Peri-extubation practices in extremely preterm infants

Thesis by

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Preface and Contribution of Authors

This thesis consists of 5 chapters: introduction (chapter 1), three studies (chapters 2-4) and an overall discussion (chapter 5).

Data for chapters 2 and 3 was used from the APEX study. The following individuals are part of the team and have contributed to conception of the study, data acquisition and data collection: Wissam Shalish, MD, Lara Kanbar, Lajos Kovacs, MD, Sanjay Chawla, MD, Martin Keszler, MD, Smita Rao, Bogdan A Panaitescu, Alyse Laliberte, Doina Precup, Karen Brown, MD, Robert E Kearney, PhD and Guilherme M Sant'Anna, MD, PhD.

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Abstract

Background: Age of first extubation is an important step in respiratory care of extremely preterm infants since prolonged use of mechanical ventilation is associated with lung injury. However, extubation practices vary and early disconnection from the ventilator is not always achievable for all patients, especially for more immature and fragile preterm infants. Once extubated, these infants require respiratory support and the two main choices are nasal continuous positive airway pressure (nCPAP) or non-synchronized nasal intermittent positive pressure ventilation (ns-NIPPV). The benefits of both modes have already been well established but evidence on which one to use as the primary choice after extubation is conflicting. Non-invasive neurally adjusted ventilatory assist (NIV-NAVA) is a promising synchronized mode of NIPPV that requires investigation in extremely preterm infants, a population at high risk of respiratory failure.

Objectives: The objectives of this Thesis were three: 1. To determine the proportion and characteristics of infants extubated early in life and to ns-NIPPV or nCPAP; 2. To explore for any association between age at extubation and initial mode of post-extubation respiratory support and clinical outcomes; 3. To investigate cardiorespiratory variability and patient-ventilator interaction in infants receiving nCPAP, ns-NIPPV and NIV-NAVA immediately post-extubation.

Methods: Infants born with birth weight ≤1250 grams and mechanically ventilated were included in the studies. In the cohort studies, demographic and outcome data was collected from medical charts using standardized data collection forms. In the prospective observational study, following extubation infants were exposed to nCPAP, ns-NIPPV and NIV-NAVA for 30 minutes

each in a random order. Heart rate and respiratory signals were acquired using electrocardiography and respiratory inductance plethysmography.

Results: Only 1/3 of all extremely preterm infants included were extubated at < 7 days of age. These infants had higher gestational age and birth weight, and better respiratory status when compared to those extubated after the first week of life. Reintubation was associated with moderate/severe bronchopulmonary dysplasia. Infants initially extubated to ns-NIPPV share a similar demographic profile of infants extubated ≥ 7 days of age. After adjustments for multiple co-variates, there were no differences in clinical outcomes between to ns-NIPPV and nCPAP. However, the use of ns-NIPPV as first choice after extubation was associated with longer duration of non-invasive support and hospital stay. The observational study comparing those modes with NIV-NAVA is ongoing.

Conclusion: Among extremely preterm infants, age of extubation and choice of initial non-invasive respiratory mode used afterwards is determined by gestational age, birth weight and respiratory status prior to extubation. Elective extubation to ns-NIPPV did improve clinical outcomes and was associated with prolonged use of respiratory support and hospitalization. The effects of NIV-NAVA is under investigation.

Résumé

Contexte: L'âge de la première extubation est une étape importante dans les soins respiratoires des nourrissons extrêmement prématurés puisque l'utilisation prolongée de la ventilation mécanique provoque des blessures aux poumons, ce qui encourage les médecins de minimiser la durée. Cependant, les pratiques d'extubation varient et la déconnexion précoce du respirateur n'est pas toujours réalisable pour tous les patients, en particulier pour les prématurés plus immatures et fragiles. Une fois extubé, il existe deux choix principaux des modes de soutien respiratoire post-extubation, soit la pression positive continue de la voie respiratoire nasale (PPC) ou la ventilation nasale à pression positive intermittente non synchronisée (VPPI-ns). Les avantages des deux modes ont déjà été établis, mais les preuves sur lesquelles choisir comme choix principal après l'extubation sont contradictoires. L'assistance ventilatoire neuro-ajusté non invasive (AVNA) est un mode synchronisé prometteur de VPPI qui nécessite une investigation chez les nourrissons extrêmement prématurés, une population à haut risque d'insuffisance respiratoire.

Objectifs: Les objectifs de cette thèse étaient les suivants: 1. Déterminer la proportion et les caractéristiques des nourrissons extubés au cours de la première semaine de vie et extubés à la VPPI-ns ou PPC; 2. Explorer toute association entre l'âge à l'extubation et le mode initial de soutien respiratoire post-extubation et les résultats cliniques; 3. Étudier la variabilité cardiorespiratoire et l'interaction patient-ventilateur chez les nourrissons recevant le PPC, la VPPI-ns et l'AVNA immédiatement après l'extubation.

Méthodes: Les nourrissons nés avec un poids de naissance ≤1250 grammes et ventilés mécaniquement ont été inclus dans les études. Dans les études de cohorte, les données démographiques et les résultats ont été recueillis des dossiers médicaux en utilisant des

formulaires de données normalisés. Dans l'étude observationnelle prospective, les nourrissons recevaient la PPC, la VPPI-ns et l'AVNA pendant 30 minutes chacun dans un ordre aléatoire. La fréquence cardiaque et les signaux respiratoires ont été obtenus en utilisant une électrocardiographie et une pléthysmographie respiratoire par inductance.

Résultats: Seulement 1/3 des nourrissons inclus ont été extubés à l'âge de <7 jours. Ces nourrissons avaient un âge gestationnel et un poids de naissance plus élevés et un meilleur état respiratoire que ceux qui avaient été extubés après la première semaine de vie. La réintubation a été associée avec une dysplasie bronchopulmonaire modérée / grave. Les nourrissons extubés à la VPPI-ns partagent un profil démographique similaire à celui des nourrissons extubés ≥ 7 jours. Après des ajustements pour plusieurs covariables, il n'y avait pas de différences dans les résultats cliniques entre VPPI-na et PPC. Cependant, l'utilisation de VPPI-ns comme premier choix après l'extubation était associée à une durée plus longue de soutien non invasif et de séjour hospitalier. L'étude observationnelle comparant ces modes avec l'AVNA est en cours.

Conclusion: Chez les nourrissons extrêmement prématurés, l'âge d'extubation et le choix du mode respiratoire non invasif initial utilisé par la suite sont déterminés par l'âge gestationnel, le poids à la naissance et l'état respiratoire avant l'extubation. L'extubation élective au VPPI-ns a amélioré les résultats cliniques et a été associée à l'utilisation prolongée du soutien respiratoire et à l'hospitalisation. Les effets de l'AVNA sont en cours d'investigation.

LIST OF ABBREVIATIONS

GA – Gestational Age

BW – Birth Weight

RDS – Respiratory Distress Syndrome

MV – Mechanical Ventilation

ELBW – Extemely Low Birth Weight

BPD – Bronchopulmonary Dysplasia

NICU – Neonatal Intensive Care Unit

SIMV – Synchronized Intermitten Mandatory Ventilation

AC – Assist Control

nCPAP – nasal Continuous Positive Airway Pressure

FRC – Functional Residual Capacity

NIPPV – Nasal Intermittent Positive Pressure Ventilation

PIP – Peak Inflation Pressure

PEEP – Positive End Expiratory Pressure

BiPAP – Biphasic Positive Airway Pressure

MAP – Mean Airway Pressure

RCT – Randomized Controlled Trial

BP-NCPAP – Biphasic NCPAP

VLBW – Very Low Birth Weight

Vt – Tidal Volume

Ve – Minute Ventilation

RR – Respiratory Rate

WOB – Work of Breathing

Pe – Esophageal Pressure

TCD – Total Compartment Displacement

TAM – Thoraco-Abdimonal Movement

NIV-NAVA – Non-Invasive Neurally Adjusted Ventilatory Assist

Eadi – Electrical Activity of the Diaphragm

NIV – Non-Invasive Ventilation

ARDS – Acute Respiratory Distress Syndrome

CMV – Conventional Mechanical Ventilation

NIV-PS – Non-invasive Pressure Support

Td – Trigger Delay

$Ti_{ventilator}$ – Ventilator Inspiratory Time

Ti_{neural} – Neural Inspiratory Time

DOL – Day of Life

ROP – Retinopathy of Prematurity

IVH – Intraventricular Hemorrhage

PVL – Periventricular Leukomalacia

NEC – Necrotizing Enterocolitis

PDA – Patent Ductus Arteriosus

FiO_2 – Fraction of Inspired Oxygen

PMA – Postmenstrual Age

SBT – Spontaneous Breathing Trial

Chapter 1 – Introduction

1.1 Prematurity and lung development

Preterm birth is highly prevalent worldwide with approximately 15 million infants being delivered prematurely every year (1). In Canada, for every 12 babies one is born prematurely (2). Many factors contribute to preterm birth such as multiple gestations, intrauterine infection, and biological and genetic markers (3). Prematurity is defined as delivery at a gestational age (GA) of less than 37 weeks and can be further classified by ranges of GA: < 28 weeks = extremely preterm; 28-31^6 weeks = very preterm; 32-33^6 weeks = moderate preterm; 34 – 35^6 weeks = late preterm and 36 – 36^6 weeks = early preterm. This thesis will focus on infants born with birth weight (BW) < 1250g or extremely preterm. Although this population is relatively small, the costs incurred from resource utilization and long hospital stays is significant; roughly 5.5 billion dollars from birth to the age of 18 years of age in the USA (4). Thus, improving the current diagnostic tools and therapies in this population is critical.

Lung development can be divided into four stages during gestation: embryonic (0-6 weeks), pseudoglandular (6 to 16 weeks), canalicular (16 to 24 weeks) and saccular (24 weeks to 40 weeks) (5). In the canalicular period, the respiratory bronchioles, alveolar ducts and primitive alveoli are formed. Notably, this phase of lung development is characterized by the differentiation of pulmonary epithelium into alveolar type I and type II cells and the formation of the blood-air barrier (6). Alveolar type I cells line the majority of the alveolar surface to form the blood-air barrier (7). Meanwhile, type II alveolar cells accumulate lamellar bodies which contain the precursor components of surfactant (7). In fact, surfactant protein can be detected at 24 weeks of intrauterine life, corresponding to the saccular period (5, 6). Surfactant is a

phospholipid that lines the alveoli leading to decreased surface tension at the air-liquid interface (8). The saccular period is distinguished by significant vascular growth and new vascularization (5). Furthermore, these changes correspond to the formation for a double capillary layer, a prerequisite of alveolar formation (5). The development of the air-blood barrier continues in this period (5).

1.2 Respiratory distress after preterm birth and the need for mechanical ventilation

Preterm infants born at this developmental stage would have lungs with surfactant deficiency leading to a clinical condition called respiratory distress syndrome (RDS) (8). Furthermore, their respiratory control center is more easily influenced by changes in acid−base status, temperature, sleep state, hypoxia, medications, and other variables (9-12). Thus, all preterm infants with RDS require oxygen supplementation and some type of respiratory support to achieve adequate ventilation and oxygenation. With increased use of antenatal steroids and improved delivery room stabilization approaches, most moderately preterm and many very preterm infants can be supported noninvasively (13). In contrast, a substantial proportion of extremely low gestational-age neonates continue to require mechanical ventilation (MV). In the Neonatal Research Network centers, almost 90% of extremely low birth-weight infants (ELBW) were treated with MV during the first day of life, and 95% of survivors were invasively ventilated at some point during their hospital stay (14). Thus, invasive ventilation is largely reserved for the relatively small number of the most immature or very sick infants. Furthermore, the spectrum of lung disease that neonatologists treat has expanded into more chronic conditions since these infants are uniquely susceptible to lung injury (15).

1.3 Pre-extubation practices

Although MV is essential for managing RDS/lung immaturity, it is associated with short and long term complications such as an increased incidence of ventilator induced lung injury (pneumothorax, pulmonary interstitial emphysema), pneumonia, bronchopulmonary dysplasia (BPD) and neurocognitive impairment (16). Thus, clinicians advocate for early disconnection from the ventilator, but the optimal age for the first extubation attempt is unknown. Currently, the main variables used by clinicians to determine extubation readiness are ventilatory settings (including oxygen needs), blood gases and presence of clinical and haemodynamic stability (17). Therefore, due to the lack of evidence concerning the most appropriate ventilator settings, level of oxygen requirement, blood gases values, and use of adjunctive therapies, a large variability in pre-extubation practice is common. In a recent international survey on periextubation practices in extremely preterm infants, 31% of Neonatal Intensive Care Units (NICU) reported using a guideline and 5% having a written protocol for weaning of the ventilator (17). Indeed, implementation of a weaning protocol has led to earlier extubations, lower failure rates and shorter duration of MV by reducing unnecessary variability in practice (18). Moreover, given the multiple ventilator modes available, it becomes difficult to agree on the best one to use and on what are the minimal extubatable ventilatory settings. Many clinicians use Synchronized Intermittent Mandatory Ventilation (SIMV) over Assist Control (AC) to wean from MV even though studies have shown that AC results in less tidal volume variability, less tachypnea, smaller changes in blood pressure and most importantly, rapid weaning from MV (19). Furthermore, only half of the respondents in the international survey reported of the use of caffeine 24 hours prior to extubation despite this drug having demonstrated to improve success

(17). Differences in practices also extend to the post-extubation phase where again, multiple options for non-invasive respiratory support, interfaces, and settings are available.

