Paediatric Diaphragm Function and Mechanical Ventilation

by
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Thesis presented in fulfilment of the requirements for the degree of Master of Physiotherapy in the Faculty of Medicine and Health Sciences at Stellenbosch University

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March 2018

Declaration

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ABSTRACT

Introduction: A relationship between diaphragm dysfunction and poor mechanical ventilation outcomes, such as prolonged duration of mechanical ventilation, weaning difficulties and extubation failure have been identified in the adult population. Most of the research of diaphragm dysfunction during mechanical ventilation has been done in the adult population and data in the paediatric population are lacking. The aim of this thesis is to report on diaphragm function in mechanically ventilated paediatric patients.

M**ethods:** A literature overview was done to describe mechanical ventilation weaning practices in the paediatric population; as well as underlying reasons for extubation failure in the paediatric population. Available data on weaning and extubation failure in the critically ill paediatric population were summarised.

A pilot study was performed to describe the inter- and intra-rater reliability of diaphragmatic ultrasound to measure diaphragm thickness in mechanically ventilated infants and children. Two researchers measured diaphragm thickness using ultrasound in five mechanically ventilated infants and children to compare measures.

A prospective observational study was performed to describe diaphragm function in mechanically ventilated infants and children. Diaphragmatic ultrasound was used to measure diaphragm resting thickness and diaphragm contractile activity, and surface electromyography was used to measure diaphragm electrical activity over a period of mechanical ventilation. Serial measures were taken each day of mechanical ventilation and patients were followed up until two days after extubation.

Results: The literature overview results showed no consensus in current clinical practice on weaning criteria or protocols, and most current practice is guided by results from adult studies. Several factors have been identified in the paediatric population that may predispose to extubation failure. Respiratory muscle function has been identified as a factor that should be assessed before an extubation attempt as it may be a contributing factor to successful extubation.

Diaphragmatic ultrasound has shown to have excellent intra-rater (Intraclass correlation coefficients between 0.77 and 0.98) and inter-rater (Intraclass correlation coefficient: 0.94) reliability to measure diaphragm thickness in mechanically ventilated infants and children.

Diaphragmatic ultrasound and surface electromyography are feasible and safe to use to measure diaphragm resting thickness, contractile activity and electrical activity in mechanically ventilated infants and children. Changes in diaphragm function occurred during mechanical ventilation in

infants and children, although all measures seem to remain within a common range in the paediatric population. Scatter plots showed that changes in diaphragm contractile activity were associated with increased mechanical ventilation duration, although not statistically significant; no other associations were made between diaphragm function and mechanical ventilation outcome.

Conclusion: More research will need to be done to identify how ultrasound and electromyography measures of diaphragm function are associated with mechanical ventilation outcome; and therefore how they could aid in predicting patients that may be at risk for poor mechanical ventilation outcomes. This thesis provides novel data on diaphragm function in mechanically ventilated infants and children which could be used as a basis for further research.

OPSOMMING

Inleiding: 'n Verhouding tussen diafragma-disfunksie en swak meganiese ventilasie uitkomste, soos langdurige tydsduur van meganiese ventilasie, speenprobleme en ekstubasie mislukking, is in die volwasse bevolking geïdentifiseer. Die meeste van die ondersoeke na diafragma-disfunksie tydens meganiese ventilasie is in die volwasse bevolking gedoen en data in die pediatriese bevolking ontbreek. Die doel van hierdie tesis is om verslag oor die diafragma-funksie in meganies geventileerde pediariese pasiënte te lewer.

Methode: 'n Literatuuroorsig is gedoen om meganiese ventilasie speen praktyke in die pediatriese bevolking; sowel as die onderliggende redes vir ekstubasie mislukking in die pediatriese bevolking te beskryf. Die beskikbare data oor speen- en ekstubasie-mislukking in die kritiese siek pediatriese populasie was opgesom.

'n Loodsstudie is uitgevoer om die inter- and intrarater betroubaarheid van diafragmatiese ultraklank te beskryf om diafragma dikte in meganies geventileerde babas en kinders te meet. Twee narvorsers het diafragma dikte in vyf meganiese geventileerde babas en kinders deur middel van ultraklank gemeet, en die metings vergelyk.

'n Prospektiewe studie is uitgevoer om diafragma funksie in meganies geventileerde babas en kinders te beskryf. Diafragmatiese ultraklank is gebruik om diafragma rustende dikte en diafragma kontraksie aktiwiteit te meet, en oppervlakselektromieografie is gebruik om die elektriese aktiwiteit van die diafragma te meet oor 'n tydperk van meganiese ventilasie. Opeenvolgende metings is elke dag geneem tydens meganiese ventilasie en pasiënte is opgevolg tot twee dae na ekstubasie.

Resultate: Die literatuuroorsig resultate toon geen konsensus in huidige kliniese praktyk oor speenkriteria of protokolle nie, en die praktyk word meestal gelei deur die resultate van studies in die volwassende bevolking. Verskeie faktore is geïdentifiseer in die pediatriese populasie wat kan lei tot ekstubasie mislukking. Respiratoriese spierfunksie is geïdentifiseer as 'n faktor wat geassesseer moet word voor 'n ekstubasiepoging, aangesien dit 'n bydraende faktor tot suksesvolle ekstubasie kan wees.

Diafragmatiese ultraklank het getoon dat dit 'n uitstekende intrarater(intraclass correlation coefficient tussen 0.77 en 0.98) en interrater (intraclass correlation coefficient 0.94) betroubaarheid het om diafragma dikte in meganies geventileerde babas en kinders te meet.

Diafragmatiese ultraklank en oppervlakselektromyografie is haalbaar en veilig om te gebruik om die diafragma se dikte tydens rus, kontraksie aktiwiteit en elektriese aktiwiteit in meganies

geventileerde babas en kinders te meet. Veranderinge in diafragma-funksie het plaasgevind tydens meganiese ventilasie by babas en kinders, alhoewel alle metings blyk om binne 'n algemene reikwydte vir die pediatriese populasie te bly. n' Strooi plot verwys dat veranderinge in diafragma kontraksie aktiwiteit is geassosieer met verlengde tydeperk van meganiese ventilasie, hoewel daar geen statistiese betekenis is nie; geen ander assosiasie tussen diafragmafunksie en meganiese ventilasie uitkoms is gemaak nie.

Gevolgtrekking: Ventilasie praktyke in die perdiatriese bevolking is nie gestandardiseer nie. Alhoewel ultraklank meting van die diafragma 'n betroubare meting is, is die interpretasie van die meting steeds onduidelik. Meer navorsing moet gedoen word om te identifiseer hoe ultraklank en elektromieografie metings van diafragma funksie geassosieer kan word met meganiese ventilasie uitkoms; en of die metings kan help met die voorspelling van pasiënte wat moontlik 'n risiko vir swak meganiese ventilasie uitkomste kan hê. Hierdie tesis voorsien unieke data om diaphragma funksie in babas en kinders wat as basis vir verdere navorsing in hierdie veld gebruik kan word.

Acknowledgements

I would firstly like to thank my supervisors, Prof Susan Hanekom, Head the Division of Physiotherapy at Stellenbosch University, and Prof Brenda Morrow from the Department of Paediatrics and Child Health at the University of Cape Town, for sharing their expansive knowledge and wisdom with me and for their continuous guidance.

I would also like to thank my co-researcher, Alison Lupton-Smith, from Stellenbosch University, for her participation in this research project, as well as for offering direction, support and for responding patiently to my endless questions.

I would like to acknowledge Dr Beyra Rossouw for generously assisting us in training with the ultrasound machine and to Tawanda Chivese, from the Biostatistics Unit at Stellenbosch University, for his assistance during data analysis.

I would also like to acknowledge the patients (and moms and dads) who participated in this study.

Finally, I'd like to express my gratitude to my family, friends and fiancé for being my encouragers and unwavering support every step of the way.

Thank you for your incredibly valuable contributions,
Maxine Terhart

"Now all glory to God, who is able, through his mighty power at work within us, to accomplish infinitely more than we might ask or think." - Ephesians 3:20

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INTRODUCTION

The paediatric diaphragm muscle

The diaphragm is the main muscle of respiration in the infant; mainly due to the undeveloped intercostal muscles and the horizontal orientation of the ribs, which puts the intercostal muscles at a mechanical disadvantage (Anraku and Shargall, 2009; Siren and Siren, 2011). Assuming the same organ proportions in neonates as adults, a full-term neonate weighing approximately 3000g would have a diaphragm weight of roughly 12g and thickness of about 2mm (Siren and Siren, 2011). The infant diaphragm reaches adult diaphragm force-generating capacity at approximately 6 months of age, as the size of the diaphragm usually directly correlates with the force production capacity of the muscle (Siren and Siren, 2011). The infant diaphragm is more susceptible to fatigue than the fully developed adult diaphragm muscle due to structural immaturity, smaller oxidative capacity as well as fewer fatigue-resistant muscle fibres (Siren and Siren, 2011). The full-term neonate has only 25% type I fatigue-resistant fibres, which increases to 50-55% at seven to eight months of age, which is consistent with the adult diaphragm (Siren and Siren, 2011). Endurance of the paediatric diaphragm is lower in comparison to adults, although diaphragm endurance in infants and children has not be sufficiently researched (Noizet *et al.*, 2005).

Mechanical ventilation in paediatrics

General paediatric mechanical ventilation (MV) practices differ in comparison to adults, not only because of airway and respiratory system immaturity, but because of cognitive and behavioural differences which pose unique challenges in patient understanding and co-operation (Kurachek *et al.*, 2003). A multi-centre study reported that 35% of the total paediatric patients admitted to paediatric intensive care units (PICUs) received MV for more than 12 hours; this percentage can vary between 30-64% (Farias *et al.*, 2004). Another study reported that 20-64% of mechanically ventilated paediatric patients receive MV for approximately five to six days (Laham, Breheny and Rush, 2013). Acute respiratory failure has been reported as the most common diagnosis for initiation of MV in 75% of all ventilated infants and children; subgroups of which included acute pulmonary disease and post-operative state (Farias *et al.*, 2004).

Adverse outcomes of MV in paediatrics includes increased duration of MV, weaning and extubation failure, which all may further increase morbidity and mortality (Kurachek *et al.*, 2003; Baisch *et al.*, 2005). In a study of 2 794 infants and children, Kurachek *et al.* (2003) reported a 6.2% planned extubation failure rate. Most extubation failure rates are low in PICUs thus strategies to decrease or predict extubation failure in the paediatric population should be directed towards the patients that are most at risk (Kurachek *et al.*, 2003). The patients that are most at risk for extubation failure are children younger than two years of age, patients on MV for prolonged periods of time, patients with

underlying neurological or respiratory disorders, patients with genetic abnormalities and patients with medical or surgical airway conditions (Kurachek *et al.*, 2003).

Factors that affect successful extubation are sufficient respiratory muscle and cough strength, in addition to resolution of the primary condition, adequate gaseous exchange, good laryngeal function, fair nutritional status and diminution of sedative or muscle relaxant medications (Kurachek *et al.*, 2003).

Diaphragm Dysfunction during Mechanical Ventilation

Unloading and disuse of skeletal muscle causing muscle wasting in critically ill patients, is associated with intensive care unit (ICU) acquired weakness and is common in the adult population (Vassilakopoulos and Petrof, 2004; Puthucheary *et al.*, 2013). Research shows that diaphragmatic atrophy occurs more rapidly in the diaphragm than in skeletal muscle in the ICU (Vassilakopoulos and Petrof, 2004).

Ventilator-induced diaphragmatic dysfunction (VIDD) has been defined as a loss of diaphragmatic force-generating capacity related to inactivity and unloading of the diaphragm muscle directly related to MV; which is one, amongst many complications that have been associated with MV in adults (Vassilakopoulos and Petrof, 2004). VIDD has been correlated with increased time on MV, weaning difficulties and extubation failure in adults (Vassilakopoulos and Petrof, 2004; Wolf *et al.*, 2011; Grosu *et al.*, 2012). This definition of VIDD excludes any other factors that may cause diaphragm dysfunction such as sepsis and medication (Vassilakopoulos and Petrof, 2004; Petrof and Hussain, 2016). In critically ill patients however, it is likely that other confounding factors will be present, thus most of the evidence of VIDD has been derived from studies on animals; although human studies have produced comparable results (Petrof and Hussain, 2016). VIDD has mostly been described in the adult population and there are little to no reports that describe VIDD in the paediatric population.

Adequate diaphragm function, in terms of muscular structure and force of the muscle, is necessary for patient-ventilator synchronicity during MV, for weaning and for successful extubation (Wolf *et al.*, 2011). Diaphragm dysfunction in adults can be identified by a decrease in diaphragm thickness and activity (Schepens *et al.*, 2015). There are no studies reporting on diaphragm atrophy and its effect on MV outcome in infants and children. Diaphragm electrical activity in paediatrics has been monitored using an invasive oesophageal electrode catheter during MV (Wolf *et al.*, 2011), however non-invasive modalities of diaphragm activity monitoring have not been sufficiently researched. In adults 18-69 hours of diaphragm inactivity during MV is related to diaphragm atrophy (Levine *et al.*, 2008); with diaphragm disuse atrophy occurring at a rate of 6% per day (Grosu *et al.*, 2012). Whether

mechanically ventilated infants and children experience the same negative effects on diaphragm function during MV as adults is unknown. The aim of this thesis is to inform current literature about diaphragm function in mechanically ventilated infants and children.

This thesis will be presented in four chapters: a literature overview on the current understanding of weaning and extubation failure in the paediatric population, a pilot study on the reliability of using ultrasound to measure diaphragm thickness in the mechanically ventilated paediatric population and an observational study on MV and its effect on diaphragm function in infants and children. The final chapter is an overall discussion of the aims and results of the thesis and recommendations for future studies. This thesis will be presented in article format.

