to the expected work of breathing after extubation.[54, 55] Evidence for this is limited in neonates, but if the post-extubation period is truly characterized by relatively high upper airway resistance, then the addition of PEEP may underestimate the true failure risk.

Clinical and physiological measurements. Researchers have mostly been interested in studying tests that rely on simple physiological measurements or bedside clinical observations because of their ease-of-use and convenience. Unfortunately, studies investigating these predictors individually have shown suboptimal results. This is not surprising, as it is unlikely that any single predictor would accurately encompass the entire spectrum of reasons for failing extubation. Consequently, studies have begun exploring more complex assessments, such as diaphragmatic function and automated biological signal analyses, to better describe the integrity and maturity of individuals' intrinsic cardiorespiratory behavior.[43] In fact, the combination of multiple predictors resulted in the most favorable performance characteristics. Although promising, such tests are presently impractical for clinical use and deserve further investigation.

The review had some limitations. There are no established method for formally assessing publication bias in diagnostic studies [56], and it was not possible to perform a bivariate random effects model due to the small number of studies evaluating most predictors (this is the preferred method for meta-analysis of diagnostic studies, since it takes into consideration the tradeoff between sensitivity and specificity within individual studies).[57] Nevertheless, the review had several strengths, including its permissive inclusion criteria, rigorous design and comprehensive data synthesis. Additionally, the review highlights some major gaps in the methodological quality of diagnostic studies of extubation readiness, emphasizing the need to standardize the

reporting process and achieve consensus on important outcomes of interest (e.g. extubation success).[58]

In conclusion, there is a lack of strong evidence to support using extubation readiness tests in preterm infants. Current predictors have low overall accuracy and add little benefit in the identification of extubation failures. Although SBTs are attractive assessment tools, higher quality studies are needed to determine the best duration, level of PEEP and definition of test pass/failure to guide their use in the most vulnerable infants. Moreover, a combination of clinical and physiological measurements during such assessments may further improve their accuracy.

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2.7 Figures and Tables

Figure 2.1 PRISMA Flow diagram

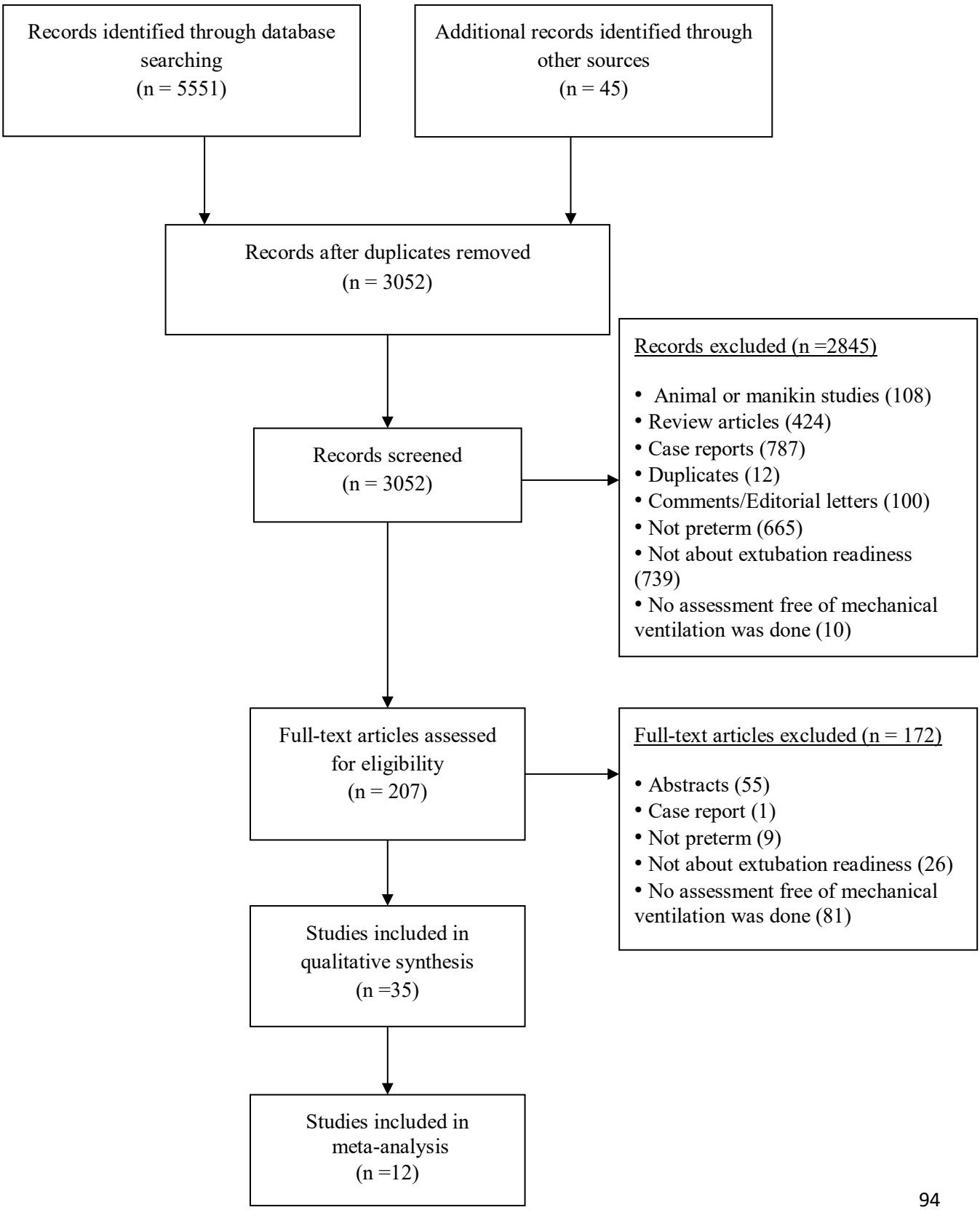


Table 2.1 Overall Characteristics of included studies

STUDY CHARACTERISTICS	
Number of patients enrolled	49 [35-59]
Single center	31 (89)
Gestational age (weeks)	26.1-32.8
Birth weight (grams)	784-1934
Day of life at time of study	2-15
Study design	
Randomized controlled trial	12 (34)
Prospective observational	22 (63)
Retrospective	1 (3)
ASSESSMENT OF EXTUBATION READINESS	
Duration of assessment	
< 3 minutes	7 (20)
3-10 minutes	14 (40)
30 min – 2 hours	8 (23)
4-24 hours	4 (11)
Not specified	2 (6)
Level of PEEP used	
Zero	6 (17)
2 to 4 cmH_2O	9 (26)
5 to 6 cmH_2O	5 (14)
Combination of 2 levels of PEEP	2 (6)
Not specified	13 (37)
OUTCOME: EXTUBATION SUCCESS	
Primary definition used	
No reintubation	26 (74)
No resumption of invasive MV	4 (11)
No reintubation or institution of CPAP	5 (14)
Time frame used for primary definition	
Anytime	1 (3)
≤ 24 hours	6 (17)
48 hours	15 (43)
72 hours	11 (31)
120 hours	1 (3)
Not specified	1 (3)

Values are expressed as median [IQR], n (%) or range.

Table 2.2 Predictors of extubation readiness

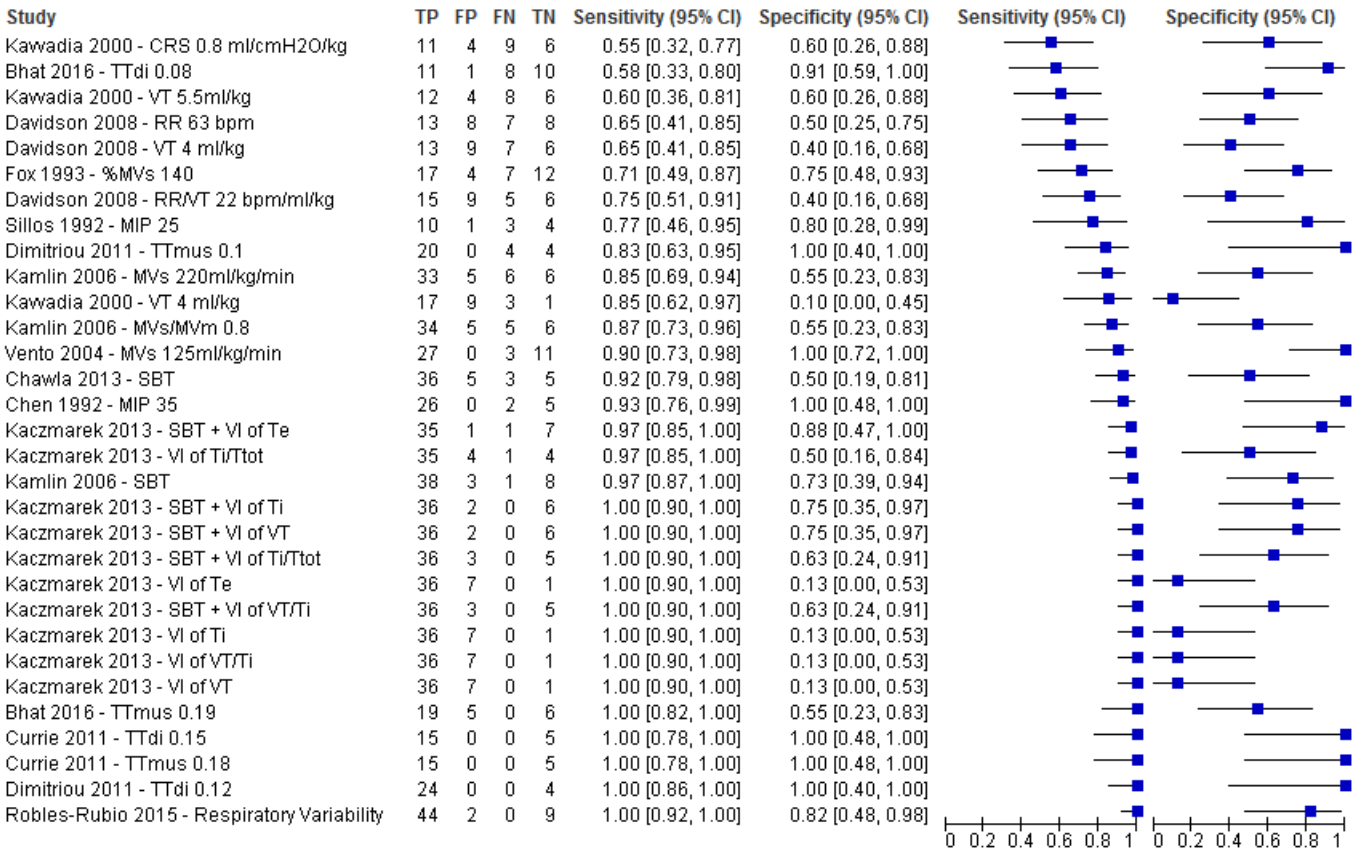
Author, year	Success	Failure	P value	AUC
VENTILATION				
Respiratory Rate, RR (breaths per min)				
Fox, 1993	81.4 (44.3-127)	75.6 (43.3-91.8)	0.52	
Smith, 1999	58 (12)	60 (11)	NS	
Vento, 2004	53 (28-67)	43 (37-56)	0.0129	
Davidson, 2008	53.4 (15.5)	65 (17.8)	0.054	
Dimitriou, 2011	74 (48-99)	68 (52-80)	0.224	
% Of baseline RR after adding external dead space				
Fox, 1993	99.4 (64.9-164)	93 (65.8-113)	0.281	
Tidal Volume, Vt (mL/kg)				
Veness-Meehan, 1990	5.1 (SE 0.3)	6 (SE 0.5)	NS	
Fox, 1993	5.32 (3-9.62)	4.64 (3.24-13.4)	0.7	
Smith, 1999	4.1 (1.4)	3.7 (1)	NS	
Kavvadia, 2000	5.8 (2-8.6)	5.4 (3.1-8.7)	NS	0.57
Kavvadia, 2000	5.8 (2-8.6)	5.4 (3.1-8.7)	NS	0.57
Vento, 2004	5.9 (4-7.8)	5.9 (4.1-8.7)	0.2512	
Kamlin, 2006				0.57
Davidson, 2008	5.3 (2.2)	4.9 (3.1)	0.563	
Dimitriou, 2011	3.2 (2-9)	2.8 (2-4.2)	0.512	
Kaczmarek, 2013	4.5 (1.8)	4.21 (1.2)	NS	
% Of baseline Vt after adding external dead space				
Fox, 1993	162 (79.3-221)	140 (68.5-206)	0.136	
Spontaneous minute ventilation, MVs (mL/kg/min)				
Veness-Meehan, 1990	341 (SE 18)	370 (SE 34)	NS	
Fox, 1993	383 (134-1090)	353 (186-784)	0.31	
Vento, 2004	309 (223-434)	240 (160-353)	0.0039	
Kamlin, 2006	314 (116)	271 (113)	NS	0.6
Chawla, 2013 (L/min)	0.26 (0.11)	0.27 (0.18)	0.86	
% Of baseline MVs after adding external dead space				
Fox, 1993	156 (89.3-230)	131 (75.2-165)	0.006	
% Time spent with MVs below 125ml/kg/min				
Vento, 2004	1.3 (0-12.9)	13.6 (8.2-45.4)	<0.0001	0.94
Minute ventilation ratio, MVs/MVm				
Kamlin, 2006				0.74
Chawla, 2013	0.81 (0.24)	0.53 (0.29)	<0.01	
Rapid shallow breathing index, RR/Vt (breaths/min/ml/kg)				
Smith, 1999	13.6 (6.7)	14.8 (4.1)	NS	
Davidson, 2008	16.5 (7.4)	21.3 (7.8)	0.074	
Dimitriou, 2011	21.9 (7.7-48.9)	22.2 (15.4-29.3)	0.896	
BREATHING PATTERN				
Inspiratory time, Ti (sec)				
Smith, 1999	0.36 (0.11)	0.39 (0.09)	NS	

Author, year	Success	Failure	P value	AUC
Kaczmarek, 2013	0.43 (0.2)	0.39 (0.12)	NS	
Expiratory time, Te (sec)				
Kaczmarek, 2013	0.58 (0.22)	0.53 (0.13)	NS	
Ratio of Ti over total respiratory cycle time, Ti/Ttot				
Currie, 2011	0.33 (0.2-0.49)	0.34 (0.31-0.42)	0.513	
Dimitriou, 2011	0.39 (0.29-0.49)	0.367 (0.34-0.44)	0.694	
Kaczmarek, 2013	0.44 (0.08)	0.46 (0.08)	NS	
Mean inspiratory flow, Vt/Ti (ml/kg/sec)				
Veness-Meehan, 1990	13.8 (SE 2.8)	14 (SE 1.3)	NS	
Smith, 1999	12 (7.3)	12.5 (3.1)	NS	
Kaczmarek, 2013	14.2 (8)	11.2 (4.1)	NS	
LUNG MECHANICS				
Compliance, C (ml/cmH_2O/kg)				
Veness-Meehan, 1990	1 (SE 0.1)	1.1 (SE 0.2)	NS	
Higgins, 1991	1.2	1.3	NS	
Kavvadia, 2000	0.94 (0.31-1.54)	0.74 (0.42-1.05)	NS	0.57
Dimitriou, 2002	0.77 (0.32-2.18)	0.79 (0.43-1.16)	NS	0.54
Vento, 2004	1.2 (0.52-1.9)	0.95 (0.62-1.5)	0.09	
Resistance, R (cmH_2O/l/sec)				
Veness-Meehan, 1990	37.4 (SE 3.8)	43.6 (SE 5.8)	NS	
Higgins, 1991	56.2	37.1	NS	
Vento, 2004	70 (27-125)	69 (49-164)	0.4	
Work of breathing (gram x cm/kg)				
Veness-Meehan, 1990	10.4 (SE 1.6)	15.1 (SE 3.9)	NS	
Higgins, 1991	7.7	8.6	NS	
RESPIRATORY MUSCLE FUNCTION				
Mean inspiratory pressure (cmH_2O)				
Dimitriou, 2002	16.7 (6.6-57.2)	11.3 (7.3-19.7)	<0.03	0.78
Currie, 2011	6.3 (3.3-11.8)	10.6 (9.1-13.6)	0.013	
Mean inspiratory pressure adjusted to weight (cmH_2O/kg)				
Dimitriou, 2002			NS	0.59
Maximum inspiratory pressure, MIP (cmH_2O)				
Chen, 1992	42.6 (7.2)	21.2 (1.8)	<0.01	
Sillos, 1992	33.8 (12.3)	23.3 (15)	<0.005	
Dimitriou, 2002	24.8 (14.1-69.3)	14.3 (9.9-21.2)	<0.01	0.9
Currie, 2011	45.5 (29.4-83)	19 (17-30.3)	0.002	
Bhat, 2016	46 (15-79)	37 (9-88)	0.42	0.57
Maximum inspiratory pressure adjusted to weight (cmH_2O/kg)				
Dimitriou, 2002			NS	0.52
Currie, 2011	29.1 (9.9-50.6)	22.1 (8-29.4)	0.074	
Maximum expiratory pressure (cmH_2O)				
Bhat, 2016	35 (6-81)	27 (15-42)	0.17	0.66
Ratio of mean inspiratory pressure/MIP				

Author, year	Success	Failure	P value	AUC
Currie, 2011	0.12 (0.04-0.32)	0.56 (0.45-0.68)	0.001	
Respiratory drive (cmH_2O)				
Currie, 2011	4.4 (2-7.7)	6.3 (4.8-7.1)	0.126	
Bhat, 2016	8 (2.8-17.7)	9.7 (1.7-18.7)	0.39	0.59
Mean diaphragmatic pressure (cmH_2O)				
Currie, 2011	7.8 (3.7-19.9)	8.5 (7.7-12.6)	0.275	
Dimitriou, 2011	8.9 (5.2-15.6)	13.7 (11.2-16.7)	0.03	
Maximum diaphragmatic pressure (cmH_2O)				
Currie, 2011	48.2 (30.1-83)	17.9 (17-33.1)	0.002	
Bhat, 2016	56.5 (30-305)	48.8 (28.4-88.7)	0.13	0.68
Maximum diaphragmatic pressure adjusted to weight (cmH_2O/kg)				
Currie, 2011	29.7 (9.9-51.9)	22.1 (8-26.7)	0.067	
Ratio of mean/maximum diaphragmatic pressure				
Currie, 2011	0.17 (0.07-0.29)	0.48 (0.38-0.65)	0.001	
Dimitriou, 2011	0.2 (0.09-0.34)	0.4 (0.28-0.49)	0.003	
Transdiaphragmatic pressure-time-product (cmH_2O/sec/min)				
Dimitriou, 2011	200 (101-417)	268 (170-332)	0.358	
Tension time index of the diaphragm, TTdi				
Currie, 2011	0.065 (0.02-0.12)	0.16 (0.15-0.2)	0.001	1
Dimitriou, 2011	0.079 (0.03-0.12)	0.142 (0.12-0.18)	0.002	
Bhat, 2016	0.04 (0.02-0.14)	0.16 (0.03-0.79)	<0.001	0.89
Tension time index of respiratory muscles, TTmus				
Currie, 2011	0.04 (0.01-0.13)	0.19 (0.19-0.21)	0.001	1
Dimitriou, 2011	0.079 (0.04-0.12)	0.145 (0.13-0.17)	0.002	
Bhat, 2016	0.07 (0.03-0.17)	0.19 (0.08-1.39)	0.003	0.82
VITAL SIGNS				
Fraction of inspired oxygen				
Vento, 2004	0.23 (0.21-0.28)	0.25 (0.22-0.3)	0.0175	
Robles-Rubio, 2015	0.26 (0.07)	0.32 (0.23)	<0.05	
Heart Rate, beats per min				
Smith, 1999	145 (13)	149 (12)	NS	
Oxygen saturation, %				
Smith, 1999	92 (2.5)	92 (3.6)	NS	
Vento, 2004	95 (88-98)	91 (88-95)	0.0004	0.75
Robles-Rubio, 2015	94 (4)	94 (3)	NS	
Transcutaneous oxygen pressure, mmHg				
Vento, 2004	72 (59-95)	60 (55-85)	0.0031	0.8
Transcutaneous carbon dioxide pressure, mmHg				
Vento, 2004	44 (37-52)	52 (46-55)	<0.0001	0.63

* Data is presented as mean (standard deviation) or median (interquartile range).
Abbreviations: SE – Standard error, AUC – area under the curve, NS – non-significant

Figure 2.2 Forest plot of sensitivity and specificity of predictor tests of extubation readiness



Forest plot of sensitivity and specificity of diagnostic tests of extubation readiness performed during a period free of mechanical inflations**.** Data is presented in order of increasing sensitivity.

Abbreviations: TP – true positive, FP – false positive, FN – false negative, TN – true negative, CI – confidence interval, VT – tidal volume, TTIdi – diaphragmatic pressure-time index, TTmus – tension time index of respiratory muscles, MVs – spontaneous minute ventilation, MVm – mechanical minute ventilation, MIP – maximum inspiratory pressure, CRS – compliance of the respiratory system, SBT – spontaneous breathing trial, VI – variability index, Ti – inspiratory time, Te – expiratory time, Ttot – total breath time, Vt/Ti – mean inspiratory flow, RR – Respiratory rate

Table 2.3 Pooled results for different predictors of successful extubation

Predictor	Study – Definition / threshold	Summary sensitivity (95% CI)	Summary specificity (95% CI)
Physiological Tests			
Vt	Kavvadia 2000 – Vt > 4 ml/kg Davidson 2008 – Vt ≥ 4ml/kg	75 (59-87)	28 (12-49)
MVs	Fox 1993 – %MVs after added dead space > 140% Vento 2004 – MVs<125 ml/kg/min for ≤ 8.1% of time Kamlin 2006 – MVs > 220ml/kg/min Kamlin 2006 – MVs/MVm > 0.8	84 (77-90)	71 (57-83)
VI of breathing pattern	Kaczmarek 2013 – VI of Ti Kaczmarek 2013 – VI of Te Kaczmarek 2013 – VI of Vt Kaczmarek 2013 – VI of Ti/Ttot Kaczmarek 2013 – VI of Vt/Ti	100 (86-100)	18 (7-38)
Clinical Tests			
SBT	Kamlin 2006 – Clinical definition Chawla 2013 – Clinical definition	95 (87-99)	62 (38-82)
Composite Tests			
SBT + VI of breathing pattern	Kaczmarek 2013 – SBT + VI of Ti Kaczmarek 2013 – SBT + VI of Te Kaczmarek 2013 – SBT + VI of Vt Kaczmarek 2013 – SBT + VI of Ti/Ttot Kaczmarek 2013 – SBT + VI of Vt/Ti	99 (97-100)	73 (56-85)
TTdi	Currie 2011 – TTdi ≤ 0.15 Dimitriou 2011 – TTdi ≤ 0.12 Bhat 2016 – TTdi < 0.08	86 (75-94)	95 (75-100)
TTmus	Currie 2011 – TTmus ≤ 0.18 Dimitriou 2011 – TTmus ≤ 0.1 Bhat 2016 – TTmus < 0.19	94 (84-98)	75 (51-91)

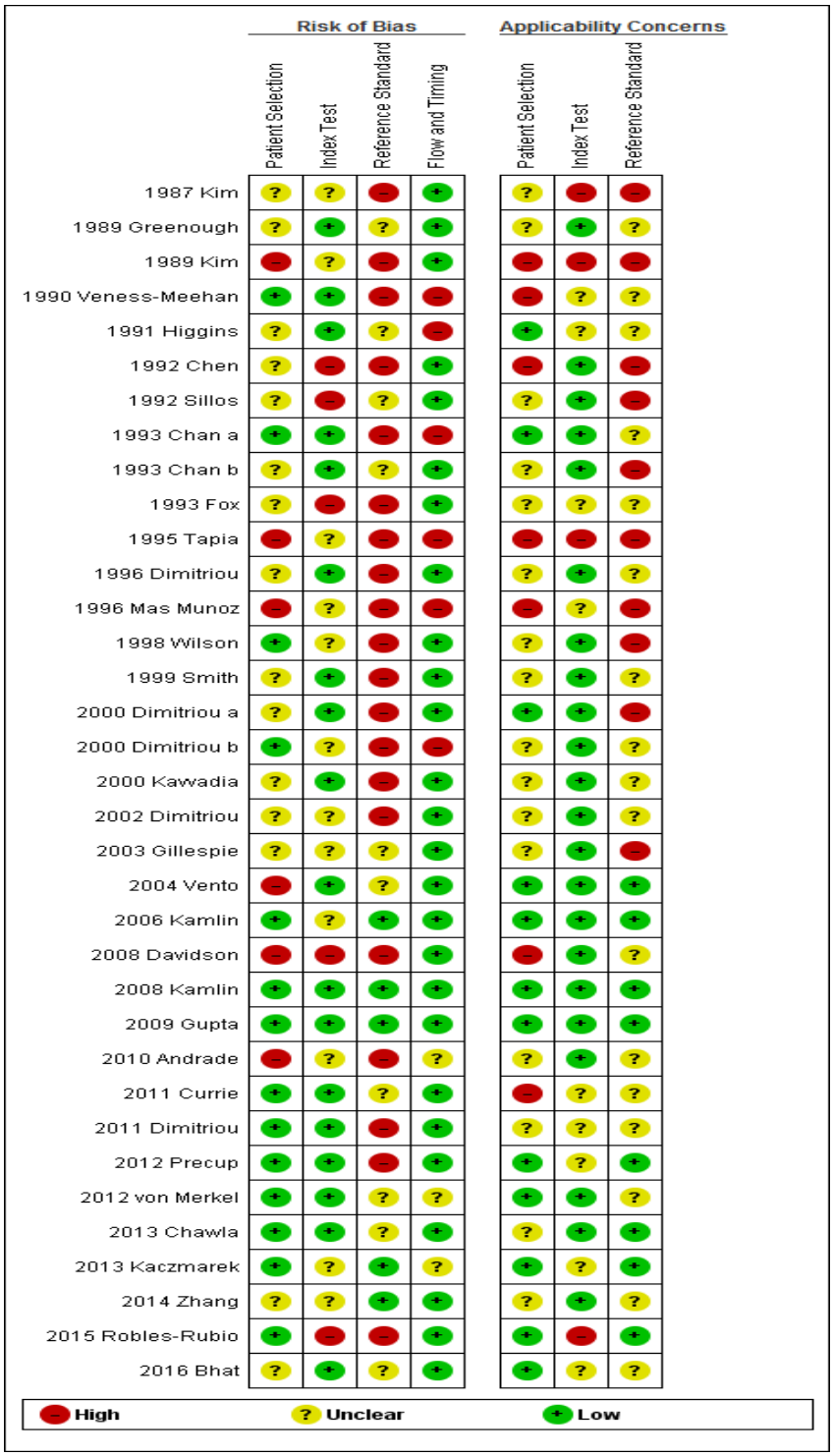
Data for which 2 or more tests could be grouped are presented.
Abbreviations: CI – confidence interval, SBT – spontaneous breathing trial, Vt – tidal volume, MVs – spontaneous minute ventilation, MVm – mechanical minute ventilation, VI – variability index, Ti – inspiratory time, Te – expiratory time, Ttot – total breath time, Vt/Ti – mean inspiratory flow, TTdi – diaphragmatic tension time index, TTmus – tension time index of respiratory muscles

2.8 Supplementary Material

Supplementary Appendix S2.1 Representative electronic search strategy from Ovid MEDLINE

#	Searches	Results
1	Airway Extubation/	(614)
2	(extub* or preextub* or detubat* or deextub* or postextub*).tw,kf.	(10470)
3	((discontin* or dis-contin* or remov* or cease* or cessat* or suspen* or withdraw* or stop* or terminat*) adj3 (respirat* or ventilat*)).tw,kf.	(2439)
4	1 or 2 or 3	(12850)
5	(newborn* or new-born* or neonat* or neo-nat* or prematur* or pre-matur* or preterm* or pre-term* or premie* or perinat* or peri-nat* or postmatur* or post-matur* or NICU).tw,kf.	(498641)
6	exp Infant, Newborn/	(539971)
7	Intensive Care Units, Neonatal/	(11032)
8	(neonat* or neo-nat*).jw.	(23372)
9	5 or 6 or 7 or 8	(813976)
10	4 and 9	(1780)
11	Animals/ not (Animals/ and Humans/)	(4228315)
12	10 not 11	(1725)
13	limit 12 to yr="1984 - Current"	(1655)
14	remove duplicates from 13	(1608)

Supplementary Appendix S2.2 Risk of bias and applicability concerns for included studies



Risk of bias and applicability concerns using the quality assessment of diagnostic accuracy studies (QUADAS-2) tool: review authors' judgments about each domain for each included study

Supplementary Appendix S2.3 Individual study characteristics

Author, year (n)	Population	Index Test	Reference Standard	Target Outcome
Cross-Sectional Design Studies (index test not used for extubation)				
Veness-Meehan, 1990 (n=50)	Inclusion: all preterm infants intubated for RDS Cohort: GA 29.7w, BW 1476g Caffeine: 40%; Surfactant: n/a	PEEP 4 Duration: ~ 1min Measurements: Vt, MVs, Ti, Ttot, C, R and WOB	Settings: FiO2≤0.4, PIP≤15 (if ≤2kg) or ≤20 (if ≥2kg), Rate≤15 (if ≤2kg) or ≤20 (if ≥2kg) Ranges: SpO2≥92%, pCO2≤56 Post-extubation: CPAP (40%) or no respiratory support (60%)	EF definition: reintubation or the need for CPAP Time frame: 72h
Higgins, 1991 (n=58)	Inclusion: extubation weight < 1000g + MV for RDS ≥24h Cohort: GA 27w, BW 838g Caffeine: 95%; Surfactant: 90%	PEEP: n/a Duration: 1 min Measurements: C, R and WOB	Settings: FiO2≤0.35, MAP≤7, Rate≤20 Ranges: SpO2 93-96% Post-extubation: CPAP (50%) or oxyhood (50%)	EF definition: reintubation or the need for CPAP Time frame: 120h
Chen, 1992 (n=33)	Inclusion: MV > 24h Cohort: GA 32.6w, BW 1774g Caffeine: < 1500g; Surfactant: n/a	PEEP 0 Duration: temporary (<5min) Measurement: MIP	Settings: 1- IMV, FiO2≤0.3, PEEP 3, PIP≤16, Rate≤4 2- ETT-CPAP 3-4 for <1h (monitor gas exchange) Ranges: pH>7.25, pCO2 30-50 Post-extubation: n/a	EF definition: reintubation Time frame: 24h
Sillos, 1992 (n=18)	Inclusion: preterm with RDS Cohort: GA 28.1w, BW 1051g Caffeine: 100%; Surfactant: n/a	PEEP 0 Duration: temporary Measurement: MIP	Settings: FiO2<0.3, Rate≤5 Ranges: pH>7.3 Post-extubation: no respiratory support	EF definition: reintubation Time frame: 24h
Fox, 1993 (n=40)	Inclusion: preterm with RDS Cohort: GA 28.3w Caffeine: 85% Surfactant: n/a	PEEP 0 Duration: ~7 min Measurements: RR, Vt , MVs with and without external dead space	Settings: IMV, PEEP 2-3, PIP 14-16, Rate 5 Post-extubation: headbox	EF definition: reintubation Time frame: 48h
Smith, 1999 (n=49)	Inclusion: BW<1500g and MV for RDS > 24h Cohort: GA 30.2w, BW1233g Caffeine: 96%; Surfactant: 71%	PEEP 5 Duration: ~6 min Measurements: HR, RR, SpO2, Vt and Ti	Settings: IMV, FiO2<0.4, PIP≤15, Rate≤15 Ranges: pH>7.26, pCO2<60 Post-extubation: headbox	EF definition: reintubation Time frame: 48h

Author, year (n)	Population	Index Test	Reference Standard	Target Outcome
Kavvadia, 2000 (n=30)	Inclusion: BW≤1500g and <1w at extubation Cohort: GA 29w, BW 1097g Caffeine: 100%; Surfactant: 47%	PEEP 0 Duration: temporary Measurements: Vt and C	Settings: 1- AC, FiO2≤0.4, PEEP 3, PIP≤14 2- ETT-CPAP for 1h with PEEP 3 (monitor gas exchange) Post-extubation: headbox	EF definition: reintubation or the need for CPAP Time frame: 48h
Dimitriou, 2002 (n=36)	Inclusion: ≤ 2w at extubation Cohort: GA 31w, BW 1569g Caffeine: 100%; Surfactant: n/a	PEEP 0 Duration: brief Measurements: inspiratory pressures and C	Settings: 1- AC, FiO2≤0.4, PIP≤16 2- ETT-CPAP for 1h (monitor gas exchange) Post-extubation: headbox	EF definition: reintubation Time frame: 48h
Vento, 2004 (n=41)	Inclusion: BW 500-1000g and MV for RDS > 24h Cohort: GA 27.4w, BW 851g Caffeine: 100%; Surfactant: n/a	PEEP 4 Duration: 2 hours Measurements: RR, Vt, MVs, C, R, SpO2, TcPO2, TcPCO2 and gas exchange	Settings: SIMV, FiO2≤0.4, PEEP≤4, PIP 18, Rate 6 Ranges: SpO2>90%, pH 7.3-7.45, pCO2 45-55 Post-extubation: CPAP	EF definition: reintubation Time frame: 72h
Kamlin, 2006 (n=50)	Inclusion: BW<1250g, MV≥24h Cohort: GA 26.8w, BW 939g Caffeine: 80%; Surfactant: n/a	PEEP 5-6 Duration: 3 min Measurements: SpO2, HR, RR, Vt and MVs	Settings: AC or SIMV, FiO2≤0.4, PEEP 5-6, Rate 20-30 (if on SIMV), Ranges: SpO2 90-95% Post-extubation: CPAP or NIPPV	EF definition: reintubation Time frame: 72h
Davidson, 2008 (n=35)	Inclusion: BW<1500g + MV from DOL 1, > 48h but < 30d Cohort: GA 31.3w, BW 1206g Caffeine: 29%; Surfactant: n/a	PEEP 3-4 Duration: 10 min Measurements: RR and Vt	Settings: SIMV, FiO2≤0.4, PEEP 3-4, PIP 14-20, Rate 12-20 Post-extubation: CPAP	EF definition: reintubation Time frame: 48h
Currie, 2011 (n=20)	Inclusion: all infants Cohort: GA 31w, BW 1602g Caffeine: < 34 weeks; Surfactant: n/a	PEEP: brief disconnection from ventilator followed by brief period on ETT-CPAP (PEEP level not specified) Duration: n/a Measurements: P0.1, MIP, Pdimean, Pdimax, Ti, Ttot, TTdi and TTmus	Settings: AC or SIMV+PS Post-extubation: CPAP (for infants <1000g)	EF definition: reintubation Time frame: 48h

Author, year (n)	Population	Index Test	Reference Standard	Target Outcome
Dimitriou, 2011 (n=56)	Inclusion: all infants MV ≥ 24h Cohort: GA 30w, BW 1390g Caffeine: 100%; Surfactant: n/a	PEEP 0 Duration: 90 seconds Measurements: RR, Vt, Ti, Ttot, PTPdi, TTdi and TTmus	Settings: AC or SIMV, FiO2<0.35, PEEP 3, PIP≤14, Rate 20 (if SIMV) Post-extubation: CPAP (if <1000g) or headbox (if ≥29 weeks)	EF definition: reintubation Time frame: 48h
Precup, 2012 (n=53)	Inclusion: BW≤1250g Cohort: GA 26.6w, BW 887g Caffeine: 70%; Surfactant: 96%	PEEP: same as baseline Duration: 3 min Measurements: ECG and RIP signals	Settings: AC or SIMV, FiO2≤0.3, MAP≤7 (if <1000g) or ≤8 (if ≥1000g) Post-extubation: CPAP or NIPPV	EF definition: reintubation Time frame: 72h
Chawla, 2013 (n=49)	Inclusion: 24-31+6/7 weeks, MV within 12h, ≥12h but <3w Cohort: GA 28w, BW 1077g Caffeine: 35%; Surfactant: 100%	PEEP: n/a Duration: 5 min Measurements: MVs Monitoring: bradycardias and desaturations	Settings: SIMV + PS, FiO2<0.35, Rate 16-20 Ranges: SpO2 88-92%, pH>7.25, pCO2<55 Post-extubation: CPAP, NIPPV, HFNC, LFNC or no support	EF definition: reintubation Time frame: 72h
Kaczmarek, 2013 (n=44)	Inclusion: BW<1250g and MV ≥ 24h Cohort: GA 26.9w, BW 938g Caffeine: n/a; Surfactant: n/a	PEEP 5-6 Duration: 3 min Measurements: SpO2, HR, Vt, Ti, Te and Ttot	Settings: AC or SIMV, FiO2≤0.4, PEEP 5-6, Rate 20-30 (if on SIMV) Ranges: SpO2 90-95% Post-extubation: CPAP or NIPPV	EF definition: reintubation Time frame: 72h
Robles-Rubio, 2015 (n=56)	Inclusion: BW≤1250g Cohort: GA 26.6w, BW 892g Caffeine: 71%; Surfactant: 96%	PEEP: same as baseline Duration: 3 min Measurements: Respiratory signals (RIP)	Settings: AC or SIMV, FiO2≤0.3, MAP≤7 (if <1000g) or ≤8 (if ≥1000g) Ranges: SpO2 88-95%, pH>7.25, pCO2 45-60 (if ≤7d) or >60 (if >7d) Post-extubation: CPAP or NIPPV	EF definition: reintubation Time frame: 72h
Bhat, 2016 (n=30)	Inclusion: preterm infants Cohort: GA 28.2w, BW 1111g Caffeine: <34 weeks; Surfactant: n/a	PEEP: brief disconnection from ventilator followed by brief period on ETT-CPAP (PEEP level not specified) Duration: n/a Measurements: P0.1, MIP, Pdimax, TTdi and TTmus	Settings: n/a Ranges: pH 7.35-7.45, pCO2 38-53 Post-extubation: CPAP (if <1000g) or no respiratory support	EF definition: reintubation Time frame: 48h

Author, year (n)	Population	Index Test	Reference Standard	Target Outcome
Studies where the index test was used to guide extubation AND compared to control group				
Kim, 1987 (n= 27)	Inclusion: BW<1250g, >28d and MV>12h Cohort: GA 28.7w, BW 1036g Caffeine: 85%; Surfactant: n/a	PEEP 2 (<1kg) or 3 (≥ 1kg) Duration: 6 hours Monitoring: apneas, bradycardias, TcPO2 and gas exchange (PaO2, pCO2)	Settings: IMV, PEEP 2 (<1kg), 3 (≥ 1kg), PIP<16, Rate 6-10 Post-extubation: no respiratory support	EF definition: resumption of IMV Time frame: n/a
Kim, 1989 (n=60)	Inclusion: all infants intubated with 3.0/3.5 ETT and MV >12h Cohort: GA 32.8w, BW 1934g Caffeine: 83% (< 37w); Surfactant: n/a	PEEP 3 Duration: 6 hours Monitoring: apneas, bradycardias, TcPO2 and gas exchange (PaO2, pCO2)	Settings: IMV, PEEP 3, PIP <17, Rate 6 Post-extubation: no respiratory support	EF definition: resumption of IMV Time frame: 6h
Tapia, 1995 (n=87)	Inclusion: BW<1500g and MV > 48h Cohort: GA 28.8w, BW 1078g Caffeine: 100%; Surfactant: 9%	PEEP 3 or 4 Duration: 12-24 hours Monitoring: apneas, bradycardias, TcPO2, SpO2 and gas exchange	Settings: IMV, FiO2≤0.4, PEEP≤4, PIP≤15, Rate 6-10 Ranges: SpO2 90-96% Post-extubation: oxyhood, CPAP or no respiratory support	EF definition: resumption of IMV Time frame: 72h
Mas Munoz, 1996 (n=54)	Inclusion: BW<1500g and DOL 3-21 at extubation Cohort: GA 31.3w, BW 1202g Caffeine: 100%; Surfactant: n/a	PEEP 2-4 Duration: 4 hours Monitoring: apneas, bradycardias, gas exchange, respiratory distress	Settings: IMV, FiO2<0.4, PIP<16, Rate<18 Ranges: pH>7.25, pCO2<55 Post-extubation: oxyhood or CPAP	EF definition: resumption of IMV Time frame: 72h
Gillespie, 2003 (n=42)	Inclusion: preterm with RDS requiring surfactant and MV ≥ 24h Cohort: GA 30w, BW 1400g Caffeine: 81%; Surfactant: 100%	PEEP 3 or 4 Duration: 10 min Frequency: q6-8h Monitoring: apneas, bradycardias, O2 needs Measurements: MVs, MVm	Settings: AC, FiO2<0.4, MAP<10, PIP<16 Post-extubation: n/a	EF definition: reintubation Time frame: 24h
Kamlin, 2008 (n=180)	Inclusion: BW<1250g Cohort: GA 27w, BW 888g Caffeine: n/a; Surfactant: 92%	PEEP 5-6 Duration: 3 min Frequency: daily Monitoring: apneas, bradycardias, desaturations	Settings: AC or SIMV, FiO2≤0.4, PIP≤25, Rate≤45 Ranges: SpO2 90-94% Post-extubation: n/a	EF definition: reintubation Time frame: 72h

Author, year (n)	Population	Index Test	Reference Standard	Target Outcome
Andrade, 2010 (n=60)	Inclusion: BW<1500g and MV ≥ 24h Cohort: GA 29.1w, BW 1023g Caffeine: n/a; Surfactant: n/a	PEEP 5 Duration: 30 min Monitoring: apneas, bradycardias, desaturations, SAS	Settings: FiO2≤0.5, MAP<12 Ranges: pH 7.2-7.4 Post-extubation: CPAP, NIPPV or Oxyhood	EF definition: reintubation Time frame: 72h
<u>Studies where the index test was used to guide extubation (no control group)</u>				
Greenough, 1989 (n=40)	Inclusion: preterm infants with RDS + MV with rates > 60 Cohort: GA 28.3w Caffeine: 100%; Surfactant: n/a	PEEP: n/a Duration: 1 hour Monitoring: gas exchange (pH)	Settings: 1- HFPPV, PIP 20, Rate 5 2- ETT-CPAP (see index test) Post-extubation: n/a	EF definition: reintubation Time frame: anytime
Chan, 1993a (n=120)	Inclusion: BW<1800g Cohort split into 2 MV groups: Acute–GA 29w, BW 1134g Chronic–GA 25.5w, BW 791g Caffeine: 100%; Surfactant: n/a	PEEP: n/a Duration: 1 hour Monitoring: gas exchange (pH and pCO2)	Settings: 1- PIP<20, Rate 5 2- ETT-CPAP (see index test) Post-extubation: CPAP (50%) and headbox (50%)	EF definition: reintubation Time frame: 48h
Chan, 1993b (n=40)	Inclusion: infants recovering from respiratory distress Cohort: GA 29.5w Caffeine: 100%; Surfactant: n/a	PEEP: n/a Duration: 1 hour Monitoring: gas exchange (pH)	Settings: 1- AC: PIP 14 (>28w) or 12 (<28w) or IMV: Rate 5 2- ETT-CPAP (see index test) Post-extubation: n/a	EF definition: reintubation Time frame: 24h
Dimitriou, 1996 (n=20)	Inclusion: preterm infants extubated ≤ DOL 10 Cohort: GA 29w, BW 1411g Caffeine: 100%; Surfactant: 65%	PEEP: n/a Duration: 1 hour Monitoring: gas exchange (pH)	Settings: 1- None provided 2- ETT-CPAP (see index test) Post-extubation: Headbox	EF definition: reintubation or the need for CPAP Time frame: 48h
Wilson, 1998 (n=35)	Inclusion: BW<2000g, MV > 24h Cohort: GA 30w, BW 1290g Caffeine: <32w; Surfactant: n/a	PEEP: same as baseline Duration: 10 min Frequency: daily Monitoring: apneas, bradycardias, O2 needs Measurements: MVs, MVm	Settings: 1- AC, FiO2<0.35, MAP<8, PIP<20, Rate≤20 2- ETT-CPAP (see index test) Post-extubation: Oxyhood or LFNC	EF definition: reintubation Time frame: 24h Also provided data for 72h/168h

Author, year (n)	Population	Index Test	Reference Standard	Target Outcome
Dimitriou, 2000a (n=20)	Inclusion: Preterm infants with CXR within 4h after extubation Cohort: GA 28w, BW 1096g Caffeine: 100%; Surfactant: 60%	PEEP 3 Duration: 1 hour Monitoring: gas exchange (pH)	Settings: 1- AC, FiO2≤0.4, PEEP 3, PIP≤14 2- ETT-CPAP (see index test) Post-extubation: Headbox	EF definition: reintubation or the need for CPAP Time frame: 48h
Dimitriou, 2000b (n=150)	Inclusion: GA≤34w + age≤14d Cohort: GA 30w, BW 1212g Caffeine: 100%; Surfactant: 66%	PEEP: n/a Duration: 1 hour Monitoring: respiratory effort + gas exchange (pH)	Settings: 1- None provided 2- ETT-CPAP (see index test) Post-extubation: CPAP or Headbox	EF definition: reintubation Time frame: 48h
Gupta, 2009 (n=140)	Inclusion: GA 24-29w or BW 600-1500g, MV for RDS Cohort: GA 27.4w, BW 1070g Caffeine: 100%; Surfactant: 99%	PEEP: n/a Duration: 10 min Frequency: q12h Measurements: MVs, MVm	Settings: 1- SIMV+PS, FiO2<0.3, Rate 20 2- ETT-CPAP (see index test) Ranges: pH 7.25-7.4, pCO2 35-49 Post-extubation: CPAP	EF definition: reintubation Time frame: 72h (Also provided data for 168h)
Von Merkel, 2012 (n=66)	Inclusion: BW<1000g, MV within 24h of life Cohort: GA 26.1, BW 784g Caffeine: 100%; Surfactant: 98%	PEEP: n/a Duration: 3 min Frequency: q6-8h Monitoring: apneas, bradys, desaturations	Settings: 1- FiO2<0.4, PIP<20 2- ETT-CPAP (see index test) Ranges: SpO2 88-96% Post-extubation: CPAP or NIPPV	EF definition: reintubation Time frame: 48h
Zhang, 2014 (n=88)	Inclusion: GA 27-32w, MV within 24h for RDS + MV≥48h Cohort: GA 30w, BW 1250g Caffeine: n/a; Surfactant: n/a	PEEP: n/a Duration: up to 5 min Monitoring: apneas, bradys, desaturations	Settings: 1- SIMV, FiO2≤0.4, PIP≤15, Rate≤10 2- ETT-CPAP (see index test) Post-extubation: CPAP	EF definition: reintubation Time frame: 48h

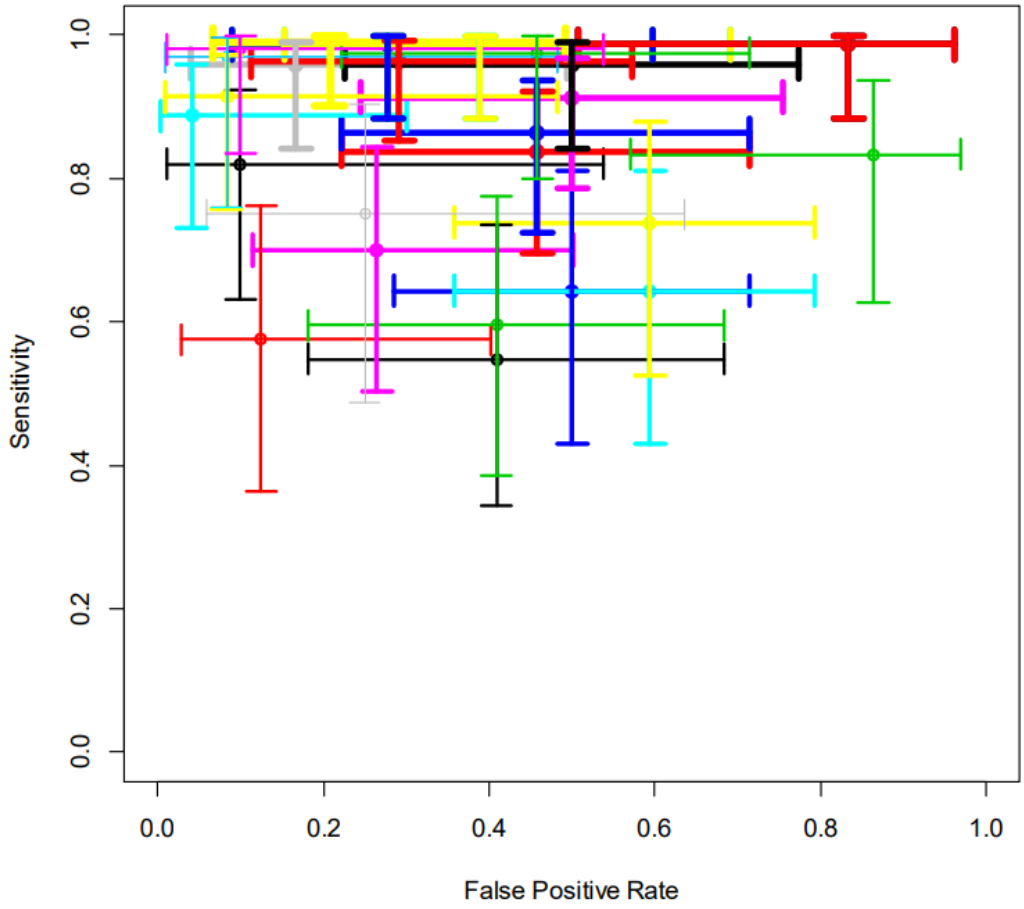
Abbreviations: RDS – respiratory distress syndrome, ETT – endotracheal tube, GA – gestational age, BW – birth weight, PEEP – positive end-expiratory pressure, n/a – information not provided, Ti– inspiratory time, Te – expiratory time, Ttot – total breath time, Vt – tidal volume, MVs – spontaneous minute ventilation, MVm – mechanical minute ventilation, ECG – electrocardiogram, HR – heart rate, RIP – respiratory inductive plethysmography, RR – respiratory rate, TcPO2 – transcutaneous oxygen pressure, TcPCO2 – transcutaneous carbon dioxide pressure, C – dynamic lung compliance, R – total lung resistance, WOB – work of breathing, MIP – Mean inspiratory pressure, Pdi – diaphragmatic pressure, P0.1 – respiratory drive, TTdi – diaphragmatic tension time index, TTmus – tension time index of respiratory muscles AC – assist control (pressure-limited), (S)IMV – (synchronized) intermittent mandatory ventilation, PS – pressure support, VG – volume guarantee, PIP – peak inflating pressure, MAP – Mean airway pressure, SpO2 – oxygen saturation, CPAP – continuous positive airway pressure, NIPPV – nasal intermittent positive pressure ventilation, HFNC – high flow nasal cannula, LFNC – low flow nasal cannula, SAS – Silverman Anderson score, n/a – information not available.