1.4 Post-extubation respiratory support

The most common type of non-invasive respiratory support used for a long time in neonatology is nasal continuous positive airway pressure (nCPAP) (17) . In this mode, a continuous distending pressure is delivered at the level of the upper airway to maintain patency, and improve functional residual capacity (FRC) and oxygenation (20). Despite its positive effects, several extremely preterm infants fail nCPAP therapy, usually defined by worsening of the respiratory status over time (21). Thus, nasal intermittent positive pressure ventilation (NIPPV) was introduced as an alternative form of non-invasive support, and became widely used over the last 15 years (17). NIPPV uses the ventilator to deliver a peak inflation pressure (PIP) above a positive end expiratory pressure (PEEP), at a predefined inspiratory time and respiratory rate (22). NIPPV may be synchronized (s-NIPPV) or not synchronized (ns-NIPPV) with the infant's spontaneous breathing. Biphasic positive airway pressure (BiPAP) is a variant type of non-invasive respiratory support that cycles between higher and lower CPAP pressures, without syncronization with the infant's breathing, and commonly using "variable flow" devices (23).

Over the last 18 years, ten randomized controlled trials have explored the differences between nCPAP and NIPPV during the post-extubation phase. A meta-analysis of these studies was recently published and concluded that NIPPV reduces the incidence of extubation failure and need for re-intubation within 48 hours to one week when compared nCPAP (24). However, several problems related to the quality of the studies included in the meta-analysis should be noted. All except for one were single center studies that enrolled a small number of patients.

Inclusion criteria varied: 7 trials enrolled very low birth weight infants (i.e. infants at moderate/low risk of requiring endotracheal re-intubation) and 2 trials enrolled premature infants < 35 or 36 weeks' gestation (extremely low risk of re-intubation) (24). Only one trial exclusively enrolled ELBW infants, the population under high risk of extubation failure and the subject of this thesis. Furthermore, amongst the studies there were important differences on the use of methylxanthines, age at extubation, and definition of failure (from 48h after extubation up to 7 days or unclear) (24). Also, different prongs were used to deliver nCPAP and NIPPV: 3 studies used nasopharyngeal prongs (single or binasal; associated with higher failure rates when used with nCPAP) and the others used short nasal prongs (24). Ventilator settings applied after extubation also varied: rates between 10 to 40 per minute, and PIP from that used before extubation to 2 to 4 cmH_2O above pre-extubation levels. The nCPAP pressures varied between 3 to 8 cmH_2O and no attempt was made to match NIPPV and nCPAP groups with respect to the mean airway pressure (MAP) delivered (24). The meta-analysis has clear limitations and the grade of evidence was recently graded as ++ low due to severe risk of bias and imprecision (25).

Of the 10 RCTs, four used ns-NIPPV, five s-NIPPV and one was a mix of both. Details of the 5 RCTs that included ns-NIPPV will be discussed with the focus on clinical and physiological studies comparing this mode of non-invasive support with nCPAP or s-NIPPV.

Khorana et al. randomized 24 infants of GA <34 weeks and BW <1500 grams to nCPAP or ns-NIPPV (26). They found no difference between the modes in the primary outcome of reintubation within 7 days (26). A randomized controlled trial (RCT) in Turkey also compared nCPAP (n=28) to ns-NIPPV (n=39) after extubation. The study included infants with GA <35 weeks and/or BW <2000 grams and used a nasopharyngeal tube as the interface (27). Reintubation within 48 hours of extubation (primary outcome) was significantly lower in the ns-

NIPPV group, with no difference in rates of BPD and BDP/death (27). The third trial enrolled smaller infants (BW <1250 grams) but ns-NIPPV was delivered by using biphasic nCPAP (BP-NCPAP) (28), where two levels of PEEP are delivered (upper and lower) (29). Some clinicians equate BP-NCPAP with ns-NIPPV where the upper level would be the equivalent of the PIP. This trial stopped prematurely due to difficulty in enrollment and lack of differences in rates of reintubation within 7 days and BPD (28). In the fourth trial, Jasani et al. enrolled very low birth weight (VLBW) infants and noted that infants randomized to ns-NIPPV instead of nCPAP spent fewer days on non-invasive support and supplemental oxygen. In this RCT, infants were older and heavier and very few infants were included in the subgroup analysis of the smallest patients (30). The fifth trial used a mix of both ns-NIPPV and s-NIPPV vs. nCPAP and enrolled infants with BW <1000 grams and GA <30 weeks. Despite no sub analysis to compare ns-NIPPV alone to nCPAP, there were no differences between ns-NIPPV/s-NIPPV and nCPAP for the primary outcome of BPD/death. The only physiological study comparing ns-NIPPV to nCPAP was performed on stable preterm infants and demonstrated decreased inspiratory effort during s-NIPPV but an increased peak expiratory effort during ns-NIPPV compared to nCPAP (31). Inspiratory and expiratory effort was measured using esophageal pressures.

1.5 Methods of synchronization

A common drawback of NIPPV is the lack of synchronization. Different technologies have been developed to provide synchronization (s-NIPPV) with varying degrees of success and will be discussed.

1.5.1 Hot wire anemometer

A hot wire anemometer is commonly used as a device to measure gas flow on the principle that heat will be dissipated as it is exposed to the flow of gas (32). The velocity of the gas affects the rate at which heat is lost (32). As the velocity of the gas increases, the electrical current needed to maintain the temperature of the hot wire increases linearly (32). The velocity is integrated to provide volume (32). This device is incorporated into some ventilators; (33) is relatively easy to use, highly sensitive and has a fast response time, but may be affected by leaks and secretions (34).

1.5.2 Pneumotachograph

A pneumotachograph is an instrument attached to the nasal mask and used to measure respiratory gas flow and volume. There is a resistive element that is kept constant and measures the pressure gradient (35). By keeping the resistance constant, pressure change becomes proportional to flow (35). Steady and consistent flow, which is characteristic of leaks, is removed and fast variations in flow due to spontaneous breathing is used to trigger the ventilator (36). The use of pneumotachographs has been shown to increase tidal volume, possibly due to the added dead space or the facial stimulation of the instrument itself (37). Much like the hot wire anemometer, a pneumotachograph is susceptible to autotriggering due to secretions and large leaks (34). It is also seen as a heavy interface for the relatively small nares of these infants (38).

1.5.3 Abdominal capsule

The abdominal capsule detects minute changes in pressure on the surface of the capsule. These changes in pressure are a result of abdominal wall movements (34). The mechanical signal of the abdominal wall is converted to an electrical signal detected by the ventilator. The major advantage of this method of synchronization is that the signal is not influenced by leaks; however it is prone to incorrect placement and may be affected by abdominal distention. In infants with RDS, subcostal retractions lead to the expansion of the abdomen during expiration, thus incorrectly triggering the capsule (38).

1.6 nCPAP vs. s-NIPPV

Studies have compared differences between nCPAP and s-NIPPV using the above described methods of synchronization.

1.6.1 Physiological studies

Over the past two decades, the potential benefit of synchronization during NIPPV has been explored during the post-extubation phase, either immediately after or when infants were stable on nCPAP (Table 1). These small studies focused on parameters such as tidal volume (V_T), minute ventilation (V_E), respiratory rates (RR), work of breathing (WOB) by using esophageal pressure (Pe), phase angle and total compartment displacement (TCD) ratio as a surrogate for WOB. The phase angle between abdominal and thoracic expansion is expressed in degrees as a fraction of the full respiratory cycle of 360 degrees (31) and TCD ratio represents the ratio of the displacement of the ribcage and abdomen compartments to the net tidal volume (39). A significant decrease in WOB was observed during s-NIPPV and only one study (Moretti

et al.) demonstrated an increase in ventilation (V_T and V_E). However, most of the patients weighed >1000 grams, had a relatively stable respiratory status and received variable pressures on both modes (Table 1).

Table 1: Physiological effects of synchronized NIPPV in preterm infants

Authors	N	Study Population	Method of synchronization	Duration of recording	Comparison ventilator mode	Major Findings on SNIPPV
Kiciman, 1998	14	BW: 1413 (730-2825) g GA: 30 (26-36) wks	Abdominal capsule	2 minutes	nCPAP	↓ TAM asynchrony
Moretti, 1999	11	BW: 1141±53 g GA: 28.1±0.5 wks	Hot wire anemometer	45 minutes	nCPAP	↓ TcPCO2, mean RR & Pe ↑ V_T & V_E
Aghai, 2006	15	BW: 1367±325 g GA: 29.5±2.4 wks	Abdominal capsule	5 minutes	nCPAP	↓ WOB (more prominent as PIP increases)
Ali, 2007	15	BW: 808±201g GA: 25.9±1.8 wks	RIP abdominal wall movements	2 hours	nCPAP	↓ WOB, phase angle & TCD ratio
Chang, 2011	16	BW: 928 (812-1130) g GA: 27.5 (25.5-30.0) wks	Abdominal capsule	1 hour	nCPAP & NIMV	↓ spontaneous inspiratory effort

Legend: BW=birthweight, GA=gestational age, nCPAP=nasal continuous positive pressure ventilation, NIMV=nasal intermittent mandatory ventilation, TAM=thoracoabdominal movement, TcPCO2=transcutaneous partial pressure of carbon dioxide, RR=respiratory rate, Pe=esophageal pressure, V_T=tidal volume, V_E=minute ventilation, WOB=work of breathing, NI-PSV=non-invasive pressure support ventilation, TCD=total compartment displacement.

1.6.2 Clinical studies

Failing extubation is a major concern for the extremely preterm population. Several RCTs have been conducted to investigate the benefit of s-NIPPV over nCPAP in reducing rates of extubation failure (Table 2). The time separation of these trials may have led to differeing respiratory care practices, however the findings were similar. A significant decrease in rates of extubation failure, defined either by clinical criteria or need for reintubation, was observed with s-NIPPV. All trials were small, used different interfaces and pressures. Of note, 3 out the 5 studies used the Infant Star ventilator with the abdominal capsule for synchronization, a device no longer available commercially.

Table 2: Clinical studies assessing extubation failure in preterm infants

Authors	N	Study Population	Method of synchronization	Time frame of extubation failure	Rates of extubation failure
Friedlich, 1999	41	BW <1500 g	Abdominal capsule	48 hours	s-NIPPV 5% vs NCPAP 37%
Barrington, 2001	54	BW <1251 g	Abdominal capsule	72 hours	s-NIPPV 15% vs NCPAP 44%
Khalaf, 2001	64	GA ≤34 wks	Abdominal capsule	72 hours	s-NIPPV 6% vs NCPAP 40%
Moretti, 2008	63	BW <1251 g	Hot wire anenometer	72 hours	s-NIPPV 6% vs NCPAP 39%
Gao, 2010	50	GA <36 wks	N/A	N/A	s-NIPPV 24% vs NCPAP 60%

Legend: BW=birthweight, GA=gestational age, nSIMV=nasal synchronized intermittent mandatory pressure

1.7 Non-invasive neurally adjusted ventilatory assist

Non-invasive neurally adjusted ventilatory assist (NIV-NAVA) is a relatively novel mode of respiratory support utilizing the electrical activity of the diaphragm (Eadi) to synchronize ventilator inflations with the patient's own spontaneous breathing (40). To capture the Eadi, a specialized catheter with microelectrodes is inserted with the tip located at the lower third of the esophagus (40). A PIP, proportional to the Eadi signal through the following equation: PIP= Eadi x NAVA level, is delivered (40). The NAVA level is a constant set by the clinician. NIV-NAVA allows an infant to control their own inspiratory and expiratory time, PIP and ventilator rate on a breath-by-breath basis (40). In circumstances where there is a loss of the Eadi signal (apnea or misplacement of catheter), a backup mode of ventilation is activated (ns-NIPPV).

1.7.1 Rationale for using Eadi triggering

The Eadi measures an infants' inherent neural respiratory drive. The brainstem is composed of respiratory centers that receive afferent inputs from the lung. These inputs relay information on lung stretch, lung de-recruitment, arterial blood gas changes, respiratory muscle loading etc. (40) Once this information is processed, an output signal is transmitted through the phrenic nerve to activate the diaphragm (40). The Eadi represents neural activation at the level of the motor units of the diaphragm (40). Based on this strategy, there is no dependence on flow for triggering and leaks do not affect triggering.