Research Questions:

- What is the effect of mechanical ventilation on the infant and paediatric diaphragm muscle?
- Is there an association between diaphragm dysfunction and poor mechanical ventilation outcome?

CHAPTER 1: LITERATURE OVERVIEW

Weaning and Extubation Failure in Paediatrics
A current understanding of the literature

Introduction

One of the most common reasons for admission to the paediatric intensive care unit (PICU) is the need for intubation and mechanical ventilation (MV) (Turner and Arnold, 2007). Weaning from MV should begin as soon as possible to prevent complications related to prolonged MV (Blackwood *et al.*, 2013; Wielenga *et al.*, 2016). One of the main concerns when weaning from MV is the risk of extubation failure and re-intubation, which is associated with significant complications (Turner and Arnold, 2007).

Background

While MV is a life-saving form of supportive therapy for critically ill patients in the intensive care unit (ICU) (Farias *et al.*, 1998), prolonged MV is also associated with significant complications and increased morbidity and mortality (Farias *et al.*, 1998; Foronda *et al.*, 2011).

Weaning from MV is a process which aids the transition from MV to spontaneous breathing by gradually reducing ventilatory support (Wielenga *et al.*, 2016). The period of weaning is typically shorter for infants due to healthier baseline lung function compared to adults; therefore recovery from a lung injury would occur more rapidly (Cheifetz, 2003). Farais *et al* (2004) reported that weaning from MV accounted for 46% of the total time spent on mechanical ventilation; however weaning could take weeks to months for some children and a few may remain ventilator dependant (Blackwood *et al.*, 2013; Wielenga *et al.*, 2016).

Most studies have defined extubation failure as the need for re-intubation and resumption of MV within 48 hours after extubation (Johnston and da Silva, 2012; Wielenga *et al.*, 2016). Extubation failure increases both morbidity and mortality (Schindler, 2005). Kurachek *et al* (2003) reported that patients failing extubation in the PICU have an increased mortality rate of 4% compared to 0.8% in those who do not fail extubation, and an increased average duration of PICU stay from seven days to 17 days (Schindler, 2005).

Recent reports have shown that paediatric extubation failure rates range between 4.1-19% (Turner and Arnold, 2007). Foronda *et al* (2011) reported that extubation failure rates may vary between 16-19% in the paediatric population and re-intubation rates range from 10-20%.

There is a lack of evidence in the paediatric population to guide health care practitioners in the care of mechanically ventilated babies and children in the PICU, specifically in the area of weaning and

extubation. Current paediatric clinical practice is largely guided by past clinical experience and evidence that has been extrapolated from studies performed on adults and premature neonates (Cheifetz, 2003; Turner and Arnold, 2007). This is an inappropriate practice due to the unique pulmonary physiology, respiratory mechanics and epidemiology of acute lung injury in infants and children (Randolph *et al.*, 2002; Johnston and da Silva, 2012). The purpose of this review is to report on current paediatric practice in the PICU/NICU regarding MV weaning and extubation failure.

Aim

To describe mechanical ventilation weaning practices and extubation failure in paediatrics

Objectives

- To identify the main indications for mechanical ventilation in paediatrics
- To identify complications associated with prolonged mechanical ventilation in paediatrics
- To describe current weaning practice in paediatrics
- To identify possible causes or underlying reasons for extubation failure in paediatrics

Methods

This scoping review follows the framework set out by the Joanna Briggs Institute (JBI) (Peters *et al.,* 2015*)*. The PEDro scale was used to assess the methodological quality of all included randomised controlled trials (RCTs). The PEDro scale is based on the Delphi list developed by Verhagen and colleagues (Verhagen *et al.*, 1998).

Searching

Searches were conducted by the primary researcher using five computerised databases, namely Pubmed, PEDro, Cinahl, Cochrane and Scopus, from the date of inception to October 2016. A combination and variations of the following key search terms were used during the search: “paediatrics” OR “children”, “mechanical ventilation” OR “artificial respiration”, “weaning”, “underlying reasons” OR “causes” and “extubation failure” OR “extubation success”. Search results were limited to articles published in English.

Selection criteria

All articles that reported on mechanical ventilation, weaning or extubation failure studies in the neonatal and paediatric population (zero-18 years old) were included. Articles that reported on mixed adult and paediatric populations were also included. All narrative reviews and commentaries were excluded from this review. Articles that were not published in English and studies performed exclusively on adults or animals were also excluded.

The primary researcher independently searched all five electronic data bases using the above-mentioned search terms. All titles, abstracts and full text articles were independently evaluated by

the primary researcher and co-researcher. Any inconsistencies regarding article inclusion or exclusion between researchers were discussed until consensus was reached. All full text articles were accessed through electronic journals. Search terms as well as a summary of the findings can be found in table form in Addendum A.

Search results

The electronic data base search yielded a total of 1349 articles across all five data bases. After elimination of 129 duplicates, 1220 titles were screened for inclusion into the review. A total of 100 articles were reviewed by abstract. 52 articles were subsequently screened as full text articles for possible inclusion. After elimination of 20 articles, a total of 32 full text articles were included. A flow diagram of search results is available in *Figure 1.1.*

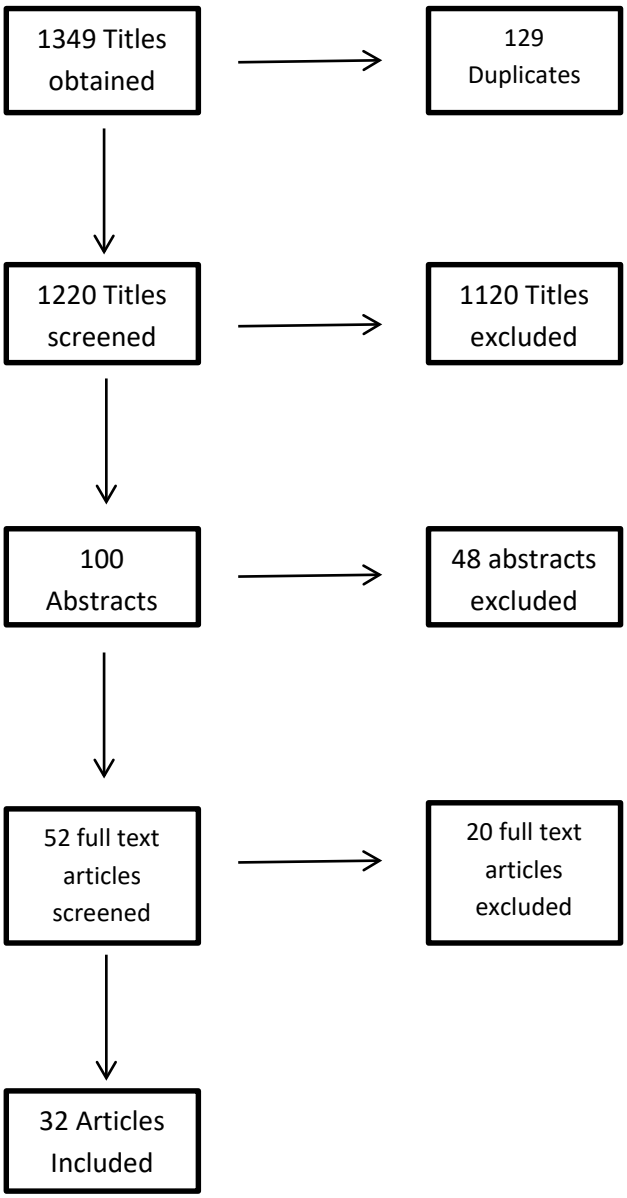

Figure 1.1 - Flow diagram of search results

Below are graphical representations of the types of studies, study designs, geographic distribution and year of publication of the included articles (*Figures 1.2 – 1.5*).