Supplementary Appendix S2.4 Tests evaluated or incorporated in clinical practice for prediction of extubation success

Author, year	Definitions of test success
PHYSIOLOGICAL TESTS	
Respiratory Rate, RR (breaths per minute)	
Davidson, 2008	RR ≥ 63
Tidal volume, Vt (ml/kg)	
Kavvadia, 2000	Vt > 4
Kavvadia, 2000	Vt > 5.5
Davidson, 2008	Vt ≥ 4
Spontaneous minute ventilation, MVs (ml/kg/min)	
Kamlin, 2006	MVs > 220
Fox, 1993	% of baseline MVs after adding dead space > 140
Vento, 2004	% time spent with MVs<125 ≤ 8.1%
Ratio of spontaneous to mechanical minute ventilation, MVs/MVm	
Wilson, 1998	Absence of apnea/brady/desat and MVs/MVm ≥ 0.5
Gillespie, 2003	Same as Wilson 1998
Kamlin, 2006	MVs/MVm ≥ 0.8
Gupta, 2009	MVs/MVm ≥ 0.5
Rapid Shallow Breathing Index, RR/Vt (breaths/min/ml/kg)	
Davidson, 2008	RR/Vt ≥ 22
Breathing patterns	
Kaczmarek, 2013	Variability index of Vt
Kaczmarek, 2013	Variability index of inspiratory time, Ti
Kaczmarek, 2013	Variability index of expiratory time, Te
Kaczmarek, 2013	Variability index of Ti/total respiratory cycle time
Kaczmarek, 2013	Variability index of Vt/Ti
Compliance of Respiratory System, CRS (ml/cmH_2O/kg)	
Kavvadia, 2000	CRS ≥ 0.8
Maximum inspiratory pressure, MIP (cm H_2O)	
Chen, 1992	MIP ≥ 35
Sillos, 1992	MIP > 25
CLINICAL TESTS	
Prolonged Endotracheal Continuous Positive Airway Pressure (CPAP) Trials (4-24 hours)	
Kim, 1987/1989	FAILURE: 1) ≥ 2 apneas/bradycardias needing stimulation within 30min; 2) any apnea/bradycardia requiring bag mask ventilation; 3) pH < 7.3
Tapia, 1995	FAILURE: 1) ≥ 3 apneas/h > 20s with bradycardias/desaturations; 2) ≥ 1 apnea/bradycardia needing bag mask ventilation; 3) pH ≤ 7.25, PaCO2 > 60, FiO2 > 0.6

Author, year	Definitions of test success
Mas Munoz 1996	FAILURE: 1) >3 apnea/h or less if bradycardia or bag mask ventilation; 2) pH < 7.2, pCO2 > 60, FiO2 > 0.6; 3) Signs of respiratory distress
1-hour Endotracheal CPAP Trials	
Greenough, 1989	pH ≥ 7.25
Chen, 1992	PaO2 50-80, PaCO2 < 50, pH > 7.25
Chan, 1993a	pH ≥ 7.25 and pCO2 ≤ 50
Chan, 1993b	pH ≥ 7.25
Dimitriou, 1996	pH ≥ 7.25
Dimitriou, 2000a	pH ≥ 7.25
Dimitriou, 2000b	Regular respiratory efforts and pH ≥ 7.25
Kavvadia, 2000	pH ≥ 7.25 with normal PaCO2 and BE ≥ -5
Dimitriou, 2002	pH ≥ 7.25 with normal PaCO2 and BE > -5
Spontaneous Breathing Trials, SBT (≤ 30-min endotracheal CPAP trials)	
Kamlin, 2006/2008	FAILURE: (1) Bradycardia >15s; (2) oxygen saturation < 85% despite 15% increase in FiO2
Andrade, 2010	FAILURE: Heart rate < 100, oxygen saturation < 85% and Silverman Anderson Score > 5
Von Merkel, 2012	Same as Kamlin 2006
Chawla, 2013	FAILURE: (1) Heart rate <100 for > 10s; (2) Oxygen saturation < 85% for > 15s; (3) Significant bradycardias requiring intervention
Zhang, 2014	FAILURE: Frequent apneas, bradycardias > 10s or desaturations > 15s
COMPOSITE TESTS	
SBT + breathing patterns	
Kaczmarek, 2013	SBT + Variability index of Vt
Kaczmarek, 2013	SBT + Variability index of Ti
Kaczmarek, 2013	SBT + Variability index of Te
Kaczmarek, 2013	SBT + Variability index of Ti/Ttot
Kaczmarek, 2013	SBT + Variability index of Vt/Ti
Tension time index of diaphragm, TTdi	
Currie, 2011	TTdi ≤ 0.15
Dimitriou, 2011	TTdi ≤ 0.12
Bhat, 2016	TTdi < 0.08
Tension time index of respiratory muscles, TTmus	
Currie, 2011	TTmus ≤ 0.18
Dimitriou, 2011	TTmus ≤ 0.1
Bhat, 2016	TTmus < 0.19
Cardiorespiratory signal analysis	
Precup, 2012	Classification based on machine learning
Robles-Rubio, 2015	Combined variability of respiratory-related metrics

Supplementary Appendix S2.5 'Cross hairs' ROC plot of predictor tests of extubation readiness



Point estimates of sensitivity and specificity for each diagnostic test of extubation readiness are represented by a weighted circle, and 95% confidence intervals are displayed by vertical and horizontal lines, respectively.

Bridging Text 2

Based on the evidence gathered from the meta-analysis presented in Chapter 2, there are clearly many gaps in our knowledge on how to assess extubation readiness in extremely preterm infants. On one hand, the current tools for predicting extubation readiness are oversimplified and lack sufficient accuracy to justify their use in clinical practice. Instead, perhaps more complex and individualized assessment tools that capture and analyze the infants' intrinsic cardiorespiratory behavior are needed. On the other hand, there is a clear lack of standardization in the way extubation failure is defined and reported in the literature, which makes interpretation of published results very difficult. This problem stems from a limited understanding of the timing, causes and clinical significance of reintubations in the extremely preterm population. For all those aforementioned reasons, we conducted a multicenter observational study primarily aimed at develop an Automated Predictor of EXtubation readiness in extremely preterm infants (the APEX study) using both clinical variables and metrics of cardiorespiratory behavior. Using APEX we also created a large clinical database of prospectively collected data pertaining to extubation, reintubation and important neonatal outcomes from this high-risk cohort.

Chapter 3 presents the protocol for the APEX study as published in *BMC Pediatrics* as open-access on July 2017.[104] In the background section, we review the evidence for using analyses of cardiorespiratory behavior in the assessment of extubation readiness, as part of the rationale for the APEX study. In the methodology section, we provide a detailed account of the study population, interventions and all the necessary information for understanding the data collection process and contents of the clinical database. Of note, the sections pertaining to the analyses of cardiorespiratory signals, machine-learning methodologies and the development/validation of the automated predictor of extubation readiness are outside the scope

of this thesis since they are being pursued by two graduate students (from the departments of biomedical engineering and computer sciences) currently completing their PhD. Rather, this thesis concentrates on the sections of the published APEX protocol pertaining to the clinical rationale for the study, the data acquisition/collection processes, and the detailed contents of the clinical database (which are used to answer the questions raised in Chapters 4 to 6).

Chapter 3 – Prediction of Extubation Readiness in Extremely Preterm Infants by the Automated Analysis of Cardiorespiratory Behavior: Study Protocol

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3.1 Abstract

Background: Extremely preterm infants (≤ 28 weeks gestation) commonly require endotracheal intubation and mechanical ventilation (MV) to maintain adequate oxygenation and gas exchange. Given that MV is independently associated with important adverse outcomes, efforts should be made to limit its duration. However, current methods for determining extubation readiness are inaccurate and a significant number of infants fail extubation and require reintubation, an intervention that may be associated with increased morbidities. A variety of objective measures have been proposed to better define the optimal time for extubation, but none have proven clinically useful. In a pilot study, investigators from this group have shown promising results from sophisticated, automated analyses of cardiorespiratory signals as a predictor of extubation readiness. The aim of this study is to develop an automated predictor of extubation readiness using a combination of clinical tools along with novel and automated measures of cardiorespiratory behavior, to assist clinicians in determining when extremely preterm infants are ready for extubation.

Methods: In this prospective, multicenter observational study, cardiorespiratory signals will be recorded from 250 eligible extremely preterm infants with birth weights ≤ 1250 g immediately prior to their first planned extubation. Automated signal analysis algorithms will compute a variety of metrics for each infant, and machine learning methods will then be used to find the optimal combination of these metrics together with clinical variables that provide the best overall prediction of extubation readiness. Using these results, investigators will develop an Automated system for Prediction of EXtubation (APEX) readiness that will integrate the software for data acquisition, signal analysis, and outcome prediction into a single application suitable for use by

medical personnel in the neonatal intensive care unit. The performance of APEX will later be prospectively validated in 50 additional infants.

Discussion: The results of this research will provide the quantitative evidence needed to assist clinicians in determining when to extubate a preterm infant with the highest probability of success, and could produce significant improvements in extubation outcomes in this population.

Trial registration: Clinicaltrials.gov identifier: NCT01909947. Registered on July 17 2013.

Trial sponsor: Canadian Institutes of Health Research (CIHR)

3.2 Background

Scope of the problem

Approximately 15,000 infants are admitted to the neonatal intensive care unit (NICU) in Canada each year, of which 11% are extremely preterm (gestational age (GA) ≤ 28 weeks) [1]. Due to lung immaturity, weak respiratory drive and surfactant deficiency, the majority of these infants require endotracheal intubation and invasive mechanical ventilation (MV) during their first days after birth [2]. In a recent large epidemiological study, 85% of extremely preterm infants required MV at some point during hospitalization, most of whom were intubated in the delivery room [3]. Amongst infants with GA of 24 and 25 weeks, 99% and 95% required MV, respectively [3]. Therefore, MV remains an integral part of respiratory management of extremely preterm infants.

Although life-saving at first, prolonged MV has been linked to several adverse outcomes, including ventilator-associated pneumonia, airway trauma and bronchopulmonary dysplasia (BPD) [4]. BPD is the most serious pulmonary morbidity, having been associated with long-term respiratory and neurodevelopmental impairments [5], as well as important social and economic burdens [6]. The duration of MV is a strong predictor for developing BPD; each additional week increases the odds of BPD by a factor of 2.7 [7]. Consequently, clinicians make every attempt to limit its duration and advocate for extubation as early as possible [8]. However, premature extubation carries its own hazards, including lung derecruitment, compromised gas exchange, inspiratory muscle fatigue and ultimately the need for reintubation [9-11]. Indeed, rates of extubation failure in extremely preterm infants have been reported in the literature to be anywhere from 10% to 70%, depending on the population studied and the time frame or criteria used to define failure [12, 13].

Extubation failure increases morbidities and mortality for several reasons [9, 14]. Not only are endotracheal intubations technically challenging [15], but they may be associated with hypoxemia, bradycardia, fluctuations in blood pressures as well as changes in cerebral function [16, 17]. In a recent prospective cohort study, 40% of intubations were associated with adverse events, and 9% of intubations were associated with severe sequelae including hypotension, chest compressions, pneumothorax and death [17]. Furthermore, reintubations risk traumatic injury to the upper airway, lung atelectasis and infection [4, 18, 19]. Together, these complications may lead to cardiorespiratory and/or neurological injuries that may result in long term disability. In fact, emerging studies suggest that reintubation may be an independent risk factor for death or BPD in this population [20, 21]. These observations are very concerning, and underscore the need for lowering the rates of extubation failure while minimizing the duration of MV.

Predictors of Extubation Readiness in Preterm Infants

Although neonatology has seen major advances in MV and post-extubation respiratory support, the scientific basis for determining whether a patient is ready for extubation remains imprecise. The decision to extubate is usually based on clinical judgment, taking into account personal experience and bedside observation of blood gases, oxygen requirements and ventilator settings [22]. As a result, there are significant practice variations and a paucity of protocols to streamline management for all components of the peri-extubation process, with decisions often being physician-dependent and not evidence-based [22, 23].

Over the years, several attempts have been made to identify objective prediction tools of extubation readiness in preterm infants. In the late 1980s-1990 for instance, it was common practice for infants to undergo a trial of endotracheal continuous positive airway pressure

(CPAP) of 2-3 cmH_2O for periods of 6 to 24h [24-26]. Infants were extubated if they had no significant apneas, bradycardias or respiratory acidosis during the trial. However, evidence from a meta-analysis refuted this practice, showing that the trial's prolonged length and low pressures increased the risk of respiratory failure [27]. Subsequently, investigators turned towards shorter assessment periods during which various clinical and physiological variables were evaluated. Unfortunately, many of these prediction tools are of limited applicability today, since they were performed before routine use of antenatal steroids or surfactant therapy. Moreover, the studies were small, single-center and enrolled very heterogeneous populations. For the most part, measures of tidal volume, minute ventilation, breathing pattern, pulmonary mechanics and diaphragmatic function failed to classify infants into their respective extubation class (success or failure) [28-30]. When prediction tools were found to have favorable sensitivities and specificities, they were not prospectively validated [31], or showed no differences in extubation failure rates when compared to clinical judgment alone [32, 33].

More recently, clinicians have shifted towards the use of short-duration spontaneous breathing trials (SBTs) for the assessment of extubation readiness in extremely preterm infants [22]. The SBT is a bedside procedure that consists of observing changes in heart rate, oxygen saturation (SpO2) and/or oxygen requirements during a short trial of endotracheal CPAP. Although the use of a standardized 30-min SBT has been standard of care for assessing extubation readiness in mechanically ventilated adults [34], the evidence for its use in preterm infants is less compelling. In one study, Kamlin *et al*. performed a 3-min SBT using endotracheal CPAP of 5-6 cmH_2O in preterm infants with birth weights (BW) < 1250 g who were deemed 'ready' for extubation [35]. The SBT showed a sensitivity of 97% and a specificity of 73% at predicting extubation success, thus it was adopted as standard of care in that institution.

However, a follow-up prospective audit of this practice found that routine use of SBTs did not improve weaning times or extubation success rates [36]. In the latest prospective observational study, the validity of a 5-min SBT was evaluated in 49 infants with GA < 32 weeks [37]. The SBT had a high sensitivity and positive predictive value, but limited specificity and negative predictive value.

Cardiorespiratory Variability and Prediction of Extubation Readiness

Variations in heart rate and respiratory rate have long been known to be influenced by the autonomic nervous system (ANS), with cardiovascular integrity depending on the correct balance between sympathetic and parasympathetic tones [38]. Autonomic dysfunction, as characterized by reduced heart rate variability (HRV), has been linked to increased mortality and cardiovascular disease in adult individuals [39]. Respiratory variability (RV), on the other hand, is reduced in conditions of hypoxia, hypercapnia and inspiratory mechanical loading [40-43]. Similarly, evidence from the adult literature has consistently demonstrated reduced HRV and RV in patients who failed weaning from MV [44, 45].

The role of HRV and RV in predicting disease in newborn infants is not understood as well. However, it has become increasingly attractive over the past years, as recent evidence suggests that loss of HRV precedes the clinical presentation of neonatal sepsis [46]. The potential for cardiorespiratory variability measurements to predict extubation readiness has led our group to explore their usefulness in the extremely preterm population. The first evaluation was conducted as part of a retrospective analysis of respiratory data collected by Kamlin et al, whereby RV indices were computed during a 3-min SBT performed prior to extubation [35]. The combination of RV and clinical response to the SBT predicted successful extubation more

accurately than either test alone [47]. However, the study used a pneumotachograph to measure respiration, a tool that has several limitations [48]. For those reasons, we conducted a pilot prospective observational study of 56 preterm infants (BW ≤1250 g) in which cardiorespiratory behavior was obtained from electrocardiogram (ECG) and respiratory inductive plethysmography (RIP) signals that captured respiratory movements from the ribcage and abdomen. Data were collected during 2 periods prior to extubation: a 60-minute recording on low ventilatory support followed by a 3-minute period on endotracheal CPAP. The primary outcome, extubation failure, was defined as the need for reintubation within 72h from extubation. The study revealed that HRV was significantly lower in infants who failed their first extubation attempt [49]. In addition, both HRV and RV measures had perfect specificity and PPV, but limited sensitivity and NPV. Nevertheless, a major factor limiting the evaluation of RV was the need for manual, breath-by-breath analysis of the respiratory signals. Manual analysis of respiratory signals is expensive, time consuming, operator-dependent and prone to errors. To circumvent this problem, it became more attractive to use an automated, continuous analysis of respiratory behavior. One such example is AUREA, a robust Automated Unsupervised Respiratory Events Analysis system developed by members of our team [50]. AUREA uses uncalibrated RIP signals to compute a number of respiratory-related metrics that are then used to classify the infant's respiratory patterns on a sample-by-sample basis. The method is fully automated, completely repeatable, standardized, and requires no human intervention. Importantly, it is more efficient than manual scoring (the most common method of analysis) and is not limited by intra- or inter-scorer variability [50].

AUREA was originally designed for older infants recovering from anaesthesia, but was later extended to support analysis of RIP data from preterm infants [51, 52]. Consequently, we

used AUREA to reanalyze the original recorded dataset from the pilot study of 56 preterm infants [53]. Exploring the utility of the metrics computed by AUREA revealed that the variability of two metrics (the instantaneous breathing frequency and ribcage movement) were significantly different between infants who succeeded and failed extubation [53]. All in all, those results indicated that cardiorespiratory signals analyzed using AUREA contained information that could be useful to predict successful extubation. However, AUREA computes many different metrics describing cardiorespiratory behavior on a sample by sample basis. Therefore, it is not straightforward to determine which metrics to use, the criteria to select the samples and how to combine them to obtain the best predictor of extubation readiness. Consequently, we applied machine learning methods to explore how to best combine features of HRV and RV to predict extubation readiness. The best results were obtained using a Support Vector Machine (SVM), an advanced machine learning classifier that uses nonlinear decision boundaries [54]. After combining 17 features computed by AUREA, the SVM produced accurate classifications with an optimal true positive rate greater than 85% and a false positive rate of less than 30% [55]. The results of this pilot study were encouraging and suggested that a classifier with such performance had the potential to reduce extubation failures by 80%.

Rationale

Both prolonged MV and the need for reintubation are associated with short- and long-term complications. Therefore, it is critical to determine the optimal timing for extubation to minimize the duration of MV while maximizing chances of success. There is promising evidence that analysis of cardiorespiratory signals can provide valuable information into the extubation readiness of extremely preterm infants. We therefore hypothesize that extubation readiness of

preterm infants can be determined accurately by using machine learning methods to combine clinical variables along with novel, quantitative and automated measures of cardiorespiratory behavior.

Objectives

This project aims to develop an automated predictor to help physicians determine when extremely preterm infants are ready for extubation, using the combination of clinical tools along with novel and automated measures of cardiorespiratory variability. The research objectives will be accomplished in this following sequence:

1- Generate a library of clinical data and cardiorespiratory signals in preterm infants prior to extubation;

2- Develop a robust model for prediction of extubation readiness, i.e. referred to as APEX (Automated prediction of extubation readiness);

3- Prospectively validate the clinical utility of this prediction model

3.3 Methods

Study design

This is a prospective, multicenter observational study aiming to develop an automated prediction tool for extubation readiness in extremely preterm infants. The study design conforms to recommendations by the TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) statement and the study protocol is reported using the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). The SPIRIT checklist is available in additional file S3.1.

Study setting

Five tertiary-level NICU's in North America are involved: the Royal Victoria Hospital, Jewish General Hospital and Montreal Children's Hospital (Montreal, Quebec, Canada), Detroit Medical Centre (Detroit, Michigan, USA) and Women and Infants Hospital (Providence, Rhode Island, USA). Approval was obtained from each institution's Ethics Review Board. Enrollment began in September 2013 and is currently ongoing. Of note, the Royal Victoria Hospital and Montreal Children's Hospital NICU's merged and moved to a new site in May 2015.

Eligibility criteria

Figure 3.1 presents a diagram representing the flow of participants through the study. All infants with BW ≤ 1250 g and requiring MV are eligible for the study. Infants are excluded if they have any major congenital anomalies, congenital heart disease, cardiac arrhythmias, or are receiving any vasopressor or sedative drugs at the time of extubation. Infants are also excluded if they are extubated from high frequency ventilation, or directly to room air, oxyhood or low-flow nasal cannula. Details of all inclusion and exclusion criteria are summarized in Table 3.1.

Extubation

There is no consensus on when an extremely preterm infant should be extubated. Thus, prior to initiation of the study, we proposed the following guidelines to consider a patient 'ready' for extubation: For infants < 1000 g - mean airway pressure (MAP) ≤ 7 cmH_2O and fraction of inspired oxygen (FiO_2) ≤ 0.3; For infants ≥ 1000 g - MAP ≤ 8 cmH_2O and FiO_2 ≤ 0.3. Nevertheless, all decisions regarding weaning, determination of extubation readiness and post-extubation management are ultimately made by the responsible physician. In general, all units

have adopted SpO_2 target ranges according to their respective institutional guidelines and have been practicing a permissive hypercapnia ventilator strategy. Caffeine therapy is commonly administered prior to extubation as part of standard care. Infants typically receive post-extubation respiratory support in the form of either nasal CPAP or non-synchronized nasal intermittent positive pressure ventilation (NIPPV), at the discretion of the attending physician. These are the two most frequently used and best regarded support modalities [22, 23]. However, since design of the study and beginning of patient recruitment, we have observed that an increasing number of infants are being extubated to heated humidified high flow nasal cannula (HHHFNC) therapy. This modality is the subject of ongoing investigations, and some uncertainty remains regarding its effectiveness in preventing extubation failures in the extremely preterm population when compared to CPAP or NIPPV [56]. This has led to adjustment of the final sample size in order to account for this new practice (see 'sample size calculation' below).

Interventions

The development of APEX (the automated prediction model of extubation readiness) involves the following steps: acquisition of cardiorespiratory and clinical data, offline analysis of all the data, derivation and prospective validation of the model. All phases of APEX development are described below.

I. *Acquisition of cardiorespiratory data*

Infants are studied prior to their first planned extubation, once deemed 'ready' by the attending neonatologist. The following cardiorespiratory signals are acquired: (1) ECG using 3 ECG leads placed on the infant's chest or limbs; (2) Chest and abdominal movements using

uncalibrated RIP with the Respitrace QDC system® (Viasys® Healthcare, USA). One RIP band is placed around the infant's chest at the level of the nipple line, and the other band around the infant's abdomen, above the umbilicus; (3) SpO_2 and photoplethysmograph (PPG) signals with a pulse oximeter (Radical, Masimo Corp, Irvine, LA.) placed on the infant's hand or foot.

All signals are amplified, anti-alias filtered at 500 Hz, and sampled at 1 kHz by a portable analog-digital data acquisition system (PowerLab version 7.3.8, ADInstruments, Dunedin, New Zealand, © 2009) mounted on a battery-powered laptop computer. Figure 3.2 shows a representative example of the signals acquired.

Data is acquired from each infant while quiet, stable and in supine position, during 2 continuous recording periods immediately preceding extubation:

1. A 60-min period while the infant receives any mode of conventional MV. These data will be used to characterize the HRV properties of the infant prior to extubation. However, this data may not be suitable for characterizing RV, since the respiratory pattern is still influenced by the ventilator.
2. A 5-min period will be used to record the respiratory parameters. During this time, the ventilation will be switched to endotracheal CPAP at the same positive end-expiratory pressure level used during the first recording period, so that the cardiorespiratory patterns are controlled by the infant.

II. *Acquisition of clinical data*

The key clinical variables recorded for each infant are summarized in Table 3.2, and the following respiratory outcomes are recorded while the infant is hospitalized in the NICU:

Extubation failure in the first 72h after extubation: This is the primary outcome for the development of APEX. Extubation failure is defined by one or more of the following criteria: (a) $FiO_2 > 0.5$ to maintain $SpO_2 > 88\%$ or $PaO_2 > 45$ mmHg (for 2 consecutive hours); (b) $PaCO_2 >$ 55-60 mmHg with a pH < 7.25, in two consecutive blood gases done at least 1 hour apart; (c) one episode of apnea requiring positive pressure ventilation with bag and mask; (d) Multiple episodes of apnea (≥ 6 episodes/6 hours). This information will be collected prospectively from the nursing flow chart and blood gas records.

Extubation failure between 72 hours and 14 days after extubation: Following the 72-hour period after extubation, infants are monitored for presence of extubation failure criteria (as described above) until 14 days post-extubation.

Reintubation: This is a secondary outcome measure and is recorded at any time point from extubation until NICU discharge. The timing and reasons for reintubation are collected in detail since the decision to re-intubate is made by the responsible physician. Therefore, the indications for reintubation may differ from the criteria defining extubation failure.

III. Data analysis

The analysis will be developed in 2 phases. Phase 1 will identify and evaluate cardiorespiratory features (metrics or patterns) that differ in infants who succeed/fail extubation. Phase II will use machine learning methods to determine the optimal combination of these features for the derivation of APEX.

Phase I: Cardiorespiratory features

All signals will be exported to MATLAB^{TM} (The MathWorks, Inc.) format for the following analysis:

A) Respiratory Signal Analysis. AUREA will be used to describe respiratory activity in terms of a series of metrics that characterize the amplitude, frequency and phase information of the RIP signals on a sample-by-sample basis [52]. These metrics are computed automatically, provide quantitative measures of the respiratory activity and include:

a. Instantaneous respiratory frequency (f_{max}): is the frequency in the respiratory band with the most power between 0.4 and 2.0 Hz.[57] It is estimated by passing the RIP signal through a bank of digital, band-pass filters; the central frequency of the filter with the highest output power at each time defines f_{max}. This yields a sample-by-sample estimate with an accuracy of 0.1Hz, or half the filter pass-band (0.2 Hz). Note that because we use symmetric, two-sided filters, there is no time delay in estimating f_{max}.

b. RMS metric: extracts the amplitude information of the respiratory signals, and is defined as the sum of the root mean square (RMS) values for the ribcage (RCG) and abdomen (ABD) RIP signals.

c. Pause metric: is based on the power of regular breathing in either RCG or ABD. Pauses are defined by a lack of respiratory effort, so the RIP signals are expected to have low relative power in the regular breathing band (0.4 – 2.0 Hz). The pause metric is defined as the ratio of power in the regular breathing band for a short window to the median regular breathing power for the entire record. This metric is close to 1 during regular breathing and lower during pauses.

d. Movement artifact metric: defined separately for ABD and RCG, compares the power in the movement artifact band (i.e., 0-0.4 Hz) to that in the regular breathing band. It is calculated using the outputs of a filter bank spanning the frequencies 0–2 Hz; each filter has a 0.2 Hz bandwidth. This metric will be close to +1 during regular breathing and shift towards -1 during movement artifacts.

e. Thoraco-abdominal asynchrony metric: estimates the phase between RC and AB using selectively filtered RIP signals to improve the signal-to-noise ratio. The filtered signals are then converted to binary signals and an exclusive-OR signal is computed, representing the phase relation between RC and AB at each sample [58]. Averaging the resulting signal over a window length N_A yields an asynchrony metric proportional to the phase shift. Once the metrics are computed, AUREA then applies k-means clustering to these metrics to assign each time sample of the RIP signals to one of 5 respiratory patterns (also illustrated on Figure 3.3):

- Pause (PAU)
- Synchronous-breathing (SYB)
- Asynchronous-breathing (ASB)
- Movement artifact (MVT)
- Unknown (UNK)

The performance of AUREA's assignment of respiratory patterns will be compared with results of an experienced manual scorer, and fine-tuned accordingly.

B) Heart Rate Analysis. ECG signals acquired during the recording periods will be analyzed by first converting the ECG signal into a point process by identifying the maxima of the R wave. The resulting signal will then be low-pass filtered using the French-Holden algorithm [59] to

generate a continuous HR signal. Instantaneous estimates of power in the: i) Very Low Frequency (VLF) = 0.01-0.04 Hz; (ii) Low Frequency (LF) = 0.04-0.2 Hz, and (iii) High Frequency (HF) = > 0.2 Hz bands will be determined by passing the continuous HR signal through a bank of band-pass filters with appropriate cut-offs. These filters will be implemented in the time domain as symmetric, two-sided finite impulse response filters, making it possible to track changes in HRV as a function of time with no delay.

C) Pulse Oximeter Analysis. The PPG signal will be analyzed to detect movement artifacts using an algorithm that computes and removes a moving average of the larger quasi-periodic pulse components. The RMS of the residual will be close to zero for clean signals and higher during movement artifacts. This metric is faster and performs better than other methods that use higher order statistics [60, 61]. Oxygen saturation and Pulse Transit Time (PTT) will be computed for artifact-free segments. The PTT estimates the time elapsed between the R-wave of the ECG and the peripheral PPG pulse [62], and has been shown to be useful in the diagnosis of Obstructive Sleep Apnea Syndrome [63].

D) Stationarity. Each metric is computed for each sample. The behavior of any given sample may vary randomly and/or as a function of time. This will likely occur during the 5-minute period on endotracheal CPAP as the infant adapts to a sudden change on respiratory load. Consequently, the time course of each metric will be inspected to ensure that it is stationary. If not, we will first try to break the data set into shorter, quasi-stationary segments. Should this fail, the metric's time-varying behavior will be described using time series analysis methods.

E) Feature Detection. We will determine which statistical properties of these metrics describing cardiorespiratory activity are likely to be useful for predicting extubation readiness. To do so, subjects will be separated into two groups, defined by extubation failure or success, and the probability density (PDF) of each metric will be computed and compared. Differences in the variability of a metric will be revealed by changes in the shape of the PDFs; increased variability should result in a broader PDF while a decrease will result in a narrower PDF. In pilot studies, we found that the interquartile range was a useful feature to quantify variability. However, the shapes of the PDFs may suggest other statistics to use as features. The respiratory patterns generated by AUREA, along with the clinical variables collected, will be subjected to a similar analysis. The set of cardiorespiratory and clinical features with discriminative ability will be selected for use with machine learning methods to build the final predictor.

Phase II: Machine learning

The machine learning phase will examine the hypothesis that subjects ready for extubation can be differentiated from those who are not by using a classifier that combines clinical variables with the features computed in Phase I.

For classification, infants will be assigned to either the SUCCESS or FAILURE groups depending on the primary outcome, extubation failure or success. We will then use discriminative classification algorithms (e.g. SVM [54] and Adaboost [64]) to construct classifiers for risk assessment. SVM is a powerful classification method, which takes existing labeled examples and constructs a non-linear decision boundary providing a class separation. New examples are then classified by comparing them to this boundary. SVM relies on two important insights: the boundary can be defined by the examples that are closest to it (called

support vectors) and any new instance can be classified by comparing it to the support vectors. This implicit way of defining the decision boundary permits the use of large numbers of attributes, and the discovery of non-linear relationships between them (rather than simple logical relationships such as "AND" and "OR"). The algorithms to be used provide non-linear classification boundaries as well as a measure of uncertainty in the labeling of each example (expressed as a "margin" between the example and the classification boundary). Unlike other learning algorithms that produce non-linear classifiers, such as neural networks, these algorithms are known to work well with limited numbers of examples, as is the case for our data, and to be very robust to noise in the input features.

IV. Prospective validation of APEX

The development of APEX as described above will use a variety of specialized software tools. These provide the flexibility necessary for exploratory research but may not be suitable for clinical use. Therefore, we will develop an integrated software system that will perform all the data acquisition, signal analysis, and classification operations needed to predict extubation outcome with a user-friendly interface suitable for medical personnel in the NICU. Prototypes of the package will be developed and tested using MATLAB's interactive environment, which supports all the needed algorithms and provides a complete set of tools for graphical interface development. Once a prototype is available, its clarity and usability will be assessed by recruiting clinicians from the NICUs (neonatologists, respiratory technicians) to test the package in a simulated setting and provide feedback. Once the package is finalized, the MATLAB compiler will be used to generate a stand-alone application that will be installed on the data acquisition machines.

The performance of APEX will then be validated in a prospective study of an additional 50 preterm infants. These will be used only to evaluate the performance of the predictor in the clinical setting. Moreover, the APEX classification algorithm and parameters will be pre-specified and used for all infants. Patient recruitment, acquisition, and follow-up will be the same as for the original study. However, immediately following completion of the cardiorespiratory recordings, APEX will carry out the signal analysis and classification computations to assign the infant to FAILURE, SUCCESS, or UNCERTAIN groups (see 'statistical methods' below). This APEX classification will not be available to the attending staff and so will not influence clinical care.

Participant timeline

At each NICU, a research coordinator screens all infants for eligibility and maintains a log of all inclusions/exclusions. Parents are approached by a study investigator who is not the attending neonatologist of that baby, and informed parental consent is obtained prior to the first planned extubation. Participants have the cardiorespiratory signals recorded immediately prior to their first planned extubation and clinical information is prospectively collected at various time points from birth until death, discharge or transfer from the NICU, as presented on the SPIRIT participant timeline in Table 3.3.

Sample size

The machine learning methods that will be used for this study have built-in mechanisms to guard against over-fitting the data (i.e., representing the training examples perfectly but having weak predictive power on new data). Consequently, traditional statistical approaches for

determining sample size do not apply [65]. Therefore, sample size was estimated by applying a methodology proposed by Obuchowski and McClish and detailed by Zhou et al [66, 67]. This method relies on estimating the prevalence of the disease of interest in the study population, estimating the variance of the receiver operating characteristics (ROC) curve based on a pilot study, and picking a required precision for the area under the curve (AUC). The prevalence of extubation failure was estimated conservatively to be 20%, based on both a review of the literature and the clinical collaborators' experience. The variance in the AUC was then estimated by applying bootstrap methods to the data acquired in our pilot study. Using these values and an AUC precision of 0.1 led to an estimated sample size of 170 babies. This sample size would provide a minimum of 5 failure cases in each fold when performing 5-fold cross-validation, thereby ensuring a reliable measurement of generalization power [68]. Nevertheless, in the face of changing practice with the increasing use of HHHFNC post-extubation, and the uncertainty related to its impact on extubation failure rates in this population, the sample size was conservatively increased to 250 patients. As for the prospective validation of APEX, the sample size of 50 infants has been chosen large enough to demonstrate the anticipated benefits and feasibility of the predictor.

Recruitment

Several strategies have been put in place to ensure steady patient recruitment at each participating site. First, the research coordinators promptly identify eligible patients and approach the parents for consent well before extubation. The coordinators follow the infant's daily status and proactively organize with the attending physician for the cardiorespiratory recordings to be made prior to extubation. In addition, in order to raise awareness of all NICU

personnel (i.e. neonatologists, nurses, respiratory therapists, neonatal nurse practitioners and trainees) about the study, routine activities have been instituted at each unit, in the form of information sessions, in-service training and presentations.

Data collection methods and data management

In order to harmonize the process of cardiorespiratory acquisition and clinical data collection, assessors from all recruiting sites will get formal training by the same research investigator. Assessors will also receive standardized instructions describing all procedures step-by-step, tips for troubleshooting signal acquisition and definitions of clinical data items. All cardiorespiratory signals will be recorded using a pre-set template from PowerLab's data acquisition system, thereby ensuring homogeneous sampling methods and a controlled vocabulary of comments added by the investigators during the recording. As for clinical data, it will be entered manually then transcribed into a standardized Microsoft Excel TM (Microsoft Corporation) template that uses multiple layers of quality control to minimize data transcription errors and regulate the type of information entered. Both cardiorespiratory signals and clinical data files will be copied to an encrypted USB key and stored in a locked cabinet that is only accessible to the research investigators. This data will be kept for a period of 7 years after the end of the study, in accordance with the Research Ethics Board guidelines.

Results from the first objective will yield a large, complex dataset that needs to be properly organized, cataloged and readily accessible to investigators from multiple disciplines and geographically-distinct institutions. To facilitate this collaboration, the cloud-based storage and sharing platform Dropbox for Business ^{TM} (Dropbox, Inc.) will be used. At the same time, it is important to ensure that the cloud-based file-sharing environment is secure and free of patient

identifiers. Thus, our group has developed and implemented an automated anonymization protocol for that purpose, as described in detail elsewhere [69]. In a nutshell, the original cardiorespiratory signals and clinical data are first transferred to a secure repository only accessible to a single administrator responsible for implementing the protocol. The files are then systematically de-identified and automatically transferred to the collaborative repository, where all team members can view the anonymized data in real time [69].

Despite the aforementioned safeguards during the data acquisition process, issues may still arise in the quality of clinical files (e.g. transcription errors, missing data or outlier values) and cardiorespiratory signals (missing or disconnected signals, inadequate recording durations). For those reasons, our group has additionally put in place an algorithm for automated validation and quality control of all files, as described in detail elsewhere [70]. Through automatically-generated summary reports, the completion status of all files is shown and problems are flagged. Moreover, the behavior of various signal properties and clinical variables are described within each site and compared between sites. As a whole, this ensures that all issues are identified and addressed in a timely fashion, that the data quality is uniform across sites and that all included files are validated prior to analysis.

Statistical methods

Machine learning algorithms

The performance of the entire machine learning algorithm (described in 'data analysis' above) will be assessed using cross-validation, a standard approach that consists of splitting the data into several sub-sets ('folds') while ensuring that the distribution of the data in each subset is similar. Some subsets are used for feature selection and classifier training, while others are

used for computing an unbiased estimate of the specificity and sensitivity of the classifiers. Each infant will be assigned to one subset of the data, such that data from the same infant will not be used both for training and testing. We will use stratified 5-fold cross-validation, which ensures that reliable estimates of the sensitivity, specificity, and variance of the predictors can be obtained. ROC curves reflecting the sensitivity and specificity trade-off will be produced and used to analytically determine the best trade-off from the point of view of clinical practice [57].

The machine learning system will produce a binary prediction of whether a baby will succeed or fail extubation. However, for use in the clinical setting, a confidence measure in the classification would be necessary. To this end, we will use a method for estimating conditional probabilities for SVM, proposed by Platt [71], and efficiently implemented by Lin et al [72]. This approach works on top of an existing support vector machine to produce an estimate of the probability that each example belongs to the class of interest. Our objective is to use these estimates to classify infants into 3 classes: (i) FAILURE: infants assigned to the failure group with high confidence; (ii) SUCCESS, infants assigned to the success group with high confidence; (iii) UNCERTAIN, infants assigned to either the success or fail groups with low confidence. Where the boundary should lie between high and low probability will depend upon the relative cost associated with a false negative (resulting in the extubation of an infant who will fail) versus that of a false positive (extending the period of ventilation for an infant who would otherwise be extubated). Given the nature of the experimental design (i.e. infants are only studied when deemed ready for extubation) we anticipate that the clinical implementation of our methods would involve delaying extubation for infants predicted to fail. We will evaluate performance based on two measures for the FAILURE class, the identification rate (IR) and the false discovery rate (FDR), defined as:

$$IR = \frac{NF_{fc}}{NF_T} \quad FDR = \frac{NS_{fc}}{NS_{fc} + NF_{fc}}$$

where NF_T = total number of failures

NF_{fc} = number of failues assigned to FAILURE class

NS_{fc} = number of successes assigned to FAILURE class

Bootstrap methods will be applied to our data to estimate the threshold value that provides the largest value for IR with an acceptable FDR.

Prospective APEX validation

The predictive validity of APEX in the clinical context will be evaluated in two ways. First, we will evaluate the accuracy with which infants are assigned to the high confidence SUCCESS and FAILURE groups by comparing the predicted and observed outcomes. We expect that infants will be assigned to these high-confidence groups with high accuracy. Second, the clinical utility of the approach will also depend on the benefits and costs associated with its potential impact on patient outcome. The benefits of using the method can be summarized in terms of the IR, the proportion of extubation failures that could potentially be prevented. The costs can be summarized in terms of the FDR, the proportional of infants incorrectly assigned to failure class. Our objectives are to obtain an IR of 0.8 and an FDR of less than 0.5. This would translate into reducing the extubation failure rate from an estimated 20% to less than 5%, at the cost of prolonging the ventilation of one infant for each extubation failure prevented.

Data monitoring and harms

The leads and bands used to measure cardiorespiratory behavior are non-invasive and come in minimal contact with the baby. Therefore, there are no risks or discomforts associated

with the study interventions. Furthermore, none of the study procedures interfere with the standard care that the participating infant will be receiving in the NICU. Any adverse events will be recorded in Case Report Forms and reported to each site's respective Research Ethics Board in accordance with the protocol and with Good Clinical Practice.

3.4 Discussion

The science of disconnecting extremely preterm infants from the ventilator remains imprecise in today's NICU. Therefore, such decision continues to be based on subjective evaluations, while clinicians try their best to balance the risks of a failed extubation against the harms of prolonged MV. No accurate predictor of extubation readiness currently exists. For the most part, available predictors are overly simplistic and fail to capture the complex and intrinsic behaviors predisposing infants to a successful extubation. Consequently, the development of an automated tool that could accurately predict successful extubation is extremely important.

To our knowledge, this is the first study to prospectively evaluate clinical and cardiorespiratory behavior of extremely preterm infants prior to extubation. Through multi-disciplinary collaboration between clinicians, biomedical engineers and computer scientists, this project aims to develop a more consistent, comprehensive, and personalized automated tool for the prediction of extubation readiness. The study includes a large sample size, is of multi-center nature and has developed a rigorous framework at all levels of the study design. This will generate the largest database of cardiorespiratory signals and clinical data relating to extubation in extremely preterm infants, therefore providing valuable insight on the complex interactions between all those variables and allowing for investigation of several questions related to this subject.

The study also has some potential limitations. Firstly, all decisions pertaining to weaning from MV, extubation, post-extubation respiratory support and reintubation are made by the responsible physician. This adds significant practice variability and a greater number of confounding factors when developing the prediction model. However, we believe that the pragmatic nature of the study makes it more reflective of clinical reality and therefore more generalizable to the real world. Besides, this concern was addressed in the derivation of the large sample size of patients. Secondly, it is important to note that the prediction model will be developed for infants who were deemed "clinically ready" for extubation by the responsible physician. This results in test-referral bias, whereby only infants pre-selected by the attending physician (based on their own personal bias of extubation readiness) are subjected to the test. Naturally, this leads to a selection of more babies with successful extubation and fewer babies with failed extubation, thereby overestimating sensitivity and underestimating specificity. Therefore, the prediction tool will only be valid in that context and cannot be generalized for all situations, until further validation [73, 74]. Lastly, it is currently unclear which criteria and time frame used to define extubation failure have the most clinical relevance for extremely preterm infants. A recent systematic review of the literature addressed this problem by evaluating extubation failure rates (defined as the need for reintubation) as a function of the time frame used. Amongst infants with BW<1000g, cumulative reintubation rates continued to increase up to 7 days post-extubation, with no sign of plateau [13]. Results of this review indicated that a time frame of 72 h could underestimate the true failure rate, and recommended using longer windows of observation in these infants. Although we have defined the primary outcome (extubation failure) as the fulfillment of pre-specified criteria within 72 hours from extubation,

we are also prospectively evaluating extubation failure using criteria up to 14 days post-extubation, as well as the need for reintubation until discharge.

3.5 Declarations

Study status: The study is currently ongoing (at the time of publication of this protocol).

Ethics approval and consent to participate: The project has received approval by the Research Ethics Board at the McGill University Health Center, which includes both the Montreal Children's Hospital and Royal Victoria Hospital (reference # 12-387), the Research Ethics Office at the Jewish General Hospital (reference #13-086), the Institutional Review Board at Women & Infants Hospital of Rhode Island (reference # 13-0090) and the Medical/Pediatric Institutional Review Board at Wayne State University in Detroit (reference # 092613MP2E). Of note, following the merger and relocation of the Montreal Children's Hospital and Royal Victoria Hospital, new ethics approval was not required since both hospitals already belonged to the same institution (the McGill University Health Center). Any proposed amendments will be discussed with each institution's Research Ethics Board and communicated with all investigators, sponsor, trial participants and trial registry (clinicaltrials.gov). All signed informed consent forms will be obtained by the trained research investigators prior to inclusion in the study.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and analyzed during the current study will be available from the corresponding author on reasonable request.

Competing interests: All authors declare that they have no competing interests

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Authors' contributions: GMS and REK are the principal investigators. LJK, CARR, DK, KB, LK, SC, GMS and REK contributed to the design and development of the study protocol. GMS, LK, SC and MK are the site investigators for the McGill University Health Center, Jewish General Hospital, Detroit Medical Centre and Women and Infants Hospital, respectively. They are responsible for supervising all research personnel at their respective sites. WS and LJK drafted the cardiorespiratory acquisition template and data collection form for standardized use across all participating units. WS trained the facilitators across all sites and coordinates in-service trainings and information sessions along with GMS, LK, SC and MK. LJK and REK developed the anonymization, validation and quality control algorithms in collaboration with WS and GMS. KB performed manual scoring of the respiratory data. DP, KB, LJK, WS, CARR, GMS and REK developed the data analysis plan. WS wrote the first draft of this manuscript. All authors read, critically reviewed and approved the final manuscript.