Given the reliance of NIV-NAVA on the diaphragm, this mode is intended for infants capable of breathing spontaneously. Infants with neuromuscular disorders, diaphragmatic paralysis or palsy, diagnosed phrenic nerve injury and receiving narcotics would not be able to benefit from this mode (40). Narcotics results in a decrease in diaphgram contraction leading to

reduced tidal volume (41). The Eadi of neonates is highly variable on a breath-by-breath basis compared to adults (40). The Eadi can be evaluated by observing the peak and/or the minimum (min) and is used as a surrogate for WOB where the Eadi peak and min represent the inspiratory effort and effort to prevent de-recruitment, respectively (40). Increasing the NAVA level is a method of unloading respiratory muscles and generating higher pressures. In other words, the NAVA level can be used to redirect the WOB from the infant to the ventilator (42). Once the respiratory muscles are sufficiently unloaded, a breakpoint is reached whereby further increases in the NAVA level will not yield higher PIPs (42). In fact, using too high of a NAVA level may lead to suppression of inspiratory drive as high pressure will be generated by decreased Eadi values (42). In this situation, infants will not need to increase their inspiratory drive to receive desired pressures.

1.7.2 Animal Studies

A few studies have explored the physiological effects of NIV-NAVA in two different animal models (Table 3). Beck et al. were able to maintain synchrony on NIV-NAVA despite large leaks, but only 30% of the pressure reached the trachea (43). At the presence of high leaks, the NAVA level had to be increased fourfold to unload the respiratory muscles and to generate higher pressures (43). Regardless of the high pressures, there was an absence of abdominal distension, a common concern of non-invasive ventilation (NIV) (43). The efficacy of NIV is hindered in the presence of upper airway obstruction, unlike in intubation whereby the endotracheal tube bypasses the upper airway. Praud et al. examined the electrical activity of the thyroarytenoid muscle, a known glottal constrictor muscle, and observed lack of constriction during NIV-NAVA when compared to NIPPV. (44) Similar results were noted in a previous

study using ns-NIPPV (45). The increase in laryngeal resistance can divert the direction of the inflation pressure towards the abdomen, leading to abdominal distension, or can be reflected in the large leaks seen during non-invasive respiratory support (44). These results support the effectiveness of NIV-NAVA compared to other non-invasive modes. More recently, Mirabella et al. concluded that NIV-NAVA is lung protective, by preventing volutrauma and barotrauma due to its ability to allow patient control of breathing pattern, with open upper airways and integration of vagally mediated lung-protective reflexes (46). Interlukin-8, an important factor in the pathway of acute respiratory distress syndrome (ARDS), was used as a biomarker of inflammation (46).

Table 3: Physiological effects of NIV-NAVA in animal models

Authors	N	Study Population	Comparison	Duration of recording	Major Findings on NIV-NAVA
Beck, 2007	10	Adult rabbits	ETT-NAVA vs. NIV-NAVA (varying NAVA levels and PEEP)	5 minutes	↑ phasic activity & respiratory muscle unloading ↓ RR
Praud, 2012	8	Term lambs	CPAP vs. PSV vs. NIV-NAVA	5 minutes	↓ glottal constrictor activity
Mirabella, 2014	20	Adult rabbits	CMV-VC vs. NIV-NAVA	6 hours	↓ lung injury score & IL-8 Recovered dynamic C_L post-ALI

Legend: CMV-VC: conventional mechanical ventilation-volume control, IL-8: interlukin-8, C_L: lung compliance, ALI: acute lung injury, ETT-NAVA: endotracheal tube-neurally adjusted ventilatory assist, NIV-NAVA: non-invasive neurally adjusted ventilatory assist, RR: respiratory rate, CPAP: continuous positive airway pressure, PSV: pressure support ventilation.

1.7.3 Clinical studies

The clinical application of NIV-NAVA in preterm infants has not been thoroughly investigated. To date, only two small studies have been conducted. Beck et al. investigated the use of NIV-NAVA in preterm infants in comparison with 2 modes of MV, conventional mechanical ventilation (CMV) and intubated-NAVA. The RR was lower on both NAVA modes (47). The criteria for breath termination (cycling off) in CMV was set to 15% of the peak flow, which was consistently earlier than the neural cycling off for the NAVA modes (47). As a result of this premature cycling off, neural expiratory time is reduced, thus increasing the RR (47). Recently, a RCT was performed in Korea comparing patient-ventilator synchrony in very preterm infants on NIV-NAVA and NIV Pressure Support (NIV-PS) (48). The following parameters were decreased on NIV-NAVA: trigger delay, ventilator inspiratory time, excessive inspiratory time and asynchrony events (48). These results are indicative of synchronization. Trigger delay (Td) was defined as the difference in time between the initial increase in Edi signal and the beginning of inspiratory flow delivered by the ventilator (48). Ventilator inspiratory time ($Ti_{ventilator}$) was defined as the time interval between the start and the end of inspiratory flow (48). Inspiratory time in excess was defined as $((Ti_{ventilator}-Ti_{neural})/(Ti_{neural})x100)$ where Ti_{neural} is the time interval between the initial increase and the maximum value of the Eadi (48). The total number of asynchrony events was reduced on NIV-NAVA, in particular, autotriggering and ineffective efforts had the greatest reductions (48). Autotriggering is the case of a pressure cycle being delivered by the ventilator in the absence of an Eadi signal whereas an ineffective effort is the opposite situation (48). Infants on NIV-NAVA demonstrated greater diaphragm unloading due to better synchronization, as reflected in the lower maximum Eadi and Eadi swing values (difference between the maximum and baseline Eadi) (48).

Table 4: Clinical NIV-NAVA studies in preterm infants

Authors	N	Study Population	Comparison	Duration of recording	Major Findings on NIV-NAVA
Beck, 2009	7	BW: 936 ± 239 g GA: 26 ± 2 wks	CMV vs. NAVA (ETT & NIV)	20 minutes	↓ neural RR & cycling off delay
Lee, 2015	15	BW: 790 (675-1215) g GA: 27 (26-28) wks	NIV-PS vs. NIV-NAVA	5 minutes	↓ Td, $Ti_{ventilator}$, Ti_{excess}, max Edi, Edi swing, PIP & asynchrony events

Legend: CMV: conventional mechanical ventilation-volume control, ETT: endotracheal tube, NIV: non-invasive ventilation, RR: respiratory rate, NIV-PS: non-invasive ventilation pressure support, Td: trigger delay, $Ti_{ventilator}$: ventilator inspiratory time, Ti_{excess}: inspiratory time in excess.

Chapter 2: Age of first extubation in extremely preterm infants: one rule does not fit all

This study was accepted and presented as a poster at the Pediatric Academic Societies Meeting (Baltimore, 2016).

2.1 Introduction

In the modern era of neonatal intensive care, MV is an intervention reserved for the sickest extremely preterm infants that failed an initial non-invasive respiratory support trial (14). In these infants, weaning and disconnection from the ventilator is a major challenge making timing of the first extubation attempt highly variable and inconsistent (49-52). This may be related to clinical instability or an inability from clinicians to recognize extubation readiness. Indeed, in the absence of accurate predictors, a trial of early extubation is commonly advocated, even if reintubation is necessary (49, 53). Although prolonged MV (> 7 days) is associated with increased risks of BPD or death, extubation failure is also postulated as an independent risk factor for those outcomes (16, 49, 50).

In a recent international survey on periextubation practices in extremely preterm infants, the majority of responders (76%) stated that extubation was attempted within the first 3 days and almost half of the responses considered failure to be an independent risk factor for morbidities and/or death (17). The decision to extubate was highly variable and based on ventilator settings, blood gases and cardiovascular stability (17) despite a precise definition, on what are the ventilator settings and blood gases at which a preterm infant can be considered for extubation with the highest chances of success, is not well established. Since there are differences between daily practice and survey answers or results obtained during RCTs, we aimed to identify the age of first extubation attempt and the factors associated with that in the population of extremely

preterm infants admitted to our institutions. A secondary exploratory analysis was performed to assess if whether or not age at extubation was associated with the combined outcome of BPD or death.

2.2 Methods

Population

All infants admitted at three Level III NICUs between September 2013 and May 2015 with BW ≤1250 grams were screened for eligibility. Only infants with GA < 28 weeks and receiving MV within the first 72 hours of life were included. Infants who died prior to extubation, self-extubated within the first week of life, had major congenital anomalies or were receiving vasopressors or narcotics at the time of extubation were excluded. The study was approved by the Research Ethics Board of the institutions.

Data Collection

Data was retrospectively retrieved from medical records of all patients except for information related to respiratory care practices of the infants enrolled in an ongoing multicenter study (Automated Prediction of Extubation Readiness – APEX study; NCT01909947) where the prospectively collected data was extracted from the research database. All information was recorded by using a standardized data collection form and included:

Patient demographics: maternal habits (smoking, drugs, alcohol), multiple pregnancies, use of antenatal steroids, premature rupture of membranes, gestational diabetes, pre-eclampsia, Group B streptococcus status, evidence of histological chorioamnionitis, mode of delivery, Apgar scores (1, 5 and 10 min), cord gas (pH, pCO_2, base excess (BE) and bicarbonate), delivery

room use of supplemental oxygen, respiratory support (CPAP, positive pressure ventilation or intubation), epinephrine and chest compressions, inborn/outborn, sex, GA, BW, weight according to gestational age (SGA, AGA or LGA), surfactant treatment (at birth or any point during hospitalization), day of life (DOL) to regain BW, administration of caffeine (and age) and use of postnatal steroids (age and duration).

Data on common comorbidities and related treatments including retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) confirmed by cerebral ultrasound, necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA) confirmed by echocardiography, pneumothorax, BPD and BPD severity (mild, moderate & severe) were also collected for the pre- and post-extubation periods, if applicable. IVH was defined as Grade I or higher (according to Papile criteria), NEC stage II or higher based on Bell's criteria, and BPD as supplemental oxygen and/or respiratory support at 36 weeks corrected GA. BPD severity was categorized as mild, moderate or severe (54). In addition, sepsis (positive blood culture), meningitis (positive cerebral spinal fluid culture) and length of NICU stay were also recorded. Phototherapy prior to extubation was also collected.

Postnatal respiratory care: detailed information regarding the postnatal respiratory course included: a) at <u>first extubation</u>: weight, corresponding pre- and post-extubation ventilator settings (including ventilator mode, PIP, PEEP, MAP, fraction of inspired oxygen (FiO_2), inspiratory time, inflation rate), the closest blood gases (pH, pO_2, pCO_2, BE, bicarbonate) and electrolytes (sodium, potassium, chloride, lactate, ionized calcium, glucose) prior to extubation (blood gases used were aterial, capillary and venous) ; b) at first <u>reintubation</u>: timing (number of hours following extubation), reason for reintubation and type of NIV respiratory support (nCPAP or ns-NIPPV) and corresponding settings prior to reintubation; c) during <u>first week of life</u>: all

collected blood gases (arterial, venous or capillary) with the corresponding ventilator settings (including patient spontaneous respiratory rate) and electrolytes at the time of blood sampling; daily nutritional data including intravenous (IV) and oral (PO) total intakes of: fluids, calories, dextrose, lipids, protein, sodium, potassium, and acetate, daily weight; d) day of life at all subsequent extubations and reintubations and e) Total number of days on each respiratory support mode.

Respiratory management during the study period. During the study period, decisions concerning ventilator weaning, extubation readiness and postextubation management were made by the responsible physician. As a general rule, a loading dose of caffeine (20 mg/kg/dose) is given ≥ 24 h prior to extubation and some type of non-invasive respiratory support is provided after extubation (nasal continuous positive airway pressure [nCPAP] or nasal intermittent positive pressure ventilation [NIPPV]). Reintubation is usually performed when: a) FiO_2 > 0.4-0.5 to maintain oxygen saturation (SpO_2) > 88% or partial pressure of oxygen > 45 mm Hg; b) partial pressure of carbon dioxide (PCO_2) >55–60 mm Hg with a pH <7.25; c) apnea requiring positive pressure ventilation with bag and mask; d) increased number of apneas (>6/6 h), or (5) significant increased WOB according to physician judgment. During the study period SpO_2 target ranges were between 88 and 92% in two Institutions and 80% to 90% in another. Extubation failure was defined as the need for reintubation within 7 days after extubation.

Data analysis

Patients were divided into two groups: extubated ≤ 7 DOL vs > 7days DOL. For both groups, blood gas values and corresponding ventilator settings during the first week of life were averaged every 24h from birth to 168h of life. Fluids and nutritional data corresponded to the daily values.

Statistical Analysis

Statistical analysis was performed with SPSS (Version 21, IBM SPSS Statistics) to determine the proportion of infants extubated within the first week of life and compare factors associated with age of extubation in infants extubated at ≤ 7 days DOL vs > 7days DOL. Normality was confirmed using the Shapiro-Wilk test. For categorical variables, the Chi-Squared or Fisher's exact test was used. The student t-test and Wilcoxon Rank Sum test were used to compare parametric and non-parametric continuous variables, respectively. A multivariate logistic regression was used to model the likelihood of developing moderate/severe BPD or death. For this analysis, potential covariates were identified using a combination of clinical judgment and statistical testing. A p-value <0.05 was considered significant.

2.3 Results

Population

During the study period a total of 237 infants were admitted in the NICUs. Of these, 100 were eligible and included in the study. The population characteristics are presented on Table 5.