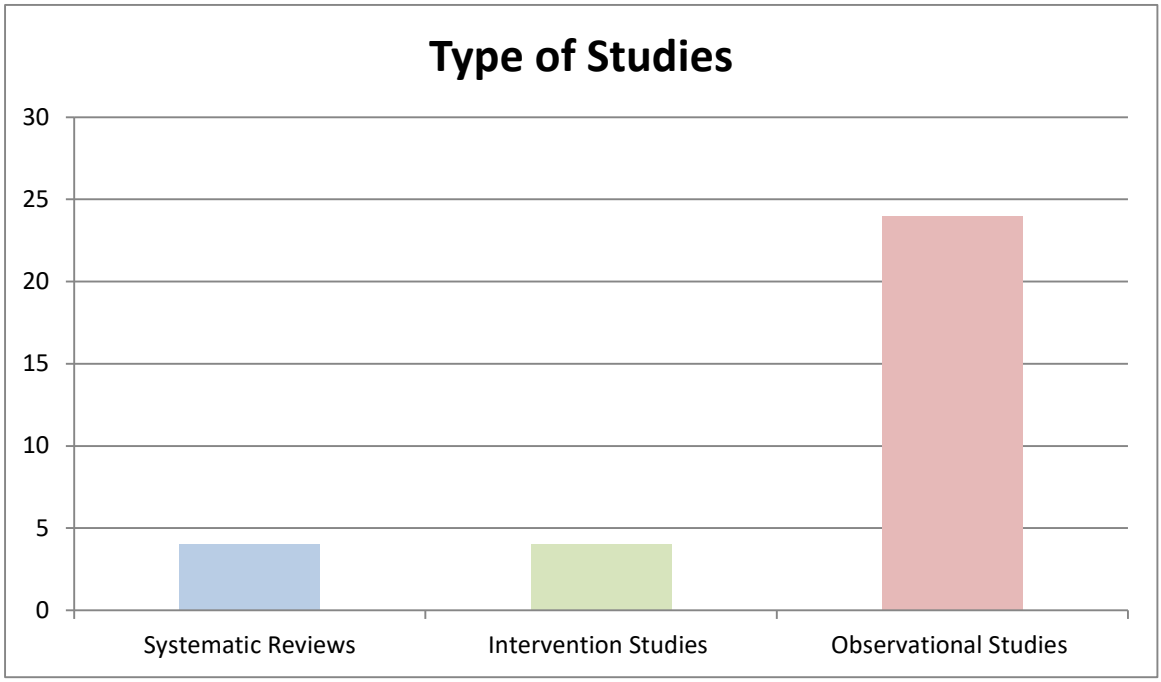

Figure 1.2 – Types of included studies

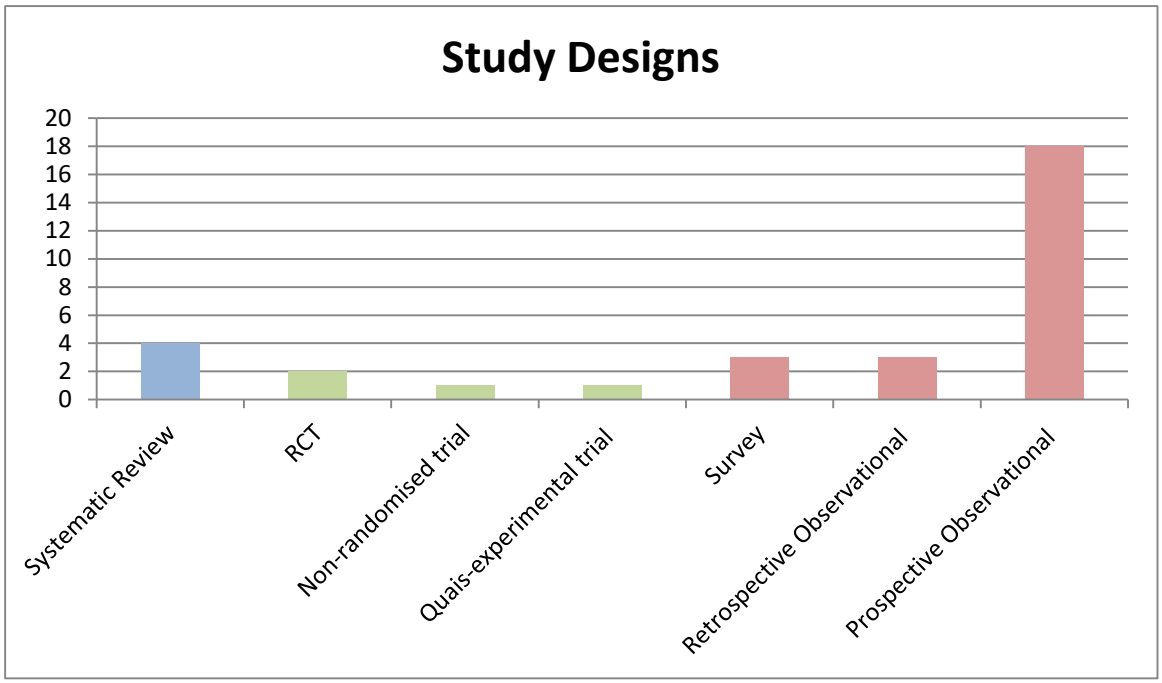

Figure 1.3 – Study designs of included studies

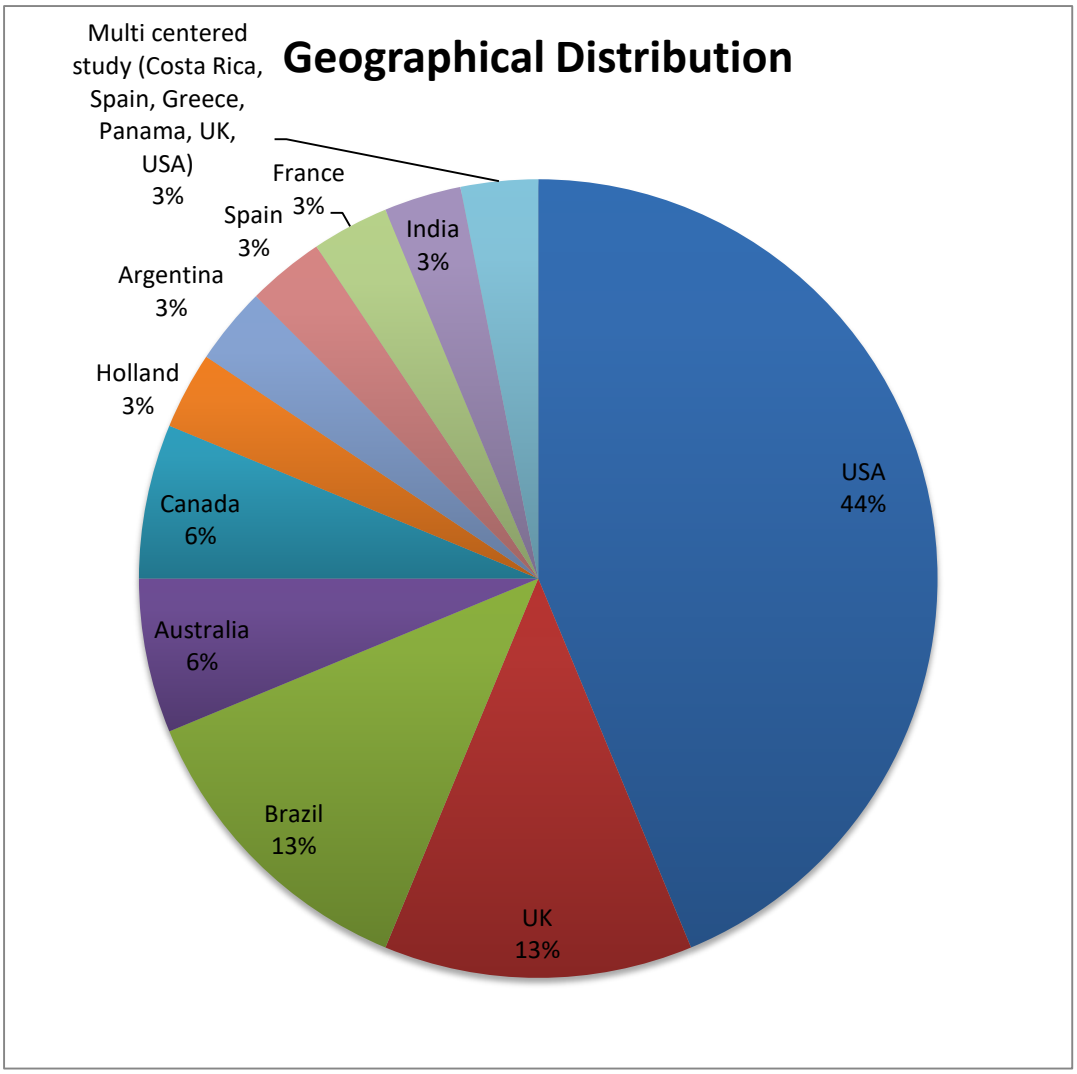

Figure 1.4 – Geographical distribution of included studies

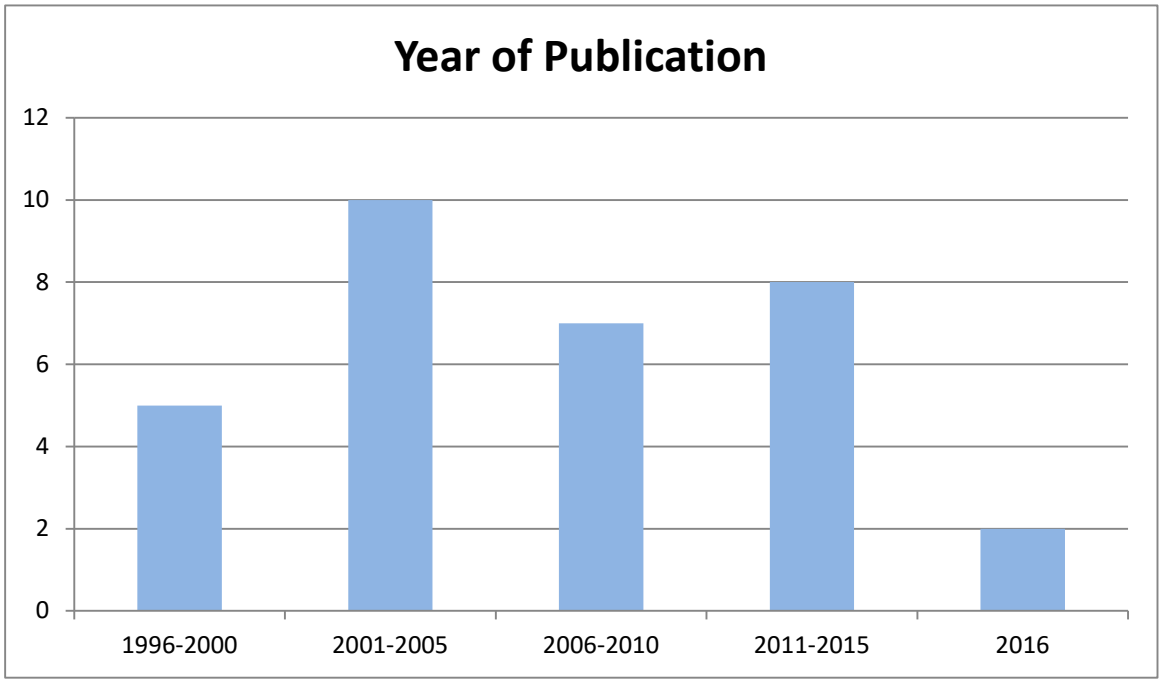

Figure 1.5 – Year of publication of included studies

Results

Systematic Reviews

Four systematic reviews were included in this review (Newth *et al.*, 2009; Blackwood *et al.*, 2013; Rose *et al.*, 2015; Wielenga *et al.*, 2016). One review reported on current practices of weaning and extubation for paediatric patients on MV (Newth *et al.*, 2009); another review reported on the effects of an automated weaning system compared to non-automated weaning (Rose *et al.*, 2015); the other two reviews compared the effects of protocolised versus non-protocolised weaning in critically ill paediatric patients (Blackwood *et al.*, 2013) and newborn infants (Wielenga *et al.*, 2016).

Newth *et al* (2009) included a total of 15 articles in their review; Rose *et al* (2015) included a total of 21 articles in their review; Wielenga *et al* (2016) included zero articles in their review and Blackwood *et al* (2013) included three articles in their review. Three reviews only included studies that were done in the PICU and/or NICU (Newth *et al.*, 2009; Blackwood *et al.*, 2013; Wielenga *et al.*, 2016) and one article included studies from adult ICUs as well as PICUs (Rose *et al.*, 2015). Newth *et al* (2009) and Rose *et al* (2015) included articles from both the adult and paediatric population their reviews. Wielenga *et al* (2016) included studies where the target population was more than 28 days old and less than 18 years of age; Blackwood *et al* (2013) included studies in which the population were exclusively neonates (gestational age ≥ 24 weeks). Two reviews (Blackwood *et al.*, 2013; Wielenga *et al.*, 2016) excluded any studies in which the participants were on non-invasive MV or had a tracheostomy.

Newth *et al* (2009) concluded that there are no clear guidelines for assessing readiness to wean or to predict extubation outcome in the paediatric population. Wielenga *et al* (2016) reported that there is a big gap in the literature regarding weaning protocols in neonates and more research needs to be done in this population. Blackwood *et al* (2013) reported limited evidence that weaning protocols can reduce the duration of MV in the paediatric population and postulated whether decreasing the duration of MV may be beneficial or harmful to paediatric patients. Rose *et al* (2015) concluded that automated weaning systems may result in reduced duration of MV, weaning and total time in the ICU or PICU. Addendum B presents a summary of the included systematic reviews.

Experimental and Quasi-experimental Studies

Two included experimental studies in this review were randomised controlled trials (RCTs) (Randolph *et al.*, 2002; Ferguson *et al.*, 2011). Randolph *et al* (2002) was published in USA and scored 6/10 on the PEDro scale; Foronda *et al* (2011) was published in Brazil and scored 5/10 on the PEDro scale.

Randolph *et al* (2002) studied the effect of weaning protocols on weaning duration and extubation success or failure in paediatrics, compared to standard care (no protocol). They randomised participants into one of two intervention groups: the PSV (pressure support ventilation) or VSV (volume support ventilation) group; or the control group which included no weaning protocol. The VSV protocol was a volume support protocol using ventilator automated continuous adjustment of pressure support; and the PSV protocol used manual adjustment of pressure support by clinicians. All participants included in this study had been receiving MV for more than 24 hours and had already failed an extubation readiness test (ERT) on minimal pressure support. There was no statistically significant difference found between extubation failure rates between groups. Failures rates were 15%, 24% and 17% for PSV, VSV and the no protocol group, respectively (Randolph *et al.*, 2002).

Foronda *et al* (2011) studied the impact of spontaneous breathing trials (SBTs) and daily evaluation of readiness to wean compared to standard care on the duration of MV in paediatric patients. Participants were randomised into the intervention group, who underwent a daily extubation readiness assessment and 2 hour SBT; and the control group who were weaned according to standard care procedures. The intervention group had a median MV duration of 3.5 days and the control group had a median of 4.7 days on MV, which is a statistically significant difference between groups (p=0.0127). There was no statistically significant difference in the number of extubation failures between groups (Foronda *et al.*, 2011).

Randolph *et al* (2002) had a sample of 182 participants younger than 18 years of age; Foronda *et al* (2011) had a sample of 312 participants older than 28 days old and younger than 15 years of age. Both studies were performed in the PICU setting and both studies used extubation outcome as one of their primary outcomes. Randolph *et al* (2002) also used duration of weaning as an outcome measure and Foronda *et al* (2011) used duration of MV and need for non-invasive MV as outcome measures. Randolph *et al* (2002) concluded that weaning protocols in paediatrics do not significantly decrease the duration of MV. Foronda *et al* (2011) concluded that the combination of a SBT and daily readiness to wean assessments decreases the duration of MV, without increasing the extubation failure rate in children.

One non-randomised controlled trial that was published in France was included in this review (Jouvet *et al.*, 2007). Jouvet *et al* (2007) studied the efficacy of a closed loop (computer-driven)

weaning system on 20 children between the ages of 1-17 years old consecutively admitted to a PICU. The efficacy of the closed loop protocol was evaluated by comparison of the participants to a historical control of 20 patients that were weaned by clinician decision alone. It was demonstrated that the closed loop protocol can be used to safely wean mechanically ventilated children. There was a non-statistically significant difference in weaning duration between the experimental and control group, with mean MV duration being 5.1 days (SD: 4.2) in the closed-loop group and 6.7 days (SD: 11.5) in the clinician decision group (Jouvet *et al.*, 2007).

Keogh, Courtney and Coyer, (2003) performed a quasi-experimental study with the aim of standardising the approach to weaning from MV in the PICU. The study was published in Australia and was performed in the PICU setting. 220 mechanically ventilated participants were included. The primary outcomes were duration of MV, duration of weaning, length of stay in the PICU and weaning outcome. Results showed longer total ventilation time (p=0.068) and length of stay (p=0.088) post-intervention compared to pre-intervention and weaning duration was comparable between groups (p=0.427). Keogh, Courtney and Coyer (2003) concluded that the use of weaning guidelines may increase MV duration, but improves outcomes of weaning and reduces the risk of weaning failure and reintubation. Longer term mechanically ventilated paediatric patients may benefit more from standardised weaning guidelines. Addendum C presents a summary of the included intervention studies.

Observational Studies

A total of twenty four observational studies were included in this review. Three were surveys (Keogh, 2004; Santschi *et al.*, 2007; Blackwood and Tume, 2015), three studies were retrospective observational studies (Edmunds, Weiss and Harrison, 2001; Restrepo *et al.*, 2004; Ferguson *et al.*, 2011) and eighteen studies were prospective observational studies (Khan, Brown and Venkataraman, 1996; Baumeister *et al.*, 1997; Farias *et al.*, 1998, 2002, 2004; Thiagarajan *et al.*, 1999; Venkataraman, Khan and Brown, 2000; Kurachek *et al.*, 2003; Baisch *et al.*, 2005; Fontela *et al.*, 2005; Bousso *et al.*, 2006; Chavez *et al.*, 2006; Harikumar *et al.*, 2009; Johnston *et al.*, 2010; Wolf *et al.*, 2011; Laham, Breheny and Rush, 2013; Saikia, Kumar and Sreenivas, 2015; Bhat *et al.*, 2016).

The weaning process was the primary outcome measure for four studies (Farias *et al.*, 2004; Keogh, 2004; Santschi *et al.*, 2007; Blackwood and Tume, 2015), weaning and MV duration was the primary outcome measure for one study (Restrepo *et al.*, 2004); and extubation outcome was the primary outcome measure for eighteen studies (Khan, Brown and Venkataraman, 1996; Baumeister *et al.*, 1997; Farias *et al.*, 1998, 2002; Thiagarajan *et al.*, 1999; Venkataraman, Khan and Brown, 2000; Edmunds, Weiss and Harrison, 2001; Kurachek *et al.*, 2003; Baisch *et al.*, 2005; Fontela *et al.*, 2005; Bousso *et al.*, 2006; Chavez *et al.*, 2006; Harikumar *et al.*, 2009; Johnston *et al.*, 2010; Wolf *et al.*, 2011; Ferguson *et al.*, 2011; Laham, Breheny and Rush, 2013; Saikia, Kumar and Sreenivas, 2015; Bhat *et al.*, 2016).