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3.6 References

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3.7 Figures and Tables

Figure 3.1 Study enrollment flow diagram template

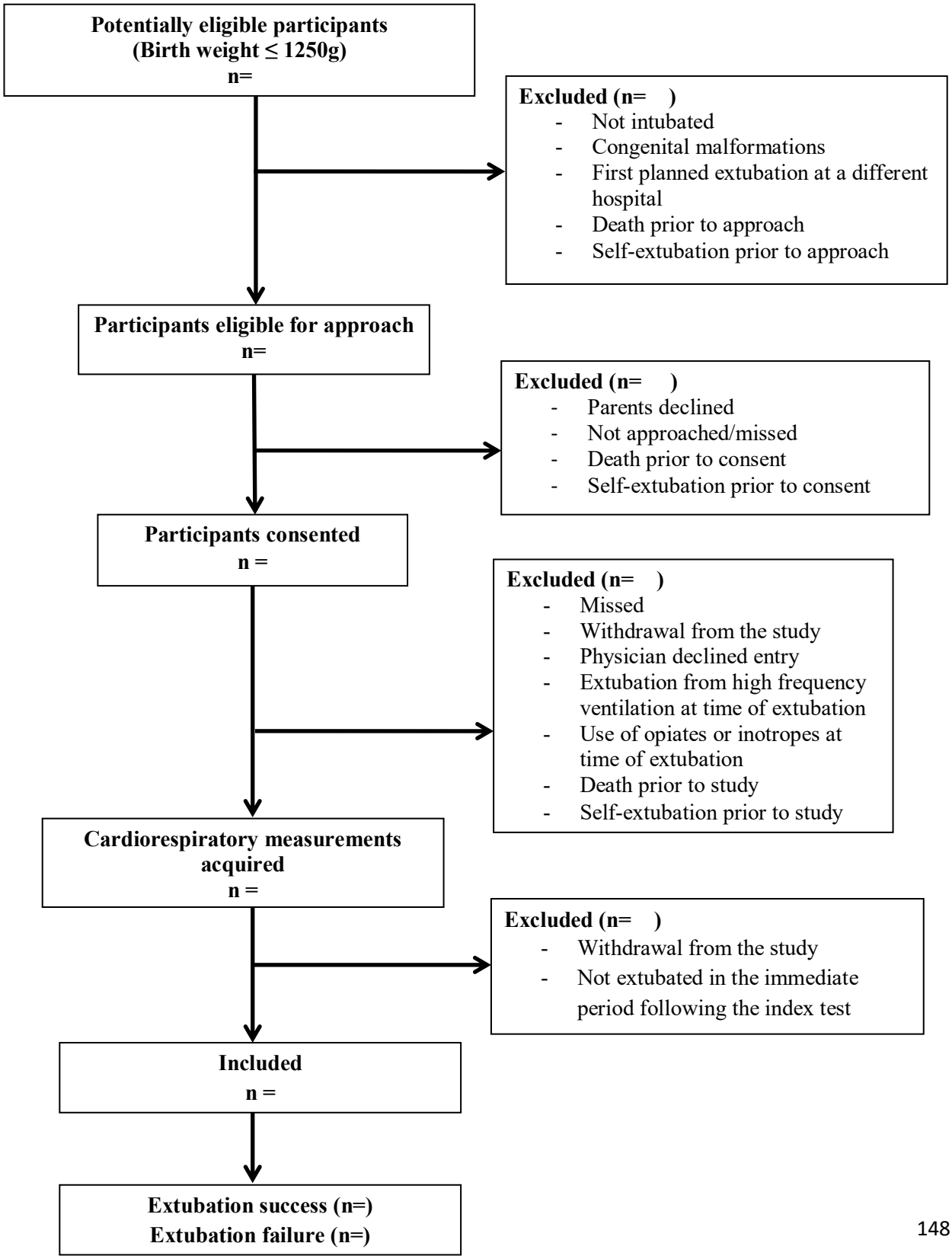
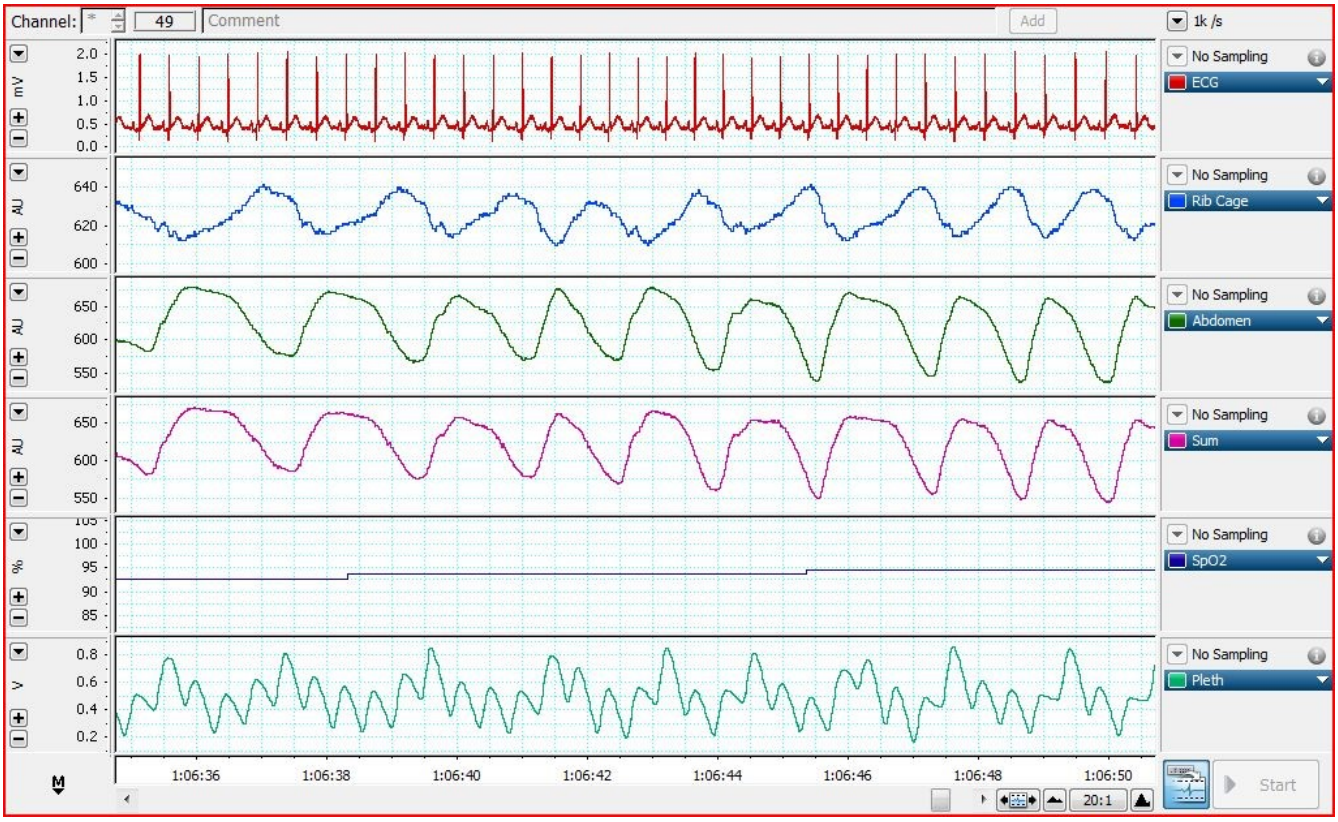


Table 3.1 Inclusion and exclusion criteria

Inclusions	Exclusions
Birth weight ≤ 1250 grams Requiring intubation/mechanical ventilation First planned extubation	Major congenital anomalies Congenital heart disease Cardiac arrhythmias Receiving any vasopressor at time of extubation Receiving any sedatives at time of extubation Extubation from high frequency ventilation Direct extubation to room air, oxyhood or low flow nasal cannula Accidental/unplanned extubation Death prior to extubation

Figure 3.2 Representative example of a cardiorespiratory recording from a preterm infant

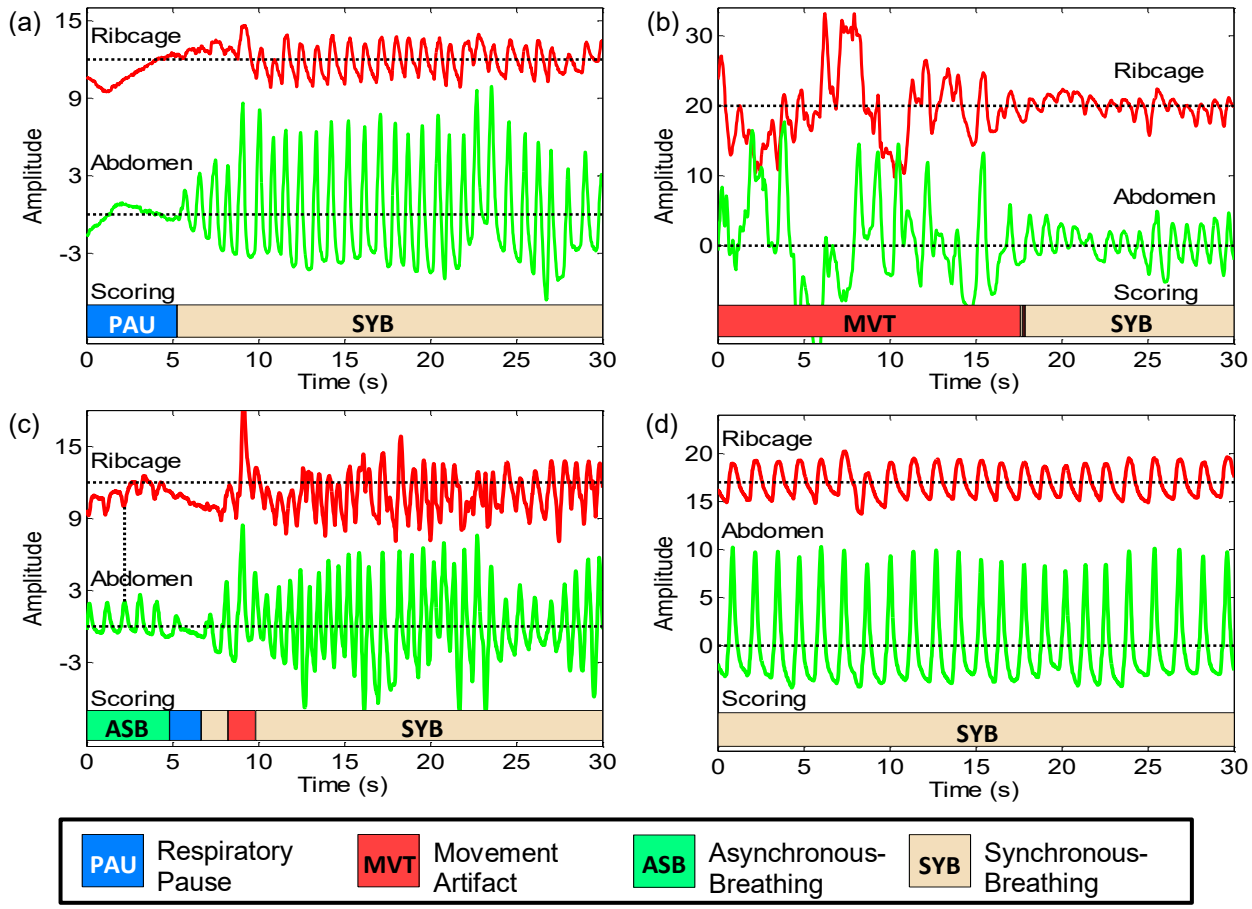


Legend: The signals displayed, from top to bottom, are: electrocardiogram, rib cage movements, abdominal movements, sum of rib cage and abdominal movements, oxygen saturation and photoplethysmography.

Table 3.2 Clinical variables to be collected for infants enrolled in the study

Antenatal and maternal variables	Mother age, parity, complications during pregnancy, maternal medications, intra-uterine growth restriction, mode of delivery, multiple birth, use of antenatal steroids, rupture of membranes, use of antibiotics during labor, histological chorioamnionitis.
Infant characteristics pre-extubation	Gender, birth weight, gestational age, Apgar scores (1, 5 and 10 min), cord blood gases, use of surfactant (age, dose), use of antibiotics and caffeine administration prior to extubation (age and dose).
Infant characteristics at time of extubation	Weight at extubation, age and post-conceptional age at extubation, ventilator mode, peak inflation pressure, positive end-expiratory pressure, mean airway pressure, tidal volume, set inspiratory time, ventilator rate, fraction of inspired oxygen (FiO_2), oxygen saturation and blood gas
Infant characteristics post-extubation	Type of non-invasive respiratory support, interface used, settings, FiO_2 and blood gas
Primary extubation outcome	Fulfilling extubation failure criteria within 72 hours from extubation
Secondary extubation outcomes	- Fulfilling extubation failure criteria up to 14 days after extubation - Need for reintubation at any time point from extubation until death or discharge (including timing and reasons for reintubation)
Other outcome variables	Total duration (in days) of mechanical ventilation, non-invasive respiratory support and of oxygen supplementation, intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, postnatal infection (defined as positive culture from the blood, urine or cerebrospinal fluid), need for postnatal steroids, bronchopulmonary dysplasia at 36 weeks post conceptual age (classified as none, mild, moderate or severe), upper airway complications, diuretics at discharge, retinopathy of prematurity and death occurring anytime in the NICU (including timing and cause).

Figure 3.3 Sample epochs of respiratory data from a preterm infant displaying the respiratory patterns detected automatically by AUREA



Legend: AUREA - Automated Unsupervised Respiratory Event Analysis system (a) Pause (PAU), (b) Movement artifact (MVT), (c) Asynchronous breathing (ASB) and (d) Synchronous breathing. Horizontal dotted lines indicate the center of each segment.

Table 3.3 Participant timeline according to the SPIRIT guidelines

	STUDY PERIOD							
	Enrolment	**Allocation**	**Post-allocation**					**Close-out**
TIMEPOINT	$-t_1$	**0**	t_1	t_2	t_3	t_4	t_5	t_6
ENROLMENT:								
Primary Eligibility screen	X							
Informed consent	X							
Study ID generation		X						
Cardiorespiratory signal acquisition								
- While the infant receives any mode of conventional mechanical ventilation			X					
- While the ventilation mode is switched to endotracheal tube continuous positive airway pressure				X				
ASSESSMENTS								
Baseline variables								
Antenatal and maternal variables		X						
Infant characteristics pre-extubation			X					
Infant characteristics at time of extubation			X					
Infant characteristics post-extubation					X			
Respiratory outcomes								
Fulfilling extubation failure criteria						X	X	
Need for reintubation						X	X	X
Other data variables								
Duration of MV Intraventricular hemorrhage Patent ductus arteriosus Necrotizing enterocolitis Type/Duration of steroids Postnatal infections	X							X
Duration non-invasive respiratory support O_2 supplementation at day of life 28 Bronchopulmonary dysplasia Upper airway complications Diuretics at discharge Retinopathy of prematurity Death								X

-t_1=birth to extubation
0= immediate period prior to initiation of data acquisition
t_1= 60-minute recording prior to extubation
t_2= 5-minute recording prior to extubation
t_3= immediate period post-extubation
t_4 = first 72h period post-extubation
t_5 = period between 72h and 14 days post-extubation
t_6= discharge, death or transfer from the neonatal intensive care unit

Additional File S3.1 SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	110
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	112
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	138
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	110, 138-139
	5b	Name and contact information for the trial sponsor	112
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	138
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	113-119
	6b	Explanation for choice of comparators	n/a
Objectives	7	Specific objectives or hypotheses	119
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	119-120

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	120
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	120, Tab 3.1, Fig 3.1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	121-129
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	130
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	121-123
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	123, Table 3.2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	129, Table 3.3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	130
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	131
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	131-132
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	131-132

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	132-134
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	134-135
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	135
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	137
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	137
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	137
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	131-132
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	138
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	138
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	n/a
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Bridging Text 3

Enrollment for the APEX study started in September 2013 and ended in August 2018. A total of 266 extremely preterm infants were included. Details regarding the flow of participants, demographics of the cohort, comparisons between sites, and overall characteristics of infants with successful or failed extubation are presented in Appendix A6.

While enrollment for APEX was ongoing and nearing completion, we used the available clinical database at the time to conduct the three studies that are presented in Chapters 4, 5 and 6 of this thesis. The first of those studies aimed to evaluate the patterns by which extremely preterm infants were reintubated during their NICU hospitalization. That is, we sought to longitudinally describe the timing of reintubations in relation to extubation (i.e. the cumulative reintubation rates over time) as well as the stated reasons why clinicians reintubated these infants. The study was published in *Pediatric Research* and the preprint of the article is presented in Chapter 4.[105]

Chapter 4 – Patterns of Reintubation in Extremely Preterm Infants: A Longitudinal Cohort Study

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4.1 Abstract

Background: The optimal approach for reporting reintubation rates in extremely preterm infants is unknown. This study aims to longitudinally describe patterns of reintubation in this population over a broad range of observation windows following extubation.

Methods: Timing and reasons for reintubation following a first planned extubation were collected from infants with birth weight ≤ 1250g. An algorithm was generated to discriminate between reintubations attributable to respiratory and non-respiratory causes. Frequency and cumulative distribution curves were constructed for each category using 24h intervals. The ability of observation windows to capture respiratory-related reintubations while limiting non-respiratory reasons was assessed using a receiver operating characteristic curve.

Results: Out of 194 infants, 91 (47%) were reintubated during hospitalization; 68% for respiratory and 32% for non-respiratory reasons. Respiratory-related reintubation rates steadily increased from 0 to 14d post-extubation before reaching a plateau. In contrast, non-respiratory reintubations were negligible in the first post-extubation week but became predominant after 14d. An observation window of 7d captured 77% of respiratory-related reintubations while only including 14% of non-respiratory cases.

Conclusion: Reintubation patterns are highly variable and affected by the reasons for reintubation and observation window used. Ideally, reintubation rates should be reported using a cumulative distribution curve over time.

4.2 Introduction

With the increasing use of early non-invasive respiratory strategies, mechanical ventilation (MV) is becoming reserved for the most immature infants with severe respiratory disease (1, 2). In an effort to avoid the complications associated with MV (3), prompt weaning and reduction of MV duration remain the ultimate goal. Unfortunately, as many as two-thirds of extremely low birth weight (ELBW) infants (birth weight ≤ 1000g) fail the initial extubation attempt and require reintubation during hospitalization (4, 5). Reintubation not only prolongs MV duration, but has also been independently associated with morbidities and mortality (4-6). For these reasons, respiratory-related studies commonly investigate strategies that can reduce rates of reintubation in these infants (7).

Reported rates of reintubation are typically defined as the proportion of infants reintubated within a pre-specified time after extubation. In general, studies aim to select an observation window that captures the majority of reintubations attributable to respiratory failure while minimizing inclusion of reintubations caused by non-respiratory events. However, since the optimal window of observation is unknown, variable ranges have been used. A recent systematic review on this subject noted that observation windows ranged anywhere from 12h to 7 days after extubation, without distinction between the causes of reintubation (8). Interestingly, amongst ELBW infants, reintubation rates significantly increased as a function of the selected observation window, without reaching a plateau by 7 days (8). Thus, the aim of this study was to longitudinally evaluate patterns of reintubation over a broad range of observation windows in extremely preterm infants, and determine the optimal approach for reporting reintubation rates in this population.

4.3 Methods

Study design

This work is a substudy of APEX, an ongoing prospective multicenter observational trial aimed at developing an automated prediction tool of extubation readiness in extremely preterm infants (Clinicaltrials.gov identifier: NCT01909947) (9). The study was conducted in 5 neonatal intensive care units (NICU) at: the Royal Victoria Hospital, Jewish General Hospital, and Montreal Children's Hospital (Montreal, Quebec, Canada); Detroit Medical Centre (Detroit, Michigan) and Women and Infants Hospital (Providence, Rhode Island). Ethics approval was attained from each institution's Research Ethics Board and informed parental consent was obtained.

Study population

Infants with birth weights ≤ 1250g and requiring MV were eligible. Only infants who underwent a planned extubation were included; an extubation was considered planned when the infant was deemed ready by the responsible clinician and extubation occurred under controlled conditions (9). Infants with major congenital anomalies, congenital heart disease, vasopressor or sedative use at extubation, extubations from high frequency ventilation and unplanned extubations (i.e. endotracheal tube dislodgement or obstruction) were excluded. All infants enrolled were followed from birth until death, discharge or transfer from the NICU. All decisions related to weaning from MV, timing of extubation, post-extubation respiratory support and reintubation were made by the responsible clinician and not influenced by the study team.

Data collection

As part of APEX, a comprehensive database of clinical variables was prospectively collected. An automated quality control and validation process was developed and applied to all

clinical files to correct for any transcription errors or outliers, as described elsewhere (10). The present study dealt with the subset of infants that were reintubated at any time point after their first planned extubation, and focused on the following variables:

(a) Demographic information: Gestational age, birth weight, sex, antenatal steroid administration, caesarian section, 5-minute APGAR score, use of surfactant and caffeine.

(b) At time of first planned extubation: post-menstrual age, weight, postnatal age, pre- and post-extubation ventilatory settings and blood gases.

(c) At the time of reintubation: The timing and reasons leading to reintubation, along with the type of respiratory support needed, were ascertained from the medical chart and/or directly from the clinical team. Data abstractors were instructed to check one or more of the following pre-selected categorical responses to indicate the reason(s) used by the medical team to proceed with reintubation: 1) apneas and bradycardias, 2) increased work of breathing (WOB), 3) respiratory acidosis, 4) increased O_2 needs, 5) upper airway obstruction and 6) other causes. The latter were defined as any other reason(s) or diagnose(s) that could explain the reintubation, such as infections (bacteremia, bronchiolitis, urinary tract infection), gastrointestinal complications (necrotizing enterocolitis (NEC), perforation, volvulus) or elective procedures, and were documented in a free-form text field in the data collection form.

Data analysis

All analyses were performed using MATLAB^{TM} (R2016a, The MathWorks Inc.). Continuous and categorical variables were described using medians (interquartile range) and counts (percentages), respectively. The timing of each reintubation was computed as the date and time of reintubation minus the date and time of first planned extubation, and grouped into 24h bins to create a broad range of observation windows. The proportion of infants reintubated for

each of the 6 categorical reasons for reintubation was determined. The free-text responses were analyzed using an automated classification algorithm (developed by WS and REK) able to detect keywords belonging to 3 additional categories of reintubation: infections (e.g. 'sepsis', 'bacteremia', 'cons', 'bronchiolitis', 'uti'), gastrointestinal complications (e.g. 'necrotizing', 'colitis', 'nec', 'volvulus', 'perf') or elective procedures (e.g. 'planned', 'elective', 'operation', 'surgery', 'procedure'). Infants reintubated for any of these 3 reasons were classified as non-respiratory; infants who were reintubated due to apneas and bradycardias, increased WOB, respiratory acidosis and/or increased O2 needs but without any other detectable etiology were classified as respiratory reintubations. In order to verify that the algorithm was accurate, a manual review of the free-text responses in the data collection forms was performed on a subset of 74 reintubated infants. The manual inspection confirmed that all reviewed infants were accurately classified into their respective categories by the algorithm.

Since the main objective of this study was to determine the proportion of infants reintubated and reasons for reintubation over a broad range of observation windows following the first planned extubation, the following sequence of analyses was conducted:

1. A frequency distribution curve was plotted to describe the number of infants reintubated per 24h bin.
2. Cumulative distribution curves were constructed to describe the reintubation rates for respiratory and non-respiratory reintubations as a function of the observation window used.
3. One-sample proportion tests were used to compare the relative probabilities of reintubation due to respiratory vs. non-respiratory reasons during 3 periods: 0-7 days, 8-14 days and >14 days after the first planned extubation. A p value < 0.05 was considered statistically significant, and 95% confidence intervals (CI) were computed.

4. The tradeoff between the ability of various observation windows to capture all respiratory reintubations (sensitivity) while limiting non-respiratory reasons (specificity) was evaluated using a receiver operating characteristic (ROC) curve.
5. A subgroup analysis was performed on infants with birth weights ≤ 1000 g to identify their cumulative rates of respiratory and non-respiratory reintubation over time.

4.4 Results

From September 2013 to June 2016 a total of 547 infants met eligibility criteria; 270 were consented and 194 included in this study (Figure 4.1). A total of 91 infants (47%) were reintubated at some time after their first planned extubation. Their demographics and pre-extubation characteristics are shown in Table 4.1. The majority (85%) of infants was reintubated from non-synchronized nasal intermittent positive pressure ventilation (NIPPV), and the most common reason for reintubation was apneas & bradycardias (65%). No infant was reintubated for upper airway obstruction. An infection (bacteremia, urinary tract infection or bronchiolitis) was reported as contributing cause in 17 infants (19%), while gastrointestinal complications (NEC, intestinal perforation or volvulus) and elective procedures accounted for 10 (11%) and 5 (5%) cases, respectively. Three infants had co-existing diagnoses of infection and NEC upon reintubation.

The automated classification algorithm identified 62 respiratory and 29 non-respiratory reintubations. The frequency distribution of reintubations over time is presented in Figure 4.2. The highest peak of reintubations occurred within 24h from extubation, representing 21% of all reintubations. A subsequent peak occurred between 25 and 168h after extubation, accounting for an additional 36% of all reintubations. A similar distribution pattern was observed for the subset

of respiratory reintubations, with the proportion of reintubations being higher at both 24h (29%) and between 25 and 168h (48%). Respiratory reintubations in the first 24h were primarily related to one or more of the following: increased WOB (61%), apneas & bradycardias (44%) and increased O_2 needs (44%). Respiratory reintubations beyond 24h were mostly due to apneas and bradycardias (73%), and to a lesser extent due to increased WOB and O_2 needs (32% each).

The cumulative distribution curve of respiratory and non-respiratory reintubation rates over time is displayed in Figure 4.3. Respiratory-related reintubation rates steadily increased as the observation window was extended from 0 to 14 days post-extubation, after which a plateau was finally reached. The rates of respiratory-related reintubations were 15% at 72h, 25% at 7 days, 29% at 14 days and 32% at discharge. In contrast, rates of non-respiratory reintubations were only 2% in the first 7 days after extubation and increased gradually, reaching 15% at discharge. The relative probabilities of respiratory and non-respiratory reintubations for 3 different time periods after extubation are shown in Figure 4.4. Infants reintubated within 7 days from extubation had a significantly greater probability of respiratory-related reintubation ($p < 0.001$, 95% CI 85-100%), whereas those reintubated beyond 14 days had a significantly greater probability of non-respiratory reintubation ($p = 0.007$, 95% CI 5-39%). Reintubations between 8 and 14 days were equally attributed to respiratory and non-respiratory causes ($p = 0.62$, 95% CI 32-81%).

Finally, Figure 4.5 shows an ROC curve that plots the proportion of respiratory reintubations (y-axis) and non-respiratory reintubations (x-axis), captured by various observation windows. Time windows of 72h, 7d, 10d and 14d captured 47%, 77%, 85% and 92% of respiratory reintubations, at the expense of also detecting 3%, 14%, 21% and 38% of non-respiratory reintubations, respectively.

For the subgroup analysis, a total of 79 out of 137 ELBW infants (58%) were reintubated at any time point after their first planned extubation, 55 of which were respiratory (70%) and 24 (30%) non-respiratory. The cumulative distribution curve of respiratory and non-respiratory reintubation rates for ELBW infants is available in Supplemental Figure S4.1 (online).

4.5 Discussion

This paper describes, for the first time, the patterns of reintubation in extremely preterm infants over a broad range of observation windows following extubation. In our cohort, nearly half the infants were reintubated at some time after their first planned extubation; two-thirds for respiratory reasons and one-third for non-respiratory causes. Reintubation rates increased consistently as the observation window was extended beyond 7 days, with differences between respiratory and non-respiratory cases. Furthermore, a comprehensive summary of the sensitivity and specificity of different observation windows at capturing respiratory reintubations without over-detecting non-respiratory causes is provided. Altogether, these findings improve the knowledge concerning reintubation of this vulnerable population and add a valuable framework for standardizing its reporting in the scientific literature.

We report that 47% of infants ≤ 1250 g and 58% of infants ≤ 1000 g were reintubated at least once during hospitalization, a finding consistent with results of other large cohort studies (4, 11). However, these reintubation rates are much higher than those reported for adult (10%) and children (6%) patients (12, 13). Given the morbidities associated with reintubation and resumption of MV, clinicians and investigators alike are increasingly searching for strategies that can reduce rates of reintubation in this population (7). Unfortunately, a heretofore these reintubation rates have not been reported in a standardized manner, making comparisons

between studies quite difficult (14). For instance, in a recent meta-analysis of interventions to improve extubation success, pooled studies used variable durations of observation (ranging from 24h to 7 days) and included infants with varying degrees of prematurity (all gestational ages < 37 weeks) (7). Our data suggest that reintubation rates changed considerably as a function of the observation window used and population studied. To illustrate, reintubation rates in our cohort would have been reported as 10% after 24h of observation, 16% after 72h or 27% after 7d, whereas limiting the study to ELBW infants could have resulted in rates of 13%, 21% or 34% for the same time points. These results support the concerns raised previously in a systematic review where reintubation rates amongst ELBW infants significantly increased over time but did not reach a plateau at 7 days post-extubation, which was not the case in larger infants (8). Therefore, in the extremely preterm population, comparison between studies that use different populations or definitions may potentially lead to inaccurate or misleading conclusions.

In studies investigating the outcome of extubation success or failure, the selected observation window has an important impact on the types of reintubation included. According to a recent international survey, most clinicians reported that extubation failure should be defined as the need for reintubation within 24 to 72h after extubation (15). The choice of a short observation window reflects the assumption that most reintubations caused by respiratory disease would occur in this time frame (5). Indeed, a recent secondary analysis of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) used a cutoff of 5 days to define extubation success based on the rationale that most reintubations during that window occurred within 48h after extubation (5). However, limiting the observation period to 5 days failed to account for an additional 243 infants who failed beyond that cutoff, hence excluding 39% of all reintubations from their analysis. In our study, we similarly observed that only a small proportion

of reintubations attributable to respiratory disease actually occurred in the first few days after extubation. In fact, limiting the observation windows to 24h, 72h and 7 days systematically underreported the true number of respiratory reintubations, failing to capture more than 70%, 50% and 20% of actual events, respectively. Such findings call into question the interpretation of studies testing interventions to prevent reintubation, since limiting the reports to short observation windows may provide a falsely reassuring estimate of the effectiveness of the intervention.

We found quite interesting that a considerable number of reintubations that occurred between 72h and 14 days after extubation had no identifiable cause other than respiratory-related symptoms (apneas and bradycardias, increased WOB, respiratory acidosis and/or increased oxygen needs). There are several plausible explanations for the need for extended observation windows to capture these respiratory-related cases. First, with the increased use of non-invasive ventilation following extubation, reintubation may be delayed rather than actually prevented. This phenomenon has actually been described in the adult population, whereby the increased use of non-invasive respiratory support has shifted the window of observation from the traditional 48h to 96h post-extubation (12, 16). Indeed, in our cohort, although infants were extubated to continuous positive airway pressure (CPAP) or NIPPV equally often, the majority had escalated to NIPPV by the time they were reintubated. This practice stems from meta-analyses demonstrating that NIPPV may be superior to CPAP in reducing reintubation rates amongst preterm infants (7, 17). However, most studies used a cut-off of 48-72h for their definitions, making it unclear as to whether extended windows of observation would have resulted in sustained benefits or not. Second, there is currently little evidence as to what constitutes a physiologically and clinically relevant definition of non-invasive support failure. As a result, the

decision to reintubate is highly subjective and generally based on clinicians' interpretation of apnea severity and/or frequency, oxygen requirements, work of breathing and gas exchange (8). A recent international survey reported that only 10% of respondents reintubated infants on the basis of standardized guidelines (15). Thus, there is significant variability within and between units regarding tolerance thresholds for reintubation. But given the concerns about reinstituting MV, it is conceivable that some clinicians would preferentially attempt to postpone reintubation as much as possible. Third, extremely preterm infants can are reintubated due to a multitude of respiratory-related reasons, including lung atelectasis, inflammation, pulmonary edema, high airway resistance and suboptimal respiratory drive. Unfortunately, indications currently used by clinicians to justify reintubation (such as increased WOB or apneas) lack specificity to distinguish between those respiratory causes. In our cohort, we observed two distinct patterns of respiratory-related reintubations, one within 24h and another between 25 and 168h after extubation, raising the hypothesis that the various respiratory disease processes leading to reintubation may actually manifest at variable time frames following extubation.

It is clear from the present analysis that extending the observation window will capture all respiratory reintubations, but at the cost of including reintubations that are unrelated to respiratory failure. In our study, reintubations due to non-respiratory causes were negligible in the first week after extubation, but became much more frequent after 14 days. The ROC curve on Figure 4.5 suggests that using observation windows between 7-14 days would offer the optimal trade-off between sensitivity and specificity for detecting respiratory reintubations.

Our study had certain limitations. The analysis was only performed for reintubations following the first planned extubation, and therefore cannot be extrapolated to those that occurred after repeat or unplanned extubations. Moreover, it is always possible that some

reintubations may have been misclassified as respiratory or non-respiratory by the medical team (i.e. misdiagnosis), during the data extraction process or by the classification algorithm. Lastly, due to the wide variability in respiratory care practices and comorbidities (e.g. postnatal sepsis or NEC) across NICUs, our results may not be generalizable to all centers. Nevertheless, the study's multicenter nature, large sample size, prospective design, thorough data quality control and rigorous analytical methods provide new and critical information for accurately reporting and analysing patterns of reintubation in extremely preterm infants undergoing their first extubation attempt. Our findings also highlight the importance of the choice of time frame and causes of reintubation when studying this population. Future research is needed to objectively characterize the various disease processes leading to respiratory-related reintubations in the first 14 days after extubation. Furthermore, the clinical implications of reintubation at different time frames and for different reasons should be explored.

In conclusion, reintubation is a very common but complex phenomenon that occurs due to multiple reasons and at variable frequencies throughout hospitalization. As a consequence, studies reporting reintubation rates at any single time point after extubation will provide an incomplete overview of the true reintubation rates, making them difficult to interpret or compare. Future studies investigating the outcome of extubation success or failure, irrespective of the definition used, should report reintubation rates as a continuum, by presenting a cumulative distribution curve over time. Ideally, this time frame should extend to at least 7 days, since it would capture most of the cases of respiratory failure without including non-respiratory related reintubations. If a longer window is chosen, distinction should be made between respiratory and non-respiratory reintubations. Finally, traditional statistical methods should preferentially be

replaced by time-to-event analysis techniques as a means to more accurately compare the effectiveness of interventions at reducing rates of reintubations.

4.6 References

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4.7 Figures and Tables

Figure 4.1 Flow of participants

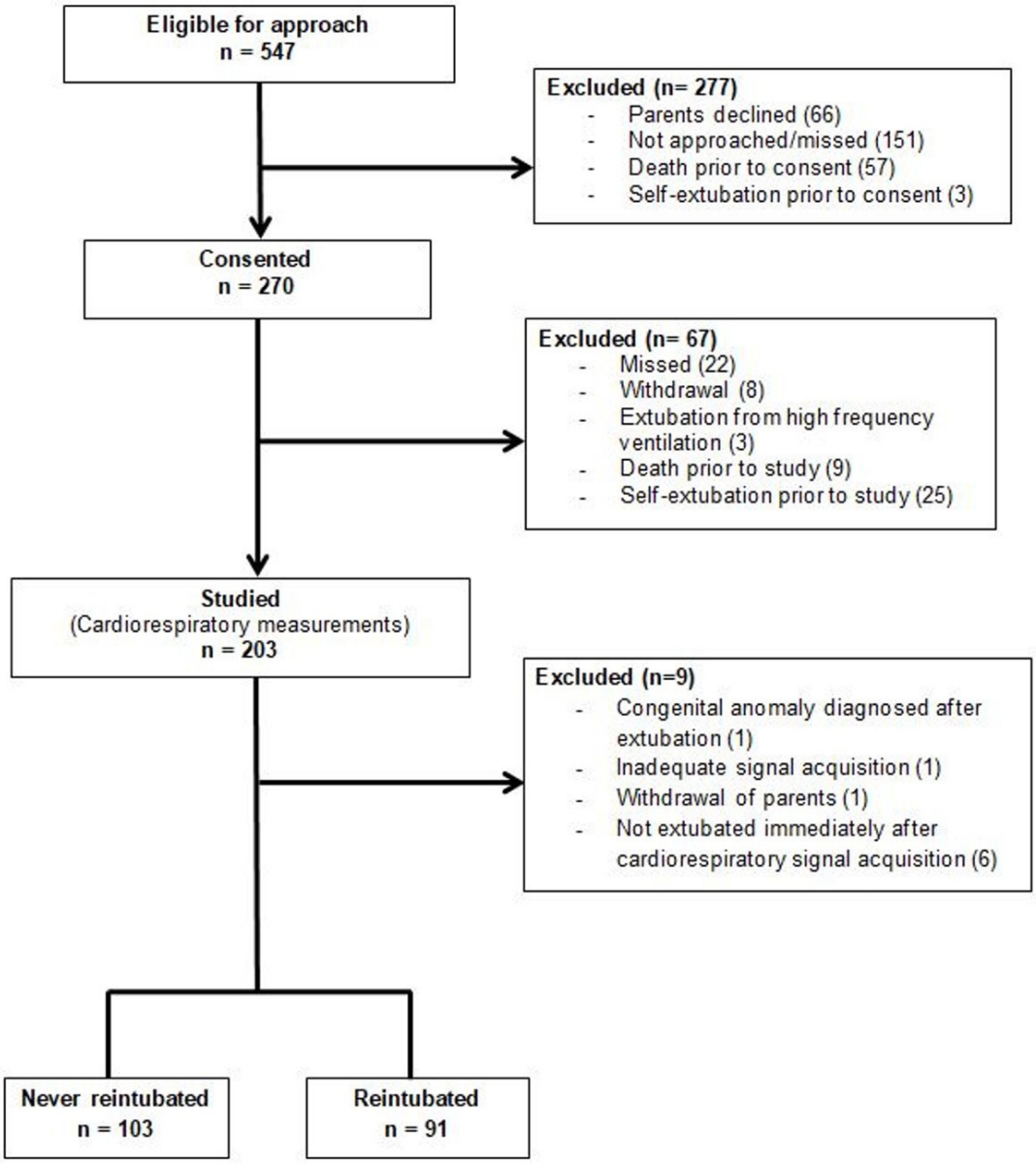


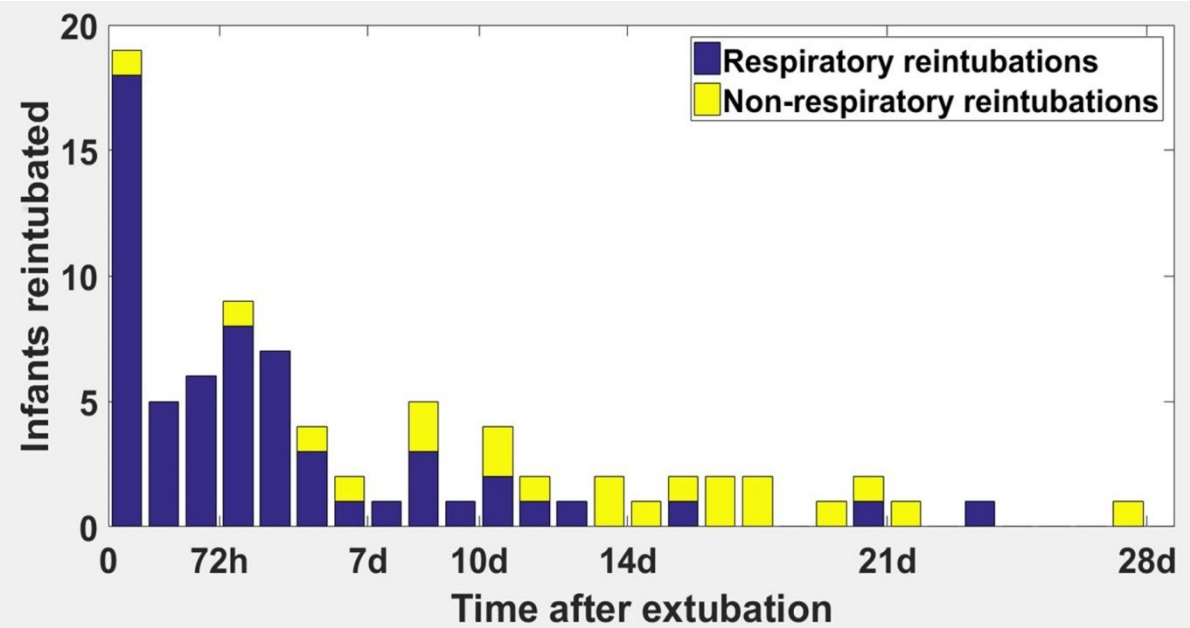
Table 4.1 Characteristics of infants reintubated and reasons for reintubation

	N = 91
Demographic information	
Gestational age, weeks	25.7 [24.7 – 26.6]
Birth weight, grams	770 [683 – 928]
Male sex, %	53 (58)
Antenatal steroids, %	80 (88)
Caesarean section, %	55 (60)
APGAR score at 5 minutes	6 [5 – 8]
Surfactant, %	87 (96)
Caffeine, %	89 (98)
Pre-extubation	
Day of life (DOL) at extubation	9 [3 – 25]
DOL ≤ 7	41 (45)
DOL > 7	50 (55)
Corrected age at extubation, weeks	27.6 [26.7 – 29]
Weight at extubation, grams	890 [730 – 979]
Mean airway pressure, cm H_2O	7.0 [6.2 – 8.2]
Fraction of inspired oxygen, %	0.25 [0.21 – 0.28]
pH	7.34 [7.30 – 7.37]
PCO_2, mm Hg	44 [36.7 – 52.2]
Base excess, mm Hg	-2.4 [-4.8 – 0.9]
Respiratory support post extubation	
Continuous positive airway pressure, %	41 (45)
Nasal intermittent positive pressure ventilation, %	46 (50)
High flow nasal cannula, %	4 (5)
Respiratory support prior to reintubation	
Continuous positive airway pressure, %	7 (8)
Nasal intermittent positive pressure ventilation, %	77 (85)
High flow nasal cannula, %	4 (4)
Others (biphasic, low flow nasal cannula or no support)	3 (3)
Reasons for reintubation (n=91)*	
Apneas and bradycardias, %	59 (65)
Increased oxygen needs, %	32 (35)
Increased work of breathing, %	26 (29)
Respiratory acidosis, %	13 (14)
Upper airway obstruction, %	0 (0)
Infections	17 (19)
Gastrointestinal complications	10 (11)
Elective procedures	5 (5)

Values are expressed as medians [IQR] or n (%)

* Infants could have more than one reason for reintubation (i.e. the sum is greater than 100%)

Figure 4.2 Frequency distribution of reintubations over time



Legend: a total of 81 reintubations are shown (an additional 10 reintubations occurred beyond 28 days after extubation)

Figure 4.3 Cumulative distribution of respiratory and non-respiratory reintubation rates over time

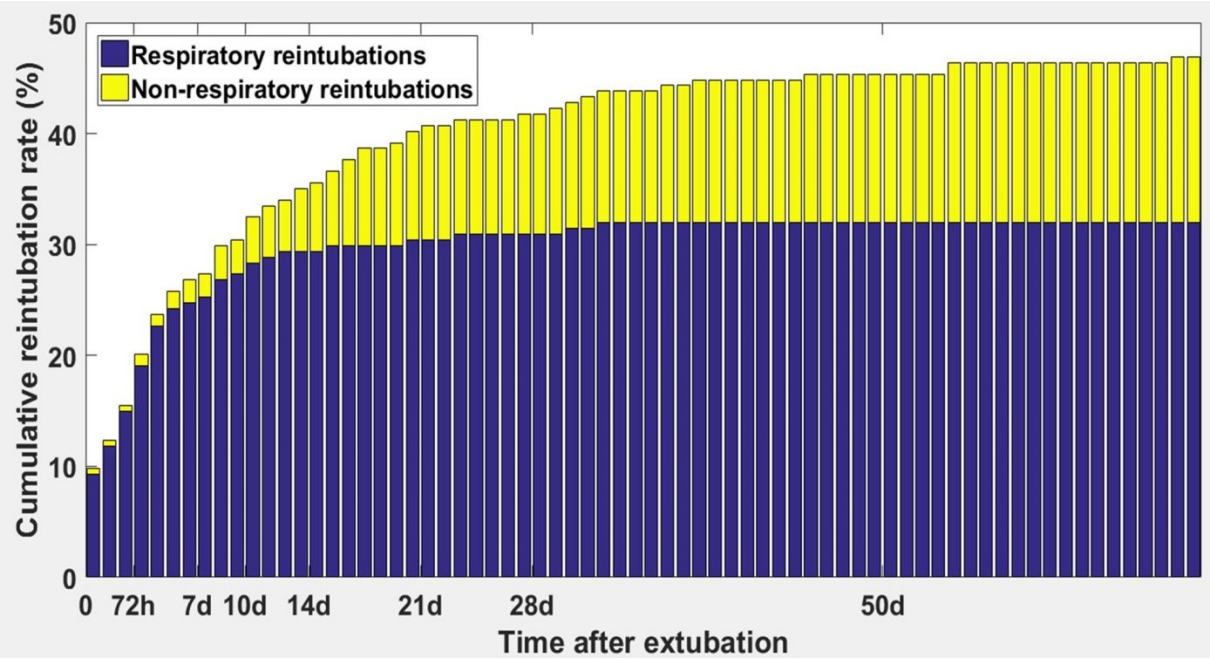
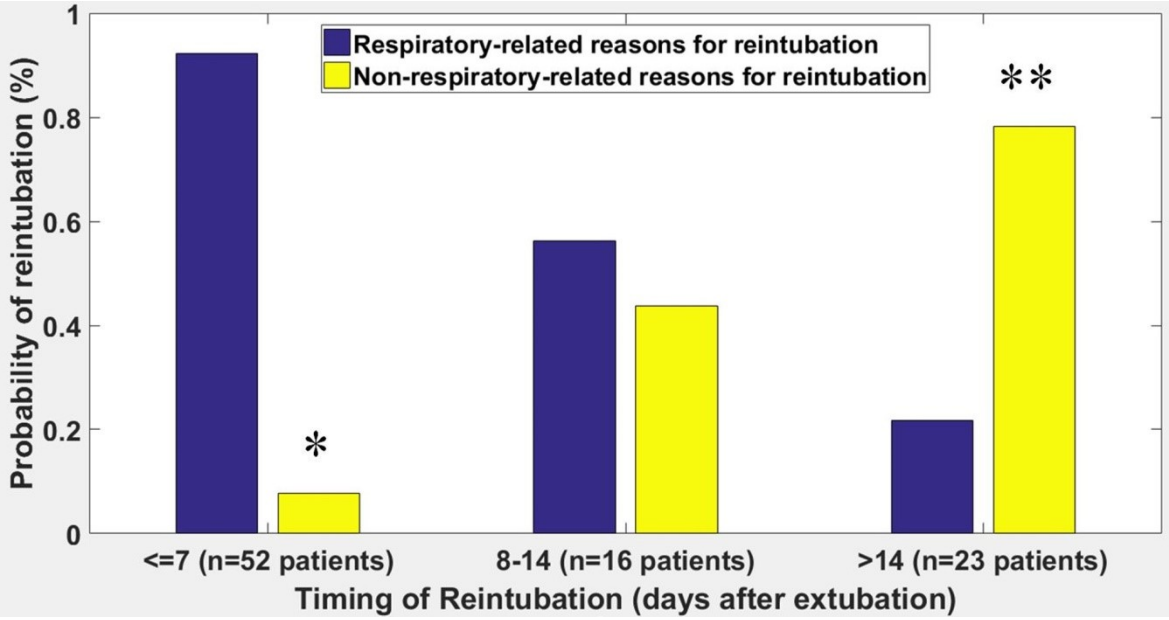
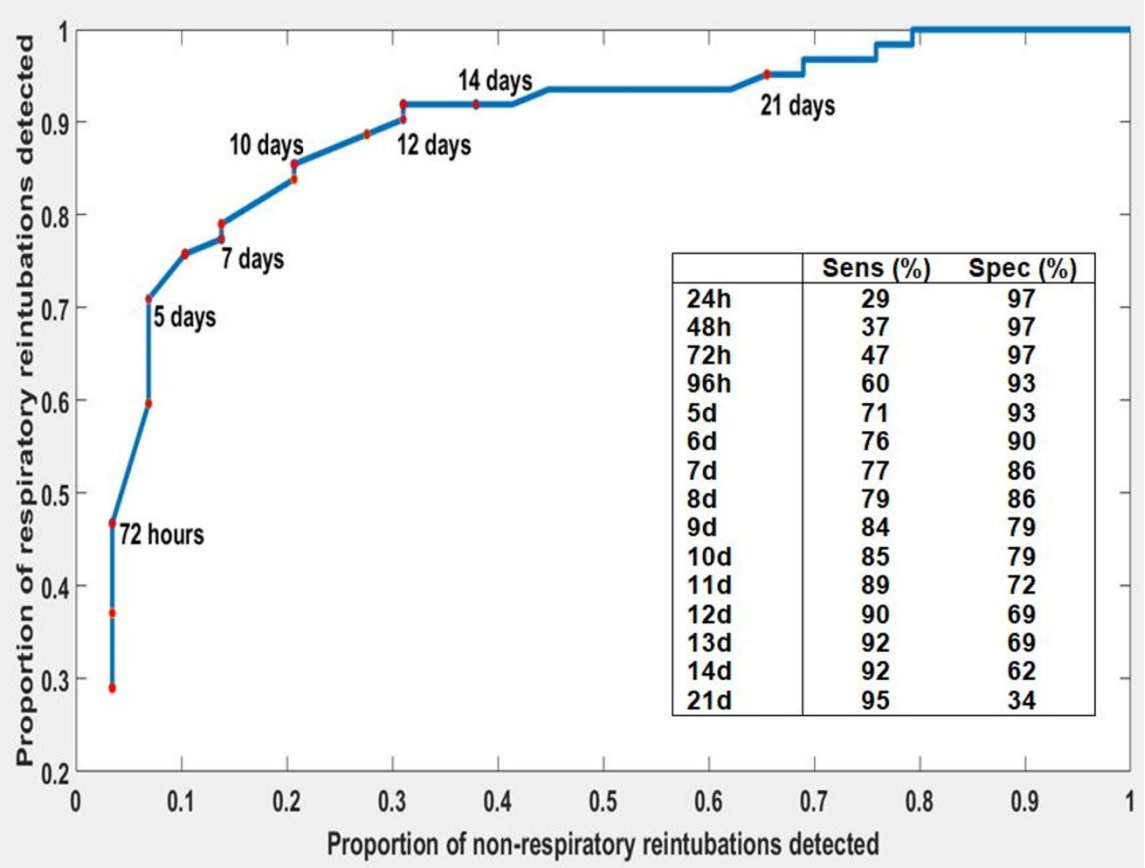


Figure 4.4 Probability of reintubation during 3 time periods following extubation



Legend: *p <0.001 (95% CI 85-100%) and ** p = 0.007 (95% CI 5-39%) for respiratory-related reasons vs non-respiratory related reintubations.

Figure 4.5 Receiver operating characteristics curve of the optimal observation window for detecting respiratory-related reintubations

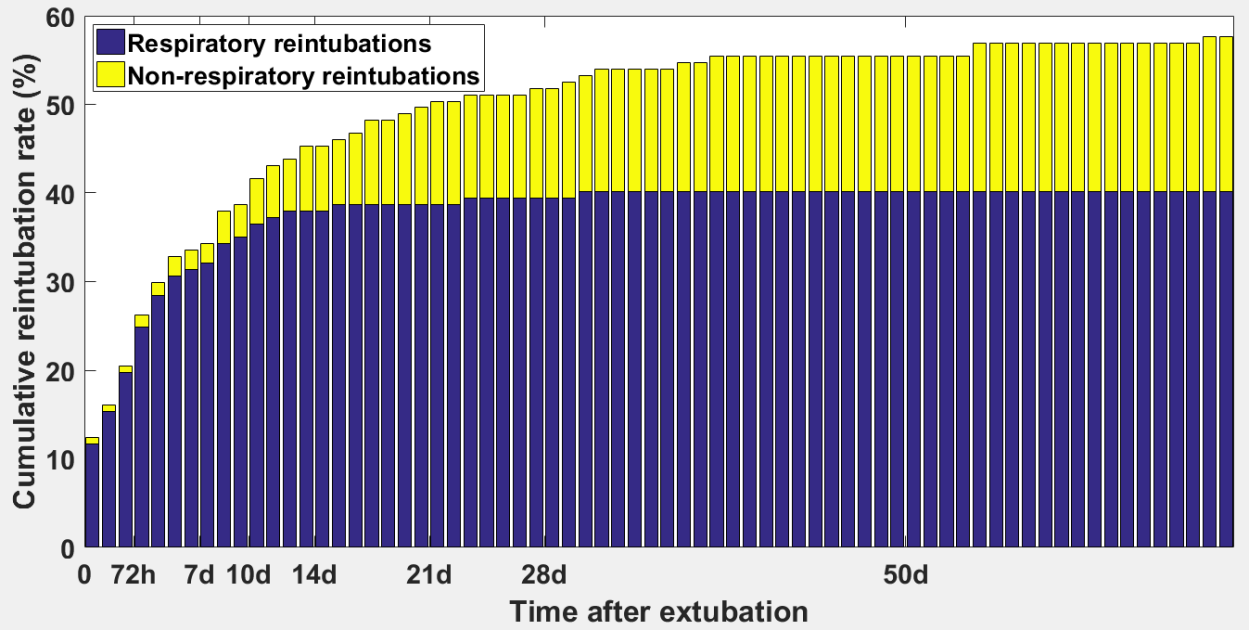


	Sens (%)	Spec (%)
24h	29	97
48h	37	97
72h	47	97
96h	60	93
5d	71	93
6d	76	90
7d	77	86
8d	79	86
9d	84	79
10d	85	79
11d	89	72
12d	90	69
13d	92	69
14d	92	62
21d	95	34

Legend: Red circles represent the sensitivity (proportion of respiratory reintubations detected) and specificity (proportion of non-respiratory reintubations detected) of different observation windows (grouped into 24h intervals) between 24h and 14 days post-extubation.