Table 5: Population characteristics

	All patients (n=100)	**Extubated at ≤ 7 days DOL (n=32)**	**Extubated at >7 days DOL (n=68)**	**OR (95% CI) or CI**	**P value**
Maternal and antenatal variables					
Gestational diabetes	7 (7)	5 (16)	2 (3)	0.16 (0.03-0.896)	0.033
Preeclampsia	12 (12)	4 (13)	8 (12)	0.93 (0.26-3.36)	1
Group B Streptococcus	11 (11)	2 (6)	9 (13)		0.504
Preterm labor	78 (78)	26 (81)	52 (76)		0.723
Rupture of membranes	31 (31)	12 (38)	19 (28)	0.65 (0.27-1.57)	0.335
Chorioamnionitis	46 (46)	14 (44)	32 (47)		0.821
Antenatal steroids	93 (93)	30 (94)	63 (93)	0.84 (0.15-4.58)	0.84
Caesarian	60 (60)	20 (63)	40 (59)	0.86 (0.36-2.03)	0.726
Singleton	80 (80)	23 (72)	57 (64)	0.5 (0.18-1.35)	0.186
Neonatal variables					
Inborn	90 (90)	28 (88)	62 (91)	1.48 (0.39-5.65)	0.568
Birth Weight, g	819.7±159.9	935±122	766±147	110-228.78	<0.001
Gestational age, weeks	26.1 [24.9-26.9]	26.8 [26.1-27.4]	25.4 [24.6-26.7]		<0.001
Apgar 5 min	7 [5 -8]	7 [6-8]	6 [5-8]		0.189
Intubation in delivery room, %	46 (46)	17 (53)	29 (43)	0.66 (0.28-1.53)	0.327
Cord pH	7.31 [7.27-7.36]	7.31 [7.29-7.36]	7.31[7.27-7.36]		0.751
Cord pCO_2	43.9 [39-48.9]	44.6 [40.2-49.8]	43.4 [37-48]		0.105
Cord Bicarbonate	20.4 [19-23]	22.5±3	20.2±3	0.85-3.59	0.002**
Cord Base Excess	-3.8 [-5.8- -1.8]	-2.51±2.79	-4.95±3.3		0.001**
Surfactant, %	97 (97)	30 (94)	67 (99)	0.447 (0.39-51.2)	0.239
Age at extubation, days	15.5 [4-27] (32)	2 [2-5] (60)	25 [15-32]		<0.001
Weight at extubation, g	940 [830-1070]	920 [820-1020]	955 [833-1098]		0.134

Caffeine pre-extubation (32 vs. 60)	89 (97)	30 (94)	59 (98)	3.93 (0.34-45.14)	0.276

Values are expressed as mean ± SD, medians [IQR] (N) or n (%). A p-value of <0.05 was considered statistically significant. Statistical results expressed as P (confidence interval) or P (odds ratio, confidence interval of odds ratio) for continuous and categorical variables, respectively.

** Variables remained significantly higher in the early extubation group after adjusting for GA and BW (cord HCO3: adjusted OR 1.29 (1.05-1.59), cord BE: adjusted OR 0.74 (0.23-2.33).

For an n<32 & n<68: data was not available; 8 patients in the late group did not have a planned extubation (died or self-extubated)

Primary outcome

Only thirty-two percent of the infants were extubated at ≤ 7 days of life (median = 2, IQR 2-5) and 68% at >7 days of life (median = 25, IQR 15-32). Demographics associated with age of extubation were GA, BW, bicarbonate and BE in the cord blood gas (Table 5). Daily blood gases, ventilator settings and caloric intake varied between the two groups. Infants extubated at ≤ 7 DOL had different blood gases and ventilator settings trajectory during the first week of life when compared to those extubated at >7 DOL (Figure 1). For most days, the pH and BE were higher, and pCO_2 and spontaneous respiratory rate were lower in infants extubated at ≤ 7 days. In addition, these infants were ventilated at significantly lower rates and mean airway pressures when compared to infants extubated at > 7 days. There were no statistically significant differences in the total fluid intake between both groups. Interestingly, infants extubated at ≤ 7 days received a higher caloric intake during the first week of life, mostly due to a greater amount of dextrose and lipid (Figure 2).

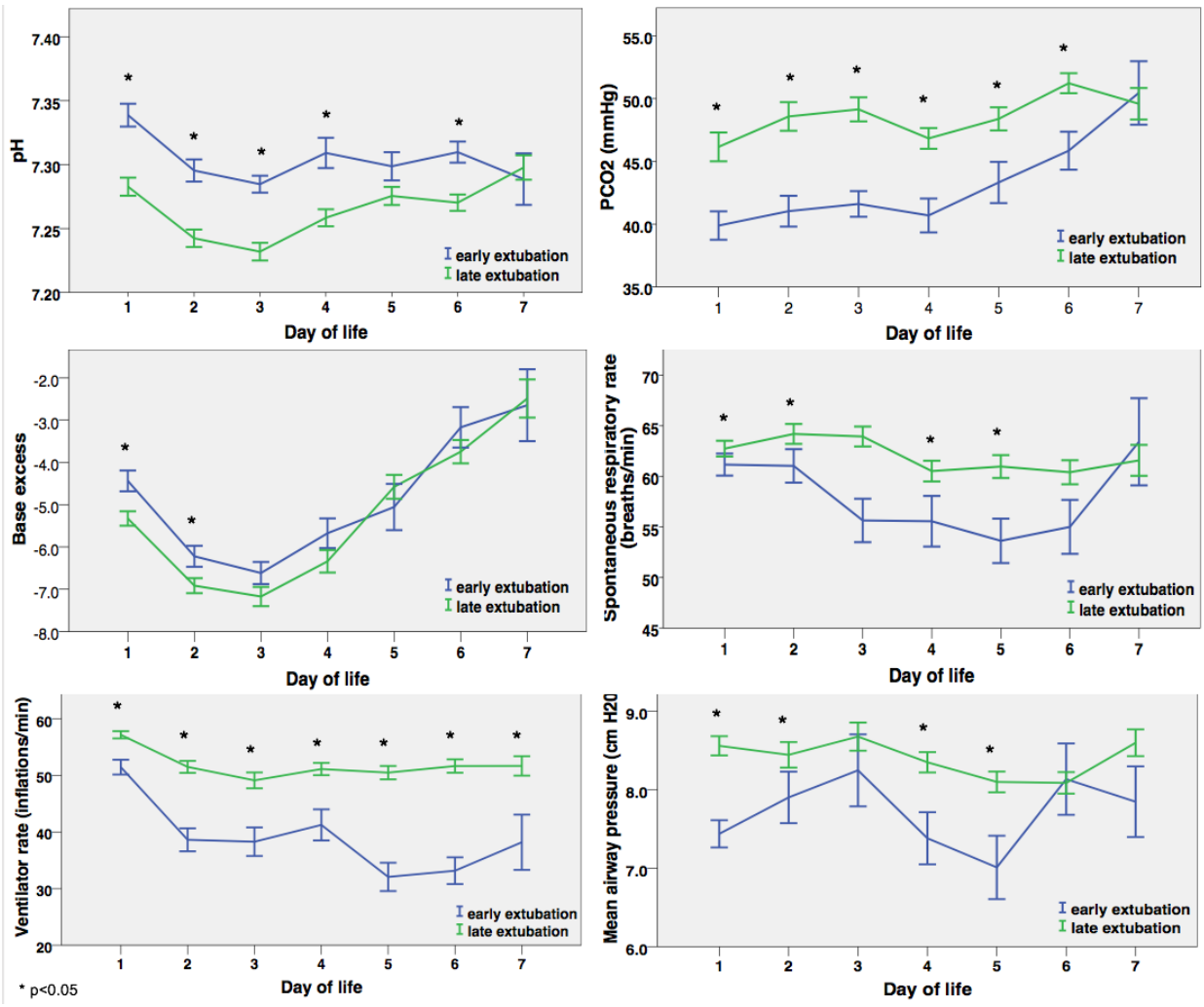


Figure 1. Blood gases and ventilator settings during the first week of life

*P value<0.05

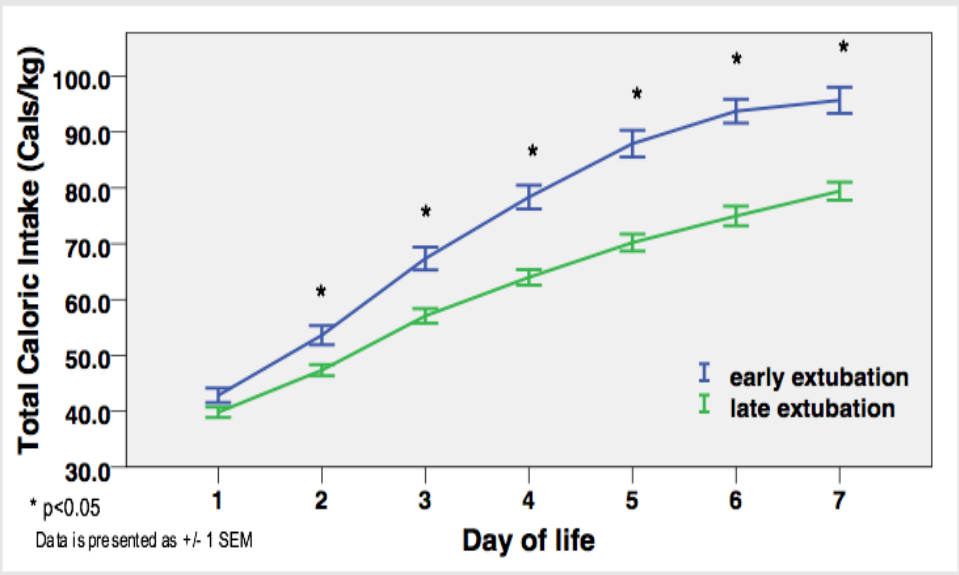


Figure 2. Total caloric intake during the first week of life

*P value<0.05

Timing of extubation and clinical outcomes

Infants extubated at ≤ 7 days spent significantly fewer days on MV with no differences on the rate of reintubation when compared to infants extubated > 7 days (Table 6). Those extubated at ≤ 7 days had lower rates of moderate/severe BPD. However, extubation at ≤ 7 days had a low accuracy (66%) for the outcome of survival without moderate/severe BPD: 47% sensitivity, 77% specificity and 53% positive predictive value. In the multivariate regression model, BPD severity was predicted using the following covariates: GA, BW, extubation at ≤ 7 days, reintubation and days spent on MV. The model highlighted the only variables associated with the outcome of moderate/severe BPD or death: reintubation and days on MV, which were significantly higher in these infants compared to those with mild BPD (Table 7). Comorbidities including ROP, IVH and PDA were more prevalent in infant's extubated at > 7 days of life. After adjusting for GA and BW, these differences were no longer significant.

Table 6: Clinical outcomes

	Extubated at ≤7 DOL (n=32)	Extubated at >7 DOL (n=68)	Unadjusted Odds Ratio (95% CI)	P value
Days to regain birth weight	9.5 [8-12] (28)	9 [7-11] (62)		0.321
Days on mechanical ventilation	5 [1-12] (31)	31 [25-39] (61)		<0.001**
Days on non-invasive respiratory support	50 [29-62] (31)	41 [30-56] (61)		0.286
Length of hospitalization	92 [73-105] (32)	108 [92-128] (67)		0.003
Reintubation	9/32 (28)	26/60 (43)	0.51 (0.2-1.29)	0.152
BPD	N=30	N=65		0.031
Mild	17 (57)	19 (29)		
Moderate	3 (10)	7 (11)		
Severe	10 (33)	39 (60)		
Necrotizing enterocolitis	4 (13)	14 (21)	1.82 (0.55-6.03)	0.411
Retinopathy of prematurity	7 (23)	30 (44)	2.82 (1.07-7.4)	0.032
Intraventricular hemorrhage	7/31 (22)	32/68 (47)	3.05 (1.16-8.02)	0.021
Patent ductus arteriosus	18/24 (75)	57/66 (86)	2.11 (0.66-6.74)	0.201
Infection	13 (41)	37 (54)	1.74 (0.74-4.09)	0.198
Death	3 (9)	3 (4)	0.45 (0.09-2.34)	0.381

Values are expressed as mean ± SD, medians [IQR] or n (%). A p-value of <0.05 was considered statistically significant. Statistical results expressed as P (confidence interval) or P (odds ratio, confidence interval of odds ratio) for continuous and categorical variables, respectively.
** Variables remained significantly higher in the late extubation group after adjusting for gestational age and birth weight
For an n<32 & n<68: data was not available; 8 patients in the late group did not have a planned extubation (died or self-extubated)

Table 7: Risk factors associated with BPD

	Mild BPD (n=36)	Moderate/Severe BPD or Death (n=64)	Univariate	Multivariate
Gestational Age	26.1 [25.3-27.2]	26.1 [24.7-26.8]	0.153 (-0.14-0.86)	0.365
Birth weight	872 (167)	791 (150)	0.014 (16.61-145.55)	0.675
Reintubation	5/35 (14)	30/57 (53)	<0.001 (OR 0.15, 0.05-0.44)	0.038
	≤7 DOL - 2/17 (12)	≤7 DOL 7/15 (47)		
	>7 DOL – 3/18 (17)	>7 DOL 23/42 (55)		
Early extubation	17 (47)	15 (23)	0.025 (OR 2.92, 1.22-7)	0.624
Length of mechanical ventilation	9.5 [2-29] (34)	28.5 [17-39] (58)	<0.001 (-19.45 - -6.913)	0.022

Values are expressed as mean ± SD, medians [IQR] (N) or n/N (%). A p-value of <0.05 was considered statistically significant. Statistical results expressed as p (confidence interval) or p (odds ratio, confidence interval of the odds ratio) for continuous and categorical variables, respectively.
In the multivariate analysis adjustments were made for gestational age, birth weight, reintubation, early extubation and length of mechanical ventilation and results expressed as p value (odds ratio and coefficient intervals) for developing moderate-severe BPD or death.