Keogh (2004) reported on the weaning process across 7 PICUs in Australia. Surveys were distributed to gather information on current management of MV weaning, as well as PICU characteristics and staffing. Keogh (2004) concluded that processes of weaning are inconsistent across Australian PICUs. Santschi *et al.* (2007) did a survey in 49 PICUs in order to characterise what the accepted physiological limits are for weaning children from MV. They found that accepted physiological limits for weaning across these PICUs are broad and there needs to be more consolidation regarding these limits before weaning guidelines can be established (Santschi *et al.*, 2007). Blackwood and Tume (2015) conducted a survey in 23 PICUs in the UK in order to describe what is considered 'usual' practice in paediatric sedation, weaning from MV and factors affecting implementation of a proposed intervention. They reported that 'usual' practices were broadly similar and that there was a lack of sedation and weaning protocols to guide staff in patient assessment and management (Blackwood and Tume, 2015).

Ferguson *et al.* (2007) performed a retrospective chart review on 538 patients younger than 19 years old, to evaluate the ERT based on a spontaneous breathing trial using pressure support. They concluded that this method of ERT may overestimate a child's readiness for extubation (Ferguson *et*

al., 2011). Edmunds, Weiss and Harrison (2001) conducted a retrospective chart review of 632 patients from a 20 bed PICU at a children's hospital over a two-year period. They found that patients are younger in age and those that have an increased duration of MV are more at risk for extubation failure (Edmunds, Weiss and Harrison, 2001). Restrepo *et al* (2004) reviewed the records of MV patients both before and after the implementation of a ventilator management program (VMP). They studied the effects of the VMP on duration of MV and weaning compared to standard care in children. They reported that the VMP was associated with reduced ventilator weaning time (Restrepo *et al.*, 2004).

Venkataraman, Khan and Brown (2000) and Khan, Brown and Venkataraman (1996) performed prospective observational studies to evaluate bedside measures of respiratory function, such as vital signs, clinical and blood gas parameters, on predicting extubation success in infants and children. They had a sample of 312 and 208 patients respectively. Khan, Brown and Venkataraman (1996) concluded that infants and children fail extubation due to poor respiratory effort, decreased inspiratory drive and increased load on the respiratory muscles and that adult indices are not reliable to predict extubation outcome in children. Venkataraman, Khan and Brown (2000) reported that bedside measurements of respiratory function can be used to predict extubation outcome in children. The results of this study also validated the results of their previously published study (Khan, Brown and Venkataraman, 1996).

Fontela *et al.* (2005) conducted a prospective observational study on 124 children to determine the incidence and associated risk factors for extubation failure in MV children. They concluded that extubation failure was most common in younger infants who received prolonged MV and sedation (Fontela *et al.*, 2005). Thiagarajan *et al.* (1999) conducted a prospective observational study on 472 patients to evaluate the effectiveness of the RSBI (rapid shallow breathing index) and the CROP index (dynamic compliance, respiratory rate, oxygenation, maximum inspiratory pressure) in predicting extubation success in children and to evaluate factors that are associated with extubation success. They concluded that the children that failed extubation had respiratory function abnormalities; and determined that the RSBI and the CROP index may be used to effectively predict extubation outcome in children (Thiagarajan *et al.*, 1999). Kurachek *et al.* (2003) conducted a prospective observational study in 16 PICUs in the United States which included a sample of 2,794 patients between the ages of 0-18 years old, with the aim of determining the incidence, risk factors and consequences of extubation failure in PICUs. They found that patients at particular risk for extubation failure are those that are younger, are intubated for long periods of time, have underlying respiratory or neurological conditions, have genetic conditions and those with airway

disorders. Deciding the precise moment for extubation in this population requires further investigation (Kurachek *et al.*, 2003).

Baisch *et al.* (2005) had a sample of 3,193 patients with a mean age of 37 months in their prospective observational study. The aim of their study was to evaluate the hypothesis that children who require re-intubation are at increased risk of associated complications. They concluded that children that require re-intubation have increased hospital length of stay, duration of MV and increased tracheostomy rate (Baisch *et al.*, 2005). Laham, Breheny and Rush (2013) conducted a prospective observational study on 319 patients from 0-20 years old to determine the ability of physicians to accurately use ventilator settings, blood gas results and other factors to predict extubation outcome. They determined that using low ventilator settings and other parameters to predict extubation readiness may unnecessarily prolong MV duration in acute cases (Laham, Breheny and Rush, 2013).

Harikumar *et al.* (2009) performed a prospective observational study on 80 children between the ages of 0.15-16 years old. They evaluated the efficacy of non-invasive tension time index of the respiratory muscles (TTmus) in comparison to tension time index of the diaphragm (TTdi) in predicting extubation outcome. They concluded that the results of TTmus correlated to that of TTdi and may be an accurate predictor of extubation outcome in children. Johnson and da Silva (2010) conducted a prospective observational study on 40 babies (1-12 months old) with bronchiolitis over a period of 18 months. They identified that lower minute volume and lower maximal inspiratory pressure may be a useful indictor of patients that are at risk for extubation failure (Johnston *et al.*, 2010).

Farais *et al.* (2004) performed a prospective multicentre cohort study across 36 medical/surgical PICUs in 7 countries and used data collection sheets to gather information on the hospital, PICU setting and patient information for all included patients. The main findings were that one in three patients that are admitted to PICU require MV and there is an 85% survival rate for patients that have been MV for more than 12 hours. Saikia, Kumar and Sreenivas (2015) conducted a prospective observational study on 92 cases by collecting pre-extubation clinical, ventilatory and laboratory parameters and calculating the extubation failure rate for each variable. They concluded that SBT failure, changes in respiratory effort as well as increased RSBI, poor cough and thick secretions are potential risk factors for extubation failure (Saikia, Kumar and Sreenivas, 2015). Baumeister *et al.* (1997) prospectively evaluated the modified CROP index and the RSBI to predict extubation outcome in paediatrics and concluded that the modified CROP index and the RSBI are useful in predicting extubation failure in the paediatric population. Farais *et al*. (1998) and Farais *et al*, (2002)

performed prospective observational studies to evaluate the accuracy of weaning indices in predicting weaning failure in the paediatric population. Farais *et al*. (1998) concluded that there is a 75% success rate for weaning paediatric patients from MV who have been assessed as ready to wean using a SBT of at least 2 hours. Farais *et al*. (2002) reported that respiratory parameters that can be measured at the bedside are poor predictors of extubation outcome in children. Wolf *et al*. (2011) investigated the electrical activity of the diaphragm during an ERT in children. They concluded that patients who generate higher diaphragmatic activity in relation to tidal volume may have better preserved diaphragmatic function and thus a better chance of passing the ERT (Wolf *et al.*, 2011).

Bousso *et al*. (2006) evaluated the ratio of dead space to tidal volume (VD/VT) as a predictor of extubation failure in children. They concluded that the VD/VT ratio cannot effectively predict the populations at risk of extubation failure (Bousso *et al.*, 2006). Chavez, dela Cruz and Zaritsky (2006) assessed the efficacy of a SBT using a flow-inflated bag in predicting extubation success in infants and children; and reported that a SBT using the flow-inflated bag is effective in predicting extubation success. Bhat *et al*. (2016) assessed the efficacy of the TTdi and TTmus in predicting extubation outcome in babies and concluded that neither TTdi nor TTmus can be recommended for use as a predictor for extubation outcome in clinical practice. Addendum D presents a summary of the included observational studies.

Discussion

Mechanical Ventilation in Paediatrics: Indications and Complications

The average duration of invasive MV in the PICU is reported to be 4 days, which may vary according to condition, age and mode of ventilation (Wielenga *et al.*, 2016). Laham, Breheny and Rush (2013) reported that roughly 30% of children that are admitted to the PICU undergo MV for an average of 5-6 days.

Signs of respiratory distress and inspiratory muscle fatigue in infants and children include tachypnea, respiratory alternans and paradoxical breathing (Khan, Brown and Venkataraman, 1996) which may be an indication for MV. When the load on the diaphragm increases the body adapts by increasing the respiratory rate (RR), using the accessory muscles for inspiration and grunting in order to sustain minute ventilation and to maintain lung volumes; which is especially evident in infants (Khan, Brown and Venkataraman, 1996). When unable to compensate, apnoea occurs (Khan, Brown and Venkataraman, 1996). Acute respiratory failure (ARF) is the most common diagnosis which indicates the need for MV (Farias *et al.*, 2004); and the most common cause of ARF in paediatrics which leads to admission to the PICU is bronchiolitis with pneumonia (Blackwood *et al.*, 2013). According to their statistics, Farais *et al.* (2004), having studied a cohort of PICUs in seven countries, reported that ARF accounted for 75% of MV paediatric patients and acute respiratory distress syndrome (ARDS) accounted for only 2% of paediatric patients on MV (Farias *et al.*, 2004). Apart from ARF, common reasons for admission to the PICU and initiation of MV are cardiac failure and neurological impairments (Randolph *et al.*, 2002). In developing countries acute pulmonary disease seems to be the most common cause for initiation of MV, whereas post-operative state is the most common reason for initiation of MV in developed countries (Farias *et al.*, 2004). Harikumar *et al.* (2009) reported that 29% of the patients included in their sample had an admission diagnosis of respiratory disease; however respiratory system involvement was present in the majority of their patients. The majority of the included children with a non-respiratory diagnosis had reduced respiratory system compliance and required significant ventilatory support. Children who had undergone liver transplantation had potential diaphragm dysfunction as a result of surgery or underlying disease (Harikumar *et al.*, 2009). In the South African context, a recent prospective study of 263 consecutive admissions to a PICU requiring invasive MV reported that the most common primary diagnoses were pneumonia, gastroenteristis, sepsis and traumatic brain injuries (Morrow *et al*., 2012). Comorbid conditions were common in this population and included congenital heart disease, history of premature birth, HIV-exposure of infection and malnutrition. The median age of the children was 3.8 months and the median duration of MV was 6 days. 17% of children received high frequency oscillatory ventilation during their admission (Morrow *et al.*, 2012).

A number of studies have reported that prolonged MV is associated with increased morbidity and mortality (Farias *et al.*, 1998; Foronda *et al.*, 2011). Complications associated with prolonged MV include nosocomial infection or pneumonia, airway injury, ventilator associated lung injury, increased patient discomfort and may result in increased need for sedation which increases the possibility of sedative dependency (Thiagarajan *et al.*, 1999; Randolph *et al.*, 2002; Harikumar *et al.*, 2009; Foronda *et al.*, 2011). Prolonged MV with associated equipment and positioning may affect a child's feeding, mobility and comfort in addition to increased health care costs, psychosocial and physical issues also associated with lengthy stay in the PICU (Blackwood *et al.*, 2013).

Other short term complications that can occur with MV include atelectasis, air leak syndrome and pneumonia. Longer-term complications include neurodevelopmental impairments or bronchopulmonary dysplasia (BPD). BPD is described as an arrest in vascular and alveolar development and is considered one of the major complications of prolonged MV in younger patients (Wielenga *et al.*, 2016). MV is associated with the unloading of the diaphragm causing deconditioning and atrophy of the diaphragm muscle as well as being associated with impaired diaphragmatic function (Fontela *et al.*, 2005). Diaphragmatic atrophy can occur within 18-69 hours of initiation of MV in humans (Levine *et al.*, 2008). There are increasing reports that even short periods of mechanical ventilation can cause inflammation in the lungs, thus emphasising the importance of discontinuation of MV as soon as possible (Foronda *et al.*, 2011; Wielenga *et al.*, 2016). Conversely, premature extubation may lead to respiratory failure, re-intubation and ultimately death (Thiagarajan *et al.*, 1999; Bousso *et al.*, 2006). It is therefore essential that timeous weaning and extubation strategies are implemented to prevent the associated complications of prolonged MV.

Guidelines for Weaning and Weaning Protocols in Paediatrics

In adults and children the weaning phase of MV accounts for about 40-46% of the total time on MV (Jouvet *et al.*, 2007). In adults there have been a number of studies demonstrating a decrease in duration of MV and shorter periods of time for patients to be moved to more spontaneous modes of MV with protocol guided weaning; however in the paediatric population the majority of studies show no significant difference between protocolised and non-protocolised weaning groups (Randolph *et al.*, 2002; Blackwood and Tume, 2015) and indicate that weaning protocols do not necessarily decrease the duration of MV (Laham, Breheny and Rush, 2013).

Generally there are three methods used in weaning protocols: 1) gradual reduction in ventilatory support; 2) an abrupt termination of ventilatory support (spontaneous breathing trial); or 3) a combination of the two (Wielenga *et al.*, 2016). Gradual reduction in ventilatory support is the most

common form of weaning (Newth *et al.*, 2009). Weaning protocols generally include objective assessments of the patient's clinical stability, level of oxygenation, mental status and pulmonary function before the weaning process is started (Blackwood *et al.*, 2013).

In a study by Blackwood and Tume (2015), who performed a survey in 23 PICUs in the UK, it was reported that none of the PICUs had reported implementing a formal set of weaning criteria to determine readiness to wean and SBTs were seldom used. Weaning from MV was generally practiced according to clinician preference and there was no consensus regarding a protocol to follow (Blackwood and Tume, 2015). A study by Keogh (2004) reporting on the current weaning practices in Australian PICUs found that all the units followed ventilation guidelines, but none had implemented weaning guidelines.

Rose *et al.* (2015) performed a systematic review of the available evidence to compare the effect of automated weaning systems on duration of weaning in adults and children compared to non-automated strategies. They reported on pooling of data from 16 studies that an automated weaning system can reduce duration of weaning by 30%; however other variables may have influenced this result. This decrease in duration of weaning may be due to the independence of the system on clinician recognition of changes to the patients' weaning status, whilst in clinician dependent systems, delays may be due to clinician availability, work load and expertise. Rose *et al.* (2015) concluded that automated weaning systems reduced total time on MV, ICU length of stay and weaning duration. Automated systems also have the potential to decrease time to first extubation, total time on MV, ICU length of stay, tracheostomy rate and effects on morbidity and mortality, re-intubation and non- invasive ventilation (NIV), amongst others (Rose *et al.*, 2015). Rose e*t al.* (2015) reported that 13 of the 21 eligible trials were published within the last 5 years which indicates an increased interest in automated closed-loop systems, where adjustments to ventilator settings are made automatically and without the need for clinician confirmation. There needs to be more research performed in paediatric populations in order to develop automated systems that are adapted to infants and children (Rose *et al.*, 2015).