4.8 Supplementary Material

Supplementary Figure S4.1 Cumulative distribution of respiratory and non-respiratory reintubation rates over time amongst extremely low birth weight infants



Bridging Text 4

In the first clinical study using the APEX cohort (shown in Chapter 4), we longitudinally described the patterns (i.e. timing and reasons) by which extremely preterm infants were reintubated during their NICU hospitalization. We found that reintubation rates varied dramatically as a function of the observation window used to define extubation failure. But in trying to ascertain which observation window to select when studying the outcome of extubation failure, we thought it crucial to additionally understand the clinical implications of different reintubations (i.e. at different time points after extubation) on important morbidities (such as BPD) and mortality. Thus, for the next study, we sought to explore the clinical impact of time interval between extubation and reintubation on death or BPD amongst infants enrolled in the APEX study. The study was published in *The Journal of Pediatrics* and the preprint of the article is presented in Chapter 5.[106]

Chapter 5 – The Impact of Time Interval between Extubation and Reintubation on Death or Bronchopulmonary Dysplasia in Extremely Preterm Infants

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5.1 Abstract

Objective: To explore the relation between time to reintubation and death or bronchopulmonary dysplasia (BPD) in extremely preterm infants.

Methods: This was a sub-analysis from an ongoing multicenter observational study. Infants with birth weight ≤ 1250g, requiring mechanical ventilation (MV), and who underwent their first elective extubation were included and prospectively followed throughout hospitalization. Time to reintubation was defined as the time interval between first elective extubation and reintubation. Univariate and multivariate logistic regression analyses were performed to evaluate associations between time to reintubation, using different observation windows after extubation (24h intervals), and death/BPD (primary outcome) or BPD among survivors (secondary outcome). Adjusted odds ratios were computed with and without the confounding effects of cumulative MV duration.

Results: Out of 216 infants included for analysis, 103 (48%) were reintubated at least once after their first elective extubation. Reintubation was associated with significantly lower gestational age/weight (at birth and extubation) and greater morbidities compared to infants never reintubated. After adjusting for confounders, reintubation within observation windows ranging between 24h and 3 weeks post-extubation was associated with increased odds of death/BPD (but not BPD among survivors), independently of the cumulative MV duration. However, reintubation within 48h from extubation conferred higher risk-adjusted odds of death/BPD compared to any other observation window.

Conclusion: Although reintubation after elective extubation was independently associated with increased likelihood of death/BPD in extremely preterm infants, the greatest risk was attributable

to reintubation within the first 48h post-extubation. Prediction models capable of identifying the highest-risk infants may further improve outcomes.

5.2 Introduction

Extremely preterm infants are often reintubated after a trial of extubation. Based on recent cohort studies, nearly 50% of very low birth weight and 60-70% of extremely low birth weight infants require resumption of mechanical ventilation (MV) at least once during their hospitalization.[1-3] However, the time to reintubation, referring to the time interval between MV courses, can range anywhere from a few hours to several weeks after extubation.[1] While prolonged MV exposure is a well-established risk factor for death and/or bronchopulmonary dysplasia (BPD) in these infants,[2, 4, 5] the direct impact of reintubation on respiratory outcomes is less well understood. Recent sub-analyses from two large randomized controlled trials showed that reintubation within 5 and 7 days after extubation independently increased respiratory morbidities and mortality.[6, 7] In contrast, the only study that adjusted for the cumulative duration of MV found that a single reintubation any time after extubation did not increase the risk-adjusted odds of BPD among survivors.[2] Importantly, all studies to date have used very different observation windows to decide which reintubations were considered clinically relevant, and made the assumption that all included reintubations, irrespective of their timing, would affect outcomes equally. Nevertheless, it is unclear whether a reintubation occurring within hours from extubation would have the same clinical implications as a reintubation occurring days or weeks later. In adults, both prompt and delayed reintubations have been associated with increased mortality.[8-10] Therefore, we sought to explore associations between time to reintubation and the composite outcome of death or BPD in a large prospective cohort of extremely preterm infants.

5.3 Methods

Study design

This study was an exploratory analysis of an ongoing multicenter observational study aiming to develop an Automated Prediction tool of EXtubation readiness in extremely preterm infants (APEX study).[11] Infants included were enrolled between September 2013 and June 2017 at five different neonatal intensive care units (NICUs) in Canada and the United States. The study was approved by each institution's Ethics Review Board and written consent was obtained from the parents.

Study population

The APEX study rationale and protocol are described in detail elsewhere.[11] In brief, infants with birth weight ≤ 1250g, requiring MV, and undergoing their first elective extubation were included. Exclusion criteria were congenital anomalies or heart defects, extubation from high frequency ventilation, extubations directly to low flow nasal cannula or no respiratory support, and deaths prior to extubation. All decisions regarding weaning from MV, extubation and reintubation were made by the treating team and not influenced by the study.

Data collection and definitions

APEX study includes a large database of clinical variables prospectively collected by trained abstractors at various time points throughout hospitalization in the NICU. Details on data collection and quality control methods are also described elsewhere.[11, 12] For the purpose of this study, the following variables were evaluated:

Exposure: For each infant reintubated, 'time to reintubation' was computed as the date and time of reintubation minus the date and time of the first elective extubation. Using that information, the exposure of interest was defined as reintubation within different observation

windows following extubation. Each observation window was binned into 24h intervals, thus creating a broad range of exposures going from 'reintubation within 24h after extubation' to 'reintubation any time during NICU hospitalization'.

Outcomes: The primary outcome was the composite of death or moderate-to-severe BPD, defined as the need for any supplemental oxygen and/or any type of invasive or non-invasive respiratory support at 36 weeks postmenstrual age.[13] Non-invasive respiratory support included any form of continuous positive airway pressure, nasal intermittent positive pressure ventilation or heated humidified high flow nasal cannula. The secondary outcome was BPD among infants surviving to discharge from the NICU.

Confounders: The cumulative duration of MV was selected a priori as an important confounder for inclusion in the final statistical model. From the database, a day of MV corresponded to a calendar day in which MV was the most employed type of respiratory support. Other potential confounding variables included: gestational age, birth weight, sex, study site, small for gestational age (defined as birth weight below the 10^{th} percentile using a Canadian reference growth curve),[14] antenatal steroids, cord pH, 5-min Apgar score, intubation in the delivery room, surfactant use, caffeine use, postmenstrual age and weight at extubation, pre-extubation hemoglobin (if sampled within the preceding 24h), pre-extubation blood gas (pH and pCO_2) and ventilator parameters (mean airway pressure and fraction of inspired oxygen), and post-extubation respiratory support. Moreover, outcomes at discharge comprised postnatal steroids use, patent ductus arteriosus, necrotizing enterocolitis (modified Bell's stage IIA or above requiring medical or surgical intervention),[15] intraventricular haemorrhage of any grade, and culture-proven postnatal infection (bloodstream, urine or cerebrospinal fluid).

Statistical analysis

All analyses were conducted using MATLAB (R2016a, The MathWorks, Natick, MA, USA). Patient characteristics were first compared between infants reintubated and those never reintubated using Wilcoxon rank sum test (for continuous variables) and Chi-square or Fisher's exact test (for categorical variables). Amongst infants requiring reintubation, a cumulative frequency graph was plotted to present the number of infants reintubated within each observation window following extubation and their respective outcomes (death, BPD or no BPD). Also, the cumulative proportion of infants that developed death/BPD was determined as a function of time to reintubation. Univariate and multivariate logistic regression analyses were used to evaluate for associations between time to reintubation and outcomes. To construct the multivariate logistic regression model, clinically relevant variables with $p < 0.20$ in the bivariate analysis were assessed using stepwise regression; only those variables with $p < 0.05$ were included in the final model. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were then computed using two models: model 1 adjusted for all variables obtained in the stepwise regression, while model 2 additionally accounted for the confounding effect of cumulative MV duration. The correlation between time to reintubation and cumulative MV duration was determined using Spearman's rank correlation, and an interaction term between the exposure of interest and cumulative MV duration was incorporated into the second multivariate model if it was shown to be statistically significant ($p < 0.05$).

5.4 Results

A total of 216 infants were included, of which 103 (48%) were reintubated at least once during hospitalization (Supplemental Figure S5.1 online). Table 5.1 compares the characteristics of infants who were reintubated or not. Infants requiring reintubation were significantly smaller and more immature at birth compared to those never reintubated. At the time of extubation, they

also had significantly lower weight and postmenstrual age, were exposed to more days on MV, and received higher fraction of inspired oxygen. Following extubation, there were no significant differences between groups with regards to the type of immediate post-extubation respiratory support used. By discharge from the NICU, infants requiring reintubation received a median of 12 additional days of MV (interquartile range, IQR 6-26 days), and had significantly greater postnatal steroid use, higher rates of patent ductus arteriosus, necrotizing enterocolitis and infection compared to infants never reintubated.

Figure 5.1 displays the cumulative number of infants reintubated and their respective outcomes (death, BPD or survival without BPD) as a function of time to reintubation. Out of 103 infants, 35 (34%) were reintubated within 3 days, 61 (59%) within 7 days and 77 (75%) within 14 days after the first elective extubation. The cumulative probability of developing death/BPD amongst reintubated infants was dependent on the observation window used: the shorter the window, the higher the probability (solid line, Figure 5.1). That is, while the overall probability of death/BPD was 83% for all reintubated infants, it was as high as 93% when limiting the observation window to infants reintubated within 48h after extubation. By contrast, the probability of death/BPD amongst infants never reintubated was 38%.

Unadjusted and adjusted associations between time to reintubation, using different observation windows after extubation, and outcomes are shown in Table 5.2 (for clearer visualization, only the most representative observation windows are presented). Adjustments were made for birth weight, study site, postnatal infection, postnatal steroids and necrotizing enterocolitis in both multivariate models, but model 2 additionally accounted for cumulative MV duration. Results for all other independent variables included in the multivariate models are

shown in Supplemental Table S5.1 online. There was no correlation (correlation coefficient r = -0.04) and no interaction ($p > 0.05$) between time to reintubation and cumulative MV days.

Primary outcome (Death/BPD): In comparison to infants never reintubated, reintubation within any observation window after extubation was associated with significantly higher odds of death/BPD in both univariate analysis and model 1 of the multivariate analysis. After accounting for the cumulative duration of MV (model 2), statistical significance persisted for the most part, but was lost once the observation window was extended to include all reintubations. Interestingly, as illustrated in Figure 5.2, the risk-adjusted odds appeared to be disproportionately higher for reintubations occurring within the first 24h and 48h after extubation compared to any other window of observation, and gradually decreased thereafter. Also, total MV duration remained significantly associated with increased odds of death/BPD in the final model (OR 1.08; 95% CI, 1.03-1.13).

Secondary outcome (BPD among survivors): In the univariate analysis, reintubation within any observation window after extubation was associated with significantly greater odds of BPD among survivors when compared to infants never reintubated. However, after accounting for confounders (including the effects of cumulative MV duration), reintubation was no longer associated with an increase in the risk-adjusted odds of BPD. In contrast, total MV duration remained significantly associated with increased odds of BPD among survivors in the final model (OR 1.13; 95% CI 1.06-1.21).

In an attempt to better understand why time to reintubation was independently associated with increased death/BPD but not BPD among survivors, a post-hoc evaluation of the causes of all infant deaths and their relationship to timing of extubation and reintubation was performed. There were a total of 10 infant deaths in the cohort: one infant never required reintubation, three

were reintubated within 24h, three between 48h-7d and three after 7d from extubation. This meant that reintubation within each of those time periods was associated with a 14%, 9% and 7% risk of death, respectively (compared to a 1% mortality for infants never reintubated). Amongst infants reintubated within the first 24h, the three deaths were attributed to: 1) pulmonary hemorrhage immediately post-extubation, 2) grade 4 intraventricular hemorrhage detected on a cranial ultrasound after reintubation (followed by withdrawal of life-sustaining therapy), and 3) fulminant necrotizing enterocolitis that became clinically manifest a few hours after extubation. The characteristics of all remaining deaths are available in Supplementary Table S5.2 online.

Finally, given the high risk of death/BPD identified for reintubations within the first 48h after extubation, a second post-hoc analysis was undertaken to determine whether other markers of illness severity were present amongst these infants. The latter had a median postmenstrual age of 27.4 weeks (IQR 26.5-28.4), weighed 820g (IQR 690-950) and were exposed to 11 days of MV (IQR 2-25) at the time of their first extubation attempt. When comparing the pre-extubation characteristics of these infants with those of infants reintubated between 48h-7 days after extubation (using Wilcoxon rank sum, Chi-square or Fisher's exact tests), no statistically significant differences could be detected (Supplementary Table S5.3 online). Moreover, there was no significant difference between groups in the number of intubation attempts required at the time of reintubation (reintubation within 48h: median 1, IQR 1-2; reintubation between 48h-7d: median 1, IQR 1-3, $p = 1$).

5.5 Discussion

In this exploratory analysis from a large prospective study, we found that time to reintubation independently modulated the odds of the combined outcome of death/BPD,

conferring the greatest risk when reintubation occurred within 48h from extubation. This significance persisted even after adjusting for the effect of cumulative MV duration. In contrast, reintubation, irrespective of the observation window used, did not increase the risk-adjusted odds of BPD among survivors. Together, these results provide novel insight to the importance of timing when evaluating the clinical implication of reintubations in extremely preterm infants.

In recent years, three large studies have investigated the effects of reintubation on death and/or respiratory morbidities in extremely preterm infants.[2, 6, 7] In a secondary analysis from a randomized trial comparing post-extubation high flow nasal cannula with continuous positive airway pressure, Manley et al. demonstrated that infants reintubated within 7 days after extubation were significantly more likely to die or require prolonged respiratory support and hospitalization.[6] In another secondary analysis from the surfactant, positive pressure and oxygenation randomized trial (SUPPORT), Chawla et al. showed that infants reintubated within 5 days from extubation had significantly greater risk of death, BPD, death/BPD and prolonged length of respiratory support and hospitalization.[7] In contrast, in a large retrospective cohort study including more than 3,000 extremely low birth weight infants, Jensen et al. found that the need for a second course of MV any time after extubation did not increase the risk of BPD (among survivors), tracheostomy or supplemental oxygen at discharge once adjustments were made for the total MV duration.[2] In trying to synthesize results from the aforementioned studies, some limitations emerge. First, each study used a different observation window to delineate which reintubations were considered clinically pertinent for evaluation. Second, studies made the presumption that all reintubations captured within their observation window would confer equal risks to the outcomes of interest. Lastly, some studies did not adjust for the cumulative MV duration in their respective analyses, making it unclear if reintubation truly affected outcomes

independently or if the adverse effects were mediated by the resumption of MV. Thus, we attempted to systematically explore these issues using our study cohort, while focusing primarily on the composite outcome of death/BPD.

The choice of observation window

In our cohort, the probability of death or BPD was highest for infants reintubated within the first few days after extubation. As the time interval between extubation and reintubation increased, a greater proportion of infants actually survived to discharge without BPD. From these findings, it is not surprising that the choice of observation window had a marked effect on the strength of the association between reintubation and death/BPD. That is, limiting the observation window to the first 48h after extubation led to the highest risk-adjusted odds of death/BPD, whereas extending the window to include more distant reintubations led to gradually weaker (and eventually non-significant) associations. As a result, a study evaluating all reintubations during hospitalization may dilute or mask the adverse effects conferred by earlier events, thereby providing a misleading reassurance about reintubation.

The independent effects of reintubation within 48h post-extubation on death/BPD

Interestingly, not all reintubations conferred equal risks of death/BPD. In fact, the need for reintubation within 48h post-extubation was associated with disproportionately higher risk-adjusted odds of death/BPD compared to any other observation window. This suggests that even though reintubation within broader observation windows (e.g. 7d or 14d) resulted in independently increased risk of death/BPD, it is likely that the significance was driven by earlier reintubations.

The characteristics of those infants who required rapid reintubation were evaluated in a post-hoc analysis. A total of 28 infants were reintubated within 48h from extubation, out of

which 26 (93%) died or developed BPD. These infants had no distinctive pre-extubation characteristics (postmenstrual age, weight, ventilatory settings, blood gases or other comorbidities), i.e. were no less 'ready' for a trial of extubation. Furthermore, we found that one-third of all infant deaths in our cohort had required a reintubation within 24h from extubation (more specifically at 30min, 7h and 8h after extubation), thus conferring a 14% risk of mortality. Careful scrutiny of the reintubations, as well as extrapolation from adult studies, leads us to speculate on some biologically plausible mechanisms that may have contributed to those results.

One likely explanation is that infants who promptly failed extubation represented an inherently sicker group. Indeed, when compared to infants never reintubated, those who required a second course of MV were significantly smaller, less mature and had more comorbidities. Altogether, these risk factors frequently result in the need for MV resumption and are also associated with increased mortality and BPD. Thus, the fact that early reintubation ($\leq$ 48h) continued to have an independent effect on death/BPD even after adjusting for confounders may have simply reflected an additional (independent) marker of illness severity. In our post-hoc analysis, we further attempted to isolate pre-extubation risk factors specific to those infants who were reintubated within 48h from extubation (Supplemental Table S5.3). Although no statistically significant factors were identified, this could have been due to the small sample size and large variance of some of the variables (e.g. pre-extubation MV days).

Another hypothesis is that infants promptly reintubated (within 48h from extubation) had a clinical deterioration that directly resulted from removal of the ventilatory support provided during MV. In adult studies, it is well established that the addition of positive end-expiratory pressure and/or pressure support during MV can significantly decrease work of breathing, reduce pulmonary wedge pressure and improve left ventricular performance.[16-19] While most patients

are capable of compensating for the transiently increased mechanical load that follows extubation, a minority may not adequately cope, thereby leading to rapid cardiorespiratory compromise and potentially catastrophic (sometimes fatal) consequences.[10, 18] Although concrete evidence for this is missing in the extreme preterm population, it is plausible that removal of invasive ventilatory support, albeit 'minimal', may have had clinically deleterious effects in the most fragile infants.

Finally, the technique of intubation in itself has been linked with increased complications, ranging from transient hemodynamic instability to cardiorespiratory arrest or death.[20] In particular, intubations with higher number of attempts, and those performed without premedication use or in an emergent setting all impart a greater risk of serious adverse events.[20, 21] From our study, although we could not ascertain most of the above risk factors, it is conceivable that infants who promptly failed their extubation attempt may have required more emergent interventions.

The confounding effects of cumulative MV duration

Reintubation unavoidably leads to prolonged exposure to MV. In our cohort, infants requiring reintubation received a median of 12 additional MV days, a finding consistent with previous data.[2] Based on recent evidence, each additional week of MV incrementally increases the risk of BPD and other respiratory morbidities.[2, 4] For that reason, it is important to adjust for its confounding effects when evaluating the independent effects of reintubation on respiratory outcomes. In our multivariate analyses, adjustments for total MV duration consistently weakened the association between reintubation (at observation windows > 48h) and death/BPD, and eliminated all associations between reintubation (at any observation window) and BPD among survivors. Thus, in concordance with results obtained by Jensen et al,[2] our findings indicate that

the increased risk of death or BPD conferred by most reintubations (especially those beyond 48h from extubation) is likely mediated by prolonged exposure to MV.

Limitations

Our study had certain limitations. First, the number of infants reintubated in the first 48h after extubation was relatively small when compared to the total number of infants reintubated, as reflected by the wider 95% confidence intervals observed as the time to reintubation was shortened. This suggests a greater degree of uncertainty with regards to the true strength of the association, and compels for larger studies to validate our results. Second, due to the small number of deaths, we only evaluated the effects of mortality as part of a composite outcome rather than a separate entity. Third, while we adjusted for several important variables known to increase death or BPD, it is possible that other confounders may have been unaccounted for. Fourth, since we only evaluated the impact of reintubations after the first elective extubation, our results may not apply to reintubations that occurred after previously failed extubation attempt(s) or after an accidental extubation.

Conclusions and clinical implications

In conclusion, results from our exploratory analysis indicate that although reintubations appear to be independently associated with an increased risk of death/BPD in extremely preterm infants, this significance is predominantly attributed to infants reintubated within ≤ 48h from extubation. Furthermore, our findings validate prior concerns that the cumulative duration of MV plays an important confounding role in the increased risk of death/BPD and BPD perceived with some reintubations. Thus, future research aimed at developing prediction models of extubation success should target the identification of reintubations that occur in the first 48h following extubation. In the meantime, given the absence of predictors capable of accurately identifying

this high-risk minority, infants should be extubated as early as deemed possible to mitigate the known risks associated with prolonged MV exposure.

5.6 References

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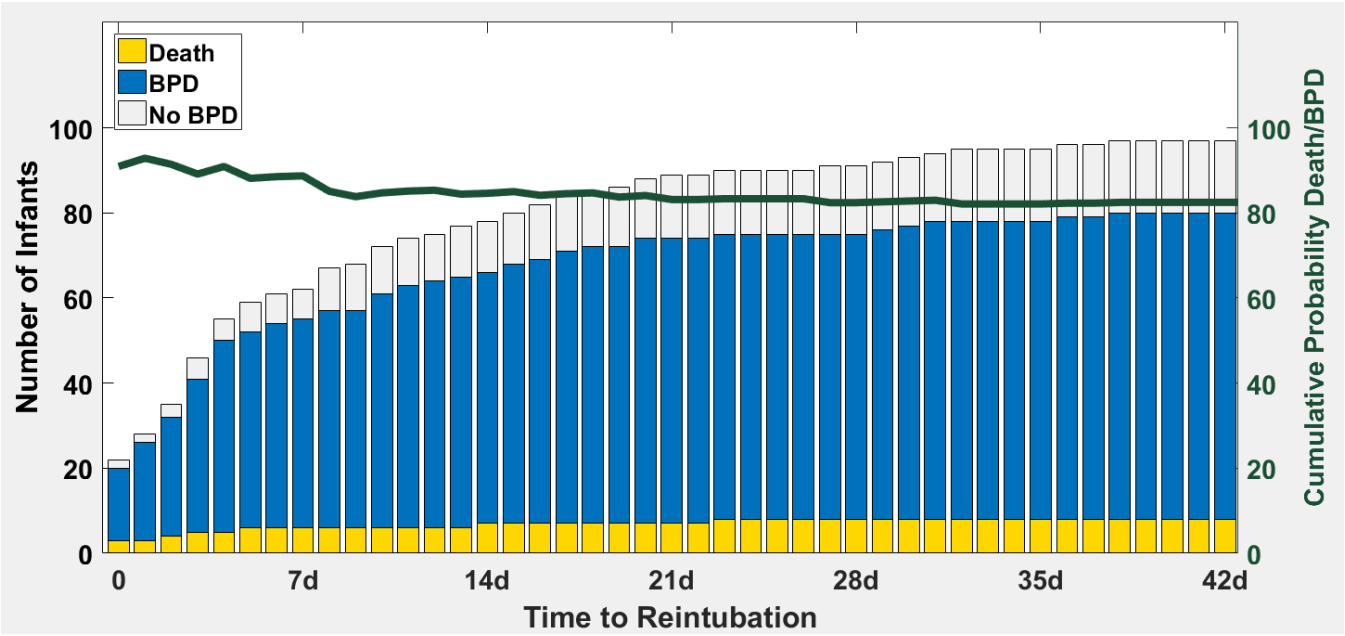
5.7 Figures and Tables

Table 5.1 Population characteristics

	Reintubated (N=103)	Never reintubated (N=113)	P value
Demographics			
Gestational age, weeks	25.6 [24.6 – 26.6]	27 [25.3 – 28.3]	< 0.001
Birth weight, grams	760 [669 – 900]	945 [750 – 1116]	< 0.001
Male sex	56 (54)	56 (50)	0.48
Small for gestational age	15 (15)	15 (13)	0.78
Antenatal steroids	92 (89)	104 (92)	0.49
Apgar score 5min[a]	6 [5 – 8]	7 [5 – 8]	0.82
Intubation in delivery room	63 (61)	47 (42)	0.004
Surfactant	97 (94)	108 (96)	0.64
Caffeine	101 (98)	109 (96)	0.69
Pre-extubation			
Postmenstrual age, weeks	27.6 [26.6 – 29]	28.7 [27.4 – 30]	< 0.001
Weight, grams	860 [730 – 974]	1040 [868 – 1153]	< 0.001
MV days	8 [3 – 25]	4 [2 – 20]	0.04
pH[b]	7.34 [7.3 – 7.38]	7.33 [7.29 – 7.38]	0.45
pCO2, mmHg[b]	44 [37 – 52]	44 [39 – 50]	0.8
Mean airway pressure, cmH_2O[c]	7 [6.2 – 8.4]	6.9 [6.2 – 7.8]	0.25
Fraction of inspired oxygen	0.25 [0.21 – 0.28]	0.21 [0.21 – 0.25]	< 0.001
Hemoglobin (≤ 24h), g/L[d]	130 [121 – 143]	138 [121 – 157]	0.07
Post-extubation			
CPAP	51 (49)	63 (56)	0.36
NIPPV	48 (47)	40 (35)	0.09
HHHFNC	4 (4)	10 (9)	0.14
Outcomes by discharge			
Additional MV days	12 [6 – 26]	0 [0 – 0]	< 0.001
Cumulative MV days	31 [14 – 40]	4 [2 – 20]	< 0.001
Postnatal steroids	66 (64)	25 (22)	< 0.001
Intraventricular hemorrhage	41 (40)	32 (28)	0.08
Patent ductus arteriosus	68 (66)	50 (44)	0.001
Necrotizing enterocolitis	23 (22)	7 (6)	< 0.001
Postnatal infection	49 (48)	33 (29)	0.01

Values are expressed as medians [IQR] or n (%). Abbreviations: CPAP – continuous positive airway pressure, NIPPV – nasal intermittent positive airway pressure, HHHFNC – heated humidified high flow nasal cannula, MV – mechanical ventilation.
[a] data available for 102 reintubated and 112 never reintubated infants. [b] data available for 97 reintubated and 97 never reintubated infants. [c] data available for 102 reintubated infants. [d] data available for 53 reintubated and 51 never reintubated infants.

Figure 5.1 Cumulative number of infants reintubated and cumulative probabilities of death/BPD as a function of time to reintubation



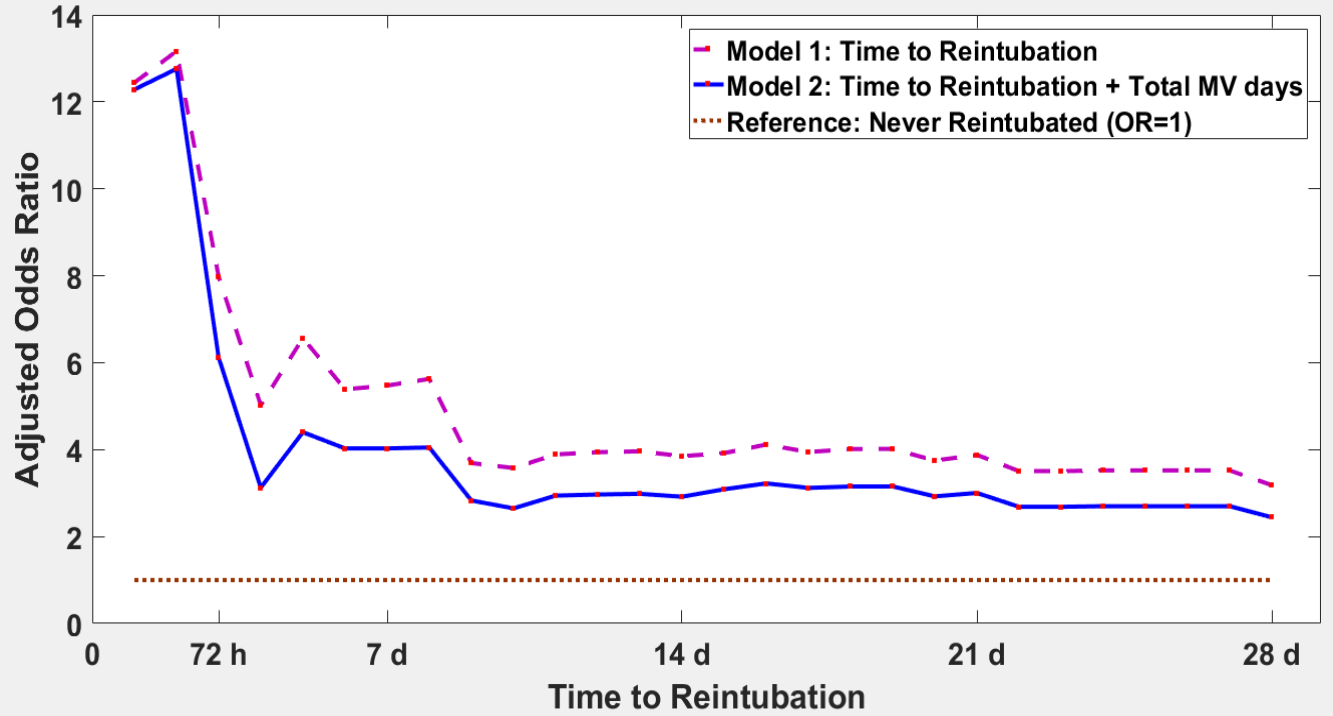
Legend: An additional 6 infants were reintubated beyond 42 days after their first planned extubation. The solid green line represents the cumulative probability of death/BPD as a function of the time interval between the first elective extubation and reintubation.

Table 5.2 Adjusted odds of death/BPD and BPD among survivors as a function of reintubation within different observation windows after extubation

	Univariate	Multivariate Model 1	Multivariate Model 2
Death/BPD			
Never reintubated	1 [Reference]	1 [Reference]	1 [Reference]
≤ 24 h	16.28 (3.59 - 73.76)	12.44 (1.77 - 87.67)	12.29 (1.27 - 118.66)
≤ 48 h	21.16 (4.74 - 94.47)	13.17 (1.93 - 89.61)	12.76 (1.38 - 117.62)
≤ 72h	17.36 (4.98 - 60.61)	7.98 (1.64 - 38.84)	6.12 (1.05 - 35.77)
≤ 5 days	16.28 (5.99 - 44.27)	6.57 (1.88 - 22.92)	4.40 (1.17 - 16.55)
≤ 7 days	12.56 (5.21 - 30.25)	5.47 (1.76 - 16.98)	4.03 (1.21 - 13.39)
≤ 14 days	8.82 (4.26 - 18.25)	3.85 (1.44 - 10.30)	2.92 (1.02 - 8.34)
≤ 21 days	8.60 (4.32 - 17.15)	3.88 (1.53 - 9.85)	3.00 (1.10 - 8.18)
Anytime	7.69 (4.06 - 14.55)	3.07 (1.29 - 7.26)	2.37 (0.94 - 5.98)
BPD among survivors			
Never reintubated	1 [Reference]	1 [Reference]	1 [Reference]
≤ 24 h	14.17 (3.09 - 64.99)	3.53 (0.64 - 19.52)	1.44 (0.22 - 9.38)
≤ 48 h	19.17 (4.26 - 86.21)	3.99 (0.74 - 21.54)	1.60 (0.25 - 10.14)
≤ 72h	15.56 (4.42 - 54.74)	3.33 (0.78 - 14.2)	1.33 (0.27 - 6.66)
≤ 5 days	15.00 (5.49 - 41.02)	3.90 (1.13 - 13.41)	1.56 (0.40 - 6.06)
≤ 7 days	11.43 (4.71 - 27.71)	3.32 (1.05 - 10.47)	1.56 (0.43 - 5.73)
≤ 14 days	8.19 (3.94 - 17.06)	2.67 (0.96 - 7.43)	1.48 (0.45 - 4.86)
≤ 21 days	7.98 (3.98 - 15.99)	2.78 (1.05 - 7.35)	1.51 (0.48 - 4.72)
Anytime	7.04 (3.69 - 13.40)	2.09 (0.85 - 5.16)	1.09 (0.38 - 3.15)

Results are expressed as OR (95% CI) and models were adjusted for birth weight, study site, postnatal infection, postnatal steroids and necrotizing enterocolitis. Model 2 was additionally adjusted for total MV days.

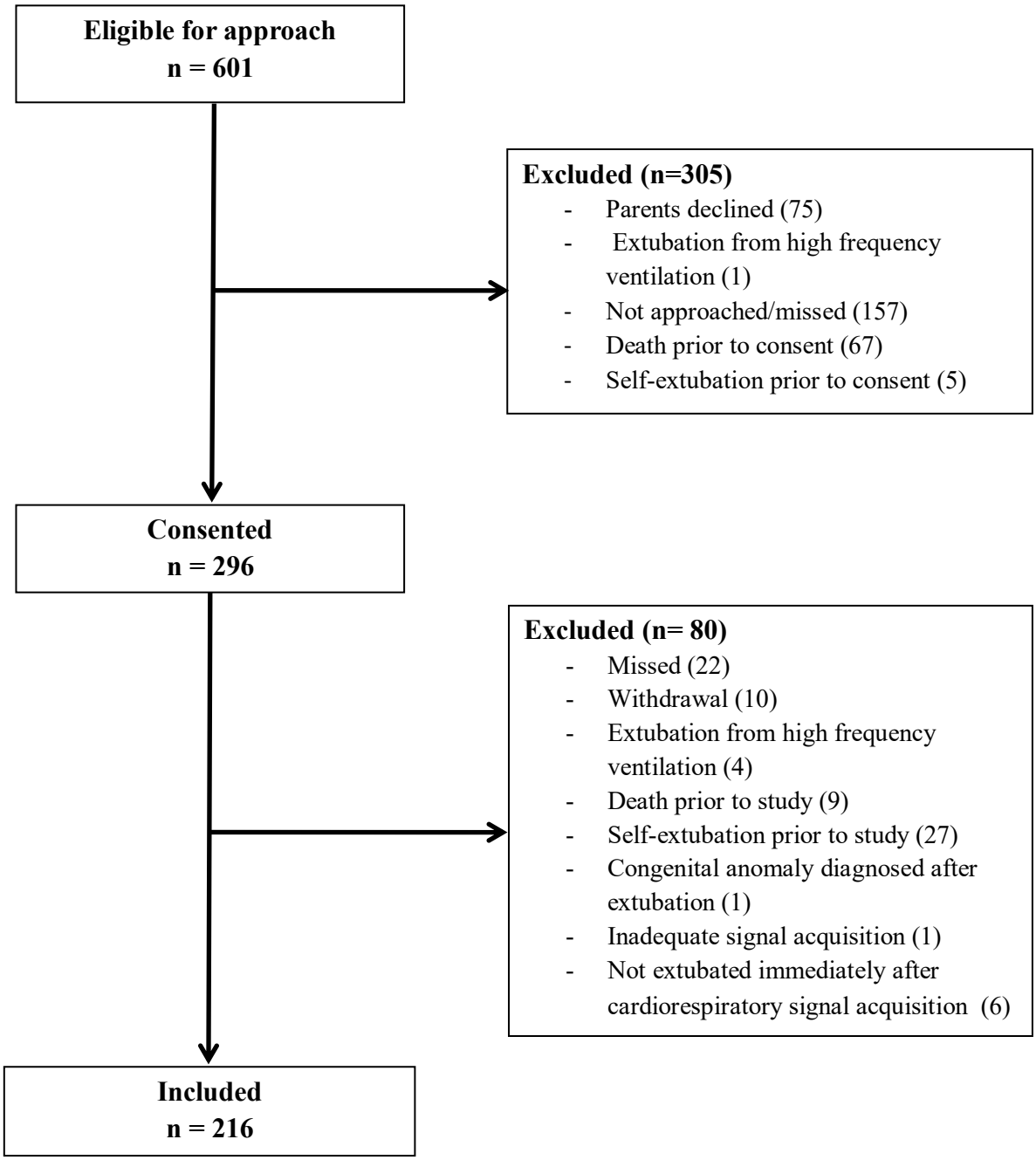
Figure 5.2 Adjusted Odds Ratio of Death/BPD as a function of time to reintubation



Legend: Each red square represents the adjusted odds of death/BPD for each time frame to reintubation, in relation to infants never reintubated. Models were adjusted for birth weight, site, postnatal infection, necrotizing enterocolitis and postnatal steroids.

5.8 Supplementary Material

Supplemental Figure S5.1 Flow of participants



Supplemental Table S5.1 Adjusted odds ratio of death/BPD and BPD among survivors for all variables included in the multivariate models

Independent variables	Multivariate Model 1	Multivariate Model 2
Death/BPD		
Need for reintubation[a]	3.07 (1.29 - 7.26)	2.37 (0.94 - 5.98)
Cumulative MV days	n/a	1.08 (1.03 - 1.13)
Birth weight	0.996 (0.994 - 0.999)	0.999 (0.996 - 1.001)
Postnatal steroids	7.23 (2.57 - 20.29)	2.86 (0.91 - 8.98)
Necrotizing enterocolitis	5.56 (1.14 - 27.09)	6.46 (1.21 - 34.58)
Postnatal infection	2.14 (0.89 - 5.14)	1.90 (0.77 - 4.72)
Study site		
Interaction term (p value)[b]	n/a	0.14
BPD among survivors		
Need for reintubation[a]	2.09 (0.85 - 5.16)	1.09 (0.38 - 3.15)
Cumulative MV days	n/a	1.13 (1.06 - 1.21)
Birth weight	0.996 (0.993-0.998)	0.999 (0.996 - 1.002)
Postnatal steroids	10.19 (3.20 - 32.50)	2.74 (0.74 - 10.08)
Necrotizing enterocolitis	6.40 (1.16 - 35.42)	7.01 (0.92 - 53.36)
Postnatal infection	2.77 (1.10 - 6.97)	2.69 (0.99 - 7.30)
Study site		
Interaction term (p value)[b]	n/a	0.50

[a] Need for reintubation any time after the first elective extubation
[b] Interaction term between need for reintubation and cumulative mechanical ventilation days. The interaction terms were not included in the multivariate model since p value was greater than 0.05

Legend: Results are expressed as OR (95% CI) and models were adjusted for birth weight - site - postnatal infection - postnatal steroid and necrotizing enterocolitis. Model 2 was additionally adjusted for total MV days.

Supplemental Table S5.2 Characteristics of infant deaths

Case	GA (weeks)	BW (grams)	DOL at extubation	Time to Reintubation	DOL at death	Cause of death
Infants reintubated						
1	26.1	980	2	0.5 h	2	Pulmonary hemorrhage
2	26.1	950	2	7 h	5	Grade 4 IVH[a]
3	26.6	890	18	8 h	20	NEC
4	25.4	710	27	51 h	74	Gram negative sepsis
5	31.7	760	2	88 h	6	NEC
6	26.7	870	5	6 d	17	Pulmonary hemorrhage
7	28.7	1090	4	15 d	19	NEC and gram negative sepsis
8	27.4	700	5	24 d	98	Chronic hypoxia[a]
9	27.4	1050	4	46 d	56	Midgut volvulus
Infant never reintubated						
10	25.1	510	68	N/A	170	Pulmonary hypertension, BPD[a]

[a] Withdrawal of life-sustaining therapy
Abbreviations: GA – gestational age, BW – birth weight, DOL – day of life, IVH – intraventricular hemorrhage, NEC – necrotizing enterocolitis, BPD – bronchopulmonary dysplasia

Supplemental Table S5.3 Characteristics of infants reintubated within 48 hours vs. those reintubated at 49 hours to 7 days after extubation

	Reintubated within 48h (N=28)	Reintubated at 49h to 7d (N=33)	P value
Demographics			
Gestational age, weeks	25.4 [24.4 – 26.5]	25.4 [24.8 – 26.1]	0.84
Birth weight, grams	745 [625 – 854]	760 [678 – 885]	0.46
Male sex	12 (43)	21 (64)	0.10
Small for gestational age	5 (18)	5 (15)	0.78
Antenatal steroids	24 (86)	31 (94)	0.28
Apgar score 5min[a]	8 [6 – 8]	6 [5 – 8]	0.19
Cord pH[b]	7.29 [7.26 – 7.33]	7.29 [7.22 – 7.35]	0.57
Intubation in delivery room	17 (61)	22 (67)	0.63
Surfactant	28 (100)	31 (94)	0.19
Caffeine	27 (96)	33 (100)	0.27
Pre-extubation			
Postmenstrual age, weeks	27.4 [26.5 – 28.4]	26.9 [26.3 – 27.8]	0.52
Weight, grams	820 [690 – 950]	820 [718 – 953]	0.85
MV days	11 [2 – 25]	6 [4 – 18]	0.97
pH[d]	7.31 [7.28 – 7.36]	7.34 [7.30 – 7.37]	0.23
pCO2, mmHg[c]	46 [38 – 57]	44 [37 – 54]	0.55
Mean airway pressure, cmH_2O	8 [6.5 – 9.4]	7.2 [6.5 – 8.3]	0.29
Fraction of inspired oxygen	0.26 [0.22 – 0.32]	0.25 [0.23 – 0.27]	0.21
Hemoglobin (≤ 24h), g/L[d]	137 [126 – 148]	128 [125 – 137]	0.24
Patent ductus arteriosus	11 (39)	16 (48)	0.47
Intraventricular hemorrhage	7 (25)	11 (33)	0.48
Necrotizing enterocolitis	2 (7)	0 (0)	0.12
Postnatal steroids	8 (29)	8 (24)	0.70
Postnatal infection	5 (18)	5 (15)	0.78

Values are expressed as medians [IQR] or n (%).
[a] data available for 27 infants reintubated within 48h.
[b] data available for 23 infants reintubated within 48h and 32 reintubated between 49h-7d.
[c] data available for 26 infants reintubated within 48h and 32 reintubated between 49h-7d.
[d] data available for 15 infants reintubated within 48h and 17 reintubated between 49h-7d

Bridging Text 5

The clinical studies highlighted in Chapters 4 and 5 focused on describing the frequency, causes and clinical implications of reintubations in extremely preterm infants. Results of these studies allowed us to have a clearer understanding of how to define extubation failure and what are the essential elements to report when trying to assess extubation readiness. In this third and last clinical study of the thesis, we returned to the focus on predictors of extubation readiness, namely SBTs. As part of the APEX study, infants were exposed to a 5-minute ET-CPAP period for the purpose of acquiring cardiorespiratory signals during a period free of mechanical inflations. But at the same time, we took note of the infants' clinical events (e.g. apneas, desaturations, bradycardias) and interventions required (e.g. stimulation, increased oxygen supplementation) during this recording. These markers of clinical stability are actually the same ones used by many clinicians to determine SBT pass or fail at the bedside. As such, from this available data, we were able to describe the clinical stability of extremely preterm infants when exposed to a 5-minute SBT, and to evaluate the accuracy of multiple SBT pass/fail definitions using various clinical event combinations. The study was published in *JAMA Pediatrics* and the preprint of the article is presented in Chapter 6.[107]

Chapter 6 – Assessment of Extubation Readiness Using Spontaneous Breathing Trials in Extremely Preterm Neonates

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6.1 Abstract

Importance: Spontaneous breathing trials (SBT) are used to determine extubation readiness in extremely preterm infants, but rely on empiric combinations of clinical events during endotracheal continuous positive airway pressure (ET-CPAP).

Objective: Describe clinical events during ET-CPAP and determine accuracy of comprehensive clinical event combinations in predicting successful extubation compared to clinical judgment alone.

Design: Diagnostic accuracy study using data obtained from the prospective Automated Prediction of Extubation Readiness (APEX) study (NCT01909947) between 2013-2018.

Setting: Multicenter (5 NICUs).

Participants: Infants with birth weight ≤ 1250g requiring mechanical ventilation were eligible. Infants deemed ready for extubation and who underwent ET-CPAP pre-extubation were included.

Intervention: For APEX, cardiorespiratory signals were recorded during 5-min ET-CPAP and signs of clinical instability were monitored.

Main Outcomes and Measures: Four clinical events were documented during ET-CPAP: apnea requiring stimulation, presence and cumulative durations of bradycardia and desaturation, and increased supplemental O_2. Clinical event occurrence was determined and compared between extubation success and failure (reintubation ≤ 7d). An automated algorithm was developed to generate SBT definitions using all clinical event combinations and compute diagnostic accuracies of a passed SBT in predicting extubation success.

Results: 259 infants with median gestational ages 26.1w and birth weights 830g were included; 147 infants (57%) had ≥ 1 clinical event during ET-CPAP. Apneas, bradycardias, desaturations

and increased O_2 needs occurred in 10%, 19%, 53% and 41% of infants, respectively. Infants with successful extubation (n=184, 71%) had significantly fewer clinical events, shorter cumulative bradycardia/desaturation durations and less increase in O_2 compared to infants that failed. In total 41,602 SBT definitions were generated, demonstrating sensitivities 51-100% and specificities 0-72%. Youden indices for all SBTs ranged from 0-0.32, suggesting low accuracy. The SBT with highest Youden index defined SBT pass as having no apnea (with desaturation requiring stimulation) or increase in O_2 requirements by 15% from baseline, and predicted extubation success with sensitivity 93% and specificity 39%.

Conclusions and Relevance: Extremely preterm infants commonly show signs of clinical instability during ET-CPAP. Moreover, the accuracy of multiple clinical event combinations to define SBTs is low. Thus, SBTs provide little added value in the assessment of extubation readiness.

6.2 Introduction

Extremely preterm infants (gestational age ≤ 28 weeks) commonly require mechanical ventilation (MV) after birth.[1] Given the known harms associated with prolonged MV, clinicians strive to limit its exposure by routinely assessing infants' readiness for extubation.[2] Currently, the decision to extubate relies on clinical judgment, through interpretation of infants' ventilatory support, blood gases and overall clinical stability.[3, 4] However, clinical judgment is subjective, leads to variable practices and is often associated with inaccurate decisions.[3] In fact, nearly one-third of infants require reintubation within 7 days after their first extubation attempt.[5]

In recent years, spontaneous breathing trials (SBTs) have increasingly been used to determine extubation readiness.[3, 4] SBTs entail a 3 to 10-minute period of spontaneous breathing via endotracheal continuous positive airway pressure (ET-CPAP), during which pass/fail is determined from a combination of clinical events (apneas, bradycardias, desaturations). To date, only two small studies have investigated SBT accuracies in predicting successful extubation compared to clinical judgment alone; a passed SBT identified almost all successful extubations (excellent sensitivity), but misclassified one-third of failed extubations (low specificity).[6-8] Of note, cutoffs to define SBT pass/fail were chosen empirically, with no background knowledge on the range of clinical events that normally occur during the trial. Thus, the objectives of this study were to describe the occurrence of clinical events in extremely preterm infants during ET-CPAP, and evaluate the accuracy of more comprehensive pass/fail definitions in predicting extubation success compared to clinical judgment alone. We conjectured that such inclusive evaluation would identify a SBT definition with better overall accuracy.

6.3 Methods

Study design and context

This is a secondary analysis from a prospective multicenter study (Automated Prediction of Extubation Readiness – APEX, clinicaltrials.gov NCT01909947), and is reported using the Standards for Reporting of Diagnostic Accuracy Studies (STARD) statement. APEX aims to develop an automated predictor of extubation readiness using machine-learning tools that integrate clinical variables and quantitative measures of cardiorespiratory behavior in extremely preterm infants deemed ready for extubation.[9] Enrollment for APEX has been completed, but the development and validation of the predictor are ongoing. As part of APEX, infants had cardiorespiratory signals acquired electronically during 5-minutes on ET-CPAP immediately preceding extubation. The rationale was to capture their intrinsic respiratory behavior without interference from mechanical inflations. Extubation was not predicated on ET-CPAP findings and no cutoffs for pass/fail were pre-specified. However, bedside clinical events that occurred during ET-CPAP were prospectively documented, hence allowing for this analysis.

Participants

All consecutive patients admitted to five tertiary care neonatal intensive care units in North America between September 2013 and August 2018 were screened for eligibility. Informed consent was obtained in accordance with research ethics boards at participating sites. APEX inclusion and exclusion criteria have been published and are detailed elsewhere.[9] Briefly, infants with birth weight ≤ 1250g, requiring MV who had cardiorespiratory signals acquired prior to their first elective extubation were included.

Test methods

Reference standard – clinical judgment: All infants were extubated per clinical judgment, i.e. once deemed 'ready' by the treating team. At the time of extubation, data pertaining to postmenstrual and postnatal age, weight, ventilator mode, mean airway pressure (MAP), fraction

of inspired oxygen (FiO_2) and blood gases (sampled within 24h pre-extubation) were collected. Of note, SBTs were not a part of clinical practice at participating sites.