2.4 Discussion

In our cohort of extremely preterm infants, only 32% were extubated at ≤ 7 days of life. These infants were more mature and with greater BW than the infants extubated later. Also, during the first week of life they had better blood gas values, lower ventilator parameters and increased caloric intake. In the exploratory analysis, age of extubation was not associated with the outcome of moderate/severe BPD and death and had a low accuracy in predicting survival without moderate/severe BPD.

Age at extubation

In a large survey with neonatologists from 5 different countries located in three continents, only 8% of the responders reported the age of first extubation attempt occurring at > 7 days of life. This is in contrast with the present study where 68% of the infants were extubated at > 7 days. Such discrepancy may reflect differences between what is known or desired when replying to a survey and the reality of daily practice, or other factors. Despite early extubation from MV being a generally recommended practice, only a few studies reported on the age at which it occurred. In the Nasal CPAP or Intubation at Birth for Very Preterm Infants (COIN) trial, more than half of the infants of the intubation group were extubated by the third day of life (55). Similar results were obtained in a trial comparing non-invasive strategies in extremely preterm infants, where the median age (IQR) of the first extubation attempt was between 3.4 (1.7-6.8) and 3.7 (1.7-7.1) days. Chawla et al. performed a sub-analysis of the SUPPORT trial and reported a median age (IQR) of first extubation between 2 (2-6) and 3 (2-9) days of life for infants that were extubated successfully or failed, respectively (56). Indeed, in the group of infants extubated at < 7 days in our study the median age (IQR) of extubation was 2 (2-5) days.

Traditionally, RCTs are only able to enroll 30 to 40% of the eligible population, and management follows research protocols. Similar results were reported by a single center retrospective analysis where respiratory practice is likely more uniform (51). This may in part explain the differences between those results and our data where respiratory practice is highly variable and staff dependent. In a single center study, the use of respiratory protocols significantly decreased the median age (IQR) at first extubation attempt from 5.0 (2-23 days) to 1.2 days (0.7-5 days) (18). Thus, in daily practice, the development and implementation of respiratory management guidelines or protocols may improve weaning and age at first extubation attempt (19).

Factors associated with age at extubation

In our cohort, infants extubated at ≤ 7 days were more mature at birth and had higher BW when compared to infants' extubated at > 7 days. This was expected since such association between age of first extubation attempt and GA and BW has been previously reported (52, 53).

The trajectory of blood gases and ventilator parameters were significantly different between the two groups. Infants extubated at ≤ 7 days of life had blood gases showing less metabolic and respiratory acidosis and required lower levels of ventilatory support. Interestingly, worse values of BE, a reliable indicator of metabolic acidosis, during the first two days of life were observed in infant's extubated at > 7 days of life resulting in these infants being intubated longer. No differences were noted in fluid intake between groups. This is important since excessive fluid intake in the first 10 days of life has been associated with the development of BPD (57). Infants extubated at ≤ 7 days of life received greater amount of dextrose and lipids when compared to those extubated at > 7 days of life.

Age at extubation and outcomes

Previous literature reported higher rates of comorbidities among infants extubated beyond the first week of life (51, 52) and those rates were lower in infants extubated ≤ 7 days in our study, yet these differences did not reach statistical significance. There is no consensus between age of extubation and extubation failure. In the only single center trial that compared the effects of different ages at extubation upon rates of extubation failure, infants achieved extubation criteria around 12h of life and a delay of 36 h to perfome extubation did not decrease rates of reintubation (58). In our study, infants extubated at ≤ 7 days did not have higher reintubation rates than those extubated at >7 days.

This is the first study to report the trajectory of blood gases, ventilator settings and fluid/nutritional intakes in the first week of life in a large number extremely preterm infants submitted to MV and undergoing their first extubation attempt. The study has some limitations such as the retrospective data collection of infants not enrolled in the APEX study and the limited power for some of the outcomes reported. It represents the respiratory management at our local institutions.

2.5 Conclusion

In our institutions, only 32% of all extremely preterm infants submitted to MV were extubated within the first week of life. Gestational age, birth weight, the trajectory of blood gases, respiratory support parameters and nutritional intake during the first week of age were associated with age at first extubation attempt. In the new era of precision medicine, more

individualized assessments using biomarkers of extubation readiness are necessary to determine the optimal age of extubation at the individual level.

Chapter 3: The use of non-synchronized nasal intermittent positive pressure in extremely preterm infants: who gets it & does it matter?

This study was accepted and presented as a poster presentation at the Pediatric Academic Societies Meeting (San Francisco, 2017).

3.1 Introduction

Non-synchronized NIPPV (ns-NIPV) and nCPAP are the most commonly used modes of non-invasive respiratory support following extubation of extremely preterm infants. nCPAP helps maintain upper airway patency, prevents atelectasis and improves oxygenation (59). However, nearly a third of infants extubated to nCPAP "fail" and require reintubation (60). As a result, the use of ns-NIPPV is becoming increasingly popular as the additional support provided by the use of positive inflations at a set ventilator rate may prevent extubation failure. However, the evidence to support the routine use of ns-NIPPV as the optimal mode of non-invasive support in the immediate post-extubation period is low (25).

Physiological studies have demonstrated no differences in tidal volume, minute ventilation, respiratory rates or inspiratory WOB between ns-NIPPV and nCPAP in stable preterm infants; yet an increase in expiratory WOB was observed with ns-NIPPV (31). A recent systematic review identified three small, single centre trials that compared ns-NIPPV with nCPAP and demonstrated a decrease in treatment failure rates (24). However, these studies enrolled larger and more mature infants, applied different ns-NIPPV devices, and used different time frames (48 hours to 7 days) to define failure (24). Given this conflicting evidence, there is remarkable practice variability amongst physicians and centers on the indications for the use of ns-NIPPV. In this study, we aimed to determine the variables used by physicians to decide on the

use ns-NIPPV or nCPAP following extubation and compare short-term outcomes between those two modes.

3.2 Methods

Population

Infants with BW ≤1250 grams and mechanically ventilated enrolled in the ongoing multicenter study called "Automated Prediction of Extubation Readiness" (APEX - NCT01909947) beginning in September 2013 . Infant's extubated to high flow nasal cannula were excluded.

Data Collection

Data was collected prospectively using a standardized data collection form and included: a) maternal & antenatal: maternal habits (smoking, drugs, alcohol), multiple pregnancies, use of antenatal steroids, premature rupture of membranes, gestational diabetes, pre-eclampsia, Group B streptococcus status, evidence of histological chorioamnionitis, mode of delivery and inborn/outborn; b) perinatal variables: Apgar scores (1, 5 and 10 min), cord gas (pH, pCO_2, base excess (BE) and bicarbonate), delivery room use of supplemental oxygen, respiratory support (CPAP, positive pressure ventilation or intubation), epinephrine and chest compressions; c) neonatal variables: BW, GA, gender, weight according to gestational age (SGA, AGA or LGA), surfactant treatment, administration of caffeine (and age) and use of postnatal steroids (age and duration). Data on common comorbidities and related treatments was collected where applicable and included ROP, IVH, PVL (cerebral ultrasound), NEC, PDA (echocardiography),

pneumothorax and BDP. IVH was defined as Grade 1 or higher according to the criteria by Papile et al. NEC stage II or higher based on Bell's criteria, and BPD as supplemental oxygen requirement >30% and/or respiratory support at 36 weeks corrected GA.

The decision to extubate and the type of post-extubation respiratory support used was made by the responsible physician. Detailed information regarding the respiratory management was collected prospectively: a) prior to the first planned extubation: blood gas values (pH, pCO_2, pO_2, BE and bicarbonate) and ventilator settings (including ventilator mode, PIP, PEEP, MAP, FiO_2, inspiratory time, inflation rate); b) after extubation: type of post-extubation support and the corresponding settings, DOL and weight of first planned extubation, age at reintubation, number of days on each type of support, number of days on supplemental oxygen, and length of stay in the NICU.

Statistical analysis

Statistical analysis was performed to compare variables associated with extubation to ns-NIPPV. Normality was confirmed using the Shapiro-Wilk test. For categorical variables, the Chi-Squared or Fisher's exact test was used and the student t-test and Wilcoxon Rank Sum were used to compare parametric and non-parametric continuous variables, respectively. A multivariate logistic and linear regression analyzes were used to determine the effect of the use ns-NIPPV on outcomes. For this analysis, potential covariates were identified by statistical testing. The covariates were then assessed for clinical relevance prior to entering the model. The statistical software used was R (version 3.3.1). A p-value <0.05 was considered significant.

3.3 Results

Population

A total of 180 infants were included. Of these, 83 (46%) were extubated to ns-NIPPV and 97 (54%) to nCPAP. Population characteristics are presented in Table 8.

Table 8: Population characteristics

	ns-NIPPV (n=83)	nCPAP (n=97)	P-value
Maternal and antenatal variables			
Preterm labor	69 (83)	72 (74)	0.148
Preeclampsia	10 (12)	18 (19)	0.230
Antenatal steroids	75 (90)	87 (90)	0.975
Chorioamnionitis	47 (57)	30 (31)	0.002
Singleton	64 (77)	76 (78)	0.842
Inborn	75 (90)	86 (89)	0.711
Neonatal variables			
Birth weight, grams	750 [664-880]	960 [760-1090]	<0.001
Gestational age, weeks	25.5±1.4	27.0±1.8	<0.001
Intrauterine growth restriction	6 (7)	21 (22)	0.007
Apgar 5 min	6 (5-6)	7 (6-8)	<0.001
Age at intubation, min	7 [3-23]	30 [10-180]	<0.001
Age at extubation, days	13 [3-27]	5 [2-15]	0.009
Weight at extubation, grams	860 [760-1005]	990 [880-1100]	<0.001
Surfactant	81 (98)	92 (95)	0.342
Caffeine	82 (99)	94 (97)	0.392
Age at initiation, days	1 [1-3]	1 [1-4]	0.590
Pre-extubation settings			
Mode			0.136
Sync intermittent mandatory ventilation	51 (61)	59 (61)	
Assist Control	30 (36)	29 (30)	
Pressure support ventilation	2 (3)	9 (9)	
Positive end-expiratory pressure, cmH_2O	5 [5-6]	5 [5-6]	0.685
Peak inflation pressure, cmH_2O	14 [13-16]	13 [12-15]	0.016
Mean airway pressure, cmH_2O	7 [6-8]	7 [6-8]	0.099
Fraction of inspired O_2	0.25 [0.21-0.28]	0.21 [0.21-0.25]	<0.001
Post-extubation settings			
CPAP level	-	6 [5-6]	-
Positive end-expiratory pressure, cmH_2O	5 [5-7]	-	-

Values are expressed as mean ± SD, medians [IQR] or n (%). A p-value of <0.05 was considered statistically significant.

Primary outcome

Infants extubated to ns-NIPPV had a lower age (at birth, intubation and extubation), weight (at birth and extubation), APGAR at 5 min and lower rates of intrauterine growth restriction. These infants had higher oxygen needs pre-extubation and a higher incidence of histologically confirmed chorioamnionitis (Table 8). There were no differences between the two groups in the use of surfactant and caffeine.

Secondary outcome

The unadjusted rates of ROP and BPD were higher in infants extubated to ns-NIPPV but after adjusting for significant variables in the multivariate linear regression the use ns-NIPPV only remained significantly associated with increased duration of non-invasive respiratory support, days on oxygen, postmenstrual age (PMA) at discharge, and length of hospitalization (Table 9). After adjustment, there was no association between ns-NIPPV use and comorbidities.