Jouvet *et al*. (2007) performed an interventional study on a closed-loop weaning protocol in a paediatric population. The closed-loop protocol is intended to decrease the total duration of MV by adjusting pressure support more frequently than when adjusted manually. Pressure support is automatically adjusted according to the patients' response and monitored breathing pattern. The median number of changes in ventilator settings per hour was recorded as 1.5 (Jouvet *et al.*, 2007), which is more frequent than what would be expected if adjusted manually. Adjustments of pressure support during MV is one of the ways in which the load on the respiratory muscles can be altered

during MV. The closed-loop system can increase the level of pressure support when necessary, to accommodate exacerbation of lung disease (Jouvet *et al.*, 2007). They reported a non-statistically significant decrease in MV duration when compared to a historical control and suggested that the system be tested first in a larger population to ensure that efficacy and tolerance of the system before implementation, however this expert closed-loop weaning system was used to wean children from MV safely (Jouvet *et al.*, 2007).

Restrepo e*t al.* (2004) studied the effect of a ventilator management protocol (VMP) in a paediatric population. They reported that although in their study the total MV time did not decrease, the time to spontaneous breathing did. Benefits of spontaneous breathing include improved ventilator-patient synchronicity and thus a decrease in sedation and allows for lower peak pressures which can reduce the incidence of ventilator-induced lung injury, however liberation from MV remains the more important outcome (Restrepo *et al.*, 2004). They also reported that the main benefit from the VMP was the effect that the protocol had on the staff of the PICU, and there was an improvement in patient care culture, which fostered better staff relationships (Restrepo *et al.*, 2004).

A recommendation made by Keogh, Courtney and Coyer (2003) is that in order for weaning guidelines to be more effective, they should be tailored to the specific needs of patients. Clinicians should thus predict and identify short- to medium- and long- term ventilated patients and adjust weaning protocols as required in order to ensure successful weaning. This may be the case for other patient populations and characteristics that may influence weaning; therefore paediatric weaning guidelines should be appropriately adjusted (Keogh, Courtney and Coyer, 2003).

It is important to determine factors that could predict or aid in identifying paediatric patients that are at risk for failure to wean. Respiratory drive, neuromuscular conduction, respiratory muscle strength and endurance are some factors that should be taken into consideration before and during weaning (Edmunds, Weiss and Harrison, 2001). Clinicians can thus prevent delayed weaning or extubation and failed extubation, as this will result in longer stay in PICU, greater health care costs and increase the risk of ventilator associated complications (Kurachek *et al.*, 2003; Schindler, 2005). It is also important as identifying these factors will be essential in providing clearer weaning guidelines.

Extubation Failure in Paediatrics

One of the main concerns with weaning from MV is the risk of extubation failure (Turner and Arnold, 2007). Several authors have reported that extubation failure is associated with significant mortality. There has been no clear explanation for this, however it could be due the increase in duration of MV after re-intubation, which increases the risk of nosocomial infection or because the patients that fail

extubation are in a state of clinical deterioration and are already at increased risk of mortality (Fontela *et al.*, 2005). Kuracheck *et al.* (2003) reported a tracheostomy rate of 14.5% and the mortality rate increased to about five times more than the patients that were successfully extubated on the first attempt.

The extubation failure rate in the paediatric population is approximately 10%, which is consistent with published data from studies done by Harikumar *et al.* (2009) who reported a rate of 10% and Laham, Breheny and Rush (2013) who reported a rate of 9% in their study. The rate of extubation failure in neonates can be as high as 22-28% (Saikia, Kumar and Sreenivas, 2015). Most extubation failures take place within the first 12 hours after extubation, with 80% of extubation failures occurring within 24 hours of extubation (Ferguson *et al.*, 2011). Baisch *et al.* (2005) found that extubation failure, although a more infrequent event in paediatrics than in adults, may lead to longer duration of intubation and MV, longer stay in the PICU and an increased tracheostomy rate. The extubation failure rate in paediatrics may be low, however it is significantly higher for those that have been intubated for >10 days and those that have existing respiratory or neurological conditions (Ferguson *et al.*, 2011). In a study by Laham, Breheny and Rush (2013) the average length of stay in the PICU for patients who were successfully extubated was 7 days, compared to 21 days for patients who were unsuccessfully extubated. Baisch *et al.* (2005) reported that children that require reintubation, after extubation failure, have increased length of hospital stay, intubation duration and PICU stay. In addition to this, Laham, Breheny and Rush (2013) also found a 3.2 fold increase in costs after a failed extubation compared to a patient that was successfully extubated.

The reason for extubation failure in younger infants may be due to physiological and anatomical factors. Infants have a higher thoracic compliance and less compliant lungs which results in them having to use more force in order to produce an adequate tidal volume, which may increase the risk of fatigue (Fontela *et al.*, 2005). The infant diaphragm muscle fibre composition only reaches adult composition (50-55% fatigue resistant fibres) at 7-8 months; as the full-term infant has about half the amount (25%) of Type I fibres than that of the adult (Siren and Siren, 2011). Type I, slow twitch muscle fibres, which are used during normal tidal breathing due to their endurance capacity, are more resistant to fatigue. Type II fast twitch (type IIA rapid oxidative and IIB rapid glycolytic) fibres are not resistant to fatigue and are mainly recruited in instances of increased breathing rate. The fewer type I muscle fibres in the infant diaphragm results in infants being more prone to fatigue of the diaphragm and fatigue occurring more rapidly than in adults, which also predisposes infants to respiratory failure. Diaphragmatic fatigue is identified by a decrease in duration of contraction and

the loss of contractility, and is often associated with failure to wean from the ventilator in adults (Anraku and Shargall, 2009).

There are also associations between longer duration of MV and extubation failure, and prolonged use of analgesics or sedatives and extubation failure (Fontela *et al.*, 2005). Fontela *et al.* (2005) reported that prolonged use of dobutamine and dopamine were associated with an increased risk of extubation failure. There are also a number of other factors that makes younger patients more vulnerable to extubation failure. Some factors include the immaturity of the upper airway which is less tolerant to endo-tracheal tubes (ETTs) and cognitive limitations which also result in the increased need for sedative or muscle relaxant use in these patients (Kurachek *et al.*, 2003).

One of the most commonly reported underlying reasons for extubation failure in infants and children is upper airway obstruction (UAO), characterised by stridor. Edmunds, Weiss and Harrison (2001), studied the rate of extubation success and failure in an American PICU and reported UAO (identified by the presence of stridor) as the most common reason for extubation failure in infants. UAO may be due to the narrowness of the subglottic larynx and the vulnerability of the mucosa to irritation and inflammatory oedema with endotracheal intubation (Edmunds, Weiss and Harrison, 2001). UAO may also be influenced by residual sedative or muscle relaxant effects as well as neurological instability (Kurachek *et al.*, 2003). UAO was also cited as being the most common reason for extubation failure and contributed to 35% of failed extubations in a study by Baisch *et al.* (2005). Post-extubation stridor was identified in 22% of the participants in a study by Laham, Breheny and Rush (2013), and the extubation success rate was 81% in those with extubation stridor and 94% in those without extubation stridor. There are some data to suggest that treatment with prophylactic systemic corticosteroids can decrease the incidence of post-extubation UAO, which may decrease the need for re-intubation in some neonatal and paediatric patients (Turner and Arnold, 2007). However Laham, Breheny and Rush (2013) reported that post-extubation stridor was identified in 22% of patients that received pre-extubation steroids and in 22% of patients who did not receive pre-extubation steroids. Extubation success rate was 85% for those that received pre-extubation steroids and 93% for those that did not (Laham, Breheny and Rush, 2013). Laham Breheny and Rush (2013) did note, however, that the presence of airway abnormalities/conditions may also have influenced this result. Kurachek *et al.* (2003) reported that patients with upper airway deformities or disorders, whether of medical or surgical origin, had almost double the risk of extubation failure compared to patients without these conditions. An ETT has the potential to exacerbate airway disorders and cause further upper airway injury, which has been found to be associated with increased risk of extubation failure in both the paediatric and adult population

(Kurachek *et al.*, 2003). Kurachek *et al.* (2003) found that ten or more days with an ETT correlated with an extubation failure rate of 17.5% in their study. Kurachek *et al.* (2003) reported that the type of ETT used, whether cuffed or uncuffed, did not significantly affect their extubation failure rate.

A number of studies in the paediatric population have attempted to identify the key risk factors for extubation failure in the paediatric population. Most current research has identified that duration of MV, younger age and medications such as sedative/analgesic drugs (Fontela *et al.*, 2005), are the main contributing factors to extubation failure in paediatrics (Fontela *et al.*, 2005; Laham, Breheny and Rush, 2013). Turner and Arnold (2007) and Newth (2009) concurred with this research reporting a significant association between extubation failure and infants aged one to three months and infants younger than 24 months in their studies, respectively. Thiagarajan *et al.* (1999) reported that children in their study that had failed extubation were younger, had been on MV for a longer duration, had an increased ventilator demand, poor respiratory system compliance and had oxygenation and ventilation defects compared to those what were successfully extubated. The populations that are particularly at risk of failed extubation as reported by Kurachek *et al.* (2003), were those less than two years of age, patients intubated for prolonged periods, patients with underlying respiratory or neurological conditions, patients with dysmorphic features or airway disorders, and advised that these at risk patients should be specifically investigated to prevent such occurrences.

Diaphragm dysfunction or ventilator-induced diaphragmatic dysfunction (VIDD) maybe be an underlying reason for failed weaning and extubation (Wolf *et al.*, 2011) as even short periods of MV can lead to diaphragmatic atrophy within 18-69 hours of initiation of MV (Levine *et al.*, 2008; Ferguson *et al.*, 2011). Contractile fatigue of the diaphragm may occur due to an increased mechanical load on the respiratory muscles for long periods of time (Wolf *et al.*, 2011). In a study by Kurachek *et al.* (2003), 40% of patients that failed extubation had insufficient respiratory muscle strength and pulmonary dysfunction, both of which may be identified and addressed before an extubation attempt (Kurachek *et al.*, 2003). Diaphragmatic function is essential for respiration and for the ability to coordinate with MV as well as to sustain spontaneous respiration after liberation from MV (Johnston *et al.*, 2010; Ferguson *et al.*, 2011). It is thus important to consider the evaluation of respiratory drive and respiratory muscle function during a period of MV, as this may be effective in predicting patients at risk for extubation failure (Johnston *et al.*, 2010), especially in babies who are already vulnerable to diaphragmatic fatigue due to the muscle fibre composition of the diaphragm. These factors should also be taken into consideration before the decision to extubate (Newth *et al.*, 2009; Blackwood *et al.*, 2013).

Other contributing factors or possible underlying reasons for extubation failure that have been reported are chronic respiratory or neurologic conditions, decreased level of consciousness, haemodynamic instability (Johnston *et al.*, 2010), sepsis, cardiac failure and apnoea (Fontela *et al.*, 2005). Saikia, Kumar and Sreenvias (2015) found that 50% of patients in their study that failed extubation had pre-morbid respiratory involvement; approximately 76% of the patients had a changed, poor or increased respiratory effort. Patients with an underlying neurological condition are also more at risk for extubation failure (Kurachek *et al.*, 2003). Progressive or static encephalopathy is associated with pharyngeal hypotonia which may lead to an impaired ability to clear pulmonary secretions (Kurachek *et al.*, 2003) and a poor cough reflex and thick secretions have also been reported to be potential risk factors for extubation failure (Saikia, Kumar and Sreenivas, 2015). It has also been postulated that in the case of extubation failure in post-operative cases, extubation failure was due to premature extubation (Saikia, Kumar and Sreenivas, 2015).

Some authors have noted that in order to achieve successful extubation one needs to achieve resolution of the primary process or reason for initiation of MV, the patient should have an intact airway and respiratory drive, the ability to perform effective gaseous exchange, must be able to clear airway secretions effectively and have sufficient respiratory muscle strength (Thiagarajan *et al.*, 1999). There should also be a reduction and eventual elimination of sedatives and muscle relaxants and their effects (Kurachek *et al.*, 2003). It is for these reasons that the decision to extubate should be made based upon standard and reproducible criteria (Bousso *et al.*, 2006), however no such criteria are available in this population at this stage.

Predicting Extubation Failure in Paediatrics

Evidently there are a number of factors that must be considered before weaning and extubating a patient from MV. Identification of a single set of criteria to predict successful extubation or extubation outcome has not yet been developed in the paediatric population (Foronda *et al.*, 2011); and adult indices of extubation outcome adapted to children have shown inconsistent results (Laham, Breheny and Rush, 2013). The use of multivariate indices that integrate a number of physiological functions are more likely to be accurate predictors of extubation outcome than univariate indices that examine only a single aspect of physiological function, and are therefore often poorer predictors of extubation outcome (Harikumar *et al.*, 2009). There have been numerous studies performed in the paediatric population in an attempt to identify the most consistent and effective means of predicting extubation outcome in this population.

Physiological Indicators

A study performed by Foronda *et al.* (2011) compared the extubation criteria of two PICUs in Brazil. They reported that the extubation criteria routinely used included: the resolution of the cause that

led to the initial need for intubation, correction of respiratory acidosis, pharmacological resolution of wheeze, $FiO_2 \leq 40\%$, $PEEP \leq 5cmH_2O$, $PIP \leq 20cmH_2O$, temperature <38.5°C, haemodynamic stability, reduced need for sedation, electrolyte balance, and no neuromuscular blocker administered within previous 24 hours (Foronda *et al.*, 2011). Haemodynamic instability, especially in mechanically ventilated patients, causes an unbalance between oxygen supply and tissue extraction which may lead to regional hypoxia. This may increase the risk of respiratory failure and apnoea in children (Fontela *et al.*, 2005).