Index test – ET-CPAP: All included infants underwent a 5-minute ET-CPAP recording prior to extubation. ET-CPAP pressure was equivalent to the positive end expiratory pressure (PEEP) preset by the clinical team on conventional MV. No pressure support was provided and the back-up rate was turned off. During ET-CPAP, a research investigator and respiratory therapist monitored the infants for apnea, bradycardia, or desaturation and intervened per clinical discretion. Interventions included increasing FiO_2 from baseline, stimulation in case of apnea and termination of ET-CPAP (i.e. resumption of MV) if necessary. Concomitantly, the following data were collected: PEEP level, baseline oxygen saturation (SpO_2) and FiO_2 just before starting ET-CPAP, presence and cumulative durations of desaturations (SpO_2<85%) and bradycardias (heart rate < 100bpm), need for additional oxygen from baseline (and highest amount provided), and total ET-CPAP duration. Once ET-CPAP was completed, the clinical team extubated infants to non-invasive respiratory support. Of note, the study design did not include blinding of ET-CPAP from the treating team. Consequently, the latter were permitted to change their minds about extubation at any time, in which case infants would be eligible for the study again (i.e. when deemed ready once more for extubation by the clinical team). In those cases, only the final ET-CPAP would be included for analysis.

Analysis

The first objective was to describe occurrences of four clinical event categories during ET-CPAP: apneas requiring stimulation, bradycardias, desaturations, and increase in oxygen supplementation from baseline. To avoid any confounding, infants transitioned to ET-CPAP with a baseline SpO2 already below 85% were excluded. The number and proportion of infants with

apneas, bradycardias, desaturations, and increased O_2 needs were determined. Also, medians and interquartile ranges were ascertained for the cumulative durations of bradycardia/desaturation and additional amount of O_2 needed.

The second objective was to evaluate the accuracy of different SBT definitions in predicting successful extubation compared to clinical judgment alone. Extubation success was defined as not needing reintubation within 7 days from extubation. First, clinical events were compared between infants who succeeded or failed extubation using Wilcoxon rank sum test, Chi-square or Fisher's exact test as appropriate. For continuous variables, probability density functions were plotted to better visualize the overlap between success and failure groups, and areas under the receiver operating characteristics curve (ROC) were computed. Next, continuous variables were transformed into binary variables using equally spaced cut-off points ranging from 0-100 seconds (for cumulative bradycardia/desaturation durations) and 0-30% (for supplemental O_2 needed), respectively. Using these variables, an automated algorithm was developed to create multiple combinations of the 4 clinical events with both 'AND'/'OR' logical operators. Examples of generated SBT definitions are shown in Table S6.1 of the Supplement. Of note, infants with missing data for any clinical event were excluded. From there, sensitivity, specificity and positive and negative predictive values of a passed SBT were computed for all derived SBTs along with their respective 95% confidence intervals. Sensitivity refers to the proportion of infants with successful extubation correctly identified by a passed SBT, while specificity refers to the proportion of infants with failed extubations correctly identify by a failed SBT (definitions and interpretation of all diagnostic terms are provided in eMethods of the Supplement). The diagnostic performance of each SBT was graphically displayed and its accuracy in predicting extubation success was estimated using Youden's index. The latter is a

measure of a test's overall discriminative power, assuming equal weight between sensitivity and specificity, and ranges from zero (poor accuracy) to one (perfect accuracy). Furthermore, the best SBT definition was identified for each of the following diagnostic goals: (1) achieve best overall accuracy (i.e. highest Youden index), (2) achieve maximal ability to detect failures (i.e. maximal specificity), and (3) achieve minimal number of misclassified infants with extubation success (i.e. maximal sensitivity).

A priori, we recognized that SBT accuracy might be influenced by the cohort's pretest probability of extubation success and the observation window used to define extubation success. To test the former, the diagnostic performance of SBTs was evaluated for infants above and below the median gestational age (a known marker of extubation success).[10, 11] To test the latter, the diagnostic performance of SBTs was computed for 4 additional definitions of extubation success, using observation windows of 24h, 48h, 72h and 5 days post-extubation.

Lastly, based on the APEX cohort's sample size and prevalence of successful extubation, and assuming a two-tailed α of 0.05, the computed SBT sensitivities and specificities would be estimated with approximately 5% and 10% precision, respectively.[12] All analyses were conducted using MATLAB (R2018a, The MathWorks, Natick, MA, USA).

6.4 Results

Out of 605 eligible participants, 278 underwent an ET-CPAP recording once deemed ready for extubation (Figure 6.1). There were 7 circumstances in which clinicians changed their minds about extubation following ET-CPAP; 4 were subsequently excluded, and 3 were later restudied once deemed ready for extubation. Therefore, 274 infants were extubated following ET-CPAP. After applying all additional exclusions, a total of 259 infants were included in this study.

Primary objective: Characteristics of patients at the time of extubation and during ET-CPAP are presented in Table 6.1 and Figure 6.2. Infants had a median gestational age of 26.1 weeks, birth weight of 830g and postnatal age of 8 days at extubation. Caffeine was administered in 98% of patients. CPAP was the most common post-extubation respiratory support (58%), followed by nasal intermittent positive airway pressure (37%) and high flow nasal cannula (5%). ET-CPAP was performed using a median PEEP of 5 cm H_2O and median interval of 32 minutes (interquartile range 21-59min) prior to extubation. Assessors decided to prematurely terminate ET-CPAP in 21 infants, based on variable thresholds of clinical events (Table S6.2 of the Supplement). During ET-CPAP, apneas, bradycardias, desaturations and increased O_2 needs occurred in 10%, 19%, 53% and 41% of infants, respectively. Cumulative durations of bradycardias and desaturations ranged from 2 to 114s and 2 to 240s respectively, while the amount of additional oxygen provided ranged from 2 to 77%. Altogether, 147 infants (57%) had at least one clinical event during ET-CPAP, with variable combinations. The combination of desaturation and increased O_2 needs was most common, occurring in 39% of infants with a clinical event.

Secondary objective: 184 infants (71%) were successfully extubated. Extubation success was associated with significantly higher age and weight (at birth and at extubation), and significantly lower respiratory support (MAP and FiO_2) at extubation compared to infants that failed (Table 6.1). During ET-CPAP, infants with successful extubation were significantly less likely to have early ET-CPAP termination or any of the four clinical events, had shorter cumulative durations of bradycardias/desaturations, and lesser amounts of O_2 compared to infants that failed (Table 6.2). When evaluated separately, the absence of the categorical clinical events predicted successful extubation with sensitivities and specificities ranging from 53-96%

and 24-69%, respectively. Moreover, the diagnostic performance of each continuous clinical event was characterized by low areas under the ROC curve (0.6-0.63) and high degree of overlap between the probability density functions (Figure S6.1 of the Supplement). After excluding seven infants with missing data, the automated algorithm was applied on the remaining 252 infants to create all combinations of the four clinical events, thus generating a total of 41,602 SBT definitions. SBTs had sensitivities, specificities, PPVs and NPVs ranging from 51-100%, 0-72%, 71-82% and 33-100%, respectively (Figure 6.3). Youden indices ranged from 0 to 0.32, suggesting an overall low accuracy. The best SBT definitions to achieve highest Youden index, maximal specificity and maximal sensitivity are provided in Table S6.3 of the Supplement. The combination of clinical events with highest Youden index defined a passed SBT as having no apnea (with desaturation requiring stimulation) or increase in O_2 requirements by 15% from baseline. Applying this definition to our cohort, 171 out of 184 infants with successful extubation would have passed SBT (sensitivity 93%) and 29 out of 75 infants with failed extubation would have failed SBT (specificity 39%). As such, 13 infants with successful extubation would have failed the SBT (hence would have remained mechanically ventilated longer than necessary), while 46 infants with failed extubation (61%) would have still passed the SBT. The best SBT that achieved maximal specificity resulted in the detection of 72% of failed extubations, at the cost of misclassifying 46% of successful extubations. Finally, the best SBT that achieved maximal sensitivity (100%) correctly identified 14 out of 75 failed extubations (19%) without misclassifying any infant with success.

A***nalyses of variability in diagnostic accuracy:*** SBT accuracies were further evaluated for infants above and below the median gestational age (pretest probabilities of 84% and 61% for successful extubation), and using different observation windows to define extubation success

(Figures S6.2 and S6.3 of the Supplement). Both analyses yielded poor SBT accuracies, as reflected by the low Youden indices (ranging from 0 to 0.36).

6.5 Discussion

In this comprehensive analysis from a large prospective cohort of extremely preterm infants, we found that over 50% of infants exhibited at least one clinical event during a 5-minute ET-CPAP recorded immediately prior to extubation. Evaluation of multiple clinical event combinations to define SBT pass/fail revealed that none could distinguish between extubation success and failure with sufficient accuracy to justify their routine use. Together, these results provide additional information on the safety and value of SBTs as currently performed.

Assessment of extubation readiness during a period of spontaneous breathing on ET-CPAP has been done for several years. In the 1980's, some preterm infants were extubated after passing a 6-24h ET-CPAP trial using PEEP levels of 2-3 cm H_2O.[13-15] This practice was abandoned once evidence showed increased risks of apnea, respiratory acidosis and extubation failure, likely due to low levels of support provided for long periods.[16] Years later, SBTs using shorter time frames (3-5 minutes) and higher PEEP levels (5-6 cm H_2O) were attempted to lessen the risks of lung derecruitment and respiratory fatigue. In two small studies, the diagnostic accuracy of SBTs was evaluated amongst infants deemed ready for extubation using empirical 'and/or' combinations of clinical events to define SBT pass/fail [6, 7]. Both studies showed excellent SBT sensitivities (97% and 92%), but only modest specificities (73% and 50%) at predicting extubation success. Interestingly, the only study to prospectively audit the impact of incorporating routine SBTs into clinical practice showed that SBT-driven extubation conferred no improvements in extubation success rates or MV durations compared to clinical judgment

alone.[17] Furthermore, a yet unpublished randomized controlled trial comparing the effects of SBT vs. clinical judgment on time to successful extubation was terminated on grounds of futility (clinicaltrials.gov NCT01471431). Nonetheless, an increasing number of clinicians worldwide have reported using SBTs in preterm infants, either as an adjunct to clinical judgment or as part of MV weaning protocols.[3, 4]

A major limitation with current SBTs is that they were defined without foreknowledge of how infants normally react to an ET-CPAP trial. In APEX, the fact that infants were exposed to a 5-min ET-CPAP recording without predefined SBT pass/fail criteria allowed us to pragmatically describe their clinical behavior. We found that episodes of apneas, bradycardias, desaturations and increased O_2 needs frequently occurred during ET-CPAP, in various combinations and wide ranges of durations and severities. While these findings highlight the important heterogeneity in patient behaviors during ET-CPAP, they also reflect a certain degree of variability in the way assessors reacted to clinical events. For example, by allowing assessors to stop ET-CPAP at their discretion, we noted important variations in thresholds for early termination. Thus, SBTs may still leave ample room for subjective interpretation, which unavoidably leads to difficult test reproducibility between assessors. A similar phenomenon of variability in SBT performance and reporting practices has been described in adults.[18]

Arguably, the documentation of clinical events during ET-CPAP would be justifiable if it could accurately predict which infants would succeed or fail extubation. In our cohort, although infants who failed extubation were significantly more likely to have clinical events compared to those successfully extubated, there was considerable overlap between the two groups. Consequently, when computing the diagnostic performance of all possible SBT definitions, none had an acceptable trade-off between sensitivity and specificity, as reflected by their low Youden

indices. In fact, given that nearly one-third of infants who failed extubation had an uneventful ET-CPAP recording, they would have been automatically misclassified by any SBT definition. Thus, the addition of a 5-min SBT to clinical judgment appears unwarranted, as it exposes infants to clinical instability without improving our ability to identify extubation failures.

Prior to initiating this analysis, we recognized that the observation window used to define extubation success might influence the SBT's diagnostic performance. We chose an observation window of 7d based on the rationale that it would capture most reintubations caused by respiratory-related reasons.[5] But it was conceivable that SBTs would be better suited for detecting reintubations occurring within shorter time frames after extubation. Similarly, we recognized that the cohort's pretest probability of extubation success might significantly alter the test's sensitivity and specificity, as previously described.[19, 20] For those reasons, we explored whether infants with higher or lower probabilities of successful extubation (based on their gestational age), or those reintubated within shorter time frames after extubation would benefit differently from a SBT. However, no improvements in SBT accuracies could be uncovered.

There are several possible explanations for why SBTs evaluated in our study did not accurately capture infants' likelihood of successful extubation. First, confounding factors such as endotracheal tube size, length, and partial obstruction (due to respiratory secretions or biofilm formation) may have influenced clinical event occurrences during ET-CPAP.[21] Second, the 5-minute trial duration may have been too short to accurately assess the infants' ability to sustain spontaneous breathing without significant apneas, especially considering that apneas are the most commonly reported cause of reintubation in this population.[5] Third, it is unclear from the available literature whether a PEEP of 5-6 cm H_2O during ET-CPAP would accurately match the patient's post-extubation physiological conditions while receiving non-invasive respiratory

support. In fact, the decrease in mean airway pressure and increased resistance associated with ET-CPAP may have further contributed to clinical instability.

An integral part of the study was that clinical events were captured continuously and subjectively through direct observation of the patient and bedside monitor. While the pragmatic nature of the assessment may be considered a limitation, it likely reflected the way SBTs are actually evaluated in clinical practice, thereby adding external validity to the study. Nonetheless, more precise information on the timing, number, duration and depth of each event, and more direct correlations between individual events may have provided further understanding of the infants' clinical behavior during ET-CPAP.

The study had some other limitations. The fact that ET-CPAP was performed only once infants were deemed ready for extubation introduced test-referral bias, meaning that inevitably more stable patients (likely to be successfully extubated) were preselected for the diagnostic test. This phenomenon has been well described to overestimate sensitivity, underestimate specificity and compromise test generalizability.[22, 23] Furthermore, due to lack of blinding of the ET-CPAP recording, extubation was postponed in seven infants who would have otherwise been extubated per clinical judgment. While these infants only represented 3% of the cohort, their inclusion may have marginally improved the specificity of the evaluated SBTs. Also, a considerable number of eligible infants were not approached or missed. Lastly, our results may not be generalizable to mechanically ventilated infants > 1250g or extubations beyond the first elective attempt.

In conclusion, extremely preterm infants commonly show signs of clinical instability during a 5-minute ET-CPAP trial. Although infants who fail extubation have significantly more clinical events compared to those successfully extubated, the accuracy of more than 41,000 evaluated SBT pass/fail definitions remained low. As such, SBTs as currently performed provide

little to no added value in the assessment of extubation readiness (especially in the identification of extubation failures) compared to clinical judgment alone. Future studies are needed to evaluate the role of SBT duration and provided PEEP levels in improving the accuracy of the test. Furthermore, ongoing analysis of the APEX study aims to evaluate the value of more complex and automated analyses of cardiorespiratory behavior during MV and ET-CPAP in better predicting extubation success.

6.6 References

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6.7 Figures and Tables

Figure 6.1 Flow diagram using the STARD template

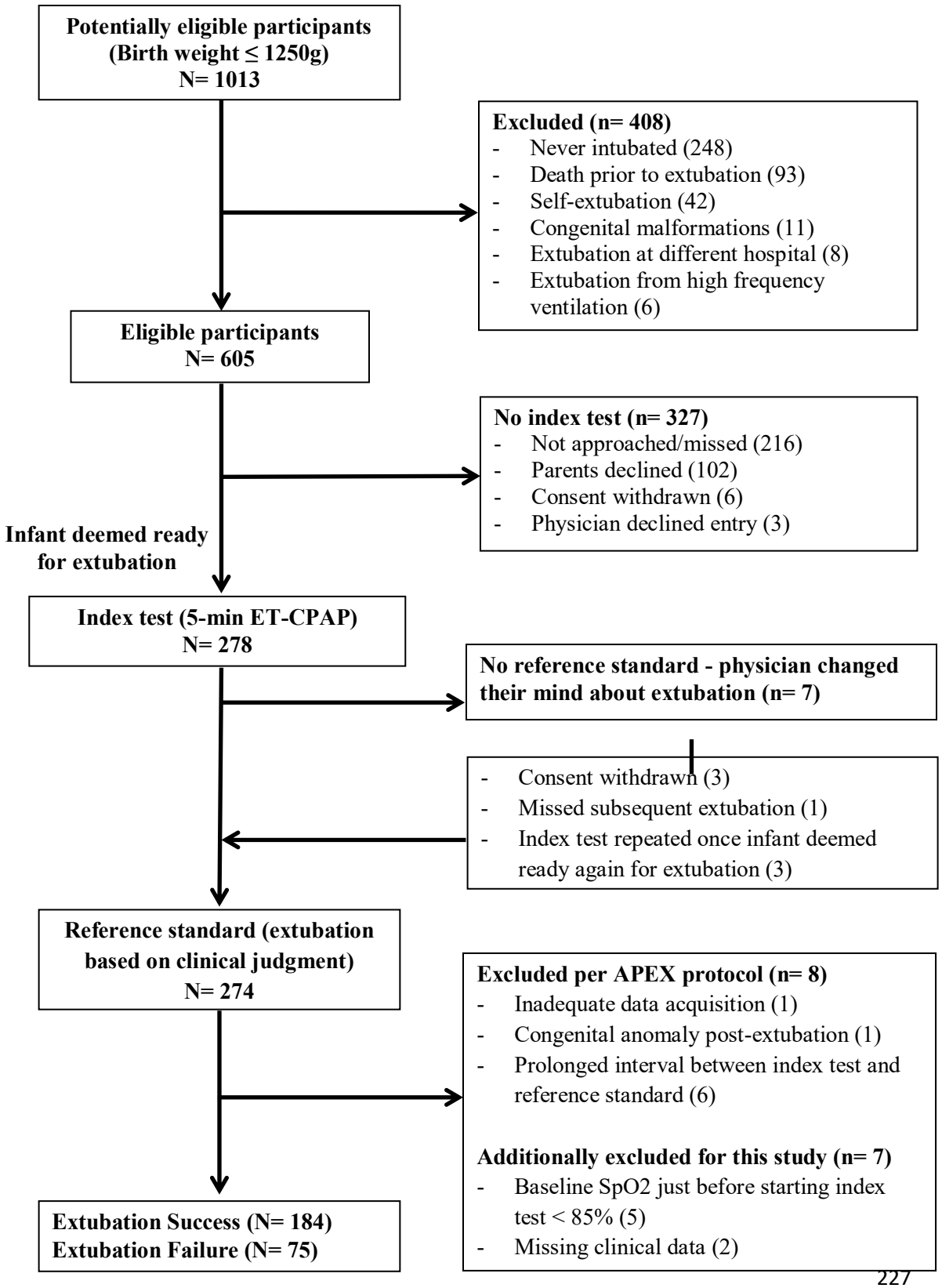


Table 6.1 Characteristics of infants prior to extubation and during ET-CPAP

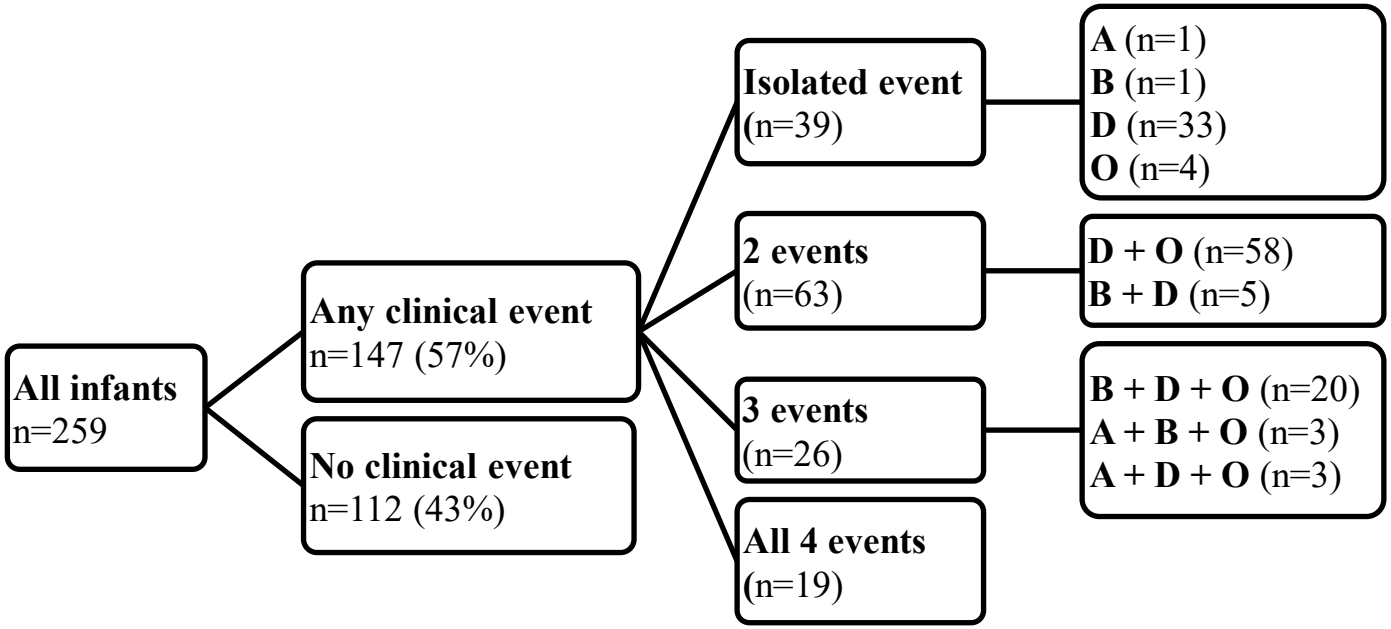
Clinical Variables	Overall Cohort (N=259)	Extubation Success (N=184)	Extubation Failure (N=75)	P Value
Demographics				
GA, weeks	26.1 [24.9 – 27.4]	26.4 [25 – 27.9]	25.4 [24.5 – 26.4]	< 0.001
BW, grams	830 [690 – 1019]	880 [715 – 1073]	740 [633 – 872]	< 0.001
Male sex, %	139 (54)	97 (53)	42 (56)	0.63
ANS, %	233 (90)	166 (90)	67 (89)	0.83
Caesarean section	173 (67)	127 (69)	46 (61)	0.23
Apgar 5 min[a]	7 [5 – 8]	7 [5 – 8]	7 [5 – 8]	0.93
DR Intubation, %	128 (49)	79 (43)	49 (65)	0.001
Surfactant, %	247 (95)	175 (95)	72 (96)	1
Caffeine, %	253 (98)	179 (97)	74 (99)	0.68
Pre-extubation				
PMA, weeks	28 [26.9 – 29.4]	28.6 [27.4 – 29.9]	27.4 [26.6 – 28.5]	< 0.001
Day of life	8 [3 – 26]	7 [3 – 27]	9 [4 – 25]	0.55
Weight, grams	940 [810 – 1080]	988 [850 – 1120]	820 [720 – 950]	< 0.001
PTV, %	133 (51)	89 (48)	44 (59)	0.13
MAP, cm H_2O[b]	7.1 [6.3 – 8]	6.9 [6.2 – 7.9]	7.5 [6.6 – 9]	0.002
FiO_2	0.23 [0.21 – 0.27]	0.21 [0.21 – 0.26]	0.25 [0.22 – 0.28]	< 0.001
pH[c]	7.34 [7.29 – 7.38]	7.34 [7.3 – 7.38]	7.32 [7.29 – 7.37]	0.21
pCO_2, mm Hg[c]	44 [38 – 51]	44 [37 – 50]	46 [38 – 55]	0.1
ET-CPAP				
Duration, min	5 [5 – 5]	5 [5 – 5]	5 [5 – 5]	< 0.001
PEEP, cm H_2O	5 [5 – 6]	5 [5 – 6]	5 [5 – 6]	0.19
Starting FiO_2[b]	0.23 [0.21 – 0.27]	0.21 [0.21 – 0.26]	0.26 [0.23 – 0.29]	< 0.001
Starting SpO_2, %[d]	94 [92 – 96]	0.95 [0.92 – 0.97]	0.94 [0.92 – 0.95]	0.03

Values are expressed as median [interquartile range] or n (%).

Abbreviations: ET-CPAP – endotracheal continuous positive airway pressure, GA – gestational age, BW – birth weight, ANS – antenatal steroids, DR – delivery room, PMA – postmenstrual age, PTV – patient-triggered ventilation, MAP – mean airway pressure, FiO_2 – fraction of inspired oxygen, PEEP – positive end expiratory pressure, SpO_2 – oxygen saturation

[a] data available for 183 infants with extubation success and 74 infants with extubation failure; [b] data available for 183 infants with extubation success; [c] data available for 152 infants with extubation success and 66 infants with extubation failure; [d] data available for 179 infants with extubation success and 74 infants with extubation failure.

Figure 6.2 Occurrence of clinical events during ET-CPAP



Abbreviations: A – apnea needing stimulation, B – bradycardia (heart rate < 100 beats per min), D – desaturations (oxygen saturation < 85%), O – increase in oxygen requirements from baseline.

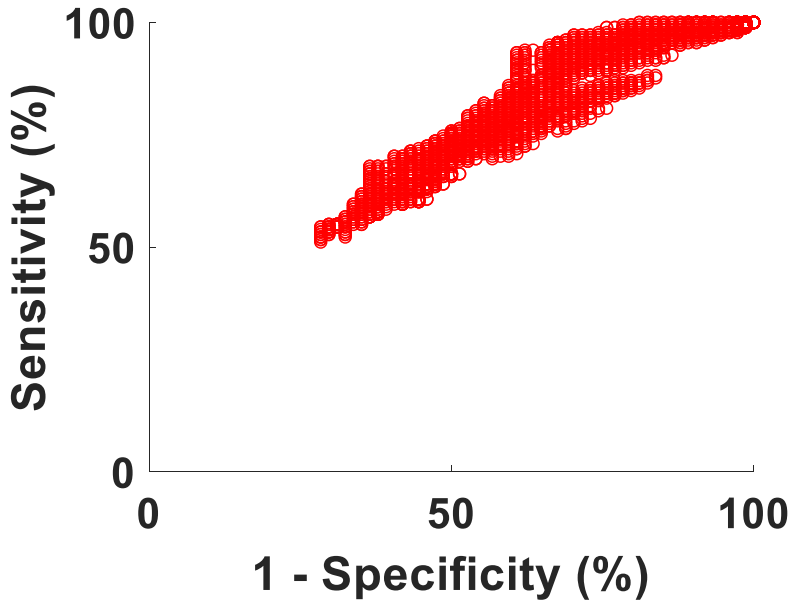
Table 6.2 Clinical events during ET-CPAP and their respective diagnostic accuracies at predicting successful extubation

Clinical Events	**ES (N=184)**	**EF (N=75)**	**Sens (95% CI)**	**Spec (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
Categorical variables						
Apnea needing stimulation	8 (4)	18 (24)	96 (93-99)	24 (14-34)	76 (70-81)	69 (51-87)
Bradycardia	24 (13)	24 (32)	87 (82-92)	32 (21-43)	76 (70-82)	50 (36-64)
Desaturation	86 (47)	52 (69)	53 (46-60)	69 (59-80)	81 (74-88)	38 (30-46)
Need for additional O_2	67 (36)	40 (53)	64 (57-71)	53 (42-65)	78 (70-84)	37 (28-47)
Early ET-CPAP termination	6 (3)	15 (20)	97 (94-99)	20 (11-29)	75 (69-80)	71 (52-91)
Any clinical event	93 (50)	54 (72)	49 (42-57)	72 (62-82)	81 (74-88)	37 (29-45)
All 4 clinical events	4 (2)	15 (20)	98 (96-100)	20 (11-29)	75 (70-80)	79 (61-97)
Continuous variables			**Area under the ROC curve**			
Desaturation (sec)	0 [0 – 59]	25 [0 – 90]	0.61			
Bradycardia (sec)	0 [0 – 0]	0 [0 – 9]	0.60			
Supplemental O_2 (%)	0 [0 – 6]	5 [0 – 18]	0.63			

Abbreviations: ET-CPAP – endotracheal continuous positive airway pressure, Sens – sensitivity, Spec – specificity, PPV – positive predictive value, NPV – negative predictive value, CI – confidence interval, ROC – receiver operating characteristics.

Legend: The left side of the Table compares the occurrence of clinical events during ET-CPAP between infants with successful or failed extubation. Categorical and continuous variables are expressed as n (%) and median [interquartile range], respectively. All comparisons were statistically significant, with $p \leq 0.01$ between extubation success and failure. The right hand side of the Table presents the diagnostic accuracy of the absence of each clinical event during ET-CPAP in predicting extubation success. The diagnostic accuracies of categorical variables are described using sensitivity, specificity, positive predictive value and negative predictive value, and are all expressed as % (95% confidence intervals). The diagnostic accuracies of continuous variables are described using area under the ROC curve.

Figure 6.3 Diagnostic performance of various SBT definitions for predicting successful extubation



Legend: The diagnostic performances of 41,602 SBT definitions are graphically presented by plotting each test's sensitivity (on the y-axis) and 1-specificity (on the x-axis). Sensitivity represents the proportion of infants with successful extubation that passed the SBT, while 1-specificity represents the proportion of infants with failed extubation that were inaccurately misclassified by the SBT.

6.8 Supplementary Material

Supplemental Table S6.1 Examples of generated SBT definitions

Definitions of SBT failure using 1 clinical event criteria: • Apnea requiring stimulation • Desaturation of cumulative duration > 60sec
Definitions of SBT failure using combinations of 2 clinical event criteria: • Any desaturation AND an increase in O_2 needs from baseline by 10% • Any bradycardia OR a desaturation of cumulative duration > 15sec
Definitions of SBT failure using combinations of 3 clinical event criteria: • A bradycardia AND desaturation of cumulative durations > 5 sec each, OR an apnea requiring stimulation • A bradycardia of cumulative duration > 5sec OR a desaturation of any duration OR an increase in O_2 needs from baseline by 5%
Definitions of SBT failure using combinations of 4 clinical event criteria: • Any one of the following: 1) a bradycardia of any duration; 2) a desaturation of any duration; 3) an increase in O_2 needs from baseline; 4) an apnea requiring stimulation • Any one of the following: 1) a desaturation of cumulative duration > 15sec AND an increase in O_2 needs from baseline by 5%; 2) a bradycardia of any duration; 3) an apnea requiring stimulation

Supplemental eMethods. Definitions of diagnostic terms

		Extubation	
		Success	**Failure**
SBT	**Pass**	True SBT pass (TP)	False SBT pass (FP)
	Fail	False SBT fail (FN)	True SBT fail (TN)

Sensitivity = TP / (TP+FN)
= proportion of infants with successful extubation that passed the SBT

Specificity = TN / (FP + TN)
= proportion of infants with failed extubation that failed the SBT

* 1-Specificity represents the proportion of infants with failed extubation that were inaccurately misclassified by the SBT

PPV = TP / TP + FP
= proportion of infants with a passed SBT that had a successful extubation

NPV = TN / TN + FN
= proportion of infants with a failed SBT that had a failed extubation

* If SBT was to be used for the assessment of extubation readiness in this cohort:
- PPV would represent the extubation success rate of the cohort
- 1-NPV would represent the proportion of infants for whom extubation was withheld due to a failed SBT that would have otherwise been successfully extubated

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Youden's index = sensitivity + specificity – 1

* Youden's index is a measure of a test's overall discriminative power assuming equal weight between sensitivity and specificity. The index ranges from 0 to 1, with 0 indicating poor accuracy and 1 indicating perfect discriminatory ability.

Supplemental Table S6.2 Characteristics of terminated ET-CPAP recordings

	N = 21
ET-CPAP characteristics	
Duration (mm:sec)	3:00 (1:42 – 4:25)
Positive end-expiratory pressure, cm H_2O	6 (4 – 8)
Fraction of inspired oxygen	0.27 (0.21 – 0.37)
Oxygen saturation, %	92 (88 – 98)
Clinical events	
Apnea needing stimulation, %	13 (62)
Presence of bradycardia, %	16 (76)
Cumulative bradycardia duration, sec	40 (10 – 83)
Presence of desaturation, %	20 (95)
Cumulative desaturation duration, sec	98 (10 – 191]
Need for extra oxygen from baseline, %	21 (100)
Amount of extra oxygen provided, %	19 (2 – 54)

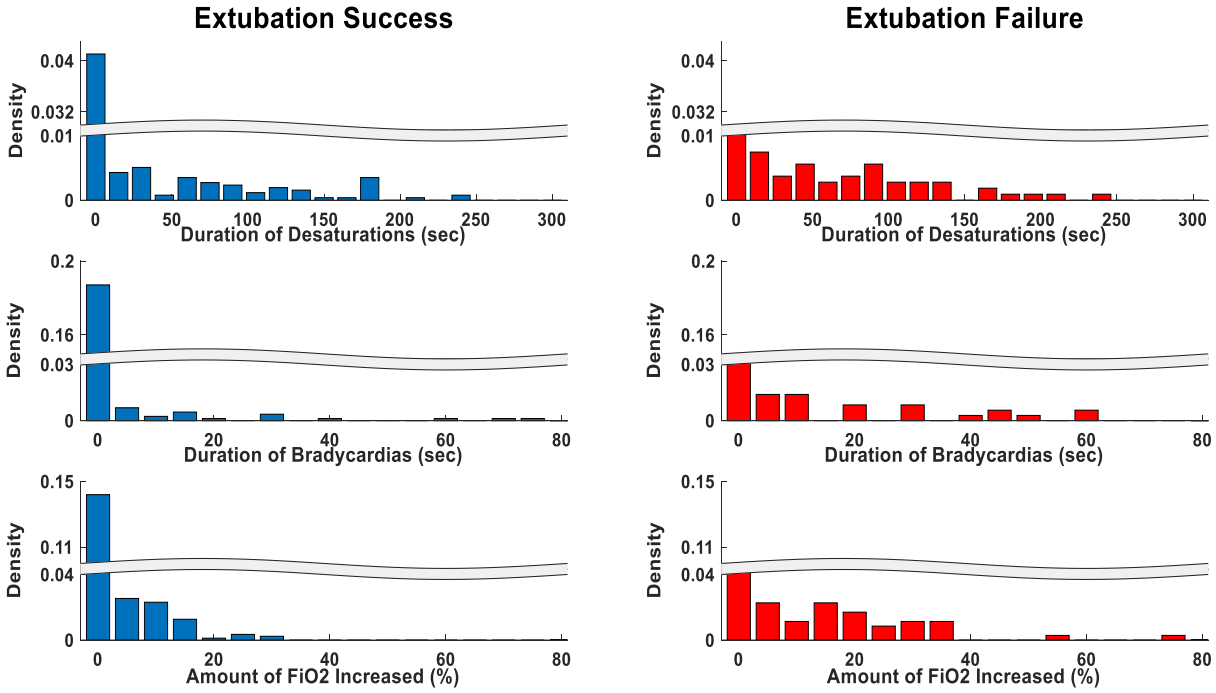
Values are expressed as median (min – max) or n (%).

Supplemental Table S6.3 Best SBT definitions and the diagnostic accuracies of a passed SBT in predicting extubation success

Criteria to define the best SBT failure definition based on the following diagnostic goals:	**Sens**	**Spec**	**PPV**	**NPV**	**Youden Index**
<u>1- Achieve best overall accuracy (i.e. highest Youden index)</u>					
(1) Apnea with desaturation requiring stimulation; or (2) A 15% increase in O_2 requirements from baseline.	93	39	79	71	0.32
<u>2- Achieve maximal ability to detect extubation failures (i.e. maximal specificity)</u>					
(1) Any desaturation; or (2) A 10% increase in O_2 requirements from baseline.	54	72	82	40	0.26
<u>3- Achieve minimal number of misclassified infants with extubation success (i.e. maximal sensitivity)</u>					
Sensitivity threshold 100% (zero misclassifications) (1) Bradycardia with cumulative duration ≥ 10 seconds; and (2) A 15% increase in O_2 requirements from baseline.	100	19	75	100	0.19
Sensitivity threshold >95% (maximum 10 misclassified infants) (1) A 15% increase in O_2 requirements from baseline.	96	32	77	75	0.28

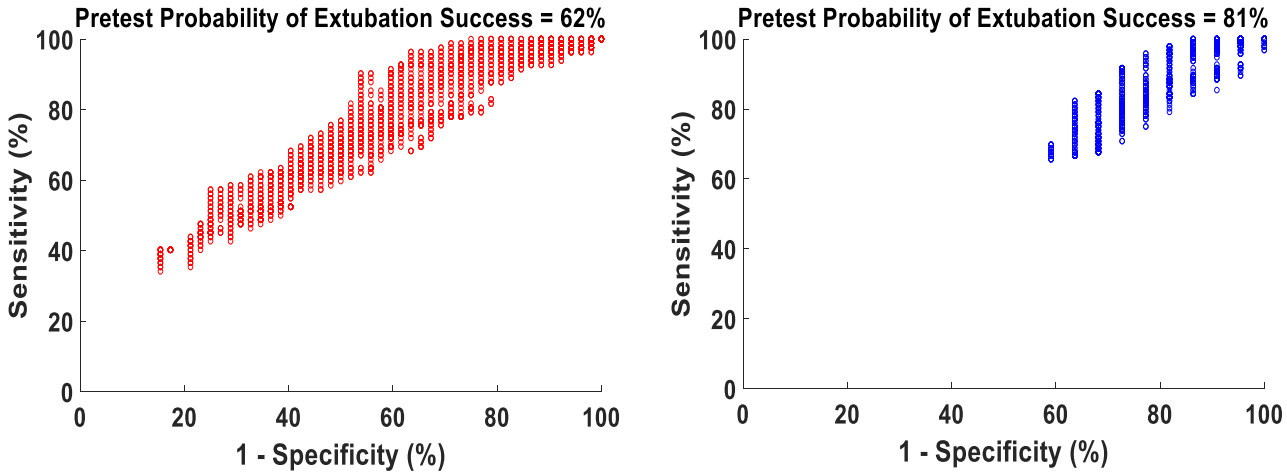
Abbreviations: SBT – spontaneous breathing trial, Sens – sensitivity (%), Spec – specificity (%), PPV – positive predictive value (%), NPV – negative predictive value (%).

Supplemental Figure S6.1 Probability density function of desaturation duration, bradycardia duration, and supplemental oxygen needed in infants who had a successful or failed extubation



Legend: Top panels: Desaturation duration; Middle panels: Bradycardia durations; Bottom panels: Additional FiO2 needed during ETT-CPAP.

Supplemental Figure S6.2 Diagnostic performance of SBTs in predicting successful extubation for infants with low or high pretest probability of extubation success



Legend: The sensitivity (y-axis) and 1-specificity (x-axis) of 41,602 SBT definitions are plotted in receiver operating characteristics (ROC) space for 2 subgroups of patients: infants with gestational age ≤ 26.1 weeks (left panel: low pretest probability of extubation success) and infants with > 26.1 weeks (right panel: high pretest probability of extubation success

Chapter 7 – Thesis Discussion

In clinical practice, the decision to extubate an extremely preterm infant is well recognized to be a challenging process. But in the absence of scientific evidence to guide this decision, clinicians typically rely on clinical acumen, experience, and personal preferences to determine whether a patient is ready or not for extubation. For some, the decision falls within the realms of the 'art of medicine'. For others, the decision is based on a calculated gamble that weighs the pros and cons of extubation. Unfortunately, in an increasingly smaller and more immature population of preterm infants, the consequences of a wrong or misguided decision can be costly. On one hand, failing to recognize an infant's potential for extubation exposes them to unnecessary and harmful exposure to MV. On the other hand, premature disconnection from the ventilator puts the infants at risk of clinical instability (while on non-invasive respiratory support), reintubation and reinstitution of MV. Considering that both prolonged MV exposure and the need for reintubation are associated with serious short and long-term complications, it is critical and highly desirable to determine extubation readiness in a timely and accurate manner in order to minimize MV duration while maximizing the chances of success. Thus, the goal of this thesis was to provide a more evidence-based and scientifically founded approach towards the assessment of extubation readiness in extremely preterm infants.

To do so, we thoroughly reviewed the literature and performed a meta-analysis to critically appraise the evidence regarding currently available predictors of extubation readiness.[103] In addition, we conducted a prospective multicenter observational study (the APEX study) from which we created a large database of prospectively collected information pertaining to the peri-extubation period from 266 extremely preterm infants.[104] Using this clinical database, we performed three sub-analyses aiming to better understand the patterns of reintubation in

extremely preterm infants, the clinical implications of reintubation, and the diagnostic accuracy of SBTs when assessing extubation readiness. All in all, we found a lack of evidence to support the use of any of the currently available predictors when compared to clinical judgment alone.[103] Moreover, in the largest and most comprehensive diagnostic accuracy study to evaluate SBTs in preterm infants, we found that the conduct of an SBT exposed many infants to clinical instability without improving the ability to accurately predict their readiness for extubation.[107] However, at the same time, we realized that that the assessment of extubation readiness in extremely preterm infants was heavily influenced by the definition used for extubation success or failure. In our large cohort, reintubations occurred at various time frames after extubation, for different causes, and had variable clinical implications on important neonatal respiratory outcomes.[105-106]

Altogether, the work presented in this thesis helped us unravel many of the complexities associated with the subject of extubation in extremely preterm infants. In this final section of the thesis, we summarize, discuss and interpret the overall findings of the thesis. In the first part of the discussion, we review the intricacies related to the definition of extubation failure and provide recommendations on how it should be reported in the literature. In the second part, we discuss the challenges with currently available predictors of extubation readiness, and provide recommendations on how to assess extubation readiness in real-world practice. In the final part of the discussion, we provide suggestions for future research to further advance our understanding on the subject.

7.1 Defining and Reporting Extubation Failures

7.1.1 Not all Failures Are the Same

Consider the following four scenarios: (a) a group of investigators aims to develop and validate a new predictor test of extubation readiness in extremely preterm infants; (b) Another group wishes to study the impact of a non-invasive therapy on reducing rates of extubation failure in this population; (c) Clinicians are undertaking a quality improvement initiative aiming to evaluate the effects of a local respiratory care bundle on extubation failure rates in their NICU; (d) a clinician performs a spontaneous breathing trial at the patient's bedside to decide if a baby is ready for a trial of extubation. All four scenarios are commonly encountered in the research world and in clinical practice. However, they all have a fundamental limitation: what exactly are the investigators and clinicians trying to predict or to prevent? What do they perceive as a successful or failed extubation? As detailed in our thesis, extubation failure can be defined in different ways and not all failures have the same causes or consequences. Based on synthesis of our findings, we suggest that when trying to predict or prevent extubation failure, one needs to consciously take into account four major factors: the definition of 'failure' used, the observation window chosen to capture 'failures', the causes of extubation failure targeted by the predictor or intervention, and the clinical relevance of the selected definition.

Definition of extubation failure used

According to the original APEX protocol, the primary outcome of the study was the prediction of extubation failure as defined by the fulfillment of preset clinical criteria (based on oxygen requirements, gas exchange, or frequency/severity of respiratory events) within 72h of extubation.[104] At the time of conception of the APEX study, the authors chose to define extubation failure based on fulfillment of clinical criteria (as opposed to needing reintubation)

because it was rightfully perceived that reintubation was a subjective decision. In theory this is absolutely true, since the vast majority of NICUs around the world make decisions about reintubation based on subjective interpretations of the patient's clinical instability rather than based on pre-defined guidelines or protocols.[60] In fact, many clinical studies have similarly opted to use predefined clinical criteria to define extubation failure for the same reasons. However in practical terms, defining extubation failure based on fulfillment of clinical criteria needs to rely on accurate monitoring and documentation of oxygen requirements, blood gas values and respiratory events (i.e. apneas, bradycardias and desaturations), including a detailed account of the timing, nature and actions needed to resolve those events. Unfortunately, as APEX enrollment progressed, it became increasingly evident that the documentation of respiratory events was inconsistent and highly variable within and across participating NICUs. As such, it was exceedingly difficult to rely on nursing reports as a means to accurately capture the exact number (and timing) of respiratory events needing intervention during the study period. In hindsight, this phenomenon is not new, since it has been demonstrated that nursing documentation of cardiorespiratory events is often incomplete and tends to underestimate the true number of apneas, bradycardias and desaturations.[100] An alternative to nursing documentation could have been to use automated electronic monitoring of physiological data (i.e. electrocardiogram signal and displayed heart rate, respiratory impedance waveform and displayed respiratory rate, and oxygen saturation) directly from the patient's bedside monitor. However, electronic monitoring and storage of the recorded signals was not available at the NICUs participating in APEX. Besides, electronic monitoring has its own limitations, since it is known to over-report cardiorespiratory events and may provide data that has not yet been shown to be of any clinical value.[108]

All things considered, defining extubation failure using either reintubation or predefined clinical criteria certainly comes with its respective sets of pros and cons. On one hand, although using 'reintubation' to define extubation failure relies on subjective and highly variable information, it remains the easiest measurable outcome and its implications can most easily be understood by all (i.e. needing reintroduction of the endotracheal tube and resumption of mechanical ventilation). On the other hand, although using 'fulfillment of clinical criteria' would provide a more accurate and generalizable definition of extubation failure, it is much harder to reliably monitor and document. Besides, there is currently no agreement in the literature on what constitutes a clinically representative or meaningful set of criteria of clinical instability that clinicians agree to label as 'extubation failure'. Therefore, due to all the aforementioned reasons, the APEX investigators ultimately chose to define extubation failure based on the need for reintubation for the development of the automated predictor of extubation readiness. Similarly, the work presented in this thesis focused on better understanding the outcome of reintubation. Having said that, in a subset of patients enrolled in APEX (i.e. all participants recruited from Montreal sites), we prospectively collected from the nursing charts hourly data concerning non-invasive respiratory support mode (and settings), oxygen requirements, and presence of bradycardias/desaturations needing intervention during the 14 days following extubation. At the time of this writing, a secondary analysis was underway looking to describe the criteria of clinical instability at which clinicians typically decided to reintubate these infants.

Observation window used to define extubation failure

Clinicians commonly believe that if a diagnostic test or intervention were able to accurately predict or prevent reintubations that occurred in the first 24 to 72h from extubation, this would be sufficient to justify their use in clinical practice. While this may be true, our thesis

demonstrated that it is not so straightforward. Extremely preterm infants can be reintubated within a very wide time span, ranging anywhere from minutes to months after their first planned extubation. As a result, the extubation failure rates can considerably change depending on the selected observation window. In our cohort, extubation failure rates would be reported as 10% after 24h of observation, 27% after 7 days, and 47% if the period of observation extended until NICU discharge.[105] Therefore, any study reporting on extubation failure that limits its observation window to less than 72h is likely under-reporting its true failure rates. Besides, as detailed in the subsections below, many of the reintubations that occur after 72h of extubation are respiratory-related (i.e. not caused by new, non-respiratory conditions such as infection or necrotizing enterocolitis) and are associated with increased risk of death/BPD. As such, studies limiting their observation windows to 72h or less are likely overlooking an important subset of reintubations that could have equally benefited from the evaluated predictor or intervention.

Lastly and perhaps most importantly, any study limiting its observation window to a single time point after extubation will fail to capture the dynamic patterns of reintubation in its cohort. For example, a unit may assert that they have very low reintubation rates in the first 48-72h after extubation. While this could indeed be a true improvement, it may also be that reintubations are simply being delayed or postponed because clinicians are trying everything possible to avoid mechanical ventilation. In fact, over the past years, clinicians have become increasingly comfortable with using very high non-invasive respiratory support settings (PEEP levels as high as 10 to 15 cm H_2O), various novel rescue modalities (nasal HFOV, nasal HFJV or non-invasive NAVA) and much higher doses of caffeine to avoid reintubation, even when evidence to support these strategies is lacking. As a result of these efforts, it is not surprising to observe that the rate of respiratory-related reintubations continues to rise well beyond 72h after

extubation. As a second example, based on the existing results of RCTs comparing NIPPV against CPAP in the post-extubation period, meta-analyses have concluded that NIPPV may be superior to CPAP in reducing rates of extubation failure in extremely preterm infants.[72] However, a crucial caveat to most of these studies is that they defined extubation failure as the need for reintubation (or fulfillment of clinical criteria) within 72h from extubation. As such, it is impossible to know whether NIPPV actually reduced failure rates, or simply postponed them by a few days. In fact, in the largest RCT of its kind (enrolling nearly 1000 ELBW infants), where extubation failure was defined as the need for reintubation anytime during NICU hospitalization, there were no differences between infants assigned to the NIPPV or CPAP groups.[99]

Thus, whenever studying or reporting extubation failure, it is extremely important to be mindful of how the chosen observation window can significantly affect the generalizability and legitimacy of the study results. In the recommendations section below, we provide some suggestions on how to improve and standardize the reporting process with regards to the choice of observation window used to define extubation failure.

Causes of extubation failure

Extremely preterm infants tend to fail extubation for a multitude of intricately connected reasons. But what's more interesting, it appears that the contributing causes of reintubation change as a function of time. These observations may have important implications for clinical practice and for research. For example, we found that reintubations attributable to non-respiratory related causes (infection or necrotizing enterocolitis) were infrequent in the first week after extubation but dominated the picture 14 days after extubation.[105] Based on this finding, we extrapolate that if an infant is reintubated for apneas and bradycardias beyond the first week after extubation (and definitely after 14 days), an infectious etiology should be ruled out.