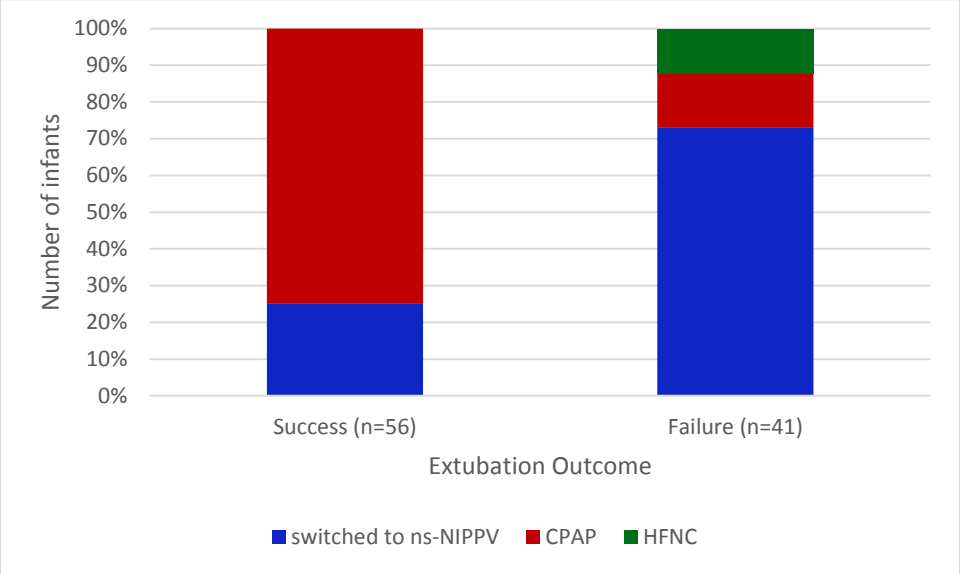
Table 9. Short-term outcomes

Clinical Outcomes	ns-NIPPV (n=83)	nCPAP (n=97)	Univariate	Linear Regression
Invasive mechanical ventilation, days	27 [8-39]	7 [3-31]	0.002	0.505 (-5.87, 11.88)
Non-invasive ventilation, days	48 [39-66]	37 [28-46]	<0.001	0.008 (2.39, 15.57)
Duration of oxygen therapy, days	76 [47-102]	29 [3-60]	<0.001	0.003 (6.63, 31.25)
Postmenstrual age at discharge, weeks	41 [39- 44]	39 [36- 41]	<0.001	0.011 (0.48, 3.65)
Length of hospitalization, days	109 [95-128]	83 [56-109]	<0.001	0.011 (3.35, 25.57)
Reintubation	46 (55)	41 (42)	0.079	0.71 (0.27- 1.53)
Intraventricular hemorrhage	27 (33)	34 (35)	0.722	0.66 (0.30-1.44)
Retinopathy of prematurity	43 (52)	22 (23)	<0.001	1.50 (0.63-3.58)
Necrotizing enterocolitis	9 (11)	14 (14)	0.473	0.36 (0.12-1.00)
Periventricular leukomalacia	6 (7)	5 (5)	0.564	2.29 (0.48- 12.72)
Bronchopulmonary dysplasia among survivors	64 (77)	42 (43)	<0.001	1.91 (0.79-4.61)
Bronchopulmonary dysplasia/death	66 (80)	48 (49)	<0.001	1.63 (0.68-3.90)

Legend: Multivariate model included: GA, BW, Apgar 5 min., day of life and weight at extubation, intrauterine growth restriction, pre-extubation FiO_2 and death. Univariate and multivariate regressions reported for ns-NIPPV. Values are expressed as median [IQR], n (%). A p-value of <0.05 was considered statistically significant.

There were no statistical differences in the rate of reintubation, defined as anytime during hospitalization, between ns-NIPPV (55%) and nCPAP (42%). Of the 46 infants exubated to ns-NIPPV and reintubated, all were on ns-NIPPV prior to the reintubation. In contrast, most infants extubated to nCPAP were switched to ns-NIPPV prior to failing extubation. Indeed, of the 97 infants extubated to nCPAP, 44 (45%) were switched to ns-NIPPV but the majority failed extubation (Figure 3).

Figure 3. Changes of non-invasive support mode in infants initiated on nasal CPAP (n=97) after extubation.



Legend: Of the 56 infants initiated on nCPAP after extubation and never reintubated (success), 25% were switched to ns-NIPPV. However, of the 41 infants initiated on nCPAP after extubation and were reintubated (failed), the majority were switched to ns-NIPPV (73%).

3.4 Discussion

In this study we were able to demonstrate that the use of ns-NIPPV instead of nCPAP is based of GA, BW and ventilatory settings, with ns-NIPPV being offered to the more immature and smaller infants receiving higher oxygen concentrations prior to extubation. This however, did not translate in better rates of successful extubation or improved outcomes. Moreover, routine extubation to ns-NIPPV led to additional days spent on non-invasive respiratory support and duration of hospital stay.

Extremely preterm infants are at high risk of extubation failure and may benefit from any additional support provided after disconnection from the mechanical ventilator. During ns-

NIPPV, PIP above the PEEP level is delivered intermittently at a set rate which may be of advantage when compared to the continuous positive pressure delivered by the nCPAP systems. Similarly to our cohort of infants, Bhandari *et al.* noted that s-NIPPV was mostly used in infants with lower GA, BW, Apgar at 1 minute and that have received more doses of surfactant (61). These infants also spent more days on oxygen and had longer hospitalization (61). In contrast, Jasani *et al.* noted a shorter duration of non-invasive respiratory support and supplemental oxygen in infants randomized to ns-NIPPV as compared to nCPAP (30). However, in this RCT infants had higher GA and BW and only a few infants were included in the subgroup analysis of the smallest infants (30) where no differences were observed between those two types of non-invasive respiratory support.

Contrary to our results, other RCTs have demonstrated a reduction in extubation failure with the use of ns-NIPPV compared to nCPAP (26, 27, 62). These studies employed different types of devices and definitions of failure. Among the ns-NIPPV devices was the biphasic nCPAP (BP-NCPAP), a system that delivers an upper and lower level of CPAP with set times and a difference between both levels of 3 to 6 cmH_2O (28). Thus, BP-NCPAP is not equivalent to the ns-NIPPV used with the ventilator. In addition, one study allowed for the use of different nCPAP devices such as bubble CPAP, ventilator CPAP and SiPAP (62). In another RCT, Ram *et al*. reported a significant reduction on extubation failure, BPD, days on MV, nCPAP and duration of oxygen therapy among infants randomized to ns-NIPPV. Again, patients in this trial had higher GA and BW and better Apgar scores at 1 & 5 minutes when compared to our study population (62). The lack of consistency of these unblinded studies concerning the studied population, devices and definitions used, makes it difficult to interpret the results. In the largest RCT comparing nCPAP to NIPPV (synchronized and non-synchronized), there were no

differences in rates of extubation failure or the combined outcome of BPD/death (63). In fact, the 95% confidence interval of the odds ratio suggests that NIPPV can potentially increase the odds of developing BPD/death (63). Importantly, these findings are comparable to those of our study.

The nasal interface used for the delivery of ns-NIPPV is prone to air leaks whereby the set pressures do not completely reach the lungs. Owen *et al*. demonstrated that over 80% of inflations were delivered 5 cmH_2O below the set PIP (64). Another problem is the lack of synchronization between patient and ventilator with several PIP's being delivered while the glotic area is closed or during the expiratory cycle. In fact, s-NIPPV has been demonstrate to improve thoraco-abdominal synchrony (33) and a meta-analysis showed lower rates of extubation failure with s-NIPPV when compared to nCPAP (24). In our cohort, 44 (45%) of the nCPAP infants were switched at some point to ns-NIPPV. Of these, 14 (14%) remained extubated. Given the lack of synchrony during ns-NIPPV, we speculate that the successful rescue of these patients might be related to the higher MAP provided during ns-NIPPV. None of the studies comparing NIPPV vs nCPAP during the post-extubation period has used equivalent MAP. This would have been important since a RCT that compared nCPAP levels of 7-9 cmH_2O with the traditional 4-6 cmH_2O showed decreased extubation failure rates in ELBW infants randomized to the higher levels (65). Although the use of ns-NIPPV as a rescue strategy may explain the lack of significance in reintubation rates between both groups, applying ns-NIPPV to all infants would have exposed most infants (55%) to this therapy unnecessarily. Furthermore, the use of ns-NIPPV immediately after extubation has not translated in better outcomes, including death/BPD.

The study has some limitations and strengths. The reason for the change from nCPAP to ns-NIPPV could not be ascertain. Furthermore, this was not a blinded RCT and no set definition

for extubation failure or nCPAP failure was used. Nevertheless, the study included almost 200 infants with BW< 1250g enrolled in a trial of extubation; a sample size larger than the majority of RCTs comparing ns-NIPPV with nCPAP.

3.5 Conclusion

In a large cohort of extremely preterm infants enrolled in an ongoing study, extubation to ns-NIPPV is mostly used in infants of lower GA, BW and receiving higher fractions of inspired oxygen. Despite reintubation being avoided by the use of rescue ns-NIPPV in a small percentage of infants on nCPAP, routine extubation to ns-NIPPV did not confer added benefits and was associated with slower weaning off respiratory support and increased length of stay.

Chapter 4: Overall Discussion

The decision to extubate can be highly variable between centers and most infants in our institution were extubated after the first week of life. These infants represent a population of lower GA and BW, worse values of blood gases, lower nutritional intake and higher ventilator settings during the first week of life. Not surprisingly, these infants required longer duration of MV and respiratory outcomes may be negatively impacted. Moreover, a higher incidence of moderate/severe BPD was observed in infants extubated for the first time > 7 days of life. However, age at extubation was not a good predictor of moderate/severe BPD. Instead, reintubation was independently associated with greater risk of this latter outcome. Given that this fragile population is at the highest risk of extubation failure, it is important to ensure an early and successful extubation. Several attempts have been made to develop better predictive tools to determine extubation readiness without success. These tools include a spontaneous breathing test (SBT) whereby an infant receives only a PEEP through the ETT (68). The duration of the SBT can vary from a few minutes to several hours and clinical signs such as desaturations and bradycardias are evaluated, measurements of lung mechanics, chest x-rays and tension time indexes (68, 69). Currently, the use of biological signals is breing explored in addition to clinical information.

Once an infant is deemed ready to be extubated, different modes of non-invasive respiratory support can be used. At our units, nCPAP and ns-NIPPV were the two modalities of choice independently of the age at extubation. Infants extubated to ns-NIPPV had lower GA and BW, and were at higher ventilator settings prior to extubation. After accounting for immaturity, rates of reintubation and other common clinical comorbidities did not differ between infants extubated to ns-NIPPV or nCPAP. The use of ns-NIPPV increased the duration of non-invasive

support and consequently the length of hospitalization. Implementation of a weaning protocol for non-invasive respiratory support may shorten the latter outcome.

Improving the respiratory management of extremely preterm infants is an important aspect of clinical care. For this reason, current practices and associated outcomes need to be assessed. In our institutions, clinicians tend to extubate the most premature infants after the first week of life and to ns-NIPPV despite no differences in important outcomes were detected and direct extubation to ns-NIPPV was associated with longer duration of non-invasive support and hospital stay.

Appendix: Respiratory behavior of extremely preterm infants receiving non-invasive respiratory support during the immediate post-extubation period

A.1 Introduction

As previously shown, the level of evidence supporting the use of ns-NIPPV over nCPAP is low (24, 63). However, when synchronization is applied during NIPPV, a decrease in WOB, TAM asynchrony and extubation failure rates has been demonstrated (31, 66, 67). Unfortunately, methods used to achieve synchronization are either no longer available or difficult to apply.

A recently developed respiratory support mode able to achieve synchronization during NIPPV is non-invasive neurally adjusted ventilatory assist (NIV-NAVA). This modality uses the electrical activity of the diaphragm to detect the respiratory effort through an esophageal catheter containing microelectrodes at the tip. Therefore, given the possible benefits of synchronization during non-invasive ventilation, NIV-NAVA is an attractive mode that needs to be evaluated in this fragile population. The primary objective of this study is to investigate for differences in cardiorespiratory behavior of extremely preterm infants receiving 3 different modes of non-invasive respiratory support immediately after extubation. The secondary objective is to investigate for differences in patient-ventilator interaction between ns-NIPPV and NIV-NAVA.

A.2 Methods

<u>Population</u>

In this prospective single center study, infants with BW ≤1250 grams and receiving mechanical ventilation are included. Infants with major congenital anomalies, congenital heart

defects, neuromuscular disease, diaphragmatic paralysis or palsy, diagnosed phrenic nerve injury, esophageal perforation, hemodynamic instability as well as infants on inotropes, narcotics or sedative agents are excluded. The study was approved by the Research Ethics Board and informed consent is to be obtained from parents. Recruitment began in January 2016

Study Design

Infants are extubated to the mode of non-invasive respiratory support determined by the responsible physician for a period of 30 minutes. After that, infants are placed on nCPAP, ns-NIPPV and NIV-NAVA in a random order, for 30 minutes each, in addition to a 10 minute transition period between modes (Figure 4). The pressure level used for nCPAP, ns-NIPPV and NIV-NAVA is the same as the pre-extubation PEEP level. For ns-NIPPV, the PIP is 10 cmH_2O above the PEEP at a rate of 20 inflations per minute. For NIV-NAVA, the NAVA level is adjusted to match the same PIP used during ns-NIPPV. In cases of apnea during NIV-NAVA, a backup ventilation is initiated at the same settings as ns-NIPPV.