A study by Farais *et al.* (2004) found that bedside measures of RR, maximum inspiratory pressure (Pimax) and rapid shallow breathing index (RBSI), represented by the frequency to tidal volume ratio (f/Vt), are poor predictors of extubation failure in the paediatric population who have passed a spontaneous breathing test with a T-piece or low level pressure support. The sensitivity of these measures never reached a value above 50% and the accuracy of these measures also did not improve when measured immediately before extubation (Farias *et al.*, 2004). Other studies that have assessed the sensitivity of these indices in predicting extubation failure have reported a sensitivity of 33-71%, 57-65% and 57-78% for Vt, RR and f/Vt ratio, respectively (Farias *et al.*, 2004).

A survey done by Santschi *et al.* (2007) concluded that during weaning the physiological limits accepted by clinicians who offered feedback on the survey were broad, which was unexplained by differences in demographics or geographic distribution. They concluded that there are very diverse opinions regarding the physiological ranges that are accepted during weaning in the absence of a defined set of criterion or evidence-based weaning guidelines (Santschi *et al.*, 2007).

Fraction of inspired oxygen (FiO_2)

There has also been some research into measures of FiO_2 and its association with extubation failure. Fontela *et al.* (2005) found that higher levels of FiO_2 (>0.4) is associated with extubation failure, and may predict extubation failure. However, an increase in FiO_2 may reflect the processes that lead to extubation failure, and is unlikely to be a cause of extubation failure in itself (Fontela *et al.*, 2005). Therefore it may be valuable to investigate the underlying reason/s for high FiO_2 prior to extubation (Fontela *et al.*, 2005).

Ratio of dead space to tidal volume

The ratio of dead space to tidal volume (VD/VT) has been used to determine the severity of diaphragmatic hernia in neonates, the degree of lung injury in MV children and as a marker in children for lung damage in ARDS (Bousso *et al.*, 2006). Hubble *et al.* (2000) reported the effectiveness of the VD/VT ratio as an appropriate measure to use for predicting extubation failure in children, however their population included older children (up to 18 years of age) which may be

why Bousso *et al.* (2006) reported contradictory results. Their population was younger and included infants, who have characteristic differences in respiratory physiology and anatomy. Young infants demonstrate less resistance to muscular fatigue, have a less effective cough and therefore are less able to remove respiratory secretions and have narrower airways (Bousso *et al.*, 2006). This may be why they found that the VD/VT ratio is ineffective in predicting extubation failure risk in their population of MV infants, because the VD/VT ratio does not take respiratory physiology and characteristics into account (Bousso *et al.*, 2006).

Ventilator settings

Factors associated with low risk of extubation failure are normal tidal volume indexed to body weight, a low FiO_2, mean airway pressure, oxygenation index, peak inspiratory pressure, high dynamic compliance, low total minute ventilation from the ventilator and normal or high mean inspiratory flow (Khan, Brown and Venkataraman, 1996). Conversely, there is an increased risk of extubation failure when: a) lower than normal tidal volumes indexed to body weight during a spontaneous breath; b) increased load on the respiratory muscles resulting in high peak inspiratory pressure or low dynamic compliance and c) decreased respiratory drive, indicated by low mean inspiratory flow (Khan, Brown and Venkataraman, 1996; Venkataraman, Khan and Brown, 2000).

They also found that Pi or Pimax to be useful predictors of extubation outcome (Venkataraman, Khan and Brown, 2000). Laham, Breheny and Rush (2013) reported that clinicians should not rely on low ventilator settings to determine a patient's readiness for extubation, especially in acute cases. Overreliance on ventilator settings for extubation readiness may lead some clinicians to extubate prematurely or to unnecessarily prolong the duration of MV. Laham, Breheny and Rush (2013) reported that low ventilator settings were associated with increased extubation failure rate in five patients with ≤1 day of MV. Laham, Breheny and Rush (2013) suggested performing daily assessments of extubation readiness, using examinations of the patient and their records to evaluate the potential risks of extubation failure. Factors such as upper airway swelling, little to no spontaneous breaths, inability to maintain the airway and to clear pulmonary secretions or signs of non-resolution of active infection may all be used as indicators for potential extubation failure (Laham, Breheny and Rush, 2013). Mean airway pressure (Paw), which reflects the average airway pressure throughout the ventilatory cycle, indicates the level of pressure support provided by the ventilator (Fontela *et al.*, 2005). Khan *et al.* (1996) and Venkatarama, Khan and Brown (2000) both reported that a high Paw before extubation is associated with extubation failure. Contradictory to this, Fontela *et al.* (2005) reported that a low Paw is associated with extubation failure, however these patients had a longer duration of MV, were on sedation for longer and were younger in age.

These factors could also have had an effect on decreasing tidal volume and increasing fatigue before extubation (Fontela *et al.*, 2005).

Extubation readiness test (ERT)

Ferguson *et al.* (2011), who studied the effectiveness of the ERT in a paediatric population, reported that the ERT used with pressure support and a spontaneous breathing trial resulted in similar extubation failure rates when compared to patients that were extubated using clinical judgement alone. One of the main reasons for this was that the ERT does not account for upper airway obstruction being a factor for failed extubation (Ferguson *et al.*, 2011). Use of an ERT may unnecessarily increase the duration of MV or may lead to overestimation of extubation readiness and thus may increase extubation failure rates (Ferguson *et al.*, 2011). Ferguson *et al.* (2011) also concluded that the ERT is not reliable when used to determine extubation readiness in patients that have been intubated for >48 hours. The extubation failure rate was more than three times higher for those who were extubated after >48 hours who had passed the ERT, than those extubated within 48 hours of intubation (Ferguson *et al.*, 2011). The most common cause of extubation failure in the study by Ferguson *et al.* (2011) was inadequate gaseous exchange due to lower respiratory tract complications, which lead them to believe that the ERT may in fact mask respiratory insufficiency. In patients that were intubated for >48 hours successful completion of the ERT was not associated with extubation success (Ferguson *et al.*, 2011).

Patients that produce higher diaphragm activity may have more preserved diaphragmatic function (Wolf *et al.*, 2011). During an ERT, Wolf *et al.* (2011) found that the paediatric patients who produced higher diaphragmatic electrical activity (Edi) per tidal volume, were more likely to pass the ERT than the children who produced a lower Edi per tidal volume.

Spontaneous breathing test (SBT)

The SBT aims to evaluate the strength of the respiratory muscles and to monitor signs of fatigue prior to extubation (Foronda *et al.*, 2011). The general duration of an SBT has been set at two hours, however there is no evidence supporting that a two hour SBT is a more effective predictor of extubation outcome than a shorter SBT; which was confirmed in a study by Chavez, dela Cruz and Zaritsky (2006). They reported, in a study of 20 patients, that a patient who fails an SBT will do so within minutes of initiation of the SBT, so shorter SBTs should be as effective in predicting extubation outcome as longer SBTs (Chavez *et al.*, 2006). A 15 minute SBT appeared to be as effective as a longer trial in predicting extubation outcome in MV children (Chavez *et al.*, 2006).

Chavez, dela Cruz and Zaritsky (2006) performed a SBT using an anesthesia bag. They found that the anesthesia bag provides CPAP which aids the maintenance of functional residual capacity, which a T-

piece does not. They reported that after having completed an SBT using a flow-inflating anesthesia bag resulted in a 92% success rate after extubation in their study. This result is well above the reported rates of successful extubation following SBTs in both adult and paediatric studies (Chavez *et al.*, 2006). This is important in children as the low elastic recoil of the chest wall predisposes them to reduced lung volumes, in this way the T-piece may promote the development of atelectasis and increase the work of breathing. The 15 minute SBT using an anesthesia bag had a 95% sensitivity in predicting extubation success in PICU patients (Chavez *et al.*, 2006).

Following the same protocol, using a two hour SBT, Saikia, Kumar and Sreenivas (2015) found in their study that failing an SBT has a strong correlation to extubation failure. Chavez, dela Cruz and Zaritsky (2006) stated that failure of an SBT is associated with but does not effectively predict extubation failure. The SBT may be more likely to predict the patients that will fail extubation rather than those who will be successfully extubated (Chavez *et al.*, 2006). Some authors have reported that combining a SBT with daily evaluation is a possible method to aid in reducing the duration of MV (Foronda *et al.*, 2011).

Dynamic compliance, respiratory rate, oxygenation, maximum inspiratory pressure (CROP) index and Rapid shallow breathing index (RSBI)

The CROP index and RSBI are multivariate indices (Harikumar *et al.*, 2009) used to predict extubation outcome in adults. Harikumar *et al.* (2009) reported that more recent studies of these indices have been limited and resulted in contradictory conclusions. They reported that the RSBI and CROP indices were found to be neither sensitive nor specific in predicting extubation outcome in children (Harikumar *et al.*, 2009). Khan, Brown and Venkataraman (1996) agreed that adult indices, such as the CROP index, are not useful predictors of extubation outcome in infants and children. The CROP and RBSI are not useful to predict extubation failure in children as they do not account for normal developmental changes in respiratory mechanics and gaseous exchange, however, it is still unknown whether an age modified score would be more appropriate (Venkataraman, Khan and Brown, 2000). A study by Baumeister *et al.* (1997) also agreed that adult indices should not be directly extrapolated for children and infants, however also demonstrated that the CROP and RSBI when modified to the paediatric population are effective means of predicting extubation outcome. Thiagarajan *et al.* (1999) reported that the CROP and RSBI was more effective in predicting extubation success than extubation failure in children.

Diaphragm tension-time index (TTdi) and respiratory muscle tension-time index (TTmus)

Ventilation is dependent on the drive of the central nervous system, the capacity of the muscles of respiration, and the load imposed on them (Harikumar *et al.*, 2009). Therefore, according to Harikumar *et al.* (2009), the factors most likely to be predictive of extubation outcome are those

evaluating the load on the respiratory muscles and effectiveness of breathing effort. The tension–time index of the diaphragm (TTdi), is a measure of the load capacity ratio of the diaphragm (Bhat *et al.*, 2016). It is derived by relating the mean transdiaphragmatic pressure per breath (Pdi) to the maximal inspiratory transdiaphragmatic pressure (Pdimax) and the inspiratory time (Ti) to the total respiratory cycle time (Ttot). A TTdi found in excess of 0.15 is indicative of an unsustainable load on the respiratory muscles and is suggested to be indicative of impending respiratory failure (Harikumar *et al.*, 2009) in adults and previous studies have reported that it is effective to use in paediatric populations (Bhat *et al.*, 2016). The measurement of TTdi is performed invasively via balloon catheter, however, TTmus which is a non-invasive measure based on airway pressure has been developed (Harikumar *et al.*, 2009).

Non-invasive tension-time index of the respiratory muscles (TTmus) reflects the respiratory drive modulated load/capacity balance of the respiratory muscles. It is ideally suited for use in the paediatric population as they are independent of the changes in respiratory muscle strength that occur with age. TTmus requires further validation in other paediatric study populations (Harikumar *et al.*, 2009). When compared with TTdi, TTmus also provided an accurate assessment of the load capacity ratio of the inspiratory muscles; and is therefore an accurate predictor of extubation outcome in ventilated children. This is a valuable finding to avoid using invasive measurements and to promote non-invasive measurements (Harikumar *et al.*, 2009).

Bhat *et al.* (2016) studied the effectiveness of the TTdi and TTmus to predict extubation outcome in term and premature infants. TTdi had an 81% specificity and 83% sensitivity overall and showed 60% specificity and 95% sensitivity in prematurely born infants in predicting extubation failure (Bhat *et al.*, 2016). The higher RR, increased chest wall compliance and immaturity of the respiratory system could have lead to a lower critical TTdi (Bhat *et al.*, 2016).

Conclusion:

This review reports on the current published evidence regarding PICU/NICU practice in terms of MV, weaning and extubation. Even though there have been several studies done in this population, this review has identified that there are many inconsistencies in current clinical practice between PICUs and clearly identifiable gaps in the research.

There are currently no clear protocols to guide the practice of MV weaning. Current evidence reports that weaning guidelines may not be useful in the PICU to decrease duration of MV and improve extubation outcome, and adult protocols are not appropriate to use in the paediatric population due to the difference in respiratory anatomy and physiology. There is evidence to suggest that weaning protocols that have been adapted to the paediatric population may be more

appropriate. More research will need to be done in order to design and implement effective weaning protocols in the paediatric population.

It is also evident that there are several underlying and contributing factors for extubation failure in infants and children. Main risk factors that have been identified for extubation failure include duration of MV, younger age and current medication or sedation. One of the main underlying reasons for extubation failure is UAO, characterised by stridor. Other underlying reasons for extubation failure that have been identified are respiratory conditions, neurologic conditions, decreased level of consciousness or haemodynamic instability; and a few articles mentioned that evaluation of the respiratory muscle condition is necessary during weaning and may have an effect on extubation success or failure. Some authors have identified respiratory muscle strength, endurance and function as factors that should be assessed during weaning to ensure successful extubation; however, this research shows that what the effect of MV is on the respiratory muscles in paediatrics is lacking. More research needs to be done on measures that can be implemented to reduce the presence of contributing factors to extubation failure in infants and children and therefore prevent or reduce the rate of extubation failure.

CHAPTER 2: PILOT STUDY

Reliability of Ultrasonic Diaphragm Thickness Measurement in Mechanically Ventilated Infants and Children

Introduction

This study assesses the reliability of using ultrasound (US) to measure diaphragm thickness in mechanically ventilated infants and children. This modality has the potential to be used in the clinical and research setting to identify paediatric patients who are at risk for extubation failure due to ventilator-induced diaphragm dysfunction characterised by a decrease in diaphragm thickness and activity.