As another example, when only concentrating on respiratory-related reintubations, we noted a difference in the manifesting symptoms over the first 7 days after extubation.[105] The most commonly stated reasons for reintubations in the first 24-48h after extubation were for increased work of breathing (61% of infants) followed by increased oxygen needs (44%) and apneas (44%). In contrast, reintubations beyond the first 48h were primarily due to increased apneas and bradycardias (73% of infants). Based on these findings, we speculate that the pathophysiology of respiratory-related extubation failures is very different in each time period. In the first 48h after extubation, the increased work of breathing and O_2 needs observed amongst reintubated infants suggests that these infants had significantly greater immaturity of the lungs and could no longer maintain alveolar stability after removal of the mean airway pressure provided by the ventilator. Alternatively, these symptoms may have resulted from some degree of upper airway obstruction caused by airway edema/inflammation around the vocal cords. Although none of the infants in our cohort were specifically stated to have stridor at the time of reintubation, it is possible that stridor may not be as easily perceptible in the smallest infants. Between 48h and 7 days after extubation, very few infants were reintubated due to respiratory distress as the primary cause. Rather, they were reintubated due to sustained respiratory events (apneas, bradycardias and desaturations) that did not respond to all available non-invasive respiratory support strategies. These events could either have been attributable to significant immaturity of the respiratory control centers (leading to predominantly central apneas), and/or could have been caused by suboptimal provision of non-invasive respiratory support leading to obstructive apneas (i.e. inadequate interface and suboptimal clearance of secretions). Altogether, it is easy to see how the definition of extubation failure can seriously affect the performance of a predictor of extubation readiness. To illustrate, a test aimed at evaluating an infant's spontaneous

respiratory drive is ill suited for predicting failures in the first 48h after extubation (since most infants do not fail from central apneas during this time period). Likewise, a test aimed at evaluating an infant's ability to sustain breathing without assistance of the ventilator (via measurements of minute ventilation, compliance, or respiratory muscle strength) is not as useful for predicting failures that occur beyond 48h from extubation. The nuances related to the choice of the ideal predictor of extubation readiness are further discussed in subsection 7.2.

Clinical relevance of the definition of extubation failure used

An important question that needs to be asked whenever trying to predict or prevent extubation failure is: "so what?" From one perspective, a failed extubation can clearly be a source of distress for the patients, their families and for the health care providers having to respond to the frequent respiratory events or having to reintubate these infants. Besides, the process of intubation in itself can be challenging and may lead to increased complications, especially when performed in an emergent setting without premedication.[102] But from a broader perspective, what exactly is the cost of a failed extubation on short and long-term outcomes? What neonatal outcome(s) are we aiming to improve by developing a predictor of extubation readiness or an intervention to reduce extubation failures? And which extubation failures confer the highest risk of morbidities/mortality (and hence should be our priority)? As highlighted in our thesis, results to these questions are not so straightforward and still not fully answered.

First, it is important to point out that all studies interested in evaluating the impact of extubation failure on morbidities/mortality in preterm infants have defined failure based on need for reintubation and not based on fulfillment of clinical instability criteria. As such, we only have evidence regarding the impact of a reintubation on outcomes in this population. Second, studies on this subject have primarily concentrated on evaluating short-term outcomes, especially

mortality during NICU stay and BPD among survivors. As such, it is currently unknown what impact reintubations have on long-term neurodevelopmental outcomes in this population.

In our study (presented in Chapter 5 of the thesis), we explored associations between the need for reintubation and the composite outcome of death/BPD in extremely preterm infants.[106] In contrast to other studies on this topic, we methodically evaluated all time intervals between extubation and reintubation in order to ascertain whether the definition of extubation failure used would have an influence on the observed results. Indeed, after adjusting for known confounders, we found that the odds of death/BPD were disproportionately greater when reintubation occurred within 48h post-extubation as compared to any other reintubation thereafter. This suggested to us that a failed extubation occurring within 48h from extubation likely carried a significantly greater cost compared to a failed extubation beyond 48h. As a matter of fact, out of 28 infants reintubated within 48h from extubation, 3 infants died soon after reintubation (from massive pulmonary hemorrhage, grade 4 intraventricular hemorrhage and fulminant necrotizing enterocolitis) and 23 infants were diagnosed with moderate-to-severe BPD. While it is possible that these infants were simply "sicker" to begin with (because we could not have accounted for all potential confounders), the fact remains that they were deemed ready for an extubation attempt by the responsible clinicians. Moreover, it is hard to refute the fact that three infants (a troublesome 11% of infants reintubated within 48h from extubation) died as a result of morbidities that led to reintubation within minutes to a few hours after extubation. Although impossible to know for certain, one may wonder whether the outcomes would have been different if those 3 infants were not extubated at that time, or if the clinician had been forewarned about their potential for immediate failure. Considering the finite number of infants in this high-risk category, our findings can only be interpreted as hypothesis generating. Nonetheless, they

certainly suggest that a key priority in studies of extubation failure should be to focus on improving our prediction or prevention of those reintubations with the highest cost, i.e. those occurring within the first 48-72 hours after extubation.

From our study, it is important to also highlight that the increased risk of death/BPD was not limited to reintubations that occurred in the first 48h after extubation.[106] In fact, definitions of extubation failure using any observation window between 72h and 3 weeks continued to be independently associated with increased risk of death/BPD, even after adjusting for known confounders (including the cumulative duration of MV). However, the odds ratios for death/BPD sharply dropped once the time intervals extended beyond 48h and continued to decline thereafter. This suggests that even though the need for reintubation in the first 3 weeks post-extubation could independently increase the risk of death/BPD, this effect is most likely attributable to reintubations in the first 48 hours. That being said, this does not mean that reintubations beyond 48 hours of extubation are clinically irrelevant. Quite the contrary, reintubations still indirectly increase the risk of death/BPD because they inevitably lead to prolonged MV exposure. Based on our study, each reintubation was associated with an additional 12 days of MV exposure.[106] Moreover, an increased cumulative MV duration was independently associated with the outcomes of death/BPD and BPD among survivors. As such, studies aimed at the prediction or prevention of reintubations (even those occurring after 48h from extubation) may be justifiable solely on the basis of reducing the overall duration of MV.

7.1.2 Recommendations for Reporting Extubation Failure

As it stands, there is tremendous variation in the way extubation outcomes are defined and reported in the literature. This makes interpretation and synthesis of the results impossible,

and hence hinders our ability to fully advance our understanding of the subject. Based on all the above discussions and after interpretation of the available evidence, we herein provide some recommendations on how best to define and report extubation failure in both the research setting and in clinical practice. These recommendations are also summarized in Table 7.1.

Definition of failure: For the time being, it is likely preferable to define extubation failure based on the need for reintubation rather than based on the fulfillment of preset criteria of clinical instability. Having said that, when designing a study, it would be advisable to provide (or mandate) participating NICUs with specific criteria for reintubation and further attempt to track compliance to these instructions. Similarly, clinicians are encouraged to develop and implement protocols or written guidelines for reintubation in their respective units, as a means to standardize the process and help with any potential future benchmarking study.

Observation window to define failure: When extubation failure is the primary outcome of a study, the choice of observation window will certainly depend on the design of the study (ex: diagnostic accuracy vs. RCT), the type of predictor (or intervention) being evaluated, and the main aims of the study. However, irrespective of the observation window selected for the primary outcome, two sets of results should be systematically reported in any study; one using a short observation window (48-72h) and another using a window of 7 days. On one hand, an observation window of 48-72h allows us to measure the effectiveness of a diagnostic test or an intervention at specifically predicting or preventing those reintubations associated with the highest risks of complications (especially death/BPD). On the other hand, an observation window of 7 days appears to have the best trade-off in terms of providing results that are representative of the cohort's overall reintubation rate, in capturing most respiratory-related

reintubations, and in targeting clinically relevant reintubations. Both sets of observation windows provide clinically pertinent results in their own way and should therefore be presented.

Presentation of results in randomized controlled trials: Given the dynamic nature of reintubations in extremely preterm infants, a cumulative distribution curve of reintubation rates for the control and intervention groups should be presented for at least the first 7 days following extubation in order to correctly capture the longitudinal effects of the intervention. In addition, for the statistical analysis reintubation rates of the control and intervention groups should be compared using time-to-event statistical methodology (i.e. Kaplan-Meier estimates, log-rank tests and Cox proportional hazards regression analyses).

Causes of failure: Ideally when evaluating a predictor of extubation readiness or an intervention to reduce reintubation rates, investigators should report as specifically and as objectively the reasons for which infants required reintubation. To do so, recording of both data derived electronically (from the bedside monitor) and manually (from the clinical chart) may provide the most thorough account of each reintubation. Such information may also help identify whether some diagnostic tests or interventions are better suited for certain types of reintubations.

Reporting serious adverse events associated with reintubation: Considering that reintubations in the first 24-48h after extubation are associated with the highest risks, it is critical to improve our reporting of serious adverse events that occur during the immediate period following extubation. These should include hemodynamic instability (requiring chest compressions and/or inotropic support), severe hypoxia, pneumothorax, pulmonary hemorrhage and death. Reporting of these serious adverse events should hopefully improve our knowledge of their true prevalence in clinical practice and should be priority targets for any future predictor of extubation readiness.

Table 7.1 Recommendations for standardizing the reporting of extubation failure

1. ***Define extubation failure based on the need for reintubation (rather than based on fulfillment of clinical criteria)***

   - Ideally, provide (or mandate) participating units with reintubation guidelines
   - If possible, track compliance to the proposed reintubation guidelines

2. ***Always report extubation failure rates at 48-72h and at 7 days post-extubation***

3. ***For randomized controlled trials:***

   - Present the reintubation rates of the control and intervention groups using cumulative distribution curves for the first 7 days post-extubation
   - Compare extubation outcomes between groups using time-to-event analyses

4. ***Provide a detailed account of the causes for each reintubation***

   - Specify if a non-respiratory-related cause was identified (ex: confirmed infection or necrotizing enterocolitis)
   - Specify the most important reasons for reintubation (e.g. apneas and bradycardias, increased work of breathing, increased O_2 needs).

5. ***Report serious adverse events that occur in the 24h following extubation***

   - Serious adverse events include: hemodynamic instability (chest compressions, inotropic support), severe or prolonged hypoxia, pneumothorax, pulmonary hemorrhage and death.

7.2 Assessing Extubation Readiness

In section 7.1, we showed how the assessment of extubation readiness could heavily be influenced by the chosen definition of extubation failure (i.e. the types of reintubations we wish to prevent). In this section of the discussion, we rather focus our attention on the complexities related to the actual assessment of extubation readiness. To illustrate with a real-world example, suppose a situation in which two extremely preterm infants (both with gestational ages of 25^{+2} weeks and birth weights of 750g) are intubated and mechanically ventilated in the NICU. At 48h of life, they are both on the same ventilatory mode and settings, namely assist control ventilation with volume guarantee of 5cc/kg, PEEP of 5 cm H_2O, rate of 30 inflations/min, mean airway pressure of 8 cm H_2O and fraction of inspired oxygen of 0.25. Given their overall stable clinical condition, should these two infants be given a trial of extubation? Are they 'ready' for transition to non-invasive respiratory support? As demonstrated in our thesis work, these commonly encountered scenarios all too often lead to variable responses and outcomes. Depending on the clinician's preferences and on the NICU's available resources and rituals, some of these infants will be deemed ready for extubation while others will remain on the ventilator. These large variations in extubation practices further stem from the fact that no accurate predictors of extubation readiness currently exist. Thus, in this section, using results gathered from the thesis, we discuss the challenges associated with clinical judgment and with predictor tests (including SBTs) for the assessment of extubation readiness. Moreover, based on the best available evidence, we provide some recommendations on how to streamline our assessment of extubation readiness in everyday practice at the bedside.

7.2.1 The Intricacies of Clinical Judgment and Extubation Readiness Tests

Clinical Judgment

When health care professionals use clinical judgment to determine an infant's readiness for extubation, they are typically integrating a number of factors, including the infant's birth demographics (e.g. gestational age and birth weight), pre-extubation conditions (e.g. postnatal age, current weight and any other ongoing comorbidities), gas exchange (e.g. pH and pCO_2), and ventilatory parameters (e.g. MAP and FiO_2) to make their decisions. However, it is not uncommon for two infants with similar clinical demographics and pre-extubation characteristics to have very different extubation outcomes. For instance, going back to the real-world example described above, we commonly face the scenario where one infant requires reintubation within a few hours (or days) after extubation while the other infant successfully remains extubated for the remainder of hospitalization. As such it is clear that clinical judgment, by itself, is ill-suited for the accurate identification and prediction of which infants are ready for extubation or not. This is not surprising, as clinical variables only represent surrogate markers of the infant's risk profile, but do not tell us anything about the infant's actual central and cardiorespiratory behavior (i.e. the actual determinants of extubation success/failure). In other words, these clinical variables do not provide concrete or reliable information about the infant's readiness for extubation in terms of their ability to sustain spontaneous breathing (i.e. mature respiratory control centers) and adequately maintain FRC on non-invasive respiratory support. That being said, through our literature review and rigorous analysis of the APEX data, we learnt several additional important facts about the complexities related to clinical judgment.

First, in the APEX cohort we observed that infants were extubated from a fairly wide range of ventilatory parameters, oxygen requirements and blood gas values. For instance, the

MAP ranged from 5 to 14 cm H_2O, the FiO_2 ranged from 0.21 to 0.53, and the pCO_2 ranged from 22 to 69 mmHg. These findings corroborate observations in a previous systematic review of the literature where we also found significant variations in what clinicians considered to be 'minimal ventilatory settings' for extubation of preterm infants. However, when looking at the range of values falling between the 25^{th} to 75^{th} percentiles, we obtain a much narrower and perhaps more useful overview of the 'acceptable' range of extubation parameters from which infants are extubated. For example, 50% of infants in the APEX study were extubated from a MAP between 6.3 and 8 cm H_2O. Any extubation from a MAP lower than 6 cm H_2O or higher than 8 cm H_2O could suggest that the infant was either weaned more than necessary or not weaned enough, respectively. Although these suggested ranges of extubation parameters are not accurate indicators of the infant's readiness for a successful extubation, they at least provide some common grounds for streamlining the weaning process and for avoiding extubations from 'extremes' outside this range.

Second, we also validated from the APEX cohort that infants with lower age/weight at birth or at extubation, and with higher O_2 requirements or MAP prior to extubation are at increased risk of reintubation (within both 72h and 7 days after extubation). However, there is significant overlap between success and failure groups for all those clinical variables. As a result, although applying a certain cutoff might correctly prevent some infants from failing extubation, it would naturally also keep many infants intubated unnecessarily longer. For example, a unit that opts to extubate infants only once their weight exceeds 1000g will certainly have lower failure rates, but will also expose infants to more MV days than they would have otherwise needed. Therefore, such simplistic thresholds for age, weight or ventilatory parameters have limited usefulness in clinical judgment and should be avoided.

Third, we also came to realize through conduct of APEX that the use of clinical judgment to determine extubation readiness also depends on various extrinsic or environmental factors that can heavily influence the infant's pretest probability of failure. As an example, when assessing an infant's readiness for extubation in the first few days after birth, it is essential to take into account why the infant required intubation and mechanical ventilation in the first place. A unit that gives surfactant prophylactically to all extremely preterm infants or that has a low threshold for intubation is likely exposing many infants to MV who may not have needed it otherwise. If the infant was intubated based on this premise, then their pretest probability of failure is lower and therefore they would benefit from an early extubation strategy (i.e. within hours after extubation). In contrast, a unit that practices CPAP in the delivery room and/or has strict criteria for intubation (and surfactant administration) is likely reserving MV to infants with the highest degree of lung and central nervous system immaturity. If the infant was intubated in that context, then their pretest probability of failing extubation is higher and so it may be justifiable to wait a few days before attempting a trial of extubation. Another example of environmental influence on clinical judgment relates to the resources available to each NICU. What is the unit's experience with non-invasive respiratory support? Is there sufficient supply and properly sized equipment for delivering optimal CPAP or NIPPV? Is the nursing (or respiratory therapist) ratio and experience level adequate for managing these infants during the critical post-extubation period? Is there qualified in-house staff at night to intervene with the post-extubation management should the infant require reintubation? All these questions are important and inevitably influence any clinician's judgment about whether an infant can be extubated or not. Unfortunately, these site-specific variables are much harder to quantify and can negatively affect the predictive ability of any assessment of extubation readiness.

Fourth, we learnt from this work that all clinical variables commonly used to assess an infant's readiness for extubation (as part of clinical judgment) are intricately connected. To illustrate, an infant with a relatively 'low' mean airway pressure may maintain adequate oxygen saturations only because they are receiving higher oxygen requirements. Conversely, an infant may appear to be very 'stable' in room air only because they are receiving a relatively 'high' mean airway pressure to maintain oxygen saturations within target ranges. Considering that MAP and FiO_2 conjointly affect oxygenation, it is important to integrate these two variables whenever assessing readiness for extubation. The respiratory severity score, which consists of MAP multiplied by FiO_2, is a simple way to integrate these two variables and has been increasingly adopted in the neonatal literature.[88] As another example, the blood gas values at which infants should be considered for extubation likely change as a function of postnatal age. In the first few days after birth, pH and base deficit are typically lower due to the metabolic acidosis that naturally occurs in all extremely preterm infants. At that point, carbon dioxide levels are also usually low as a compensatory mechanism. But as time elapses, the metabolic acidosis is resolved and the infant gradually develops inflammatory lung disease with compensated respiratory acidosis (i.e. chronic CO_2 retention). Thus, an infant in their third postnatal week may tolerate extubation from a higher pCO_2 (ex. 55 mmHg) better than an infant with the same CO_2 in the first few days of life. Considering the non-linear relationship that often exists between these clinical variables, it becomes easy to see why clinical prediction models (or calculators of extubation success/failure) using logistic regression may be misleading. For that reason, non-linear methods (ex: using Bayesian analyses or decision trees) may be better suited for handling these important clinical variables when trying to develop an estimator of extubation readiness.

Extubation readiness tests

Over the decades, clinicians have tried in many different ways to improve the assessment of extubation readiness in preterm infants with objective tests measuring various clinical and physiological parameters. As highlighted in our systematic review and meta-analysis, a total of 31 different extubation readiness tests have been evaluated in preterm infants.[103] Unfortunately, none convincingly had sufficient accuracy, power (i.e. low sample size) or external validity to justify recommending them in clinical practice. There are many interesting reasons why the evaluated predictors have lacked precision or widespread adoption as adjuncts to clinical judgment in the assessment of extubation readiness:

(1) Studies have so far reported extubation failure using various definitions and observation windows, which makes the interpretation and extrapolation of individual results very problematic (as explained extensively in section 7.1).

(2) Studies evaluating the diagnostic performance of a predictor test often included infants with very high pretest probabilities of successful extubation. For instance, some studies had very broad inclusion criteria that could include infants with gestational ages anywhere from 24 to 37 weeks, while other studies performed the diagnostic test on infants who were already quite mature at the time of extubation (e.g. more than 3 weeks of age) or who were extubated from unusually low ventilatory settings.[103] By including infants with high pretest probabilities of success (i.e. infants who would have otherwise likely been successfully extubated without any diagnostic test), this diminishes the diagnostic performance of the test on those infants who would have most benefited (i.e. those infants with equivocal or high risk of failure).

(3) There was some confusion across studies as to what exactly were the intended goals of the diagnostic test. In some studies, tests were primarily meant to serve as a tool to accelerate

weaning from the ventilator (i.e. achieve high sensitivity). In others, tests were targeted at reducing extubation failure rates (i.e. achieve high specificity). But irrespective of the desired goals, all studies determined the optimal cutoff point of their diagnostic test by assigning equal weights to sensitivity and specificity. Arguably, a different methodological approach would have been necessary if the goal was to favor the attainment of maximal sensitivity or maximal specificity. Moreover, infants in most studies were submitted to the diagnostic test at a time when they were already deemed ready for extubation by the responsible clinician. As such, a test with high sensitivity becomes less useful because it only validates the clinicians' intuition to extubate without really affecting the weaning duration. Lastly, it is highly conceivable that the same evaluated predictor test could simply not perform both tasks with equally high accuracy. In fact, the adult literature makes a clear distinction between weaning tests and extubation readiness tests. In mechanically ventilated adults, it is recommended to first undergo a separate weaning test (while still on high ventilatory settings) to assess their potential for an extubation assessment.[93] If they pass the weaning test, only then are they submitted to an additional trial to determine readiness for extubation.

(4) The vast majority of diagnostic tests only incorporated a single clinical or physiological parameter. Therefore, the test could only evaluate one of the many causes for which preterm infants fail extubation. For example, a predictor that measures lung compliance or minute ventilation may capture failures caused by underdeveloped or injured lungs, but may not as precisely capture failures attributable to immature control of breathing. As another example, a SBT is primarily designed to assess an infant's spontaneous respiratory drive, but does not provide as much information about the infant's pulmonary function or respiratory muscle strength. Besides, no diagnostic test can possibly predict reintubations caused by upper airway

obstruction, whether during the immediate period after extubation (i.e. as a result of airway edema/inflammation) or during the days following extubation (i.e. as a result of suboptimal provision of non-invasive respiratory support).

(5) A large number of the evaluated diagnostic tests required significant instrumentation (such as placement of esophageal catheters or respiratory inductive plethysmography bands) or were not very user-friendly. As a result, many of the diagnostic tests have remained in the experimental phase and thus cannot be reproduced.

For all the above reasons, extubation readiness tests as performed today in preterm infants do not appear to be warranted in clinical practice, neither as a tool to accelerate weaning nor as a tool to reduce extubation failure rates. Interestingly, although adult intensive care units (and to a lesser extent pediatric intensive care units) have adopted various extubation readiness tests in clinical practice, the evidence for their use is not entirely convincing. Most studies in adults have consisted of RCTs comparing protocolized weaning against standard of care (i.e. weaning and extubation per clinical discretion); the protocols themselves all included an extubation readiness test, such as a SBT.[68] While the evidence was compelling that protocols were associated with expedited weaning and reduced MV, it is not clear whether the outcomes improved as a result of the extubation readiness tests themselves or from the mere presence of a standardized weaning protocol. Besides, those same trials did not show a statistically significant reduction in reintubation rates with the use of protocols compared to clinical judgment.[68] Moreover, in a comprehensive review of predictors of weaning and extubation success from 65 diagnostic accuracy studies in adults, most predictors had poor accuracies compared to clinical judgment alone, especially with regards to the identification of extubation failures.[109] Similar uncertainties exist about the usefulness of extubation readiness tests in pediatric population.[110]

Spontaneous breathing trials

Of all the evaluated predictors, SBTs have gained the most traction in NICUs across the world because they are overall easy to implement, are relatively straightforward to perform at the bedside, and require no further equipment or sophisticated measurements. In fact, all that is required for the conduct of the trial is a predetermined duration, a fixed level of support and a definition of SBT pass/fail. But as highlighted in our international survey and systematic review of the literature, clinicians have used a wide variety of test durations, PEEP levels and pass/fail definitions when conducting the trial.[60, 103] None of the evaluated SBTs so far have demonstrated convincing superiority over clinical judgment alone, either in terms of accelerating weaning or reducing extubation failure rates. In fact, a yet unpublished RCT (clinicaltrials.gov NCT01471431) evaluating the impact of daily SBT vs. standard of care on weaning duration in preterm infants had to be terminated on grounds of futility. Furthermore, based on our comprehensive diagnostic accuracy study using the APEX cohort, after evaluating over 40,000 combinations of clinical events to define SBT pass/fail, we found that a 5-minute SBT exposed 56% of infants to clinical instability without accurately predicting whether they would later fail or succeed extubation.[107] Thus, for all the aforementioned reasons, SBTs cannot be recommended as part of routine use for the assessment of extubation readiness in preterm infants.

There are many inherent problems with the SBT as practiced today that can explain its lack of accuracy. First, we do not know what should be the optimal duration of the trial. On one hand, a short trial (e.g. 3-5 minutes) may be inadequate to realistically assess the infant's ability to sustain breathing without having clinically significant apneas. On the other hand, a long trial (e.g. several hours) may lead to lung derecruitment, especially if the SBT is performed under

settings where the infant is receiving less ventilatory support compared to their baseline pre-extubation settings. Second, we do not know how much ventilatory support (and what ventilator mode) to provide during the trial. As it stands, most clinicians use endotracheal CPAP with or without pressure support for their SBT. However, this type of ventilator support may significantly increase the work of breathing of the infant, especially if breathing through a 2.5 endotracheal tube. The possibility of partial obstruction or biofilm deposition through that tube could increase the resistance (and aggravate the imposed work of breathing) even further. In fact, it is very plausible that the imposed work of breathing during SBT may be significantly higher than the one immediately post-extubation, especially since infants are typically placed on CPAP or NIPPV with mean airway pressures commonly exceeding 6 cm H_2O (sometimes as high as 10 cm H_2O). Even when pressure support is provided during the SBT, there is a potential for respiratory fatigue and loss of functional residual capacity. This is because in the pressure support mode, the patient determines their own inspiratory times. Since preterm infants have very short inspiratory times and fast respiratory rates, there is a theoretical potential that the achieved mean airway pressures will be significantly lower during pressure support than during the infant's pre-SBT ventilatory settings. Third, the determination of SBT pass/fail can be very subjective since it relies on the clinician's reaction at the bedside and their inherent perceptions of the infant's actual readiness for extubation. In fact, this phenomenon was observed in our pragmatic APEX study but has also been well described in adults.[111] Therefore, even though SBTs are meant to be more objective than clinical judgment, they are still susceptible to some degree of bias during their conduct or their interpretation.

The ideal predictor

After having deconstructed all the intricacies involved in the assessment of extubation readiness, it becomes easy to see how the development of a perfect predictor is virtually impossible. In an ideal world, the perfect predictor would need to fulfill all of the following conditions. (1) The measurements/assessments done for the predictor should be able to encompass all or most of the causes for which infants fail extubation. (2) The level of difficulty of the assessment (i.e. the chosen duration and level of support) should replicate, as much as possible, the expected conditions of the infant during the post-extubation period. (3) The assessment should not expose infants to unnecessary clinical instability, unless this transient instability will exclusively identify infants who would have failed extubation. (4) The predictor should have a very high specificity for detecting and thus preventing high-risk failures (i.e. reintubations occurring in the first 48-72h after birth and associated with the highest risk of morbidities/mortality). (5) The predictor should be simple to use, objective, non-invasive and easily reproducible from one assessor to the next.

Unfortunately, none of the predictors evaluated so far have come anywhere close to fulfilling the above conditions. However, the APEX study has made some important strides in trying to achieve these goals. As detailed in Chapter 3, the APEX study aims to develop an automated and objective predictor of extubation readiness using machine-learning methods that combine clinical information with metrics of cardiorespiratory behavior derived from the analysis of cardiac and respiratory signals in extremely preterm infants.[104] For one, assessment of cardiorespiratory behavior through signal analysis has its merits because it provides information about the patient's maturity, breathing patterns, and respiratory drive in an automated and unsupervised fashion. Moreover, the use of machine-learning methods allows for integration of both clinical

and physiological information into one comprehensive predictor, and may be better suited for handling non-linearly correlated data. The development and validation of the APEX predictor of extubation readiness has recently been completed and is the thesis subject for two other graduate students in the fields of biomedical engineering and computer science, respectively.

7.2.2 Recommendations for the Assessment of Extubation Readiness in Clinical Practice

As it stands, there is unfortunately no perfect way to systematically and accurately determine when an infant is ready for extubation. However, after thoroughly reviewing the evidence and personally being present for hundreds of extubations of extremely preterm infants (as part of the data acquisition and data collection for the APEX study), herein are provided a few suggestions on how to streamline and improve decisions during the assessment of extubation readiness in clinical practice. Of note, these recommendations only apply to extremely preterm infants undergoing their first planned extubation attempt during the first 4-6 weeks of life. A summary of those recommendations is also provided in Table 7.2.

First, it is primordial to recognize that although a failed extubation appears to independently increase the risk of adverse outcomes, there are also complications associated with prolonged MV exposure. For that reason, until more accurate predictors become available for identifying high-risk failures, it is probably best to attempt extubation as early as deemed possible. To do so, health care professionals (clinicians, nurses and respiratory therapists) should routinely discuss as a team (ex: during daily morning rounds) whether the patient could be extubated. Infants should not be kept intubated based on arbitrary one-rule-fit-all criteria (ex: “once the corrected age exceeds 28 weeks gestation” or “once the weight exceeds 1000g”), or based on unfounded rationales (ex: “to allow the baby to grow”). If the patient is nowhere near

'ready' (e.g. high ventilatory parameters, high oxygen requirements, or poor respiratory drive), clinicians should proactively optimize conditions so that the patient could more promptly achieve extubation potential (by using adjuvant therapies such as diuretics, postnatal steroids and caffeine). Moreover, considering that the NICU is often a very busy environment with rapid turnover of personnel, weaning from MV can often be forgotten or inconsistent. For that reason, NICUs are encouraged to implement and develop evidence-based weaning protocols, ideally driven by respiratory therapists and/or nurses, in order to expedite weaning from the ventilator and avoid missed opportunities for extubation.

With regards to actual 'readiness criteria' from which infants should be extubated, it is clear that there is no one-size-fits-all solution. As such, instead of having prescriptive criteria with rigid thresholds, the readiness criteria should serve two main purposes: (1) To provide a safe but wide-enough range of parameters that clinicians are already commonly using for extubation in everyday practice, and (2) to weed out the possibility of extubation from more outlying conditions (e.g. extubation from very low or very high ventilatory settings, which could either unnecessarily prolong MV exposure or increase the chances of reintubation, respectively). Based on extubation practices in the APEX study, the middle 50% (or interquartile range) of clinicians extubated from a MAP of 6 to 8 cm H_2O, a PEEP of 5-6 cm H_2O, a ventilator rate of 20-30 inflations/min and FiO_2 between 0.21 and 0.3, with pH values ranging between 7.3-7.4 and pCO2 38-51 mmHg. When in pressure-controlled modes of ventilation PIP levels ranged between 12 and 15 cm H_2O, whereas in volume-controlled modes the tidal volumes ranged between approximately 4 and 5 ml/kg. Altogether, these parameters provide a sense of acceptable parameters from which clinicians should consider infants for extubation. Of note, in the case of a clinical study evaluating the outcome of extubation failure, investigators should

ideally provide their respective units some guidelines on extubation while also reporting the settings from which infants were actually extubated.

Last but not least, when an infant is deemed ready for extubation according to clinical judgment, it is not advisable to perform a SBT or ET-CPAP trial (whether with or without pressure support) to validate the decision to extubate. The change in ventilatory mode required to perform the test may expose the infants to unnecessary clinical instability without improving the ability to identify which ones will fail extubation. Instead, it might be more helpful to simply take a few minutes to observe the infant at the bedside while they are on their pre-extubation ventilatory parameters. The clinician could make note of the infant's level of alertness or reactivity during nursing care and their breathing patterns. Finally, it is advised that the clinician be present at the time of extubation to observe the infant's work of breathing, to promptly address any signs of upper airway obstruction, and to ensure optimal provision of non-invasive respiratory support (proper suctioning, patient positioning and interface placement). All in all, until a more accurate predictor test becomes available, it is preferable to only use clinical judgment (in the sequence described above) for the assessment of extubation readiness.

Table 7.2 Recommendations for the assessment of extubation readiness in clinical practice

1. ***Infants should routinely and proactively be assessed for their extubation potential***

   - Discuss as a multidisciplinary team during morning rounds
   - Identify strategies to expedite weaning and reduce mechanical ventilation duration
   - Infants should not be kept intubated solely based on their age or weight

2. ***Develop and implement respiratory therapist and/or nursing-driven weaning protocols***

3. ***The following are an acceptable range of parameters from which to consider infants ready for extubation:***

   - Mean airway pressure: 6 to 8 cm H_2O
   - Fraction of inspired oxygen: 0.21 to 0.30
   - Peak inflation pressure (on pressure-controlled ventilation): 12 to 15 cm H_2O
   - Tidal volume (on volume-controlled ventilation): 4 to 5 ml/kg
   - Ventilator rate: 20 to 30 inflations/min
   - pH prior to extubation: 7.3 to 7.4

4. ***Spontaneous breathing trials or any other endotracheal CPAP tests (with or without pressure support) are not advised***

7.3 Conclusions and Future Directions

To conclude, the thesis provided a comprehensive and structured appraisal of the complexities surrounding the assessment of extubation readiness and reintubation in extremely preterm infants. By describing peri-extubation practices and outcomes of a large cohort of infants, we were able to better understand the risk factors, frequency, etiology and consequences of reintubation in this population. Moreover, after systematically reviewing the literature and conducting a large diagnostic study on SBTs, we shed some light on the safety and accuracy of various diagnostic tests, especially SBTs, at predicting extubation readiness. Altogether, these learnt notions lay the groundwork for future studies interested in this complex subject, and provide some guidance on how to define extubation failure, which populations to target and how to report outcomes in a standardized fashion. Moreover, the knowledge acquired from this thesis provides a more evidence-based and 'minimal risk' approach towards assessment of extubation readiness in the real world, when trying to make the best decision at the bedside for the patient.

At the same time, the thesis has uncovered many remaining gaps in knowledge where future research is still urgently needed. Perhaps one of the more pressing issues revolves around unraveling the specific reasons why extremely preterm infants fail their extubation attempt. As it stands, in the absence of adequate monitoring or documentation of respiratory events, it is impossible to know in real-time the exact reasons why infants develop apneas (whether obstructive, central or mixed), increased work of breathing, increased oxygen requirements or respiratory acidosis. Besides, it is currently not possible to instantaneously evaluate whether the infants are adequately receiving the pressures delivered by the non-invasive respiratory support device. Therefore, it is critical that we develop ways to improve our monitoring, documentation and differentiation of clinical events while automatically ensuring that the patients are receiving

optimal delivery of non-invasive respiratory support. By understanding the unique causes leading to clinical instability in extremely preterm infants, we may be able in the future to personalize diagnostic tests and interventions in a way that is tailored towards each patient's needs or risk factors. Furthermore, considering that both extubation and reintubation practices are highly variable within and across NICUs, it is often very difficult to infer conclusions from any clinical study or to generalize results to any given NICU. As such, it may be useful to develop an 'extubation readiness score' and a 'clinical instability index' for infants undergoing extubation and reintubation, respectively. This may create a more standardized terminology when comparing studies and facilitate benchmarking initiatives across NICUs. Finally, with the increased awareness that some failed extubations may be associated with severe morbidities and even death, the highest priority is to develop a predictor capable of accurately identifying those failures. Hopefully, final results of the automated predictor of extubation readiness derived from APEX will have promising results and move the science forward on this subject.

Appendix

A1. Non-Invasive Respiratory Strategies to Avoid MV in Extremely Preterm Infants

Over the past two decades, a number of trials have investigated the efficacy of less-invasive respiratory support strategies at reducing the need for MV (and hence improving outcomes). For the purpose of this literature review, we identified all trials from three recently published systematic reviews and meta-analyses evaluating these different non-invasive strategies.[112-114] Trials published after the year 2000, with >30 patients per intervention arm, with available data on the need for MV within at least 7 days after birth, and including extremely preterm infants (i.e. gestational age < 28 weeks or birth weight < 1250g), were evaluated. From each included trial, we extracted the type of non-invasive respiratory support strategy/strategies, the mean or median gestational age of the studied cohort, and the proportion of infants who required invasive mechanical ventilation within 7 days (or more) after birth. A total of 17 articles were included, as shown on Table A1.1 below.[59,115-130]

Table A1.1 Randomized controlled trials evaluating the effects of different non-invasive respiratory support strategies on the need for mechanical ventilation in extremely preterm infants

Study, year	Non-invasive respiratory support strategy	Cohort gestational age (weeks)	Need for MV (%)
Kugelman, 2007	CPAP	28.2	62
	NIPPV	29	31
Morley, 2008	CPAP	26.9	59
Kishore, 2009	CPAP	30.8	41
	NIPPV	30.7	19
Rojas, 2009	CPAP	29.3	39
	INSURE	29.3	26
Finer, 2010	CPAP	26.2	67
Dunn, 2011	CPAP	28.1	52
	INSURE	28.1	59
Gopel, 2011	CPAP	27.5	73
	LISA	27.6	33
Meneses, 2011	CPAP	30.1	64
	NIPPV	29	58
Ramanathan, 2012	INSURE/CPAP	27.8	58
	INSURE/NIPPV	27.8	23
Tapia, 2012	CPAP/INSURE	29.8	30
Kandraju, 2013	CPAP/early INSURE	30	24
	CPAP/late INSURE	30	37
Kanmaz, 2013	LISA	28	40
	INSURE	28.3	49
Dilmen, 2014	Early INSURE	28.3	35
	Late INSURE	28.7	46
Kribs, 2015	LISA	25.3	75
Lista, 2015	CPAP	26.8	69
	CPAP/sustained inflation	26.8	59
Duman, 2016	NIPPV	29.1	70
	NIPPV+INSURE	28.8	38
Oncel, 2016	CPAP/MIST	29.1	40
	NIPPV/MIST	29.2	27

Abbreviations: CPAP – continuous positive airway pressure, NIPPV – nasal intermittent positive pressure ventilation, INSURE – intubation-surfactant-extubation, LISA – less invasive surfactant application, MIST – minimally invasive surfactant therapy

A2. International Survey on Peri-Extubation Practices in Extremely Preterm Infants

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ABSTRACT

Objective: To determine peri-extubation practices in extremely preterm infants.

Design: A survey consisting of 13 questions related to weaning from mechanical ventilation, assessment of extubation readiness and post-extubation respiratory support was developed and sent to clinical directors of level III NICUs in Australia, Canada, Ireland, New Zealand and USA. A descriptive analysis of the results was performed.

Results: 112 / 162 (69%) units responded; 36% reported having a guideline (31%) or written protocol (5%) for ventilator weaning. Extubation readiness was assessed based on ventilatory settings (98%), blood gases (92%), and presence of clinical stability (86%). Only 54% ensured that infants received caffeine ≤ 24 hours prior to extubation. 16% of units systematically extubated infants on the premise that they passed a Spontaneous Breathing Test with a duration ranging from 3 minutes (25%) to more than 10 minutes (35%). Nasal CPAP was the most common type of respiratory support used (84%) followed by NIPPV (55%) and high flow nasal cannula (33%). Reintubation was mainly based on clinical judgment of the responsible physician (88%). There was a lack of consensus on the time frame for definition of extubation failure, the majority proposing a period between 24-72 hours; 43% believed that EF is an independent risk factor for increased mortality and morbidity.

Conclusions: Peri-extubation practices vary considerably; decisions are frequently physician-dependent and not evidence-based. The definition of extubation failure is variable and well defined criteria for re-intubation are rarely used. High quality trials are required to inform guidelines and standardize peri-extubation practices.

INTRODUCTION

Mechanical ventilation (MV) is commonly used to support extremely preterm infants but has important associated complications.[56] Therefore, clinicians prefer to use non-invasive ventilation initially to avoid mechanical ventilation, but when intubation is required, they try to remove the endotracheal tube as soon as possible. However, the process leading towards extubation is complex, requires careful planning and involves three major steps: weaning, assessment of extubation readiness, and provision of post-extubation support.[131] Furthermore, definitions of extubation failure and the criteria for reintubation are inconsistent and rates of extubation failure appear to be high.[101] Unfortunately, there is little high quality evidence to guide clinicians during this peri-extubation period, leading to wide variations in practice,[132] which can affect important outcomes.[133]

Protocols are widely used to reduce unnecessary variations in practice and improve outcomes.[134, 135] Therefore, the development and implementation of protocols for the three major steps involved in the peri-extubation period have been recommended by the American College of Chest Physician and the American College of Critical Care Medicine in adults.[136] In pediatric and neonatal patients, the evidence is much less compelling.[137, 138] However, improvements in outcomes have been reported by some centers, including faster weaning from MV with the use of a respiratory therapist driven protocol,[70] earlier extubation with the routine performance of a spontaneous breathing trial to assess extubation readiness,[139] and lower bronchopulmonary dysplasia (BPD) rates with application of strict guidelines for nasal continuous airway pressure (CPAP) therapy.[140] Therefore, we designed a survey to identify peri-extubation practices across 5 countries in 3 different continents. We also aimed to examine the criteria used to define extubation failure and the need for re-intubation.

METHODS

A survey consisting of 13 questions related to peri-extubation practices, involving some aspects of weaning from mechanical ventilation, assessment of extubation readiness and post-extubation respiratory support was developed after review of the literature and consultation with experts in neonatal respiratory care (see online supplementary material). All questions focused on the respiratory care of extremely preterm infants, i.e. those less than 28 weeks gestation. The questionnaire was distributed electronically between October 2013 and February 2014, with bi-monthly reminders. All level III NICU clinical directors were identified using the official medical directory for each country (Canada, USA, Ireland, Australia and New Zealand). Consent was inferred by completing the survey, and the study was approved by the Research Ethics Board at McGill University Health Centre in Canada.

We asked about the use of guidelines or protocols for ventilator weaning and the professional group responsible for making the decisions about weaning. We also ascertained the earliest age when the first extubation attempt would be considered, as well as criteria used to assess extubation readiness. More specifically, we inquired about the use of a spontaneous breathing trial (SBT), a challenge whereby the infant is breathing spontaneously through the endotracheal tube for fixed time duration while clinical status is assessed. After providing a broad definition of SBT, we asked respondents whether they used the SBT in their unit, and if so the duration of the trial and criteria used to determine its success or failure. Furthermore, we asked about the types of respiratory support used immediately following extubation.

We also assessed whether units had specific criteria to guide re-intubation. We asked respondents to define extubation failure (EF), the rate of EF in their unit and whether they considered EF to be an independent risk factor for mortality and morbidity in these infants.

RESULTS

The questionnaire was sent electronically to 158 NICU's out of which 112 (71%) responded: 62/93 (67%) from United States, 21/30 (70%) from Canada, 14/21 (67%) from Australia, 5/6 (83%) from New Zealand and 8/8 (100%) from Ireland. Two responders skipped the question about their country.

Peri-extubation practices

Weaning from mechanical ventilation. Thirty-six percent of the NICUs reported having a guideline (31%) or written protocol (5%) for ventilator weaning. Decisions about weaning were made by the one or more of the following: staff neonatologist (99%), neonatal fellow (71%) or nurse practioner (54%).

Assessment of extubation readiness. Extubation readiness was assessed based on multiple criteria, including ventilatory settings (98%), blood gases (92%), and presence of clinical and hemodynamic stability (86%). Fifty four percent of respondents ensured that infants received caffeine within 24 hours prior to extubation. Only 16% of units routinely extubated infants on the premise that they passed a SBT, but up to 38% at least sometimes used it as part of their assessment. The SBT was of variable duration, ranging from 3 minutes (25%) to more than 10 minutes (35%). Most of the centers were either neutral (55%) or disagreed (23%) with the idea that a SBT could help to predict extubation readiness. Following weaning and assessment of extubation readiness, the first attempt to extubate was performed anytime from immediately after surfactant administration (18%) up to more than 14 days of life (1%), although the majority of centers extubated between 1 to 3 days of life (Figure A2.1).

Post-extubation respiratory support. Nasal CPAP was the most common type of post-extubation respiratory support used (84%) followed by NIPPV (55%) and high flow nasal cannula (33%). A minority of centers (10%) reported using low flow nasal cannula, oxyhood or no support during the immediate post-extubation phase.

Definition and criteria of extubation failure

The decision to re-intubate was mainly based on clinical judgment of the responsible physician (88%); only 12% of units had well defined criteria to guide re-intubation. There was a lack of consensus on the time frame for definition of extubation failure, with the majority proposing a period between 24 and 72 hours (Figure A2.2). Most respondents (79%) estimated having an EF rate between 10 and 30% in their unit. At the same time, 43% believed that EF was an independent risk factor for increased mortality and morbidity.

DISCUSSION

Using a simple and pragmatic survey we were able to obtain very important information about peri-extubation practices from a large number of units across 5 countries located in 3 continents. The descriptive analysis revealed significant variations in practices, with a lack of specific guidelines or protocols to streamline management. It also identified some approaches that were inconsistent with current evidence. Our results are concerning because this survey has been conducted in an era where intubation and mechanical ventilation are increasingly reserved for the sickest preterm infants who fail a trial of non-invasive support and are therefore under higher risk of extubation failure, increased morbidities and mortality.

Practice variability most commonly stemmed from a lack of, or conflicting evidence to support one respiratory approach over another. For instance, weaning from mechanical ventilation continues to be performed in a non-standardized manner, mostly by the staff neonatologist or neonatal fellow on service. This physician-dependent model contrasts with adult and pediatric acute care practices, whereby the use of health care professional-driven protocols for ventilation weaning has become standard of care.[69, 141, 142] The evidence to support MV protocols in the preterm population, although promising, is still scarce.[70, 132] Similarly, the decision to extubate is also subjective and non-evidence based, primarily relying on ventilator settings, blood gases and the presence of clinical stability.[131]

In the absence of accurate and objective predictors of extubation readiness, we found a growing interest in using a SBT as part of the assessment process. This strategy has been recently reinvestigated in three small, single center studies.[80, 139, 143] However, in clinical practice we noted the use of variable duration of the SBTs, ranging from less than 3 to more than 10 minutes. Such findings highlight the need for more evidence to evaluate the routine use of SBTs as a regular assessment tool, particularly with regards to the duration, criteria for success or failure, and accuracy.

In relation to post-extubation respiratory support, extremely preterm infants were most frequently extubated to CPAP, followed by NIPPV and HFNC. All three therapies have been demonstrated in large randomized control trials to be effective in reducing the risk of extubation failure.[99, 113, 144] The significantly higher CPAP usage could be explained by its familiarity, cost, ease of use and the extensive body of literature in the past decade. NIPPV, on the other hand, was not as consistently adopted by units. We observed very similar rates of NIPPV use when compared with two other surveys in Ireland [145] and England.[146] This could be explained by the

fact that several questions related to ventilator settings (pressures and rates) and use of synchronization during NIPPV remain unanswered.[147, 148] Although a meta-analysis of several small, single center studies concluded that NIPPV was superior to CPAP after extubation [149], the large pragmatic multinational RCT failed to demonstrate any reduction in BPD, mortality or the combined outcome.[99]

In some instances, we observed that outcomes of clinical research were not always readily translated into clinical practice, even when evidence of effectiveness already existed. Indeed, 10% of centers still reported extubating extremely preterm infants to low flow nasal cannula, oxyhood or no support, despite the evidence favoring the use of CPAP, NIPPV or HFNC. Similarly, only 54% of respondents took into account the administration of caffeine prior to extubation, despite substantial evidence in favor of its use.[150]

Evidence is lacking to support any criteria or specific time frame to define extubation failure in extremely preterm infants, which was apparent in our survey. Indeed, the large majority of the respondents used a time frame of ≤ 72h to define extubation failure (93%), which mainly reflects what studies have traditionally used. This short time frame has recently been challenged.[101] When looking at infants below 1000 grams, reintubation rate rises in proportion to the observation period, even when the definition extends to 7 days. In other words, using extubation failure definitions of 72 hours or less may underestimate the true failure rate and therefore give centers false reassurance about their clinical practice and outcomes. Finally, nearly half the respondents believed that extubation failure was an independent risk factor for increased mortality and morbidity despite the lack of strong evidence in the neonatal population. We speculate that this belief may come from the strong evidence from the adult [151, 152] and pediatric literature [153, 154] and the multiple mechanisms involved in the process of endotracheal re-

intubation, re-opening of atelectatic lungs (biotrauma) and re-initiation of mechanical ventilation, all potentially harmful to the preterm lungs. Therefore, a consensus regarding the definition of extubation failure is needed to determine acceptable reintubation rates and to understand the risks associated with reintubation in the extremely preterm population.

Our study had some important limitations. Responses were provided by a single individual and may not have been representative of the collective unit practice. The responses may also have reflected what people say they do, but not necessarily what they actually do in clinical practice. We deemed that the clinical medical directors of each unit would be best suited to represent their unit. Our survey was simple and pragmatic. This helped us achieve a good response rate but meant that more details were not sought.

Conclusions

Our survey demonstrated that peri-extubation practices in extremely preterm infants vary considerably. Decisions are frequently physician-dependent and not always evidence-based. A small proportion of units use SBT's but the duration and perceived usefulness of the test vary considerably. The definition of extubation failure is highly variable and well defined criteria for re-intubation are rarely used. Thus, the results of this survey should be used to further stimulate research that can provide evidence to inform guidelines and standardize peri-extubation practices in modern neonatology.