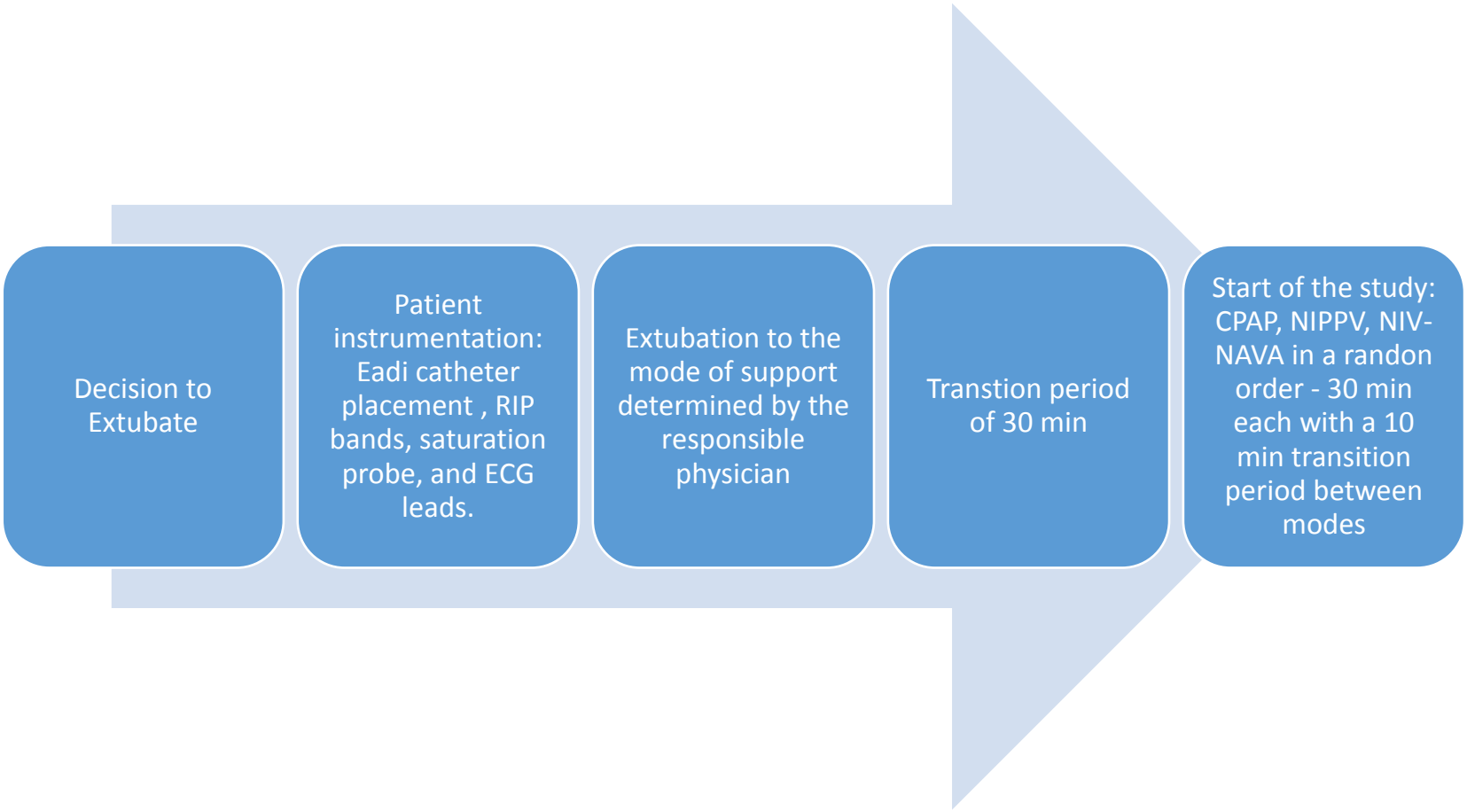


Figure 4. Timeline of the study

Instrumentation

All instrumentation is done prior to extubation. Chest and abdominal wall movements are recorded using Respiratory Inductive Plethysmography (Respitrace QDC®, Viasys® Healthcare, USA) by placing two respibands around the infant's chest and abdomen (Figure 5).

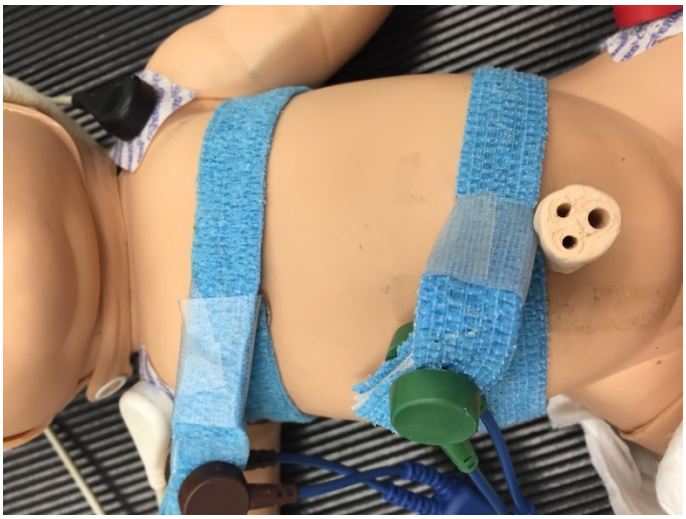


Figure 5. Placement of respibands. The chest band is placed at the level of the nipple and the abdominal band is placed above the umbilicus.

Heart rate is measured using electrocardiography (ECG) signals by applying three ECG leads: two on the chest and one on the thigh (Figure 6).

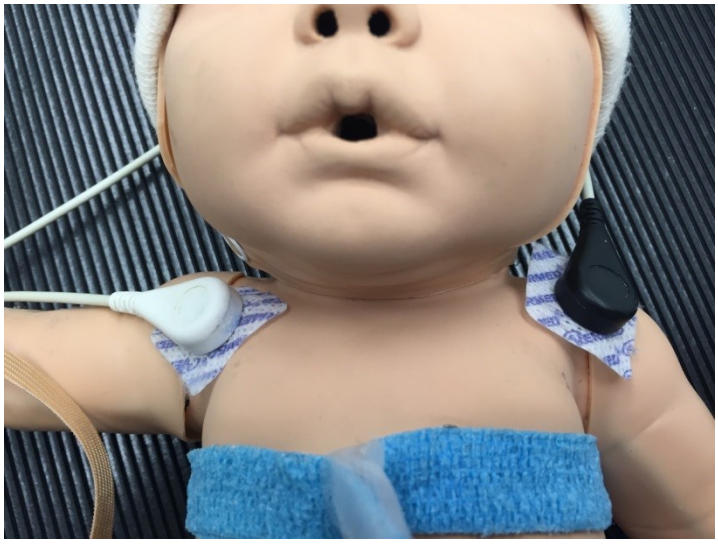


Figure 6. Placement of ECG leads

Oxygen saturation is measured using pulse oximetry (Masimo Radical, MasimoCorp, Irvine, LA) by placing an oxygen saturation probe around the right wrist (Figure 7).

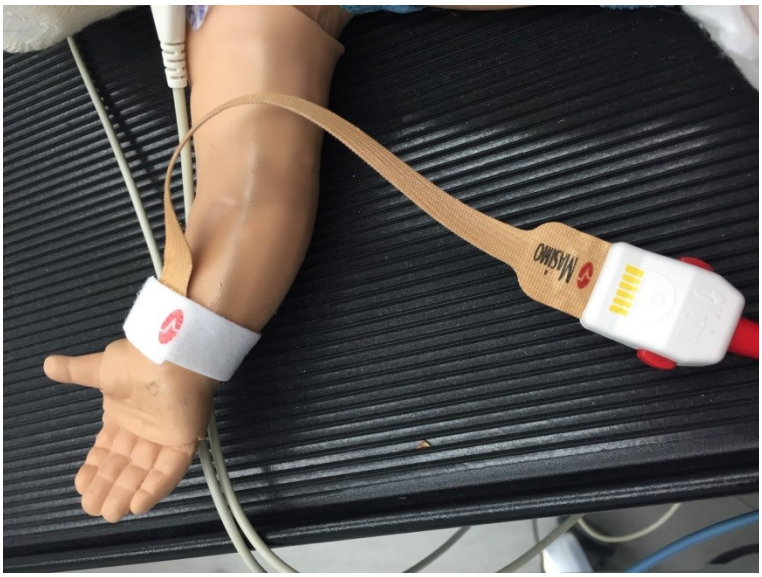


Figure 7. Placement of saturation probe

The cardiorespiratory signals are acquired using the Power Lab data acquisition system (ADInstruments, Bella Vista, Australia). The Eadi catheter will be placed with the tip at the

lower third of the esophagus and adequate positioning checked according to manufacturer specifications using the ventilator screen. The Edi catheter is correctly positioned when the second and third wave channels are blue (Figure 8). The EMG from the diaphragm and the pressure waveform are acquired through the NAVA tracker software (Maquet, software version 2.0).

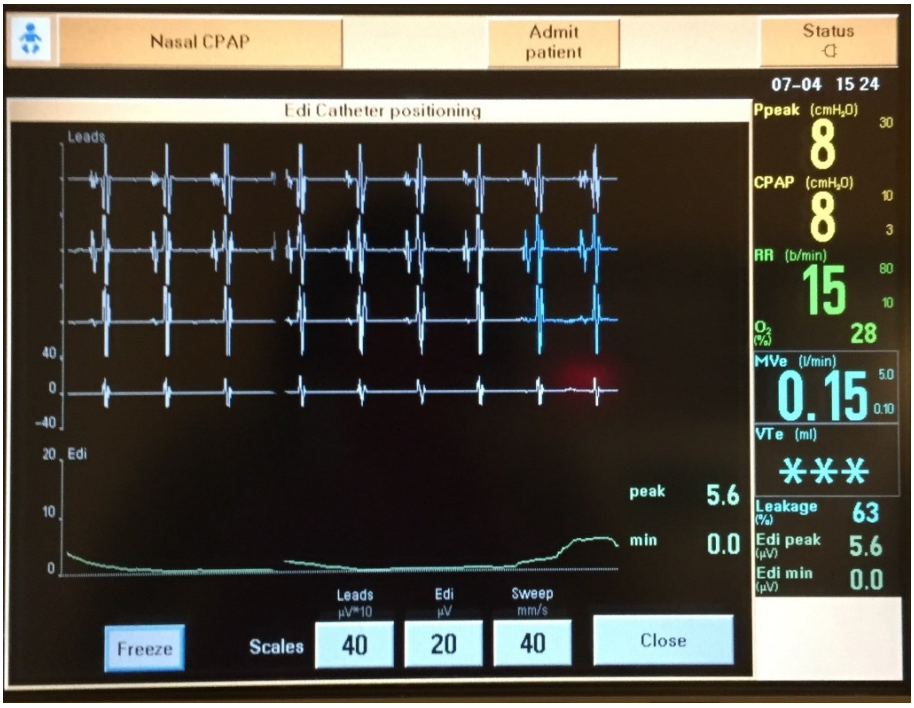


Figure 8. Verification of Eadi catheter position on the Servo-I ventilator

Data Collection

All maternal, perinatal and neonatal demographic data, respiratory care data and patient outcomes are being collected as previously described in chapter 3.

Signal analysis

Cardiorespiratory variability

Respiratory signals will be analyzed using AUREA (Automated Unsupervised Respiratory Events Analysis). This data acquisition system categorizes the RIP signals into the following events: pause, movement artifact, asynchronous and synchronous breathing. Heart rate variability will be analyzed from ECG signals using time and frequency domain methods, ideally using two 5 minutes segments of data. For the oxygen saturation signal, the mean and standard deviation will be calculated.

Patient-ventilator interaction

The visual display of the waveforms will allow for the placement of different time cursors. From these time cursors, the following parameters can be calculated: trigger delay, cycling off delay, number of breaths with premature cycling off, asynchrony index, wasted inspiratory efforts, relationship and proportionality between ventilator assist and patient's respiratory requirements, neural inspiratory and expiratory time and ventilator inspiratory and expiratory time.

Statistical analysis

Appropriate statistical tests will be performed to compare variables between nCPAP, ns-NIPPV and NIV-NAVA. A p value < 0.05 will be considered statistically significant.

A.3 Results

To date, twenty-four out of 30 infants have been studied. Signals on all 3 modes from one infant (Study ID: GLN_NAVA_011) is presented in Figure 9.