Background

Diaphragmatic atrophy can occur even during brief periods of mechanical ventilation (MV) and can begin within 18-69 hours of initiation of MV (Levine *et al.*, 2008; Ferguson *et al.*, 2011). Schepens *et al.* (2015) studied the progression of diaphragm atrophy in adult ventilated patients using US and reported that after just one day of MV there was already a substantial decrease in diaphragm thickness with the biggest decrease occurring within the first 72 hours of MV. Although diaphragm atrophy during full MV support has been well described in adults, paediatric data are lacking and research in this field is warranted (Emeriaud *et al.*, 2014). The diaphragm is the main muscle of respiration and infants rely even more so on the diaphragm for respiration than adults due to physiological and anatomical differences in the respiratory system (Anraku and Shargall, 2009; Siren and Siren, 2011). Diaphragmatic atrophy is associated with diaphragm dysfunction (Schepens *et al.*, 2015), which has been linked to weaning difficulties and extubation failure in adults.

US is a non-invasive tool which can be used to visualise and evaluate the structure and function of the diaphragm (Sarwal, Walker and Cartwright, 2013). The non-invasive and risk-free nature of US also makes it appropriate to use with critically ill infants and children (Goligher *et al.*, 2015). The costal part of the diaphragm is relatively close to the surface of the skin therefore a high resolution and low penetration US probe (between 7.5-15 MHz) can be used to effectively visualise and measure the thickness of the diaphragm (Gibson *et al.*, 2002). Diaphragm thickness can be measured using US at different lung volumes, during tidal breathing and during static inspiratory efforts (Gibson *et al.*, 2002). The measurement is rapid and produces accurate and reproducible results in most adult individuals (Gibson *et al.*, 2002; Sarwal, Walker and Cartwright, 2013). To the best of our knowledge, there are no studies using US to monitor diaphragm thickness in the paediatric population.

This study aimed to evaluate the inter- and intra-rater reliability of using ultrasound to measure diaphragm thickness in mechanically ventilated infants and children in the PICU for future use in research and clinical practice.

Research Objectives:

- To assess the inter-rater reliability of using ultrasound to measure diaphragm thickness in mechanically ventilated infants and children
- To assess the intra-rater reliability of using ultrasound to measure diaphragm thickness in mechanically ventilated infants and children

Research design and Methodology

A prospective observational study was conducted in the paediatric intensive care unit (PICU) at Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, South Africa; a 22-bed multidisciplinary PICU in a tertiary academic hospital. The PICU admits approximately 1 400 children per annum, with an estimated 9% mortality rate. Ethical approval was obtained from the Human Research Ethics Committees of the University of Cape Town (179/2013) and the University of Stellenbosch (S16_05_087) (Addendum E and F). Written informed consent was obtained from the parent or legal guardian of the child (Addendum G).

All intubated and mechanically ventilated patients between zero and two years of age, admitted to the PICU of RCWMCH were eligible for inclusion if they had received MV for $\leq$ 24 hours. Patients were excluded from this study if they**:** were chronically ventilated patients; likely to be extubated within 24 hours of intubation; haemodynamically unstable; prematurely born neonates; had thoracic burns and/or dressings covering the thoracic area; had current or previous diaphragmatic abnormalities, hernias or known diaphragmatic paralysis; were diagnosed with neuromuscular diseases or spinal paralysis; if they had marked abdominal distension; or if they were unable to be turned from prone into the supine position for therapeutic or oxygenation purposes.

Procedure

Researchers underwent a short training session on the use of diaphragmatic US by a qualified professional, prior to starting this study.

After obtaining informed consent from the patients' parent or legal guardian, baseline data and US measurements were recorded using standardised data capture sheets (Addendum H and I). Diaphragm thickness measurements were obtained once a day for two days at roughly the same time of the morning by the same researcher and co-researcher; provided the child did not have any new condition which excluded him/her from the study (e.g. new development of ascites or abdominal distension).

Measurements were stopped if the patient became uncomfortable or distressed, or if any other urgent medical care was required and resumed afterward if the patient was deemed stable by the attending clinician.

US Methodology

Bedside US methodology, as described previously by Gibson *et al.* (2002), was implemented. With the patient in a semi-supine position (head-up at +/- 30 degrees), the Sonosite EDGE® Ultrasound System (Sonosite Fujifilm Inc., Bothell, WA, USA) was used in two-dimensional B-mode for identification of the right hemi-diaphragm, followed by an M-mode recording of breaths in order to identify diaphragm thickness at end-expiration and end-inspiration as depicted in Addendum J (Images A - C). Using the freeze-frame function, end-expiratory and end-inspiratory thickness identified; and the on-screen callipers were then placed in the centre of the upper and lower boarder of the diaphragm to measure thickness in centimetres (cm) as depicted in Addendum K (Images D - E). Measurements were taken at the end of inspiration and expiration, respectively, and the average thickness over three breaths was used for analysis. The thickness at end-inspiration and end-expiration was documented on the daily data capture sheet for each participant. After completion of measurements the researcher ensured that the patient's chest was clean from US gel, the patient was returned the nursing position and was comfortable and stable.

Inter-rater reliability

Measurements of diaphragm thickness using ultrasound were taken on the same patient for two consecutive days by the primary researcher and co-researcher, one immediately following the other. The area of measurement on the chest of the patient was cleaned between measures (i.e there were no markings or US gel residue on the patient's skin to indicate the placement of the US probe by the first researcher).

Intra-rater reliability

The primary researcher took measurements of diaphragm thickness using the same ultrasound machine at two different times (+/- 30 minutes apart) on the same participant. The area of measurement on the chest of the patient was cleaned between measures (i.e there were no markings or US gel residue on the patient's skin to indicate the previous placement of the US probe).

Statistical analysis

Intraclass Correlation Coefficients (ICC) were calculated using IBM SPSS (version 24, IBM) program and Microsoft Excel software was used to create Bland-Altman plots using the measurements of end-expiration and end-inspiration. As described previously, ICC < 0.4 indicates poor agreement; ICC

between 0.40 and 0.59 indicates fair agreement; ICC between 0.60 and 0.74 indicates good agreement and ICC between 0.75 and 1.00 indicates excellent agreement (Cicchetti, 2001).

Results

145 PICU patients were screened by the primary researcher for inclusion into the study from 18 July 2016 - 31 August 2016. 12 patients met the inclusion criteria and due to unobtained consent, only five (three male) patients were ultimately included in this reliability study. Baseline demographic data of included participants can be found in Table 2.1.

Table 2.1 –Included participant characteristics

Participant	**Age (months)**	**Sex**	**Diagnostic Category**	**Duration of MV (days)**	Spontaneously breathing* (Y/N)	
					Day 1	Day 2
1	7	Male	GIT	3	Y	Y
2	9	Female	Pulmonary	4	Y	Y
3	6	Male	Cardiac	1	Y	Y
4	16	Male	Cardiac	1	Y	Y
5	1	Female	Cardiac	3	N	Y
Mean (SD)	**7.8 (5.4)**	**-**	**-**	**2.4 (1.3)**		

**Spontaneously breathing at initial assessment each day*

Yes (Y); No (N)

Inter-rater reliability

The ICCs for the average of end-expiration on day one and day two showed an excellent correlation with the coefficients being 0.77 and 0.98 respectively. The ICC for the end-inspiration readings for day one and day two also showed excellent agreement with the ICCs being 0.80 and 0.91 (Table 2.2).

Table 2.2 – Inter-rater reliability Intraclass Correlation Coefficients

Average measures	Day	Intraclass Correlation*	95% Confidence Interval	
			Lower Bound	Upper Bound
End-expiration	1	0.766†	-0.620	0.975
	2	0.983†	0.836	0.998
End-inspiration	1	0.798†	-0.272	0.978
	2	0.912†	0.367	0.990

Two-way mixed effects model where people effects are random and measures effects are fixed.

* Type A intraclass correlation coefficients using an absolute agreement definition.

† This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

The Bland-Altman plots showed broader limits of agreement (LOA) for day 1 end-expiration compared to day 2, however all the points lie within the upper and lower LOA on both days. For day

1 end-expiration the points lie slightly further from the mean line, but are distributed evenly above and below the mean line indicating little to no bias; whereas on day 2 all the points lie much closer to the mean line but are not as evenly distributed above and below the mean line. For end-inspiration on both day 1 and day 2, the LOA are narrow and all the points lie between the upper and lower LOA. On day 2 the points are more evenly distributed above and below the mean line than day 1. All the points for day 1 and day 2 lie relatively close to the mean line besides one outlier that lies closer the lower LOA on day 1 (Addendum L).

Intra-rater reliability

The ICCs for end-expiration and end-inspiration both showed an excellent correlation at 0.94 between measures 1 and 2 (Table 2.3).

Table 2.3 – Intra-rater reliability Intraclass Correlation Coefficients

Average measures	Intraclass Correlation*	95% Confidence Interval	
		Lower Bound	Upper Bound
End-expiration	0.942†	0.464	0.994
End-inspiration	0.936†	0.405	0.993

Two-way mixed effects model where people effects are random and measures effects are fixed.

* Type A intraclass correlation coefficients using an absolute agreement definition.

† This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

The Bland-Altman plots for end-inspiration had slightly narrower LOA than end-expiration. All the points fall between the upper and lower LOA for both end-expiration and end-inspiration; and all the points are distributed equally above and below the mean line which indicates little to no bias (Addendum M).

Discussion

The aim of this study was to assess the reliability of obtaining diaphragm thickness measures using US in a mechanically ventilated paediatric population. The inter- and intra-rater reliability of US was evaluated by comparing measurements of diaphragm thickness between researchers and by comparing one researcher's measurements on two separate occasions, respectively. Ultimately it is hoped that this tool could be incorporated into clinical practice to identify diaphragm dysfunction in mechanically ventilated infants and children, to predict those at higher risk of extubation failure.

Based on the results of the tests of inter-rater reliability it is evident that there is excellent agreement between researchers. The observed improvement in agreement between researchers from day one to day two could indicate that the accuracy of measures will improve over time with

practice and experience, as positioning of the US probe is patient-specific due to differences in chest size, age, etc. Measurements of end-inspiration showed slightly better agreement than measurements of end-expiration. The results also indicted that the agreement of measures between researchers improved from day 1 to day 2; although on day 1 the measures of end-inspiration showed better agreement than measures of end-expiration and on day 2 end-expiration showed better correlation than end-inspiration. The intra-rater reliability also showed excellent correlation, with both end-inspiration and end-expiration having very high ICC values. There was slightly better agreement between the first and second readings for end-expiration than end-inspiration, which is consistent with what was found between researchers on day 2. This could be due to the variability of diaphragm thickening at end-inspiration between spontaneous and non-spontaneous breaths, which would not significantly affect thickness at end-expiration as the diaphragm will return to resting thickness after a spontaneous or non-spontaneous breath; thus these measures would stay more consistent. Another reason for better reliability with end-expiration measures could be that expiration is longer than inspiration and is therefore easier to identify and measure the point of end-expiration than end-inspiration.

A possible reason for the observed difference in measures between researchers may relate to individual differences in calliper positioning during the process of measuring the diaphragm muscle. Ideally, for both inter- and intra-rater reliability, the measures of diaphragm thickness would be done simultaneously. However, given the specificity of the area and placement of the US probe on the chest wall, this was not possible. Goligher *et al.* (2015) reported that there is a direct relationship between the level of contractile activity of the diaphragm, i.e activity during spontaneous and non-spontaneous breaths, and changes in diaphragm thickness in adults. Thus, given breath by breath variability, and differences in spontaneous versus non-spontaneous breaths over time, it was expected that measurements obtained would differ even for the same patient between breaths; which likely affected the results obtained for both inter- and intra-rater reliability.

Limitations of the study

This study was performed on a small sample of five infants and children, using only two raters. Future research should aim to increase the participant sample size and rater numbers for improved reliability of the results and to establish the generalizability of these measures to a larger sample of patients. Researchers could not accurately assess whether the measured breath was spontaneous or non-spontaneous during measurements which could also be seen as a limitation of this study; due to the difference in diaphragm thickness during a spontaneous or non-spontaneous breath. A suggestion for future research or practice of this method would be to assess and measure only the spontaneous breaths if possible. Given the relatively short time between inter-rater measurements,

it is possible that there was some recall bias, however the results of this study demonstrated that the methodology and the repeatability of these measures was reliable and can be used effectively in the clinical research setting.

Conclusion

The results of this study indicate an excellent inter-rater and intra-rater reliability when using ultrasound as a measure for diaphragm thickness in mechanically ventilated infants and children. Using US to measure diaphragm thickness was not only an appropriate and safe modality, due to the nature of US being portable, non-invasive and radiation-free, but it is also feasible to use in this population. Given the negative effect of MV on the diaphragm, measures of diaphragm thickness over a period of MV may be used to identify patients that have developed diaphragm dysfunction. Using these measures and plotting a trend may make it possible for clinicians to identify diaphragm dysfunction. Thus, these measures may be useful as a predictor for infants and children that may be at risk for weaning difficulties and extubation failure. Ultimately, it is hoped that this measure could be implemented in the clinical setting to identify mechanically ventilated paediatric patients with diaphragmatic atrophy or dysfunction.

CHAPTER 3: PRIMARY STUDY

Mechanical Ventilation and its Effect on Diaphragm Function in Infants and Children.
An explorative study.