Figure A2.1. Age at first extubation attempt

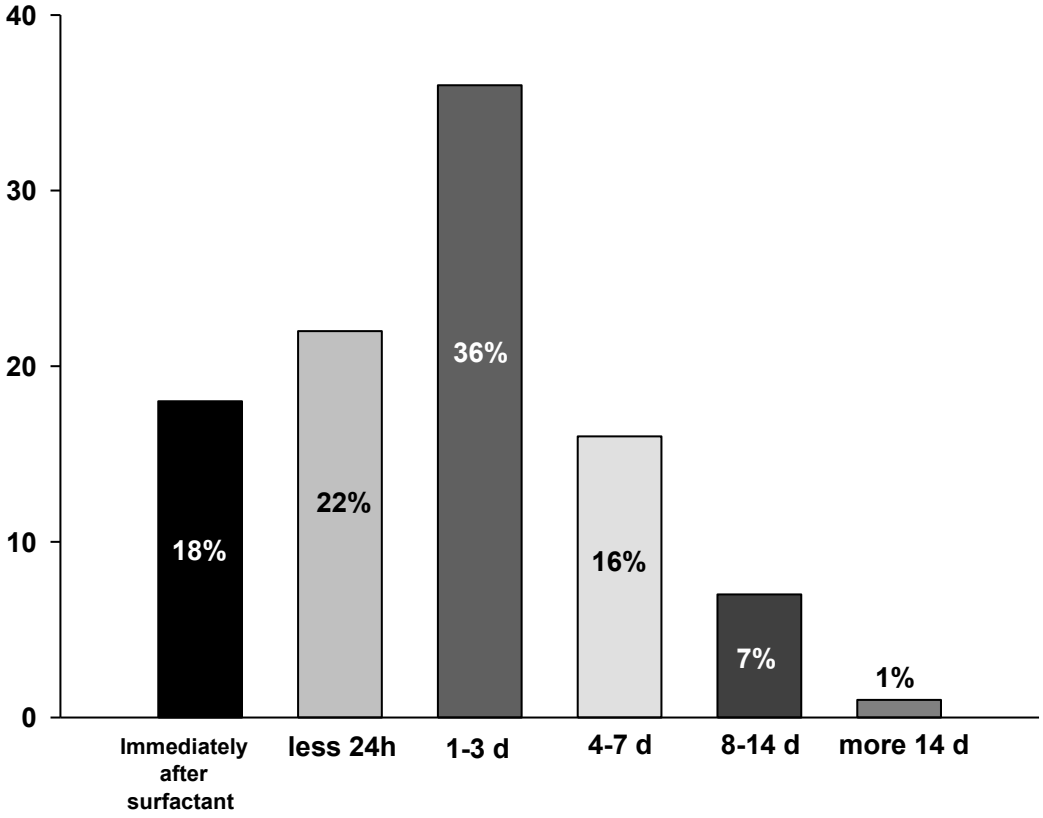
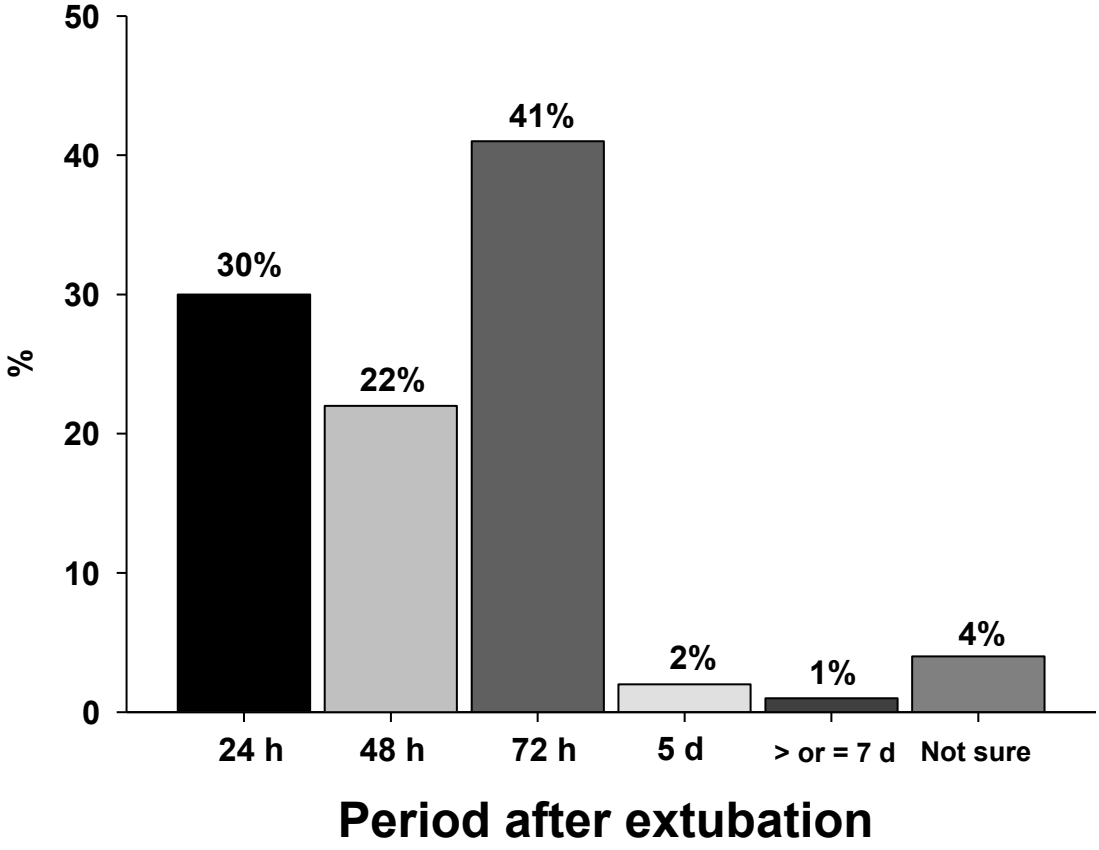


Figure A2.2. Time frame used to define extubation failure.



Online Supplementary Material – Questions of the Peri-extubation Practices Survey

1. How does weaning of extremely premature infants (<28wks) from mechanical ventilation occur in your unit?

    a. Using a strict written protocol e.g. if blood gases satisfactory reduce rate/tidal volume/pressure by x amount
    b. Using a less formal set of written instructions (guidelines) providing suggestions of how to reduce ventilator support
    c. No written protocols or instructions – allows individual clinicians to manage each case according to their interpretation

2. Which clinical group is responsible for making decisions about ventilator weaning (select all that apply)?

    a. Attending neonatologist
    b. Residents
    c. Neonatal fellows
    d. Respiratory therapists
    e. Nurses
    f. Nurse practitioners

3. In your unit, extremely premature infants (<28 weeks) are extubated from mechanical ventilation based on what criteria (select all that apply)?

    a. Ventilator settings
    b. Blood gases
    c. Clinical/hemodynamic stability
    d. Received caffeine within the last 24hrs
    e. Passed a spontaneous breathing trial

4. On average, the 1st extubation attempt of these infants (< 28 weeks) occurs at:

    a. Immediately after surfactant (Intubation-Surfactant-Extubation, INSURE)
    b. Less than 24 hours of life
    c. 1 to 3 days of life
    d. 4 to 7 days of life
    e. 8 to 14 days of life
    f. > 14 days of life

5. What respiratory support is used during the immediate post-extubation period in these infants < 28 weeks (select all that apply)?

    a. Nasal Intermittent Positive Pressure Ventilation
    b. Nasal CPAP
    c. High Flow Nasal Cannula (≥2L/min)
    d. Low Flow Nasal Cannula (<2 L/min)
    e. Oxyhood
    f. No respiratory support is initially applied

6. In your opinion, extubation failure should be defined as need of re-intubation within____after extubation:

    a. 24 hrs
    b. 48 hrs
    c. 72 hrs
    d. 5 days
    e. ≥ 7 days
    f. Not sure

7. Approximately, what is the overall rate of extubation failure, defined as the need for reintubation ≤ 72 hrs post-extubation, in extremely premature infants (< 28 weeks) in your unit?

    a. < 10%
    b. Between 10 and 30%
    c. > 30%

The spontaneous breathing trial (SBT) is a simple technique performed to assess extubation readiness in patients receiving mechanical ventilation to provide information on the spontaneous breathing ability. This test is already the standard of care in many adult and some pediatric intensive care units but only a few studies have evaluated its usefulness in the neonatal population.

8. How often do you use SBT before extubation of extremely preterm infants (< 28 weeks) in your unit?

    a. All the time
    b. Usually
    c. Sometimes
    d. Never

9. What is the duration of the SBT in your unit?

    a. < 3 minutes
    b. 3 minutes
    c. 5 minutes
    d. 10 minutes
    e. > 10 minutes
    f. We do not use the spontaneous breathing trial in our unit

10. What is considered SBT failure in your unit?

    a. Desaturation or bradycardia for longer than 15 seconds despite a 15% increment in FiO_2
    b. Any one of the following criteria: significant bradycardia (heart rate < 100 beats per minute for more than 10 seconds), oxygen desaturation (< 85% for > 15 seconds) or significant bradycardia requiring intervention
    c. Other
    d. We do not use the spontaneous breathing trial in our unit

11. In your opinion, can SBT help predict extubation readiness in extremely premature infants (< 28 weeks)?

    a. Strongly agree
    b. Fairly agree
    c. Neutral/don't know
    d. Fairly disagree
    e. Strongly disagree

12. In your unit, extremely preterm infants (< 28 weeks) are re-intubated based on:

    a. Clinical judgment of the responsible physician
    b. Well defined re-intubation criteria

13. In your opinion, is extubation failure an independent risk factor for increased mortality and morbidity in these infants (< 28 weeks)?

    a. Yes
    b. No
    c. Not sure

A3. The Use of Mechanical Ventilation Protocols in Canadian Neonatal Intensive Care Units

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Abstract

Objectives: To identify the proportion of Canadian neonatal intensive care units with existing mechanical ventilation protocols and to determine the characteristics and respiratory care practices of units that have adopted such protocols.

Methods: A structured survey of 36 questions about mechanical ventilation protocols and respiratory care practices was mailed to the medical directors of all tertiary care neonatal units in Canada and circulated between December 2012 and March 2013.

Results: Twenty-four out of 32 units responded to the survey (75%). Of the respondents, 91% were medical directors and 71% worked in university hospitals. Nine units (38%) had at least one type of mechanical ventilation protocol, most commonly for the acute and weaning phases. Units with pre-existing protocols were more commonly university-affiliated and had higher ratios of ventilated patients-to-physician or respiratory therapist, although this did not reach statistical significance. The presence of a mechanical ventilation protocol was highly correlated with the co-existence of a protocol for non-invasive ventilation ($p<0.001$, OR 4.5 [95% CI: 1.3-15.3]). There were overall wide variations in ventilation practices across units. However, units with mechanical ventilation protocols were significantly more likely to extubate neonates from the assist control mode ($p=0.039$, OR 8.25 [95% CI: 1.2-59]).

Conclusion: Despite the lack of compelling evidence to support their use in neonates, a considerable number of Canadian neonatal intensive care units have adopted mechanical ventilation protocols. More research is needed to better understand their role in reducing unnecessary variations in practice and improving short- and long-term outcomes.

INTRODUCTION

The provision of mechanical ventilation (MV), along with its processes of weaning and discontinuation, are critical components of the Neonatal Intensive Care Unit (NICU). Over the past decade, a rising body of literature has emerged in support of lung protective strategies and ways to achieve timely weaning and discontinuation from MV. In spite of that, there is excessive practice style variation amongst neonatal practitioners in their decision-making about MV for similar patient states.[155, 156] Heterogeneous MV practices are resource-intensive and could negatively affect patient care in the face of multiple changes and inconsistent treatment plans.[132] One way of harmonizing MV practices is through the development and implementation of MV protocols. A protocol, by definition, is a precise and detailed plan with definite inclusion and exclusion criteria that provide standardized pathways for caring for patients with specific conditions.[157, 158] Protocols have been extensively studied in adult and pediatric populations. They have notably been established for the treatment of sepsis, glycemic control and weaning from mechanical ventilation,[159-161] with results showing improved clinical outcomes associated with decreased medical costs. MV protocols have in fact repeatedly produced faster weaning times when compared to usual, physician-driven care,[162] while conferring shorter duration of MV and length of ICU stay in both adult and pediatric patients.[163, 164] In 2001, a collective task force of pulmonary and critical care experts issued evidence-based guidelines recommending that all ICU's should develop and implement weaning protocols designed for non-physician health care professionals (e.g. nurses, respiratory therapists) as part of their standard of care.[69]

Although MV protocols have been incorporated into daily practice in over 70% of adult ICU's in North America,[158, 165] their use in pediatric and neonatal ICU's is unknown. We conducted a survey with the aim to determine the extent to which MV protocols have been

integrated into current practice in Canadian NICU's. We also sought out the factors that drive certain NICU's to implement MV protocols, and whether these protocols affect ventilatory practices.

METHODS

Questionnaire development

A structured questionnaire (see Supplementary file) was derived through reviewing the literature and consulting respiratory therapists (RT) and NICU physicians at our institution. The framework was also inspired by a recent Canadian survey on the use of MV protocols in adult ICU's.[165] We asked a total of 36 close-ended questions regarding hospital/ICU characteristics, MV practices and MV protocols. In our survey, we defined protocols as "standardized plans which can give step by step instructions or specific rules to follow in a given situation. They must be specific enough that given a particular set of circumstances, multiple clinicians would generally make the same decision or act in the same way".

Study design

The survey was mailed in a pre-posted envelope to the medical directors of 32 tertiary-care (level III) NICU's in Canada capable of providing life-sustaining respiratory support. The list was generated using the 2011 directory of newborn intensive care units and neonatologists, published by the American Academy of Pediatrics. The medical directors from each unit were requested to complete the questionnaire, or alternatively assign it to one of the respiratory therapist (RT) leaders from their unit. The survey was circulated between December 2012 and

March 2013 with monthly email reminders and was anonymous. Informed consent to participate was inferred by return of the completed survey.

Analysis

The primary outcome was the proportion of Canadian NICU's with any MV protocol. The protocols were subdivided into the following categories: acute (≤ 7 days of MV), chronic (> 7 days of MV) and weaning phases, high frequency oscillatory ventilation (HFOV) and high frequency jet ventilation. We also inquired about the presence of any other respiratory support protocols for non-invasive ventilation (NIV) or use of surfactant, caffeine or inhaled nitric oxide. As a secondary outcome, we assessed whether the following hospital/ICU characteristics were associated with the presence of MV protocols: hospital type (university versus community), presence of medical or respiratory therapist (RT) trainees, presence of daily multidisciplinary rounds, ratio of patients to physician, ratio of ventilated patients to RT and RT responsibilities with regards to ventilator changes. We further assessed whether the presence of MV protocols influenced MV practices, including the choice of ventilation mode (following intubation or pre-extubation), weaning strategies and post-extubation respiratory support. Finally, in units where MV protocols were available, we sought to determine how those protocols were developed, implemented and maintained.

Results from the questionnaires were entered into a database (Microsoft Office Excel 2007) and analyzed using IBM SPSS version 21. We used the Fisher exact test and Mann-Whitney test for comparing dichotomous and continuous data, respectively. A p value < 0.05 was considered to be statistically significant.

RESULTS

The survey was sent to 32 neonatal units (20 university hospitals and 12 community hospitals with university affiliation). Twenty-four out of 32 units completed the survey (75%). Most of the questionnaires were completed by medical directors (N=22; 91%) and the other two were completed by the RT leader. The majority of respondents were from university hospitals (N=17; 71%) and the remaining were from community hospitals with university affiliation (N=7; 29%). All but one respondent worked in a "closed unit" (all admissions and patient care decisions were coordinated by a single physician).

Use of MV and other respiratory support protocols

Nine units (38%) had at least one written protocol for invasive MV. The most common protocols, present in 7 units, were for the acute and weaning phases of MV. Protocols for the chronic phase of MV and for HFOV were present in 4 units. Six out of 9 units had more than one MV protocol, with an average of 2 MV protocols per unit.

Seven of the 24 units that responded had a protocol for NIV (29%) and the presence of a MV protocol was highly correlated with the co-existence of a protocol for NIV (p value < 0.001, OR 4.5[95% CI [1.3-15.3]). The most common NIV protocol was for high flow nasal cannula, HFNC (N=6; 86%) followed by both continuous positive airway pressure (CPAP) and low flow nasal cannula (N=5; 71%). With regards to other measures of respiratory support, protocols for surfactant, inhaled nitric oxide and caffeine administration were present in 67%, 67% and 38% of the 24 units, respectively.

Factors associated with the use of MV protocols

Table A3.1 summarizes the association between hospital/ICU characteristics and the presence of MV protocols. There were no statistically significant differences overall. Protocols were more commonly used in university than in community hospitals (N=8; 89% vs. N=1; 11%, p=0.191). Medical trainees were present in all 9 units that had a MV protocol, as compared to 11 out of 15 units (73%) without a protocol (p=0.259). Despite having all units offer 24 hours/7 days per week RT coverage, units with MV protocols had a modestly higher ratio of ventilated patients per RT (9.2 vs. 5.6, p=0.050). Similarly, MV protocols were more commonly available in units that provided RT's with exclusive or joint responsibility (as opposed to no responsibility) for making changes on the ventilator (N=9; 100% vs. N=10; 67%, p=0.118). The presence of MV protocols was not significantly affected by the staff-to-patient ratio (19.8 vs. 15.9, p=0.184) or nurse-to-ventilated patient ratio (1.6 vs. 1.5, p=0.815).

Mechanical ventilation practices and association with MV protocols

There were wide variations in overall MV practices across the 24 units (Table A3.2). Forty-six percent of respondents did not specify the initial mode of ventilation, while 20% used either one of assist control (AC) with volume guarantee, AC with pressure control or synchronized intermittent mandatory ventilation (SIMV) with pressure support. The most common pre-extubation mode was SIMV (N=17; 74%) followed by AC or volume guarantee (N=10; 44%) and HFOV (N=7; 30%). The most frequent post-extubation respiratory support was CPAP (N=23; 96%), but 46% of respondents (N=11) extubated to nasal intermittent positive pressure ventilation (NIPPV) or HFNC. All units titrated oxygen concentration (FiO2) based on oxygen saturation (SpO_2) targets. Plateau pressures were only limited 50% of the time and positive end-expiratory pressure (PEEP) was titrated inconsistently based on measurements of

FiO_2, blood gases, SpO_2 and chest x-ray evaluations (range 25-38%). Blood gases and other CO_2 monitoring devices were used to determine ventilator changes in only 57% of cases. None of the units included daily spontaneous breathing trials as part of their ventilation practices.

Overall, the presence of MV protocols did not confer any major changes in MV practices. However, units with MV protocols were more likely to use AC as their preferred pre-extubation mode (75% vs. 27%, OR 8.25 [95% CI: 1.15-59], p=0.039) compared to units without protocols, where SIMV was the most common mode (N=12; 80%). They also more commonly used blood gases and other CO_2 monitoring tools for making changes to the ventilator, although this did not reach statistical significance (75% vs. 47%, OR 3.43 [95% CI: 0.52-22.8], p=0.379).

Protocol development and implementation

All 9 existing MV protocols were developed by a multidisciplinary team and the majority were supported by ongoing staff education (N=8; 89%). Six units (67%) required a physician order prior to initiating the MV protocol. Access to the protocol was variable, but most commonly it could be found on the hospital intranet (N=7; 78%). Nevertheless, the actual protocol adherence was only monitored in 5 units (56%) and 7 respondents (78%) did not know whether the protocol had been revised since inception.

DISCUSSION

We have found from our survey that 38% of Canadian tertiary-care NICU's currently have protocols to guide the use of MV. This observation strikingly contrasts with the adult intensive care, where evidence-based recommendations have accelerated the widespread use of protocols for MV.[69, 165] Compared to the adult literature, there is a paucity of data on the role of

MV protocols in the neonatal population. Only one single Canadian observational study by Hermeto et al. showed that the implementation of an RT-driven ventilation protocol for premature infants resulted in earlier extubation with an increased number of successful extubations and shorter duration of MV, even two years after implementation of the protocol.[70] On the other hand, some other respiratory support strategies such as inhaled nitric oxide and surfactant administration have been protocolized in over two thirds of Canadian NICU's, suggesting that protocols are becoming increasingly used in neonatal respiratory care.

Our survey also reveals a wide variability in ventilation practices across Canadian NICU's, which is consistent with similar findings from recent European and Australasian studies.[155, 156, 166] With the advent of technology and the accessibility to different modes and devices, provision of MV has become tremendously variable between institutions. To add to the complexity, most NICU's are structured in such a way that patients are exposed, on a daily basis, to a very high turnover of health care professionals, each with their own sets of experiences and backgrounds. This phenomenon has two major implications. First, several benchmarking studies done by American and Canadian neonatal networks have shown significant variation among centers in the incidence of important neonatal outcomes such as bronchopulmonary dysplasia, nosocomial infections and mortality.[133, 167-169] This clustering persisted even after correcting for variables known to affect these outcomes, suggesting that differences in clinical practice may play an important role.[133] The authors of these studies have advocated that neonatal outcomes could be improved through standardization of care and attenuation of these clinical practice variations. Secondly, it has been well demonstrated that evidence-based recommendations from clinical research are either slow to appear, overused or inappropriately applied in clinical practice.[157, 170] For instance, volume guarantee ventilation continues to be underused, even with

evidence to suggest that it may reduce ventilator-induced lung injury and duration of MV.[171] Furthermore, SIMV appears to be the most widely used mode for weaning and extubation, despite the evidence that AC provides less work of breathing, more homogeneous tidal volumes and faster weaning from MV when compared to SIMV.[63, 64] However, in the presence of MV protocols, the use of AC pre-extubation was significantly higher than SIMV, supporting the idea that protocols may promote evidence-based practice and discourage outdated approaches. In addition, units with MV protocols are significantly more likely to extend this culture into developing protocols for NIV, a therapy that has gained rising adoption as part of the shift towards more protective lung strategies.[99, 113, 172] A similar finding was observed in a survey in adult ICU's, where 73% of units had 3 or more clinical protocols and only 2% had 1 protocol.[158] This movement could reflect the units' positive experiences or perceived improvement in patient care delivery with protocols.

Thus, we believe that NICU's may benefit from the development and implementation of neonatal MV protocols, given their potential to reduce practice variability and improve patient safety. Using best available evidence, protocols should delineate all aspects of MV, including intubation criteria, preferred ventilator modes and settings, monitoring, weaning and post-extubation management. MV protocols should also be population and disease-specific. When evidence is lacking, protocols offer a great opportunity to involve all health care professionals and reach consensus as a team. MV protocols can further compensate for resource limitations; allowing busy clinicians to perform other tasks in the NICU while respiratory therapists can perform changes in a timely fashion. We noted a trend towards increased MV protocol use in units where the ratio of ventilated patients per RT or physicians was higher, but this did not reach

statistical significance, likely due to the small sample size. Evidence-based guidelines on how to construct clinical protocols exist and are beyond the scope of this paper.[132, 134, 173]

Our study had some limitations. Given its nature, the survey was vulnerable to response bias, in that some medical directors may not have responded because they did not have any MV protocol in their institution. This would lead us to overestimate the proportion of Canadian NICU's with MV protocols. However, we obtained a relatively high response rate (75%), and the fact that questionnaires were anonymous may have minimized this bias. The person completing the questionnaire may have had limited knowledge of the existence or contents of MV protocols. We deemed that clinical medical directors would be the most likely individuals to know about the latest projects in their respective units, and gave them the opportunity to delegate their respiratory therapy leader in case of time constraints or lack of awareness. Finally, results of the survey only describe the claimed MV practices, but this may not necessarily have reflected actual current practices in the unit, which may have changed since completion of the survey.

Despite the lack of evidence to support the use of mechanical ventilation protocols in neonates, 38% of Canadian NICU's have already moved forward with its development and implementation. MV protocols are preferentially being adopted in academic institutions where staffing coverage is limited, and appear to lead to potentially better practices. More research, in the form of randomized control trials or plan-do-study-act quality improvement initiatives, is needed to better understand the role of MV protocols in reducing unnecessary variations, improving clinical outcomes and decreasing medical costs.

Table A3.1: Association between hospital/ICU characteristics and the presence of mechanical ventilation protocols

	Protocol (n=9)	No Protocol (n=15)
Type of Hospital		
University hospital	89%	60%
Community hospital with university-affiliation	11%	40%
Medical trainees present	100%	73%
Daily multidisciplinary rounds	100%	87%
RT Coverage (24h per day)	100%	100% (13/13)
RT students in-training	100%	87%
RT's and ventilator changes		
Not responsible	0%	33%
Exclusively responsible	33%	20%
Jointly responsible with MD	67%	47%
Ratio of ventilated patients per RT	9.2 (5) [b]	5.6 (3) [b]
Ventilated patients per RT		
1 to 5 ventilated patients per RT	25% (2/8)	50% (7/14)
6 to 10 ventilated patients per RT	50% (4/8)	43% (6/14)
More than 10 ventilated patients per RT	25% (2/8)	7% (1/14)
Ratio of ventilated patients per RN	1.6 (0.5) [b]	1.5 (0.5) [b]
Ventilated patients per RN		
1 ventilated patients per RN	33%	40%
1.5 ventilated patients per RN	22%	20%
2 ventilated patients per RN	44%	40%
Ratio of patients per MD	19.8 (3) [b]	15.9 (8) [b]
Patients per MD		
1 to 10 patients per MD	0%	29% (4/14)
11 to 20 patients per MD	78%	57% (8/14)
Over 20 patients per MD	22%	14% (2/14)

Abbreviations: RN, registered nurse; RT, respiratory therapist; MD, medical doctor
[a] Total percentage may be greater than 100% in this category, as respondents could choose more than 1 answer.
[b] Mean (standard deviation).

Table A3.2: Association between MV practices and the presence of MV protocols.

	Protocol (n=9)	No Protocol (n=15)	Overall (n=24)
Initial mode of MV			
Not specified	56%	40%	46%
Assist control – volume control	33%	20%	25%
Assist control – pressure control	11%	20%	17%
Synchronized intermittent mandatory Ventilation with pressure support	0%	20%	13%
Use of blood gas, transcutaneous and end-tidal CO2 for titration	75% (6/8)	47%	57%
Use of permissive hypercapnia [a]			
PCO_2 allowed to rise to a preset maximum	33%	27%	29%
PCO_2 allowed to rise as long as pH is within a preset range	67%	80%	75%
Plateau pressures limited	50% (4/8)	50% (7/14)	50% (11/22)
PEEP titrated [a]			
Based on predetermined SpO2 levels	33%	27%	29%
Based on arterial blood gas results	22%	26.7%	25%
Based on set FiO2	44%	33%	38%
Based on chest X-ray evaluation	22%	40%	33%
Mode of MV pre-extubation [a]			
Assist Control [b]	75% (6/8)	27%	44% (10/23)
Synchronized intermittent mandatory ventilation	63% (5/8)	80%	74% (17/23)
Volume guarantee	63% (5/8)	33%	44% (10/23)
High frequency oscillatory ventilation	50% (4/8)	20%	30% (7/23)
High frequency jet ventilation	13% (1/8)	0%	4% (1/23)
Type of post-extubation support [a]			
Low flow nasal cannula	56%	20%	33%
High flow nasal cannula	44%	47%	46%
Continuous positive airway pressure	100%	93%	96%
Non-invasive positive pressure ventilation	67%	33%	46%

[a] Total percentage may be greater than 100% in this category, as respondents could choose more than 1 answer

[b] Statistically significant result (p value 0.039, OR 8.25 [1.15-59])

Online Supplementary Material – Questions of the Canadian Survey

Professional completing this survey:

- ☐ Physician
- ☐ Respiratory therapist leader

Demographic Information

1. Which of the following best describes your hospital?
   - ☐ University hospital
   - ☐ Community hospital
   - ☐ Community hospital with University affiliation
   - ☐ Don't know

2. According to the Ministry of Health and social services an intensivist-led ICU management model is one in which all admissions and patient care decisions are coordinated by a single physician who has Royal College accreditation or equivalent training in critical care medicine. This is referred to as a "closed" unit. Based on this definition is your ICU a "closed" unit?
   - ☐ No
   - ☐ Yes
   - ☐ Don't know

3. Do resident physicians train in any of your intensive care units? (Select all that apply)
   - ☐ No
   - ☐ Yes, Pediatric residents
   - ☐ Yes, subspecialty residents training in critical care medicine
   - ☐ Yes, subspecialty residents training in other fields
   - ☐ Yes, fellows who are not part of a formal University-affiliated training program

4. On average, what is the assigned ratio of registered nurses (RNs) to?
   Ventilated/intubated patients in your largest intensive care unit?
   1 RN to _____ ventilated patient(s).

5. What is the approximate ratio of staff physicians on duty to patients in your intensive care unit?
   1 staff MD to _____ patient(s)

6. Does your intensive care unit have Respiratory Therapist (RT) coverage?
   - ☐ No (Please skip to Question 11)
   - ☐ Yes, 8 - 11 hours a day in hospital but no after hours coverage
   - ☐ Yes, 8 - 11 hours a day with on call coverage after hours
   - ☐ Yes, 12 - 16 hours a day in hospital but no after hours coverage
   - ☐ Yes, 12 - 16 hours a day, with on call coverage after hours
   - ☐ Yes, 17 - 23 hours a day in hospital but no after hours coverage
   - ☐ Yes, 17 - 23 hours a day, with on call coverage after hours
   - ☐ Yes, 24 hours a day, 7 days a week

7. Does your hospital train Respiratory Therapy students?

- ☐ Yes
- ☐ No

8. Are the Respiratory Therapists responsible for changes to the ventilator settings for mechanically ventilated patients?

- ☐ No
- ☐ Yes, exclusively
- ☐ Yes, and physicians can also make changes in the ventilators settings.
- ☐ Yes, and physicians and registered nurses can also make changes in the ventilator settings.

9. What is the ratio of Respiratory Therapists to ventilated/intubated patients in your intensive care unit?

1 RT to _____ patient(s)

For this questionnaire, we define protocols as "standardized plans which can give step by step instructions or specific rules to follow in a given situation. They must be specific enough that given a particular set of circumstances, multiple clinicians would generally make the same decision or act in the same way." Non-physician health professionals may follow the protocol's rules without specific orders (other than an order to initiate the protocol).

10. Do you have a written protocol governing any aspect of mechanical ventilation (invasive or non-invasive)?

- ☐ No
- ☐ Yes

11. If yes, which one? (Select all that apply)

- ☐ Mechanical ventilation – acute phase (≤ 7 days)
- ☐ Mechanical ventilation – chronic phase (> 7days)
- ☐ Mechanical ventilation – weaning protocol
- ☐ High frequency Oscillatory Ventilation
- ☐ High frequency Jet Ventilation
- ☐ Nasal Intermittent Positive Pressure Ventilation
- ☐ Nasal CPAP
- ☐ High flow nasal cannula therapy
- ☐ Low flow nasal cannula therapy

12. If you indicated in Question 10 that a mechanical ventilation protocol exists in your hospital, would you be willing to enclose a copy of it with this questionnaire?

- ☐ No
- ☐ Yes, I will attach a copy to this questionnaire

13. In your unit, is the initial mode of ventilation specified?

- ☐ No, the initial mode of ventilation is not specified

- ☐ Yes, the initial mode of ventilation is assist control/volume control
- ☐ Yes, the initial mode of ventilation is assist control/pressure control
- ☐ Yes, the initial mode of ventilation is synchronized intermittent mandatory ventilation (SIMV) with pressure respiratory (PS)
- ☐ Yes, other _____ (please state initial mode)

14. In your unit, are specified blood gas (ABG, CBG, VBG) or end tidal CO2 ($ETCO_2$) or transcutaneous ($TcPCO_2$) limits used to determine ventilation changes?
- ☐ No, there are no BG, $TcPO_2$ or $ETCO_2$ limits
- ☐ Yes, there are BG, $TcPO_2$ or $ETCO_2$ limits stipulated to govern changes in ventilation

15. Does the unit ventilatory practice allow for the development of elevated PCO_2? (permissive hypercapnia) in certain circumstances? (Select all that apply.)
- ☐ No, the ventilation protocol does not allow for permissive hypercapnia
- ☐ Yes PCO_2 is allowed to rise to a preset maximum
- ☐ Yes, PCO_2 is allowed to rise as long as pH is within a preset range

16. Are plateau pressures limited as part of the ventilation practice?
- ☐ No plateau pressures are not limited as part of the ventilation protocol
- ☐ Yes, they are limited to ≤ 30 cm H_2O
- ☐ Yes, they are limited to a value > 30 cm H_2O

17. Is FiO_2 titrated? (Select any that apply)
- ☐ No
- ☐ Yes, it is changed according to predetermined SpO_2 levels
- ☐ Yes, it is changed based on ABG results

18. Is PEEP titrated? (Select all that apply)
- ☐ No
- ☐ Yes, it is changed according to predetermined SpO_2 levels
- ☐ Yes, it is changed based on ABG results
- ☐ Yes, minimum PEEP is determined by set FiO_2
- ☐ Yes, lung inflation evaluated by chest X-ray anteroposterior view

19. Does the ventilation practice include daily spontaneous breathing trials (SBT) for patients who meet preset criteria?
- ☐ No, there is no inclusion of spontaneous breathing trials in the protocol
- ☐ Yes, spontaneous breathing trials are included in the protocol for mechanically ventilated patients who meet preset criteria
- ☐ Yes, spontaneous breathing trials are included in the protocol for all mechanically ventilated patients

20. If yes, how are SBTs most commonly performed?
- ☐ Patient remains on the ventilator and is switched to minimal Pressure
- ☐ Support (PS) with minimal PEEP
- ☐ Minimal CPAP (no PS) via the ventilator

☐ Other (please describe):

_____

If your unit has a ventilation protocol

21. Is overall adherence to the protocol monitored?
    - ☐ No, adherence is not monitored
    - ☐ Yes, adherence is measured with the use of chart audits
    - ☐ Yes, adherence is measured in some other way (please describe)
    - ☐ Not applicable

22. Is a physician order required to initiate the mechanical ventilation protocol?
    - ☐ No
    - ☐ Yes

23. How can the staff access the mechanical ventilation protocol? (Select all that apply)
    - ☐ A copy is kept at each bedside/ventilator
    - ☐ It is printed on laminated cards for staff to carry
    - ☐ A printed copy is kept in the intensive care unit
    - ☐ It is available on the hospital intranet
    - ☐ A poster of the protocol is posted in the intensive care unit
    - ☐ Other (please specify):

    _____

24. Was the development of the mechanical ventilation protocol a multidisciplinary endeavor?
    - ☐ No, it was developed by the physicians
    - ☐ No, it was developed by the Respiratory Therapists
    - ☐ Yes
    - ☐ Don't know

25. Is the use of the ventilation protocols supported with ongoing staff education?
    - ☐ No
    - ☐ Yes

26. Have the ventilation protocols been revised since their inception?
    - ☐ No
    - ☐ Yes
    - ☐ Don't know

The following questions deal with practices in your intensive care unit.

27. Does your ICU(s) have daily multidisciplinary rounds?
    - ☐ No
    - ☐ Yes

28. If multidisciplinary rounds do occur in your intensive care unit, who routinely attends? (Select all that apply)

- ☐ Staff physicians
- ☐ Medical trainees
- ☐ Registered nurses
- ☐ Respiratory Therapists
- ☐ Clinical Pharmacists
- ☐ Physiotherapists
- ☐ Social Worker
- ☐ Clinical Nutrition
- ☐ Speech Language Pathology
- ☐ Other (please specify):

_____

29. Does your intensive care unit utilize any of the following in the treatment of refractory hypoxemia? (Select all that apply)

- ☐ High frequency oscillatory ventilation (HFOV)
- ☐ High frequency jet ventilation (HFJV)
- ☐ Inverse ratio ventilation
- ☐ Airway pressure release ventilation (APRV)
- ☐ Inhaled nitric oxide
- ☐ Extracorporeal membrane oxygenation (ECMO)
- ☐ Prone positioning
- ☐ Neuromuscular blockade

30. What route of intubation does your NICU use?

- ☐ Nasal
- ☐ Oral
- ☐ Both

31. Who usually does the intubation in your unit? (Please choose by order)

- ☐ Residents
- ☐ Respiratory therapist
- ☐ Neonatologist
- ☐ Neonatal nurse practitioner

32. After extubation the neonate is placed on:

- ☐ Low flow nasal cannula
- ☐ High flow nasal cannula
- ☐ CPAP
- ☐ NIPPV

33. For neonates who are mechanically ventilated, do you have a protocol for caffeine administration?

- ☐ No
- ☐ Yes, all babies mechanically ventilated receive caffeine immediately after intubation
- ☐ Yes, all babies mechanically ventilated receive caffeine 1- 2 days prior to extubation

34. Do you have a protocol for nitric oxide use?
    - ☐ Yes
    - ☐ No

35. Do you have a protocol for surfactant administration?
    - ☐ Yes
    - ☐ No

36. What is the mechanical ventilation mode used prior to extubation?
    - ☐ High Frequency Oscillatory Ventilation (HFOV)
    - ☐ High frequency Jet ventilation (HFJV)
    - ☐ Assisted control Ventilation (AC)
    - ☐ Synchronized intermittent mandatory ventilation (SIMV)
    - ☐ Volume guarantee ventilation
    - ☐ 3 minute spontaneous breathing trial while providing endotracheal CPAP

Your participation in this survey is greatly appreciated.
Please return the survey in the enclosed pre-addressed stamped envelope.
If you answered yes to Question 12, please attach a copy of your mechanical ventilation protocol to this questionnaire. Your protocol will be treated confidentially.

A4. Respiratory Care Protocols in Neonatal Intensive Care

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Abstract

Neonatal respiratory care involves physicians with variable backgrounds treating multiple respiratory problems and populations with a number of invasive and non-invasive devices and strategies. Unfortunately, there is a lack of strong evidence to guide the most adequate management for several specific situations. Altogether, this complexity leads to significant practice variability that can affect patient and health care outcomes. Respiratory care protocols, guided by evidence and/or consensus, are an attractive solution to promote standardization of care and reduction of unnecessary practice variations. Indeed, despite the limited evidence supporting the use of respiratory protocols in neonates, a significant number of units have already developed and implemented them into clinical practice. Respiratory care protocols appear to promote evidence-based practices, discourage outdated approaches and ultimately improve patient safety.

Introduction

The hallmark of neonatology relies on adequate provision of respiratory care, most commonly in the form of non-invasive respiratory support or mechanical ventilation (MV). Also, adjunctive therapies such as surfactant, caffeine, postnatal steroids and inhaled nitric oxide play important roles. Over the past decade, a large number of strategies to guide respiratory care practices have been investigated in an attempt to improve neonatal short- and long term outcomes, including length of MV, extubation failure rates, bronchopulmonary dysplasia (BPD) and neurodevelopment. Unfortunately, there is often limited or conflicting evidence to guide clinicians, leading to highly variable practices and a wide display of outcomes across Neonatal Intensive Care Units (NICU). One way to decrease unnecessary variations in practice is through the use of clinical protocols. This chapter will aim to: (1) describe the variability of respiratory care practices in neonatology; (2) evaluate the impact of practice variability on patient and health care outcomes; (3) review the evidence for using respiratory care protocols in neonates and (4) provide an overview on how to develop and implement these protocols in the NICU.

Variability of respiratory care practices in neonatology

In the modern era of neonatology, with the introduction of many new technologies and adjunctive therapies, the provision of adequate respiratory care has become very complex and challenging. Several local, national and international surveys have been undertaken to describe how these therapies are utilized across NICUs, consistently revealing wide intra- and inter-center variability.

Respiratory care management in the Delivery Room (DR)

Approximately 10% of neonates require some degree of respiratory assistance after birth.[174] Since the inadequate delivery of respiratory support may have serious repercussions, it is crucial for health care providers to have a solid foundation in neonatal resuscitation while staying up-to-date with recent advances in the field. A number of national and international expert consortiums regularly publish evidence-based guidelines to help providers during this critical period.[174] Despite those recommendations, surveys from around the world continue to demonstrate wide variations in many aspects of respiratory care management in the DR.

The most striking illustration of variability is ventilation during neonatal resuscitation. Units provide positive pressure ventilation (PPV) using various methods, including the flow-inflating bag (2-63%), self-inflating bag (6-96%), T-piece / Neopuff (1-79%) and ventilator (16-49%).[175-182] These can be delivered via face mask, binasal prongs, single nasal prong or a nasopharyngeal tube. Many institutions have more than one device at their disposal. Although positive-end-expiratory-pressure (PEEP) is now commonly used during PPV, many centers that use the self-inflating bag do not apply it with a PEEP valve or manometer.[179] In addition, delivered peak inflation pressures (PIP) vary with regards to the maximal level and duration of the inflation.[178, 181] Continuous positive airway pressure (CPAP) in the DR has gained popularity over the past years, particularly for the preterm population. But its use varies between 50-85% across countries, with units setting different gestational age thresholds (anywhere from 24-32 weeks) above which they would attempt CPAP.[175, 176, 178, 182] For those infants who get intubated, 3-45% of units have reported using CO_2 detectors.[177, 179-182] Moreover, there are variations in the preferred routes of intubation (oral vs. nasal) and types of endotracheal tubes used (straight vs. shouldered).[178]

The second most prominent source of variability in the DR relates to oxygenation. Despite evidence-based recommendations on the use of pulse oximetry, oxygen blenders and resuscitation of term infants with room air, some units have not yet adopted these practices.[174] Routine use of PO and O_2 blenders ranges from 30 to 100% and 36 to 100% across units, respectively.[175, 178-183] Although guidelines recommend pre-ductal saturation measurements, one survey showed that only 37% of units placed their saturation probes correctly.[176] Similarly, 7 to 56% of units have been reported to initiate resuscitation in 100% oxygen.[176, 177, 180, 183] In the case of preterm infants, the starting concentration of oxygen varies considerably (between 21-100%), with some providers starting high and tapering down and others doing the contrary.[181] Oxygen is commonly titrated based on pre-defined oxygen saturation targets, but some units still adjust according to color and heart rate.[179]

Invasive mechanical ventilation

With the rapid advent of technology, clinicians can now choose from a wide range of ventilators and modalities for invasive MV. Some surveys have reported as many as 12 different brands of ventilators for delivering conventional MV and at least 4 different types of machines for providing high frequency oscillatory ventilation (HFOV), with many units having more than one type at their disposal.[155, 166, 184] There are currently over 10 different MV modes available, including assist control (AC, pressure or volume controlled), intermittent mandatory ventilation (IMV, with or without synchronization, with or without pressure support), HFOV (with or without volume control), high frequency jet ventilation (HFJV) and neurally adjusted ventilatory assist (NAVA). Use of all these ventilators and modalities is rarely guided by patient disease or best evidence, but rather by availability, familiarity and personal preferences.[61, 155, 166, 184-186]

A noticeable observation from recent surveys reveals that volume-targeted ventilation (VTV) has yet to gain widespread adoption during MV, despite established evidence for its use as a lung-protective strategy.[171] There are significant geographical variations in VTV use, ranging from 5 to 60%.[61, 155, 156, 166, 185, 187] With regards to the preset tidal volume (V_T), the recommended target is generally 4-7ml/kg. However, surveys have demonstrated that some units use V_T targets as low as 3-4ml/kg and as high as 10ml/kg.[156, 187] Another prospective observational study showed that as many as 18% of units used V_T levels higher than 7ml/kg.[166] These extremes of low and excessive V_T may predispose to inadequate ventilation and volutrauma, respectively.

Furthermore, tools used for monitoring and titrating MV settings are quite heterogeneous. For instance, gas exchange can be monitored using $PaCO_2$ levels in the blood, transcutaneous CO_2, end tidal CO_2 or near-infrared spectroscopy.[61, 188] There is generally no consensus on the blood gas route (venous, arterial or capillary), frequency of sampling and thresholds for titrating. Although some evidence suggests that permissive hypercapnia may be a lung protective strategy during MV, a recent survey in the US showed that clinicians aimed for various target PCO_2 levels, anywhere between 45 and 65 mmHg.[189] Ventilator settings are also titrated in many different ways. In one Canadian survey, PEEP could be titrated on the basis of oxygen saturation, pulse oximetry, blood gas, fraction of inspired oxygen (FiO_2) or chest x-ray findings.[61] The indications and frequency of performing chest x-rays in intubated neonates is also rarely delineated and subject to individual preferences.

There are many other aspects of MV that lend themselves to practice inconsistencies. Endotracheal tubes (ETT) are secured using various taping methods. Infants are suctioned via the ETT at different frequencies and techniques. Practices relating to infant positioning (supine vs.

prone) or the ability to do kangaroo care during MV are also nurse or clinician dependent. Most importantly, the use of sedation during MV is so controversial that it has led to very changeable practices; some clinicians always provide opiates and/or sedatives to intubated patients, while others sometimes or never use it.[185, 186]

Peri-extubation practices

In order to limit complications associated with MV, infants are often extubated as early as possible. The process of extubation is quite complex and consists of three important steps: weaning from MV, assessment of extubation readiness and provision of post-extubation respiratory support. Significant variations in practice exist for all components of this process, with decisions often being physician-dependent and not always evidence-based. For instance, SIMV appears to be the most commonly used weaning mode across surveys,[61, 155, 185] despite the evidence that AC confers more homogeneous V_T and faster weaning when compared to SIMV.[63] Furthermore, in a recent international survey focused on extremely preterm infants, extubation readiness was primarily assessed based on the subjective interpretation of ventilator settings, blood gases and overall clinical stability.[60] In addition, 16% of infants were extubated infants on the basis of passing a spontaneous breathing trial (SBT), although the trial was often conducted in variable ways. The timing of extubation was extremely variable, with some units removing the ETT immediately after surfactant administration while others only after 2 weeks of MV. Finally, 10% of the centers still reported extubating extremely preterm infants to low flow nasal cannula, oxyhood or no respiratory support despite the undisputed evidence favoring the use of non-invasive ventilation in this population.[190]

Non-Invasive Ventilation (NIV)

Continuous Positive Airway Pressure (CPAP) – Since its discovery in the late 1970's, CPAP has been extensively studied in neonates. Consequently, it is by far the most widely used NIV mode across the world. Although CPAP has been well established and widely adopted for the treatment of apnea of prematurity and following extubation of preterm infants, its use as a primary therapy for respiratory distress syndrome (RDS) has only recently gained attraction. A recent study comparing epidemiological data from the Vermont Oxford and Italian Neonatal Networks revealed significantly high coefficients of variation in the use of CPAP as a primary therapy, ranging from 0 to 80%.[191] To provide CPAP, a variety of devices (ventilator, infant flow SIPAP or bubble) and interfaces (nasal prongs, nasal mask, nasopharyngeal tubes, nasal cannula) are used.[145, 184] There is no clear consensus on the level of CPAP to be applied as well as on how to wean and discontinue CPAP therapy. For instance, cycling off CPAP and transitioning from CPAP to HFNC therapy are common non-evidence based practices.

Nasal Intermittent Positive Pressure Ventilation (NIPPV) – NIPPV has also gained popularity, with rates of use varying from 18 to 88% in different parts of the world.[145, 146, 191, 192] It is most commonly applied as a rescue mode for infants who fail CPAP, to prevent intubation in infants with RDS or immediately after extubation. This variability in usage mainly stems from conflicting evidence on its effectiveness as well as limited understanding of its mechanisms of action, clinical indications and optimal means of delivering the pressures. Similar to CPAP, units may have at their disposal up to 5 different devices and interfaces for delivering NIPPV.[145, 146, 192] Synchronized NIPPV is still used by some units, but for the majority it is no longer commercially available.[146, 192] This is particularly important because the only studies demonstrating physiological and clinical benefits have used synchronized NIPPV.[192]

Furthermore, there is no consensus on what constitutes best settings (PIP, PEEP and rate) and how to optimally wean NIPPV.

High Flow Nasal Cannula (HFNC) – Well before any clinical trials had established its safety and effectiveness, HFNC had been widely used across units. Surveys revealed that between 50 to 77% of units were using it.[191, 193, 194] The most common indication was in the immediate post-extubation period. In two surveys, 33% of extremely preterm infants (≤ 28 weeks) and 12% of infants with birth weight ≤ 1kg were extubated directly to HFNC, respectively.[60, 194] This is particularly concerning, given the lack of evidence for infants below 26 weeks and experts cautioning against its routine use in this population.[74] Another popular application for HFNC is as an alternative to CPAP or as a weaning step between CPAP and no respiratory support. However, no evidence currently exists to support any of those practices.[195] With regards to the actual delivery of HFNC, current evidence (from the literature and manufacturers) recommends using no more than 8L of flow and a nasal cannula that allow some degree of leakage around the nares (around 50%). In spite of that, there is wide variability in HFNC delivery; one survey reported that as many as 15% use maximal flows greater than 8L, over half of respondents apply nasal cannula that exactly fit the nostrils and 23% apply measures to keep the mouth closed.[193] All these actions have the potential to deliver unreliable and dangerously high levels of pressure.