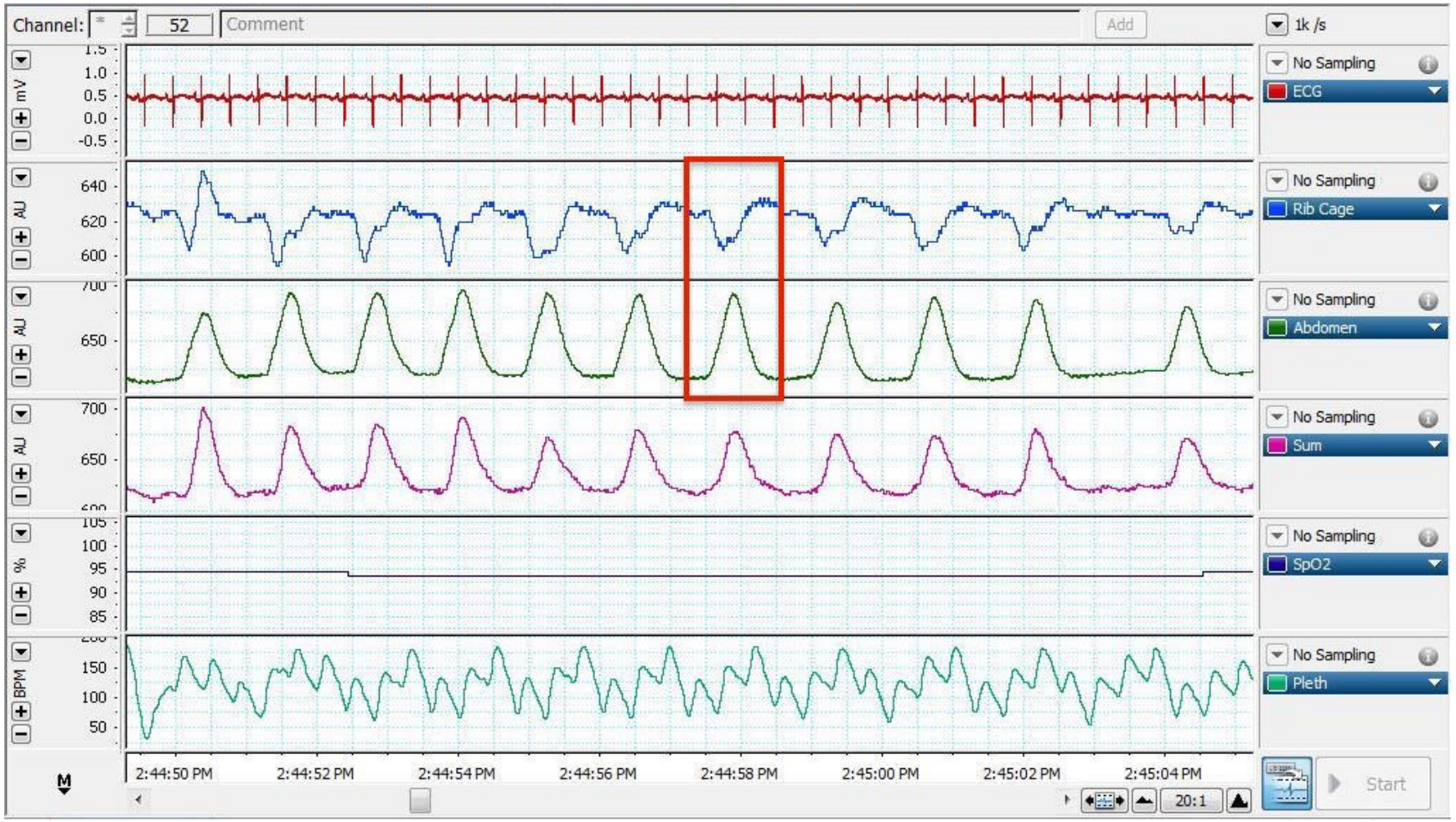


Figure 9a. Snapshot of cardiorespiratory signals during nCPAP. Rib cage and abdomen RIP waveforms are represented in blue and green, respectively. The red box highlights asynchronous breathing whereby the rib cage moves inward and abdomen moves outward during inspiration.

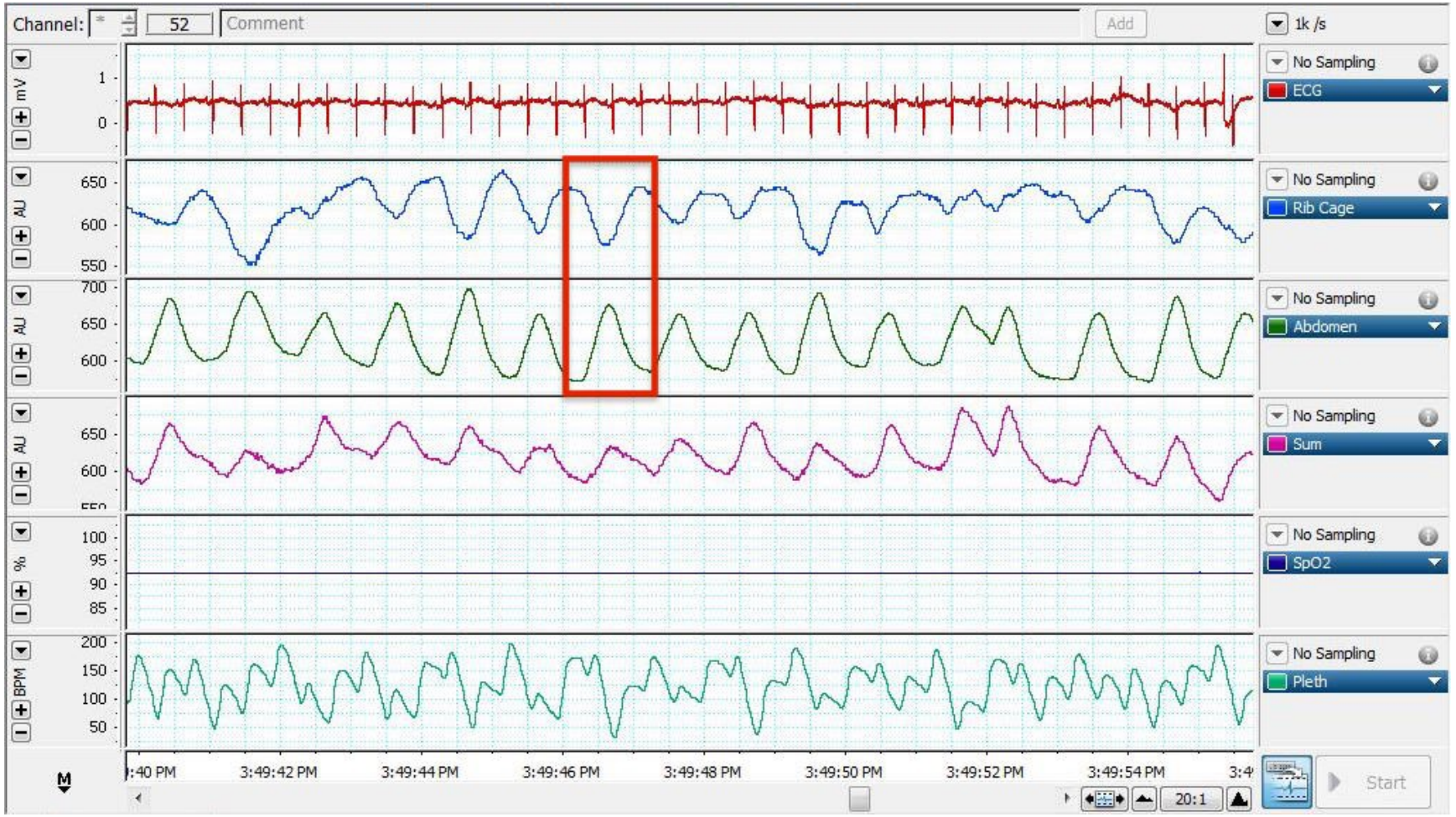


Figure 9b. Snapshot of cardiorespiratory signals during ns-NIPPV. Rib cage and abdomen RIP waveforms are represented in blue and green, respectively. The red box highlights asynchronous breathing.

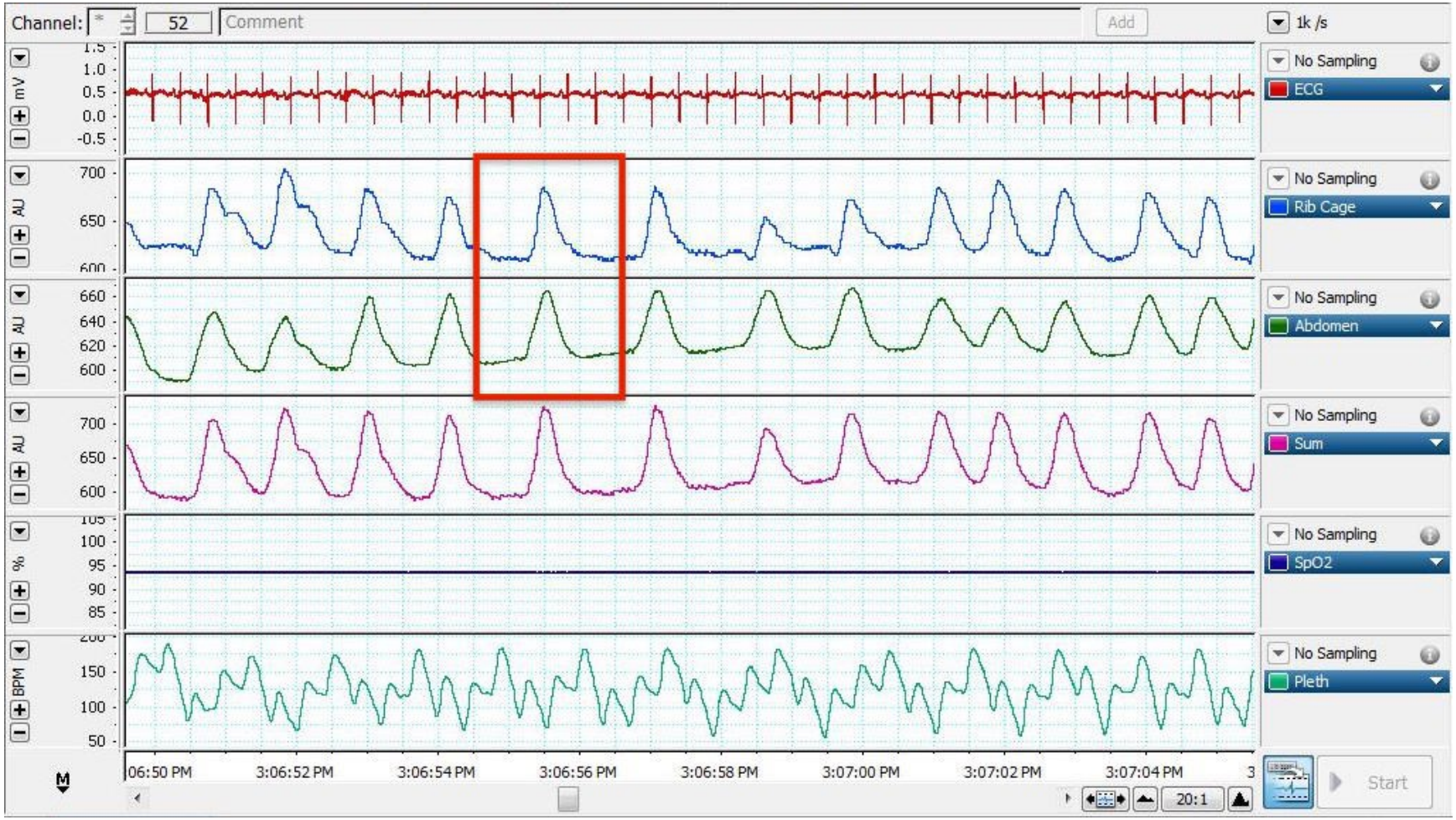


Figure 9c. Snapshot of cardiorespiratory signals during NIV-NAVA. Rib cage and abdomen RIP waveforms are represented in blue and green, respectively. The red box highlights synchronous breathing.

We hypothesize that there will be differences in cardiorespiratory behavior in extremely preterm infants receiving nCPAP, ns-NIPPV and NIV-NAVA during the immediate period after extubation. Results of this study can potentially help distinguish the optimal mode for a particular infant. In addition, an infant's cardiorespiratory behavior can provide insight into respiratory outcomes such as extubation failure. However, sleep/wake status was not recorded during the study. This is a limitation as heart variability may be higher when an infant is awake. Preliminary results of a study done by our research group showed that infants who failed extubation had greater heart rate variability during the switch from nCPAP to ns-NIPPV when compared to infants successfully extubated. We also anticipate improved patient-ventilator interaction when infants are receiving NIV-NAVA compared to ns-NIPPV. Enhanced synchronization may result in better respiratory outcomes and extubation success.

4.4 Conclusion

NIV-NAVA is a promising therapy that is being used in some centers across the United States and in Europe. In addition to the specific ventilator, the use of NIV-NAVA requires placement of a special esophageal catheter. Given the extra instrumentation and costs, the implementation of such a therapy requires extensive training and protocolization. Thus far, there have been no technical issues with the use of NIV-NAVA. However, correct placement of the catheter needs to be verified periodically as it can change position with movements. Although analysis has not been completed, some observations were made. Anecdotally, paradoxical breathing appears to improve on NIV-NAVA compared to the other modes. Further analysis may highlight additional advantages of NIV-NAVA.

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