Other modes of NIV – More novel NIV modes have recently made their way into clinical practice despite the lack of evidence to support their use. Two such examples include non-invasive HFOV (nHFOV) and non-invasive NAVA. A recent European survey reported that 17% were using nHFOV for diverse indications, mainly for CPAP failure or as primary therapy. There were significant variations in the types of equipment, interfaces and settings used to

deliver nHFOV, with little information about its safety profile.[196] Similarly, NIV-NAVA is increasingly applied in many NICUs across North America using evidence mainly based from animal data, retrospective clinical studies and case series.[197]

Adjuvant therapies

Caffeine –A succession of animal, pharmacological and clinical evidence over the years has led to widespread caffeine use in neonates. The most influential publication of all was the large, multicenter Caffeine for Apnea of Prematurity (CAP) trial, which showed that caffeine significantly reduced incidence of bronchopulmonary dysplasia and cerebral palsy in preterm infants.[198, 199] Nonetheless, in the real world, caffeine practices continue to be highly variable and not always reflective of current evidence. For example, two recent surveys reported 54% and 77% of units respectively ensured that extremely preterm infants were loaded with caffeine prior to extubation.[60, 185] This is contrary to recommendations advocating for caffeine use in order to improve chances of successful extubations in preterm infants.[200] As another example, the use of prophylactic caffeine for the prevention of apnea has been heavily debated. The latest Cochrane review (2010) did not support routine use of prophylactic caffeine,[201] but a series of recent retrospective studies have shown that early administration of caffeine (in the first 48h of life) significantly reduced length of MV and improved short term respiratory outcomes in preterm infants.[202, 203] As a result, the off-label use of prophylactic caffeine has risen from 22% (at the time of the CAP trial) to 60-75%.[202, 204, 205] The first dose is given anytime between days 1 to 25h of life and for a duration ranging of 2 to 119 days.[205] There are also noticeable differences in practices related to monitoring and discontinuation of caffeine. Ten percent of units still routinely measure caffeine levels.[204] The timing of caffeine cessation often depends on the unit's

pre-specified gestational age cutoff (anywhere from 32 weeks to greater than 35 weeks). A significant proportion of units also discontinue caffeine once the infant has become apnea-free for 5-7 days (81%), ≤ 4 days (11%) or ≥ 8 days (8%).[204]

Surfactant – The introduction of surfactant is probably one of the most important and life-saving discoveries in the history of neonatology. It improved survival and reduced important morbidities associated with MV, especially for the extremely preterm population. However, the role of surfactant in everyday practice has markedly evolved over time. Originally, surfactant was mainly recommended as prophylaxis for all extremely preterm infants and was preferably administered in the first 2 hours of life.[206] Nowadays, clinicians are trying to avoid MV all together and are therefore looking for alternative ways to administer it using less invasive routes.[207] As such, use of prophylactic surfactant varies anywhere between 0 and 90%.[183-185, 191, 208] Most units use the INSURE (intubation-surfactant-extubation) method, but other strategies are increasingly tried.[209] When surfactant is provided as rescue therapy, clinicians use different clinical indications (e.g. FiO_2 thresholds), number of doses and methods of administration (e.g. infant's position, rate of infusion, pressures and lung recruitment maneuvers used pre and post administration).[185, 208, 209]

Inhaled Nitric Oxide (iNO) – The use of iNO for persistent pulmonary hypertension and acute hypoxic respiratory failure has been comprehensively studied in late preterm and term infants. In spite of that, there exists wide practice variations related to iNO administration in this population. Clinicians assess illness severity in a variety of ways (e.g. oxygenation index, pre-post ductal saturation difference, O_2 requirements, and echocardiographic findings), have different thresholds or indications to start iNO and use variable starting doses (5-20ppm) and maximal doses (20-40ppm).[210, 211] Moreover, there is no standard approach for monitoring and

weaning iNO (blood gases, oxygenation index, oxygen saturation and/or O2 needs), especially in patients who are non-responders to the therapy. The most striking observation of all is the rising off-label use of iNO in preterm infants less than 34 weeks gestation, despite firm position statements and consensus guidelines recommending against it. In fact, a number of surveys and large epidemiological studies have documented wide regional and inter-hospital variations in iNO use, indications, age of initiation, dosage and duration of therapy for this group.[211-213] This raises great concern, especially when iNO is associated with staggering health costs and has not been demonstrated to improve short or long term outcomes in this population, with potential to cause harm in the subset of extremely preterm infants less than 1000g.[214]

The impact of respiratory care practice variability

For the many reasons explained in the first session of this chapter, variability in respiratory care practices is extremely prevalent. The NICU is a fast paced environment where decisions are often made on the go and clinicians don't always have the time or sufficient knowledge to make the most informed decisions. In addition, units are often restrained in their ability to adopt a certain practice by its cost, ease-of-use or resource requirements (space, personnel, etc.). Most importantly though, despite the abundant existing literature, the evidence to justify most respiratory care practices is often limited or conflicting, leading clinicians to interpret study results in various ways, or shape their practices according to different background experiences and personal beliefs.

There are many implications of practice variability on patient outcomes (Table A4.1). In cases where high-grade evidence exists to guide respiratory care practices, it is easy to perceive how deviations (e.g. evidence-based therapies are introduced too late, too soon or are misused

for certain populations and conditions) can negatively affect patients. But even in cases where the evidence is unclear, the mere presence of variability has been linked to marked differences in pulmonary morbidities across NICUs. For example, rates of extubation failure range from 20 to 70% in preterm infants;[81, 98] this means that units with low extubation failure rates may perhaps be exposing infants to prolonged periods of MV while units with high failure rates may be disconnecting infants from the ventilator too soon. Both prolonged MV and the need for reintubation have been associated with serious, preventable morbidities.[56, 86] In a similar way, rates of unplanned extubation vary between 1% and 80% depending on unit MV practices and ETT fixation methods.[215] These accidental extubations also expose infants to unnecessary complications, including hemodynamic instability, need for reintubation, and prolonged MV.[215] Moreover, several benchmarking studies have demonstrated important variations in the incidence of BPD across centers, which persist even after adjusting for variables known to affect this outcome.[133, 216] Authors of these studies have suggested that differences in clinical practice may actually be affecting this clustering effect. Similar observations have been made for non-respiratory related outcomes, including survival and neonatal sepsis.[167, 169, 217]

Practice variability has potentially negative consequences that go even beyond patient outcomes (Table A4.1). It is not uncommon for a single patient to be exposed to several ventilation modes or therapies throughout hospitalization, or for a family to receive conflicting opinions regarding their child's respiratory management. This could be a great source of anxiety for the parents and may weaken their alliance with the health care team. Besides, this could create a lot of confusion amongst nurses, respiratory therapists and trainees, leading to lesser opportunities for productive teaching or learning. Finally, with little continuity or predictability

of management, it becomes quasi impossible to effectively audit respiratory care practices or perform any quality control studies in the unit.

The role of respiratory care protocols in neonates

One way of harmonizing practices is through the use of respiratory care protocols. Protocols are a set of guidelines or rules to follow for a pre-specified population with a pre-specified condition. They have been extensively studied in critically ill adult and pediatric patients, namely for sepsis, sedation, hyperglycemia and MV. In these patients, MV protocols have consistently been demonstrated to improve outcomes by reducing costs, decreasing MV duration and shortening length of stay.[68, 164] They also have been shown to reduce rates of extubation failure as well as unplanned extubations.[218, 219] As such, MV protocols have been considered standard of care and have been developed and implemented by over two-thirds of adult ICU's.[69, 165]

In contrast, the evidence for using respiratory care protocols in neonates is still limited. Studies are small, single center and retrospective or observational in nature. In one Canadian study, the implementation of a respiratory therapist-driven MV protocol for premature infants with birth weight < 1250g resulted in earlier extubation, greater number of successful extubations and shorter duration of MV.[70] In another study, the implementation of a standardized SBT protocol for extubation of extremely preterm infants resulted in faster weaning times with no impact on extubation failure rates.[139] In a further study, the implementation of a nurse-driven comfort protocol in ventilated preterm infants significantly reduced the amount of morphine used which translated in fewer days on MV and a shorter course of hospitalization.[220] Lastly, the use of a standardized surfactant protocol allowed clinicians to audit their practice and identify

strategies to reduce adverse events associated with surfactant administration.[221] The results of this quality control initiative led to later modifications of the surfactant protocol, which has recently been published.[222]

Despite the lack of strong evidence, it is interesting to observe that many units have already developed and implemented respiratory care protocols. In a recent Canadian survey, we showed that 38% of NICUs had at least one MV protocol while 29% had a protocol for NIV.[61] In another international survey, 36% of units reported having a guideline or written protocol for ventilator weaning.[50] Protocols for CPAP and NIPPV are available in approximately 20% of units,[61, 146, 192] while guidelines for HFNC are present in 25 to 50% of units.[61, 193, 194]

But the most striking trend is the increasing use of iNO protocols in practice. With the rising costs of iNO treatment, there have been many incentives from clinical managers and hospital administrators to audit iNO practices within their respective units. As a result, it's no surprise that almost two-thirds of units have developed and implemented iNO protocols.[61] To our knowledge, there have been no studies directly evaluating the impact of implementing iNO protocols in neonates, but there is some evidence from the pediatric literature that iNO protocols reduce practice variability, decrease iNO usage and thus lower costs without affecting mortality.[223, 224] As such, several local, national and international committees have published evidence-based guidelines to assist NICUs in developing their own institutional protocol.

Finally, there is a rising body of evidence recommending the development and implementation of clinical protocols for other specific neonatal practices or conditions. Some of these include pain control, sedation, feeding and delivery room management of extremely preterm infants (i.e. the golden hour).[225-227] But the area in which protocols have been most well studied remains the respiratory management of neonates with congenital diaphragmatic hernia

(CDH). In this population, implementation of a standardized, evidence-based protocol for respiratory care (e.g. using gentle ventilatory approaches, permissive hypercapnia etc.) has reliably led to lesser practice variations, improved survival and decreased morbidities.[228-230]

Development and implementation of respiratory care protocols in the NICU

From the above sections, there is no doubt that respiratory care protocols confer many benefits, but under some circumstances they may also have some disadvantages (Table A4.2). Developing and implementing a respiratory care protocol is not an easy task. It requires mobilization of many collaborators, careful scrutiny of a large body of evidence and ongoing monitoring to ensure adequate application of the protocol in practice. This section will outline the key principles for effectively developing and implementing respiratory care protocols in clinical practice (also summarized in Table A4.3).

Pre-conception

Well before any protocol is drafted, it is important to take the time to get buy-in from all members of the team who will eventually be using the protocol. This includes nurses, nurse practitioners, respiratory therapists, neonatologists and their respective professional leadership. Many providers are often unaware of the negative impacts of variability on health care outcomes. Others may feel skeptical about the benefits of protocols, potentially fearing that it will take away from their ability to individualize patient care. Thus, it is of utmost importance to provide a clear rationale for using a certain protocol in the unit. Showing unit-specific data that highlights practice variations and compares outcomes with other centers may be a useful step to further justify the need for a protocol. Thus, by involving all stakeholders as early as the pre-conception

phase, all team members will feel included and invested in the realization of the project. This will further aid in improving later rates of adherence and compliance to the protocol.

Once buy-in is obtained, the next crucial step is to create a working group that will be in charge of preparing the protocol. A member from each discipline involved in providing respiratory care (e.g. neonatologist, respiratory therapist, nurse, pharmacist and respirologist) should be encouraged to participate in this group. By using such approach, all key disciplines are represented and given the opportunity to share their perspectives. This multidisciplinary endeavor should lead to a stronger, more comprehensive and especially more inclusive protocol.

Preparation of the protocol

The development of a sound protocol depends heavily on the accuracy of its content. If a protocol is based on outdated or low quality evidence, it may actually lead to undesirable or even harmful effects. For that reason, it is essential to perform a thorough review looking for the best available evidence in the literature. Ideally, protocols should be based on results from randomized controlled trials, systematic reviews and meta-analysis. In the absence of such high quality evidence, other studies should be carefully scrutinized with a critical mind. Additional information should be sought out from expert opinion or from other units who already have had some experience with that specific protocol. Furthermore, epidemiological databases can be a useful resource to identify centers that have better outcomes in a certain aspect of respiratory care and collaborate with them in order to identify potentially better practices responsible for these positive outcomes.

With regards to the information contained in the protocol, it should preferably be patient-specific, disease specific and easy to follow. A protocol that is too flexible or unclear may lead to

variable interpretations and misuses. In contrast, a protocol that is too rigid, detailed or overly specific may become inapplicable for most patients. Thus, careful attention should be placed on developing a protocol that englobes most targeted patients but that also leaves some room for individualized decision-making.

Implementation and monitoring

Once the protocol is completed and approved by the necessary regulatory authorities, a number of steps need to be undertaken in order to ensure its adequate implementation. First, the protocol needs to be made readily available to all health care providers who will use it. Different channels can be used to disseminate the protocol, including the hospital intranet, monthly newsletters, posters in the unit, printed copies at the bedside and small laminated cards for staff to carry. Second, the protocol should be formally presented at educational sessions, in-services and special rounds with the aim to raise awareness, answer peoples' questions and clarify their concerns.

Following implementation, an effort should be made to monitor adherence to the protocol in an ongoing manner. In the absence of monitoring, it is not uncommon for protocol compliance rates to decrease with time. Thus, it is important to regularly monitor protocol usage in the unit in order to identify any major issues and promptly correct them. Regular refresher sessions may also be useful to reinforce the protocol. Finally, it is plausible that with time, new evidence-based recommendations will be made available and hence the protocol might become outdated. As such, protocols should be revised periodically and resubmitted for approval.

Conclusion

Neonatal respiratory care involves prompt lung recruitment and adequate ventilation and oxygenation during the transition period immediately after birth to management of a variety of respiratory conditions. For that, a number of different technologies and adjunctive therapies are available with lack of high level of evidence for several of them. Thus, it is not surprising that practice variability is a reality. Respiratory care protocols are an attractive tool to promote practice standardization and reduce unnecessary variations and health care related costs. Despite the limited evidence supporting their use in neonates, a significant number of NICUs have already developed and implemented clinical protocols into practice. Overall, respiratory care protocols appear to promote evidence-based practices, discourage outdated approaches and ultimately improve patient safety.

Table A4.1. Impact of respiratory care practice variability

On patients

- Potential for using non-evidence based practices
- Potential for increased errors and morbidities
- Unpredictable management
- Lack of continuity
- Parental distress

On workplace

- Increased costs
- Increased resources
- Confusion of health care team
- Inconsistent learning environment for trainees
- Reduced potential for quality control initiatives

Table A4.2. Pros and cons of respiratory care protocols

Pros

- Reduces unnecessary variability in care
- Streamlines care
- Quick adoption of new information at the bedside
- Educational aids for trainees and allied health care team
- Improves communication
- Decreases costs
- Decreases errors
- Improves patient safety

Cons

- Inappropriately used for certain patients or conditions
- Oversimplified or too prescriptive
- Designed around low quality evidence
- Potential loss of individualization of care
- Potential to be obsolete if not kept current

Table A4.3. General principles for effectively developing and implementing respiratory care protocols

Pre-Conception

- Obtain buy-in from all stakeholders
- Form a multidisciplinary working group
- Take into account that developing and implementing protocols require ample time, organization and resources

Development

- Easy to use
- Patient and disease-specific
- Avoid "cookbook medicine"
- Does not replace clinical judgment

Implementation

- Readily available
- Regular educational sessions
- Regular monitoring of adherence and compliance
- Periodical revision to accommodate for new evidence or clinical practice patterns

A5. The myth of minimal ventilatory settings for extubation in preterm infants

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In neonatology, the term "minimal ventilatory settings" to describe extubation readiness is used ubiquitously, despite the lack of known definition on what constitutes "minimal" settings. For that reason, we performed a systematic review of the literature to determine if "minimal" ventilatory settings for extubation could be defined. The main rationale, methodology and results of this work are presented in Chapter 1.4.1. In this appendix, details are provided on the flow diagram of included studies and the overall study characteristics. At the time of writing of this thesis, the systematic review was being updated to incorporate studies published between 2013 and 2018, and the manuscript was still in preparation.

Figure A5.1 Flow diagram of included studies

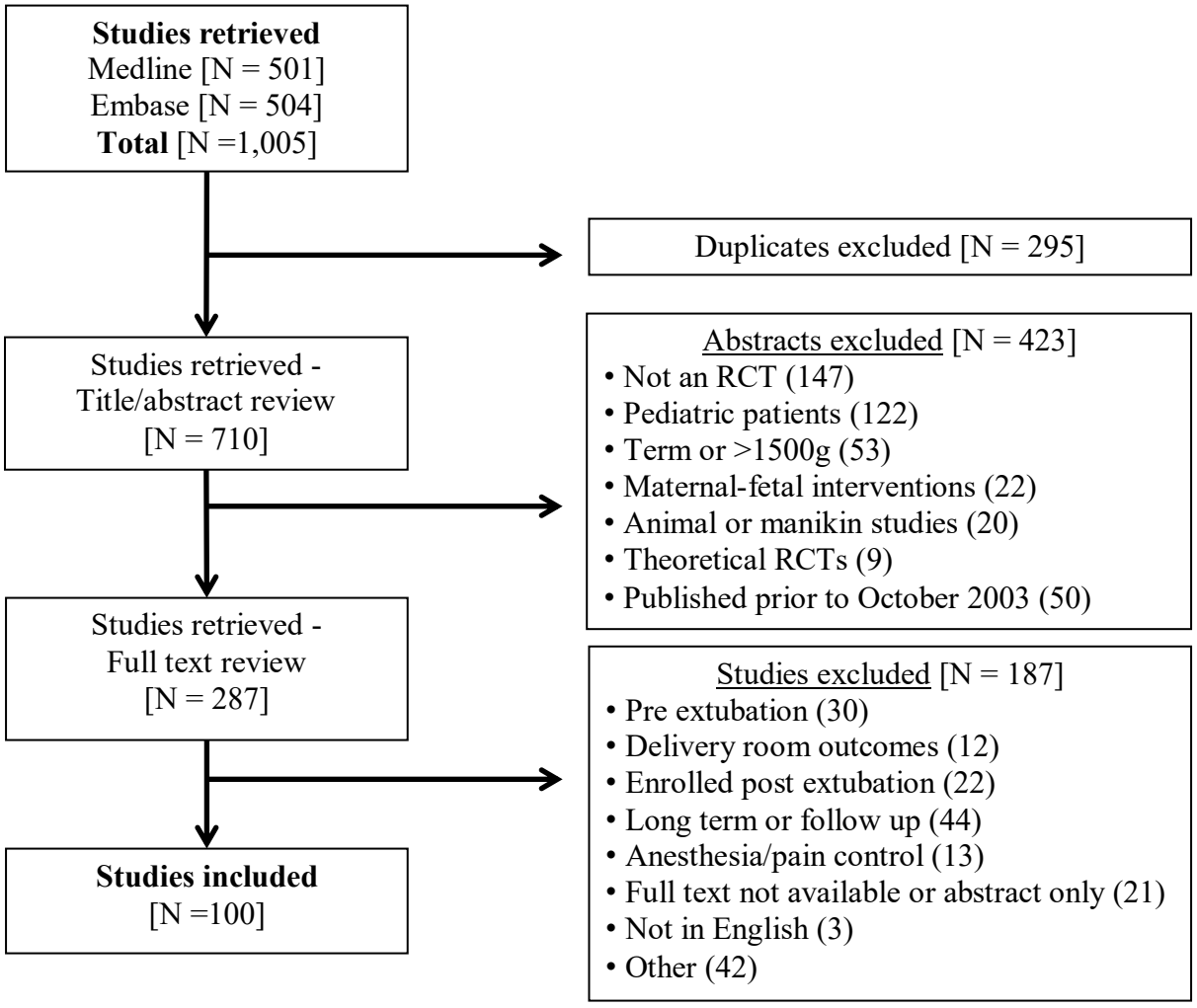
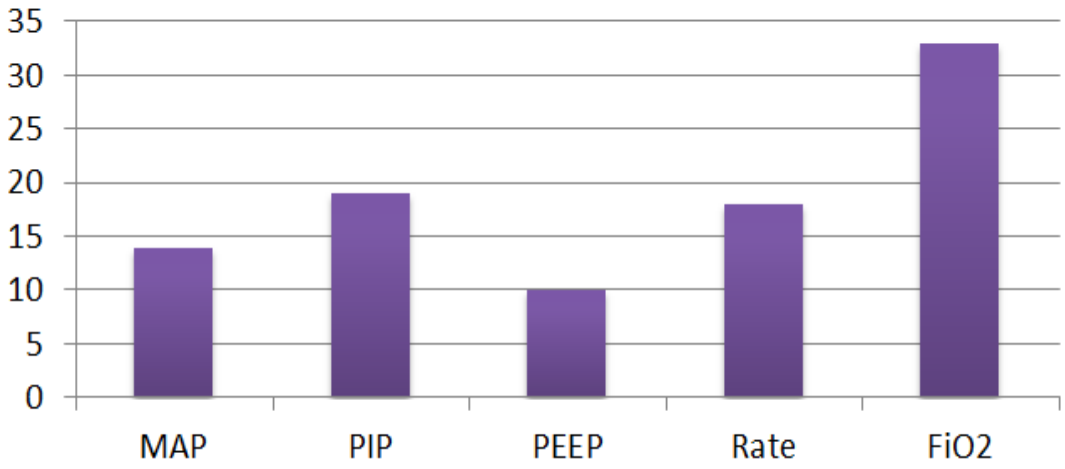


Table A5.1 Characteristics of included studies.

	Minimal Ventilatory Settings Provided [n=37]	**Minimal Ventilatory Settings not Provided [n=63]**	**p-value**
Country of Origin			0.195
International	2 (5%)	4 (6%)	
United States	10 (27%)	20 (32%)	
Canada	2 (5%)	1 (2%)	
Europe	3 (8%)	4 (6%)	
Asia	7 (19%)	14 (22%)	
Central/South America	0 (0%)	2 (3%)	
Australia/New Zealand	0 (0%)	7 (11%)	
Publication Year			
2003-2008	17 (46%)	40 (64%)	
2009-2013	20 (54%)	23 (36%)	
Median number of patients / study	88 (40-162)	132 (60.5-243)	0.48
Birth weight	1020 ± 262 g	1114 ± 336 g	0.15
Gestational age	27.8 ± 1.6 weeks	28.1 ± 2.2 weeks	0.43

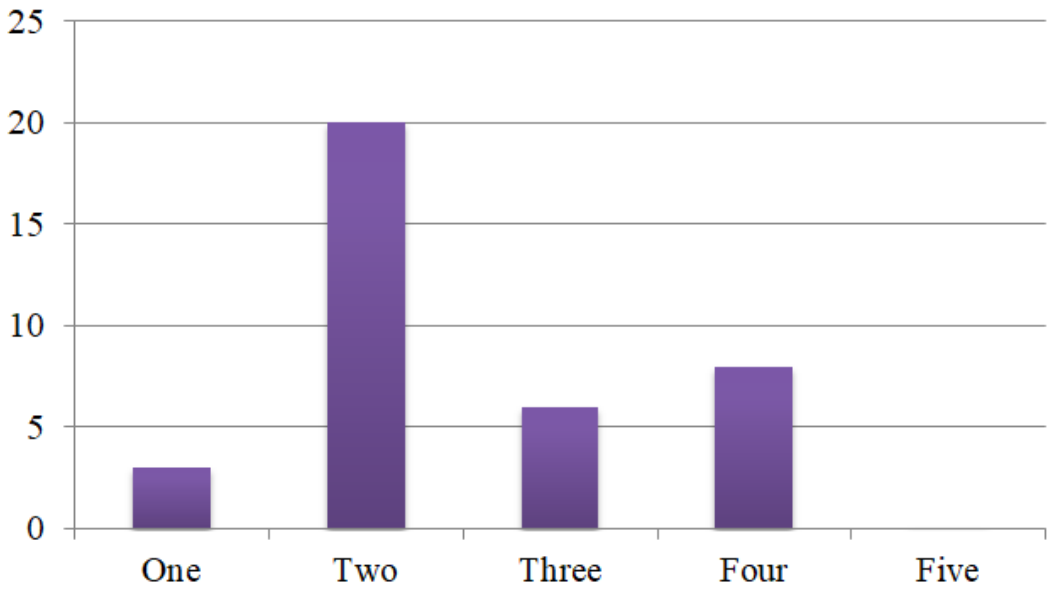
Legend: Results are presented as n (%), median (interquartile range), and weighted means ± standard deviation. Note that international studies included centers in more than one nation.

Figure A5.2 Number of studies reporting minimal settings per ventilatory parameter



Abbreviations: MAP – mean airway pressure; PIP – peak inflation pressure; PEEP – positive end-expiratory pressure; FiO_2 – fraction of inspired oxygen; PCO_2 – partial pressure of carbon dioxide.
Legend: The figure presents the number of studies reporting a minimal setting for each of the ventilatory parameters.

Figure A5.3 Number of minimal settings presented per study



Legend: The figure shows the number of studies that provided one, two, three, four and five minimal settings from which to extubate preterm infants. Studies most commonly provided two minimal ventilatory settings (n=20).

A6. Final demographics and patient characteristics from the APEX study

The following section of the Appendix provides details regarding the flow of participants in the APEX study, demographics of the cohort, comparisons between sites, and overall characteristics of infants with successful or failed extubation.

Flow of participants (Figure A6.1)

Between September 2013 and August 2018, there were a total of 1013 infants potentially eligible for enrollment in the APEX study. Of those, 765 (76%) required intubation and mechanical ventilation during the course of their NICU hospitalization. After excluding infants who were not intubated, those with congenital malformations, and those who already had their first extubation at a non-participating site, 746 infants were eligible for approach in the APEX study. Of those, consent was obtained from 357 participants. Unfortunately, when the time came for extubation, some of these infants could not be studied because of unavailable research personnel, withdrawal of consent by the parents, decline of entry into the study by the clinicians on service, or extubation from high frequency oscillatory ventilation. In a few other cases, infants could not be studied because they either had a self-extubation or died prior to their first extubation attempt. As a result, cardiorespiratory data could only be acquired from 274 infants. Amongst those 274 infants, 6 were excluded because extubation did not take place immediately after cardiorespiratory data acquisition, 1 was excluded due to a new diagnosis of choanal atresia after extubation, and 1 was excluded due to poor data quality. Thus, a total of 266 infants were included in the APEX cohort for future analysis.

Demographics of the cohort (Table A6.1)

Table A6.1 presents the characteristics of the infants at birth (including maternal and delivery information), prior to extubation, at the time of extubation, post-extubation, at reintubation and upon discharge from the NICU. The Table first highlights that the APEX study primarily included very small and extremely premature infants, hence the infants at the highest risk of failing extubation. In addition, the Table provides an overview of what actually happens in real world practice with regards to extubation and reintubation of these high-risk infants. As expected from the pragmatic nature of the study, the peri-extubation practices of the cohort were tremendously heterogeneous for all aspects of respiratory care.

Site comparisons (Table A6.2)

Infants were enrolled from a total of 5 participating institutions: 3 in Canada (Montreal Children's Hospital, Royal Victoria Hospital, Jewish General Hospital, Montreal, Quebec) and 2 in the United States of America (Women & Infants Health, Providence, Rhode Island and Hutzel Women's Hospital, Detroit, Michigan). Of note, the Royal Victoria Hospital merged with, and therefore became part of the Montreal Children's Hospital in May 2015. To preserve anonymity, the sites were numbered from 1 through 5 and compared using nonparametric statistical tests (Kruskal-Wallis for continuous variables and Chi square for categorical variables) to see if there were any overall differences between the groups. As highlighted in Table A6.2, patient characteristics at birth (i.e. gestational age and birth weight) were similar between sites except for significant differences in antenatal steroid use (Site 3 appeared to have lower rates of utilization compared to other sites). However, there were important differences between sites at the time of extubation. Notably, there were significant differences in the postmenstrual age,

weight and day of life at extubation, with Site 1 predominantly extubating at a later stage when infants were bigger and more mature. As a result of extubating at a later age, Site 1 naturally had significantly higher use of postnatal steroids and diagnoses of patent ductus arteriosus prior to the first extubation attempt. Furthermore, there were significant differences in the ventilatory parameters used at extubation, including the preferred ventilator mode (e.g. patient triggered vs. synchronized intermittent mandatory ventilation), the use of volume-controlled ventilation, the PEEP, MAP and FIO_2. Interestingly, Site 3 appeared to tolerate much higher ventilatory parameters (i.e. higher MAP, PEEP and FIO_2) at the time of extubation. Moreover, there were significant differences in the preferred modes of non-invasive respiratory support following extubation; Sites 1 and 6 preferred extubation to CPAP (with Site 6 primarily using the bubble CPAP system) while Sites 2 and 5 almost exclusively preferred extubation to NIPPV. Also, Sites 1 and 5 allowed extubation to HFNC following extubation in their extremely preterm infants. Finally, the reintubation rates (during NICU hospitalization) also differed significantly between sites, ranging anywhere from 39% (in Sites 1 and 2) to 75% (in Site 5).

Comparisons of infants with successful and failed extubations (Table A6.3)

Whether using an observation window of 72 hours or 7 days, infants with failed extubation were significantly smaller and more immature at birth and at the time of extubation compared to infants with successful extubation. Moreover, infants with failed extubation were extubated from significantly higher mean airway pressures and oxygen requirements compared to successfully extubated infants.

Figure A6.1 Flow of participants in the APEX study

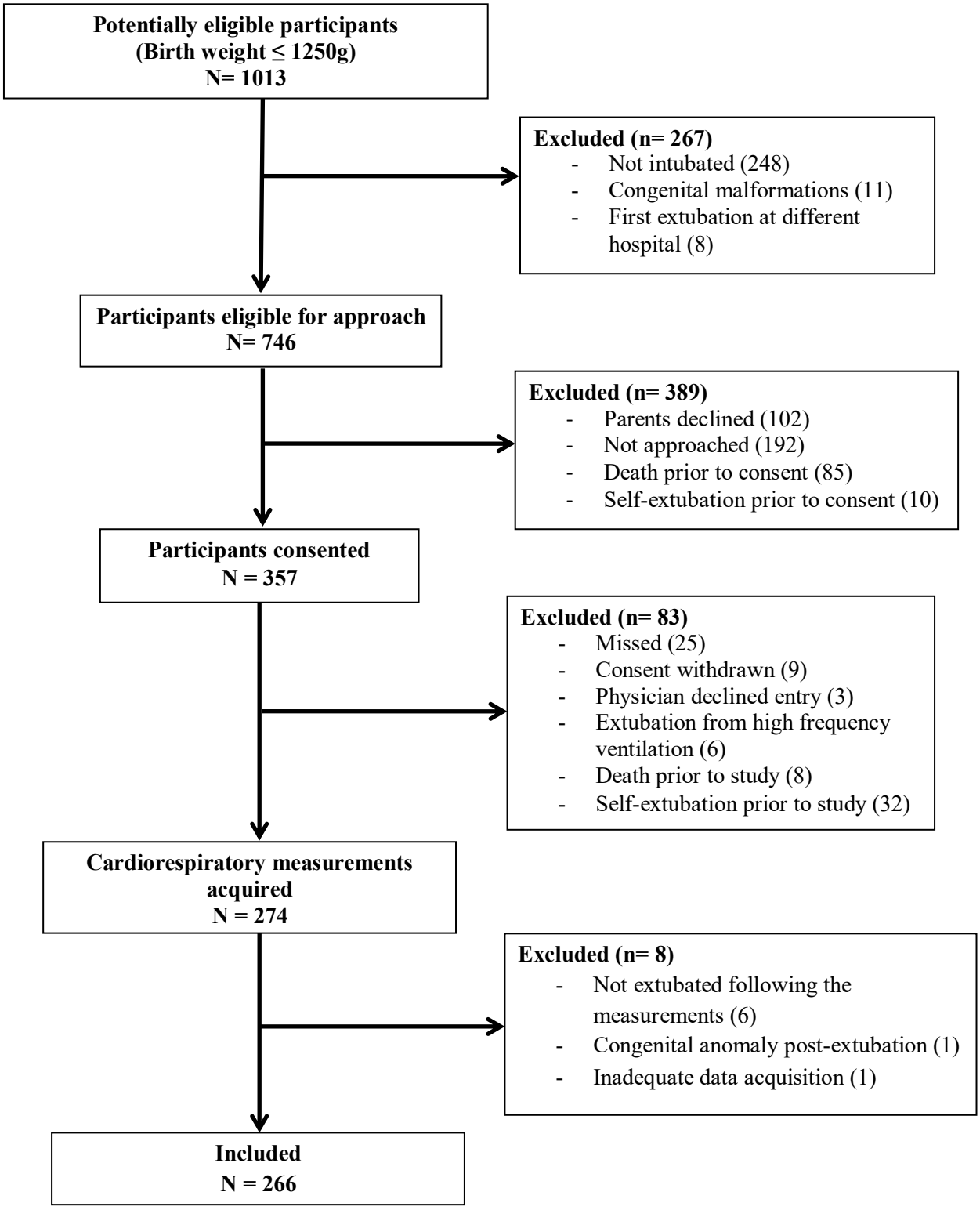


Table A6.1 Demographics of the APEX cohort

Demographic Information (n=266)	Median [IQR] or n (%)	Range
Demographics at birth		
Gestational age, weeks	26.1 [24.9-27.4]	23-31.7
Birth weight, grams	830 [690-1015]	390-1250
Small for gestational age, %	34 (13)	
Head circumference, cm (n=258)	23.5 [22-25]	18.5-31
Male sex, %	141 (53)	
Singleton, %	211 (79)	
Inborn, %	237 (89)	
Pregnancy history		
Maternal gravida	2 [1-4]	1-9
Maternal gestational diabetes, %	17 (6)	
Maternal preeclampsia, %	45 (17)	
Maternal infection during pregnancy, %	32 (12)	
GBS positive, % (n=152)	29 (19)	
Preterm labor, %	204 (77)	
Intrauterine growth restriction, %	44 (17)	
Antenatal steroids, %	240 (90)	
Antenatal steroids, number of courses (n=264)	1 [1-1]	0-3
Prolonged rupture of membranes, %	103 (39)	
Duration of ruptured membranes, hours	72 [19-212]	1-1128
Suspected clinical chorioamnionitis, %	88 (33)	
Confirmed histological chorioamnionitis, % (n=226)	113 (50)	
Delivery information		
Caesarean section, %	177 (67)	
Apgar score at 1 minute (n=263)	4 [2-6]	1-9
Apgar score at 5 minutes (n=264)	7 [5-8]	1-10
Apgar score at 10 minute (n=174)	7 [7-8]	1-10
Cord pH (n=237)	7.3 [7.24-7.34]	6.6-7.47
Cord pCO_2, mmHg (n=227)	47 [41-55]	31-124
Cord HCO_3, mmHg (n=222)	22 [19-24]	11-31
Cord base excess, mmol/L (n=225)	-3.8 [-5.9 to -1.7]	-25.6 to 3.6
Maximum fraction of inspired oxygen, FiO_2 (n=234)	0.8 [0.4-1]	0.25-1
Need for bag mask ventilation, %	247 (93)	
Duration of bag mask ventilation, minutes (n=177)	5 [2.9-9]	0.3-45
Continuous positive airway pressure (CPAP), %	137 (52)	
Need for chest compressions, %	11 (4)	
Need for epinephrine, %	3 (1)	
Need for intubation in delivery room, %	130 (49)	

Demographic Information (n=266)	Median [IQR] or n (%)	Range
Characteristics prior to extubation		
Age at intubation, minutes	20 [5-120]	0 to 17d
Number of intubation attempts (n=261)	1 [1-2]	1-6
Surfactant, %	254 (95)	
Number of surfactant doses (n=261)	1 [1-2]	1-4
Caffeine, %	260 (98)	
First day of initiation (n=259)	2 [1-4]	1-58
Loading dose, mg/kg elemental caffeine (n=256)	10 [10-10]	5-11
Maintenance dose, mg/kg elemental caffeine (n=231)	4 [2.5-5]	2-10
Pneumothorax, %	14 (5)	
Ventilator-associated pneumonia, %	32 (12)	
Patent ductus arteriosus (PDA), %	100 (38)	
PDA treatment with mediation or ligation, % (n=100)	34 (34)	
Intraventricular hemorrhage (IVH), %	70 (26)	
Postnatal steroids prior to extubation, %	79 (30)	
Days on postnatal steroids prior to extubation (n=79)	9 [5-17]	1-57
Use of diuretics, %	100 (38)	
Necrotizing enterocolitis (NEC), %	11 (4)	
Surgical NEC, % (n=11)	5 (45)	
Infection, %	43 (16)	
Characteristics at the time of extubation		
Postmenstrual age, weeks	28 [26.9-29.4]	24.6-38.7
Day of life	7.5 [3-25]	1-104
Weight at extubation, grams	935 [800-1080]	550-2700
Temperature of the infant, ° C (n=264)	36.6 [36.4-36.9]	32.9-38
Temperature in the incubator, ° C (n=261)	33.6 [31.6-36]	27.2-38.6
Laboratory test results within 24h from extubation		
Blood gas done, %	223 (84)	
pH (n=223)	7.34 [7.29-7.38]	7.16-7.54
pCO_2, mmHg (n=223)	44 [38-51]	22-69
HCO_3, mmHg (n=223)	22 [20-26]	16-37
Base excess, mmol/L (n=223)	-2.8 [-5 to 0.4]	-9.6 to 10
Bilirubin level, umol/l (n=153)	87 [67-109]	17-235
Hemoglobin level, g/L (n=122)	135 [121-151]	83-181
Phototherapy at the time of extubation, %	51 (19)	
Ventilator parameters at the time of extubation		
Patient triggered ventilation, %	135 (51)	
Synchronized intermittent mandatory ventilation, %	131 (49)	
Volume guarantee	101 (38)	
Positive end expiratory pressure, cm H_2O	5 [5-6]	4-9
Mean airway pressure, cm H_2O (n=265)	7 [6.2-8]	4.7-14

Demographic Information (n=266)	Median [IQR] or n (%)	Range
FiO_2	0.23 [0.21-0.27]	0.21-0.53
Oxygen saturation, % (n=265)	95 [93-97]	85-100
Peak inflation pressure, cm H_2O (n=147)	14 [12-15]	10-22
Tidal volume, ml/kg (n=101)	4.8 [4.2-5.3]	2.8-6.2
Rate, inflations/min (n=252)	20 [20-30]	10-60
Inspiratory time, sec (n=259)	0.35 [0.35-0.4]	0.2-0.7
Post-extubation characteristics		
Continuous positive airway pressure (CPAP), %	151 (57)	
Bubble CPAP system, % (n=151)	48 (32)	
CPAP level, cm H_2O (n=151)	6 [5-7]	5-12
CPAP FiO_2 (n=151)	0.23 [0.21-0.3]	0.21-0.77
Nasal intermittent positive pressure ventilation (NIPPV), %	101 (38)	
NIPPV PIP, cm H_2O (n=101)	15 [14-18]	8-26
NIPPV PEEP, cm H_2O (n=101)	6 [5-7]	3-10
NIPPV Rate, inflations/min (n=101)	30 [27-40]	15-50
NIPPV FiO_2 (n=101)	0.29 [0.25-0.35]	0.21-0.7
High flow nasal cannula (HFNC), %	14 (5)	
Blood gas done within 24h after extubation, %	213 (80)	
pH (n=213)	7.32 [7.29-7.36]	7.05-7.56
pCO_2, mmHg (n=213)	45 [38-53]	24-105
HCO_3, mmHg (n=212)	23 [20-26]	15-37
Base excess, mmol/L (n=212)	-2.6 [-5 to 0.3]	-10 to 12
Reintubation characteristics		
Any reintubation during hospitalization, %	128 (48)	
Time to reintubation, hours (n=128)	99 [21-317]	0.5 to 96d
Reintubation within 24h post-extubation, % (n=128)	34 (13)	
Reintubation within 72h post-extubation, % (n=128)	51 (19)	
Reintubation within 7 days post-extubation, % (n=128)	79 (30)	
Reintubation within 14 days post-extubation, % (n=128)	97 (36)	
Non-invasive respiratory support at the time of reintubation		
CPAP, % (n=128)	10 (8)	
CPAP level, cm H_2O (n=10)	6 [6-8]	5-15
CPAP FiO_2 (n=10)	0.28 [0.21-0.5]	0.21-1
NIPPV, % (n=128)	105 (82)	
NIPPV PIP, cm H_2O (n=105)	17 [16-20]	10-28
NIPPV PEEP, cm H_2O (n=105)	6 [6-8]	4-14
NIPPV Rate, inflations/min (n=105)	40 [30-40]	16-60
NIPPV FiO_2 (n=105)	0.38 [0.3-0.5]	0.21-1
Main reason for reintubation:		
Increased work of breathing, % (n=128)	21 (16)	
Respiratory acidosis, % (n=128)	4 (3)	

Demographic Information (n=266)	Median [IQR] or n (%)	Range
Stridor, % (n=128)	0 (0)	
Apneas and bradycardias, % (n=128)	73 (57)	
Increased oxygen needs, % (n=128)	15 (6)	
Number of reintubation attempts	1 [1-3]	1-7
Final outcomes at discharge		
Death, %	10 (4)	
Bronchopulmonary dysplasia (BPD) in survivors, % (n=256)	240 (94)	
Mild BPD, % (n=256)	88 (34)	
Moderate BPD, % (n=256)	47 (18)	
Severe BPD, % (n=256)	105 (41)	
Cumulative days on mechanical ventilation	19 [4-36]	1-270
Cumulative days on non-invasive respiratory support	43 [32-55]	0-138
Cumulative days on CPAP	13 [5-25]	0-78
Cumulative days on NIPPV	4 [0-13]	0-50
Cumulative days on HFNC	18 [8-29]	0-90
Cumulative days on supplemental oxygen	47 [13-93]	0-251
Need for postnatal steroids, %	128 (48)	
Cumulative days of postnatal steroids (n=127)	16 [10-30]	1-211
Upper airway complications, %	13 (5)	
Vocal cord injury, % (n=13)	4 (31)	
Tracheomalacia, % (n=13)	1 (8)	
Subglottic stenosis, % (n=13)	5 (38)	
PDA, %	155 (58)	
PDA requiring no treatment, % (n=155)	103 (66)	
PDA requiring medical treatment only, % (n=155)	45 (29)	
PDA requiring surgical treatment only, % (n=155)	3 (2)	
PDA requiring medical and surgical treatment, % (n=155)	4 (3)	
NEC, %	34 (13)	
Medical NEC (n=34)	17 (50)	
Surgical NEC (n=34)	17 (50)	
Infection, %	102 (38)	
Retinopathy of prematurity %	97 (36)	
Total length of NICU hospitalization, days	101 [76-122]	2-308

Values are expressed as medians [IQR] or n (%).

Table A6.2 Comparisons between APEX sites

Variable	Site 1 (n=106)	Site 2 (n=31)	Site 3 (n=37)	Site 4 (n=24)	Site 5 (n=68)	Overall P Value
At birth						
GA, weeks	26.6 [25-27.6]	26.4 [25.1-27.5]	26.1 [24.5-27.9]	25.8 [24.7-26.5]	25.7 [24.6-26.8]	0.2
BW, grams	850 [710-1050]	880 [738-990]	810 [675-1050]	769 [587-975]	770 [675-940]	0.35
Male, %	52 (49)	16 (52)	22 (59)	11 (46)	40 (59)	0.6
ANS, %	99 (93)	29 (94)	28 (76)	23 (96)	61 (90)	0.02
C-section, %	72 (68)	24 (77)	21 (57)	16 (67)	44 (65)	0.6
SGA, %	16 (15)	3 (10)	6 (16)	4 (17)	5 (7)	0.07
Apgar 5 min	7 [6-8]	6 [5-7]	6 [4-8]	6 [5-7]	6 [4-8]	0.002
Cord pH	7.3 [7.25-7.34]	7.31 [7.27-7.34]	7.31 [7.23-7.38]	7.26 [7.21-7.31]	7.3 [7.25-7.7.33]	0.35
Intubation age, h	0.4 [0.3-2.5]	0.3 [0.1-2.8]	0.1 [0.03-0.5]	0.05 [0.03-0.1]	0.2 [0.1-3.3]	< 0.001
Pre-extubation						
PDA, %	43 (41)	12 (39)	3 (8)	9 (38)	33 (49)	0.001
IVH, %	31 (29)	6 (19)	8 (22)	7 (29)	18 (26)	0.8
PNS, %	41 (39)	4 (13)	4 (11)	7 (29)	23 (34)	0.004
NEC, %	1 (1)	1 (3)	1 (3)	2 (8)	6 (9)	0.1
Infection, %	20 (19)	2 (6)	2 (5)	3 (13)	16 (24)	0.06
At extubation						
Day of life	17 [4-28]	3 [2-12]	5 [2-13]	6 [2-30]	8 [4-25]	0.001
PMA, weeks	29 [27.7-30]	27.3 [26.3-28.8]	28 [26.6-29.4]	28 [26.6-29.1]	27.6 [26.6-29.3]	< 0.001
Weight, grams	975 [840-1090]	900 [811-1023]	870 [678-1051]	870 [700-1008]	895 [780-1080]	0.03
pH	7.33 [7.29-7.37]	7.31 [7.29-7.36]	7.34 [7.29-7.38]	7.37 [7.33-7.41]	7.34 [7.3-7.38]	0.08
pCO_2	44 [36-51]	44 [39-48]	46 [41-54]	39 [34-49]	45 [41-51]	0.1
AC/PSV, %	23 (24)	24 (80)	12 (34)	0 (0)	56 (93)	< 0.001
VG, %	24 (23)	8 (26)	22 (59)	0 (0)	47 (69)	< 0.001
PEEP, cm H_2O	5 [5-5]	5 [5-5]	7 [7-8]	5 [4-5]	5 [5-6]	< 0.001
MAP, cm H_2O	6.5 [6.1-7.3]	7 [6.5-7.8]	9 [8-10]	6.4 [5.9-7]	7.5 [6.3-8.5]	< 0.001
FiO_2	0.21 [0.21-0.25]	0.21 [0.21-0.24]	0.25 [0.21-0.3]	0.26 [0.22-0.29]	0.25 [0.21-0.29]	< 0.001

Variable	Site 1 (n=106)	Site 2 (n=31)	Site 3 (n=37)	Site 4 (n=24)	Site 5 (n=68)	Overall P Value
Post-extubation						
CPAP, %	77 (73)	10 (32)	20 (54)	0 (0)	44 (65)	< 0.001
NIPPV, %	20 (19)	21 (68)	17 (46)	19 (79)	24 (35)	< 0.001
Reintubation						
Within 24h, %	11 (10)	2 (6)	8 (22)	2 (8)	11 (16)	0.3
Within 72h, %	15 (14)	2 (6)	11 (30)	6 (25)	17 (25)	0.05
Within 7d, %	23 (22)	4 (13)	15 (41)	11 (46)	26 (38)	0.005
Within 14d, %	31 (29)	7 (23)	15 (41)	14 (58)	30 (44)	0.02
Anytime, %	41 (39)	12 (39)	17 (46)	18 (75)	40 (59)	0.005
Timing, hours post-extubation	120 [21-322]	284 [122-456]	26 [6-88]	120 [65-274]	91 [21-368]	0.05

Values are expressed as medians [IQR] or n (%).
Abbreviations: GA – gestational age, BW – birth weight, ANS – antenatal steroids, SGA – small for gestational age, PDA – patent ductus arteriosus, IVH – intraventricular hemorrhage, PNS – postnatal steroids, NEC – necrotizing enterocolitis, PMA – postmenstrual age, AC – assist control ventilation, PSV – pressure support ventilation, VG – volume-guaranteed ventilation, PEEP – positive end-expiratory pressure, MAP – mean airway pressure, FiO_2 – fraction of inspired oxygen, CPAP – continuous positive airway pressure, NIPPV – nasal intermittent positive pressure ventilation.

Table A6.3 Characteristics of infants with successful and failed extubation within 72h and 7d post-extubation

	OBSERVATION WINDOW: 72 hours			OBSERVATION WINDOW: 7 days		
Variable	**Success (n=215)**	**Failure (n=51)**	**P value**	**Success (n=187)**	**Failure (n=79)**	**P value**
At birth						
GA, weeks	26.1 [25-27.8]	25.3 [24.3-26.4]	0.002	26.4 [25-27.9]	25.4 [24.4-26.4]	< 0.001
BW, grams	860 [710-1050]	730 [610-840]	< 0.001	880 [713-1074]	740 [623-872]	< 0.001
Male, %	116 (54)	25 (49)	0.5	98 (52)	43 (54)	0.8
ANS, %	196 (91)	44 (86)	0.3	169 (90)	71 (90)	0.9
Histological chorio, %	97/183 (53)	16/43 (37)	0.06	80/159 (50)	33/67 (49)	0.9
SGA, %	27 (13)	7 (14)	0.8	23 (12)	11 (14)	0.7
Apgar 5 min	7 [5-8]	7 [5-8]	0.8	7 [5-8]	7 [5-8]	1
Cord pH	7.3 [7.24-7.34]	7.28 [7.24-7.31]	0.07	7.31 [7.25-7.34]	7.29 [7.24-7.33]	0.1
Intubation in DR, %	98 (46)	32 (63)	0.03	79 (42)	51 (65)	< 0.001
Pre-extubation						
PDA, %	80 (37)	20 (39)	0.8	67 (36)	33 (42)	0.4
IVH, %	55 (26)	15 (29)	0.6	45 (24)	25 (32)	0.2
PNS, %	61 (28)	18 (35)	0.3	54 (29)	25 (32)	0.7
NEC, %	8 (4)	3 (6)	0.4	8 (4)	3 (4)	1
Infection, %	32 (15)	11 (22)	0.2	28 (15)	15 (19)	0.4
At extubation						
Day of life	7 [3-26]	13 [4-25]	0.6	6 [3-27]	9 [4-25]	0.6
PMA, weeks	28.4 [27.1-29.7]	27.3 [26.6-28.5]	< 0.001	28.6 [27.3-29.8]	27.3 [26.5-28.4]	< 0.001
Weight, grams	960 [820-1100]	810 [710-950]	< 0.001	985 [843-1118]	810 [710-950]	< 0.001
pH	7.34 [7.29-7.38]	7.32 [7.28-7.37]	0.1	7.34 [7.29-7.38]	7.32 [7.29-7.37]	0.2
pCO_2	44 [37-50]	46 [40-55]	0.08	44 [37-50]	45 [38-54]	0.2
AC/PSV, %	89 (41)	26 (51)	0.2	77 (41)	38 (48)	0.3
PEEP, cm H_2O	5 [5-6]	5 [5-6]	0.1	5 [5-6]	5 [5-6]	0.2
MAP, cm H_2O	7 [6.2-7.9]	7.9 [6.3-9]	0.02	6.9 [6.2-7.9]	7.5 [6.5-9]	0.003
FiO_2	0.21 [0.21-0.26]	0.26 [0.21-0.3]	< 0.001	0.21 [0.21-0.26]	0.25 [0.21-0.28]	< 0.001

Values are expressed as medians [IQR] or n (%).
Abbreviations: GA – gestational age, BW – birth weight, ANS – antenatal steroids, chorio – chorioamnionitis, SGA – small for gestational age, DR – delivery room, PDA – patent ductus arteriosus, IVH – intraventricular hemorrhage, PNS – postnatal steroids, NEC – necrotizing enterocolitis, PMA – postmenstrual age, AC – assist control ventilation, PSV – pressure support ventilation, PEEP – positive end-expiratory pressure, MAP – mean airway pressure, FiO_2 – fraction of inspired oxygen.

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