Introduction

Mechanical ventilation (MV) has been associated with significant complications; one of them being diaphragm dysfunction (Vassilakopoulos and Petrof, 2004) Diaphragm dysfunction refers to changes in the structure or force of the diaphragm muscle (Schepens *et al.*, 2015) and can occur due to the unloading effect of MV on the diaphragm (Grosu *et al.*, 2012). Signs of diaphragm dysfunction include diaphragmatic weakness, atrophy, fatigue, decreased endurance and decreased electrical activity (Vassilakopoulos and Petrof, 2004; Wolf *et al.*, 2011; Grosu *et al.*, 2012; Schepens *et al.*, 2015). Diaphragm dysfunction specifically related to MV, or ventilator-induced diaphragm dysfunction (VIDD), is defined as a loss of force-generating capacity of the diaphragm. This definition of diaphragm dysfunction is related only to the effect of MV on the diaphragm muscle and excludes other contributing factors of diaphragmatic dysfunction such as sepsis, medications, metabolic and electrolyte imbalances and shock (Vassilakopoulos and Petrof, 2004; Petrof and Hussain, 2016). Complications of VIDD are prolonged duration of MV, weaning difficulties and extubation failure (Vassilakopoulos and Petrof, 2004). Most of the evidence on diaphragm dysfunction has been described in the adult population, and data on diaphragm dysfunction in the paediatric population are lacking.

Research has shown that changes in diaphragmatic force generating capacity and structure, which characterise diaphragm dysfunction, can be measured (Schepens *et al.*, 2015). Ultrasound (US) is a non-invasive modality that can be used to measure the structure of the diaphragm and, as discussed in chapter 2, is reliable to use in this population. Repeated measures of resting diaphragm thickness, which is the thickness of the diaphragm at end-expiration, can be used to identify changes in the thickness of this muscle which could be a means by which diaphragm atrophy or hypertrophy could be identified and monitored over time. The thickening fraction, which is the ratio of thickening of the diaphragm muscle from end-inspiration to end-expiration, can be used to measure and monitor the contractile activity of the diaphragm muscle.

Invasive measures of diaphragm electrical activity by means of oesophageal electrodes in mechanically ventilated infants and children have been described in the literature. Surface electromyography (EMG) being a non-invasive modality may be safer and associated with less risk than invasive measures, which may make application of this measure in critically ill patients more

appropriate. Hutten *et al* (2010) reports that more study on the validity of non-invasive measures in comparison to invasive measures are required; however these measures are being used in the critical care setting and provide insight into respiratory muscle activity (Hutten et al., 2010).

For the purposes of this study, we will be observing diaphragm function in terms of diaphragm electrical activity, contractile activity and atrophy in the mechanically ventilated paediatric population. Diaphragmatic US and EMG can be used to identify and measure the structure and movement of the diaphragm. These modalities are feasible, reliable, non-invasive, painless and safe to use in the critically ill paediatric population (Gibson *et al.*, 2002; Grosu *et al.*, 2012; Sarwal, Walker and Cartwright, 2013).

Study objective

To describe diaphragm function, in terms of diaphragm thickness, contractile and electrical activity, in mechanically ventilated infants and children.

Methodology

Research design
Prospective observational study.

Research setting
This setting for this study is described in Chapter 2.

Ethical considerations
Ethical considerations, such as ethical clearance and informed consent, are described in Chapter 2. Ethical clearance forms and informed consent forms can be found in Addendum E, F and G.

Sampling
All patients admitted to the paediatric intensive care unit (PICU) at Red Cross War memorial Children's Hospital (RCWMCH) from 18 July 2016 – 1 April 2017 were screened for inclusion using the same inclusion/exclusion criteria as described in Chapter 2.

Procedure
Baseline data were obtained from existing patient medical files and diaphragm measurements were recorded using standardised data capture sheets (Addendum H and I). Daily measurements of diaphragm function were obtained within 24 hours of intubation until two days post-extubation by the same researcher, at approximately the same time in the morning; given the patient had not developed a new condition which would exclude them from measurements for that day study. Measurements were stopped if patients became distressed, uncomfortable or if urgent medical care was required and were resumed once the patient was deemed stable by the attending clinician.

Ultrasound Methodology
Bedside US methodology, as described in Chapter 2 was implemented. The reliability of US to measure diaphragm thickness in mechanically ventilated infants and children is described in Chapter 2.

Resting diaphragm thickness (i.e. end-expiratory thickness) and diaphragm contractile activity (i.e. the thickening fraction, TF) were assessed for the purposes of this study. TF was calculated using the following formula (Sarwal, Walker and Cartwright, 2013):

*TF = ((thickness at end-inspiration – thickness at end-expiration)/thickness at end-expiration) * 100*

Surface Electromyography Methodology
A Dipha® (Inbiolab BV, Groningen, Netherlands) EMG device was utilised with the methodology and electrode placement as described by Hutten *et al.* (2008). Electrodes used for measurement of the intercostal muscle activity were omitted for the purpose of this study.

Patients remained in supine (with 30 degrees head-up) during EMG. When possible, patients were measured during quiet sleep or during periods of minimal movement and EMG recordings were continued until an uninterrupted measurement of 30 breaths was obtained, which varied between patients. Only data obtained during periods of minimal peripheral movement were analysed. The gating method was performed automatically during data acquisition by the Polybench software (Inbiolab BV Groningen, Netherlands) in order to remove any activity signals obtained from the heart (Maarsingh *et al.*, 2000).

The mean sum of activity from the left and right hemi-diaphragms were obtained and processed (Addendum N) using Polybench software (Inbiolab BV, Groningen, Netherlands). Data were collected on electronic data spreadsheets using Microsoft Excel (Windows 10).

Statistical analysis

The IBM SPSS (version 24, IBM, USA) program was used to test data for normality using the Shapiro-Wilks W test. Means and standard deviations for normally distributed data or medians and interquartile ranges for non-normally distributed data were calculated. Relationships between variables were identified using Spearmans correlations and scatter plots (presenting both R and R^2 values). Differences between sub-groups were measured using a two-way ANOVA, using Statistica version 13 (StatSoft Inc, Tulsa, USA). Preliminary data analysis was done in consultation with a statistician at the Biostatistics Unit, Division of Epidemiology and Biostatistics, Stellenbosch University. A significance level of $p \leq 0.05$ was chosen.

Adult studies show that diaphragm atrophy begins within 48 hours of initiation of MV (Grosu *et al.*, 2012), thus patients were grouped according to whether they had an initial increase or decrease in TF from day 1 to day 2 of MV. Patients were also grouped according to whether or not they were breathing above the set ventilator rate on the first day of MV.

Results

Twenty-five participants were included and full data were obtained for twenty four participants (67% male; 6.5 (median) months), which were used in the final analysis. Table 3.1 represents included participant characteristics at baseline. After discharge from the PICU to the general ward US measures could no longer be taken due to hospital protocol and limited availability of the US machine; therefore post-extubation US measures for some participants are lacking. One participant died after one day's measurement, thus was excluded from analysis. Three participants (12.5%) had no EMG measurements taken due to sternotomy incisions precluding electrode placement. Eight extreme EMG values were removed due to presumed technical error, with extreme values (ranging from 41.5 – 523.6µV). *Figure 3.1* is a flow chart of participants and data through the study.

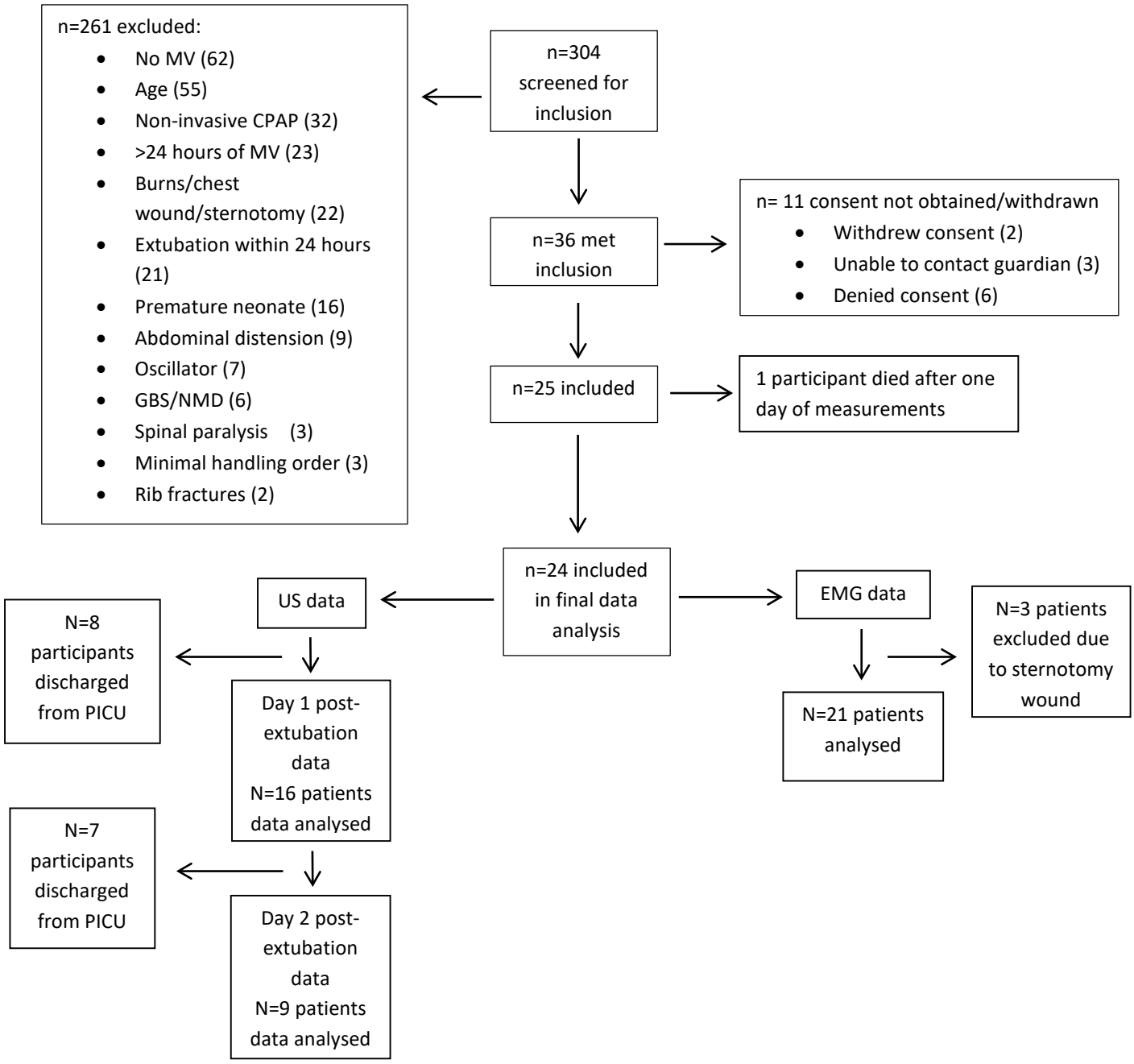

Figure 3.1 – Flow chart of participants and data through the study

Abbreviations: mechanical ventilation (MV), continuous positive airway pressure (CPAP), Guguillain-Barre syndrome (GBS), neuromuscular disease (NMD),ultrasound (US), electromyography (EMG),paediatric intensive care unit (PICU)

Participant characteristics and outcomes

One participant started MV on invasive continuous positive airway pressure (CPAP), all other included participants started on pressure control (PC) ventilation on day 1 of MV. Eighteen (75%) participants spent 100% of their total ventilator time on PC. On the last day of MV the participants were mechanically ventilated on either PC (92%) or invasive CPAP (8%). On the first day post-extubation the patients were either extubated to nasal prong oxygen (NPO_2) (42%), non-invasive CPAP (38%), high flow oxygen (4%) or room air (RA) (17%). By the second day post-extubation the patients were either on NPO_2 (33%), non-invasive CPAP (25%) or RA (42%). Fourteen (58%) patients were recorded as taking additional breaths over and above the set ventilator rate and ten patients were not taking any additional breaths on day 1 of MV. Modes of ventilation used and amount of support received can be found in Addendum O. One patient (4%) never received any sedation, however all other patients were either sedated with morphine (n=15, 63%), midazolam (n=3, 13%) or a combination of the two (n=5, 21%). Only one patient received a neuromuscular blocking agent (n=1, 4%) for the first two days on MV. Table 3.1 represents included participant characteristics at baseline (day 1 of MV) and MV and PICU outcomes.

Table 3.1- Characteristics and outcomes of included participants (n=24)

Sex	
Male (%)	16 (67%)
Female (%)	8 (33%)
Age	
0-12 months	16 (67%)
>12 months	8 (33%)
Median months (IQR)	6.5 (13.25)
Weight	
<5kgs	10 (42%)
>5kgs	12 (50%)
No recorded weight	2 (8%)
Median (IQR)	5.50 (2.7)
Diagnostic Category	
GIT (%)	7 (29%)
Pulmonary (%)	4 (17%)
Cardiac (%)	8 (33%)
Trauma (%)	1 (4%)
Post-op (%)	2 (8%)
Neurologic (%)	2 (8%)
Sedation duration	
Mean days (SD)	2.83 (1.88)
MV duration	
Median days (IQR)	3 (3)
Discharged to gen. ward (%)	23 (96%)
Deceased (%)	1 (4%)

Ultrasonic measures of diaphragm function

Daily measures of diaphragm end-expiratory thickness and TF for all participants are charted in Addendum P.

Resting diaphragm thickness

During mechanical ventilation

Diaphragm resting thickness was within the range of 0.06cm to 0.22cm for the first three days of MV. All measures of diaphragm thickness during MV are charted in *Figure 3.2* (image A). There was no significant difference in resting diaphragm thickness during MV between the groups that had either an increase (n =9) or decrease (n =9) in TF from day 1 to day 2 of MV (p = 0.77) (*Figure 3.3* – image A).

After mechanical ventilation

The range of resting diaphragm thickness on the last day of MV and for two days post-extubation was 0.08cm-0.21cm; *Figure 3.2* (image B) charts these measures. There was no significant difference in resting diaphragm thickness on the last day of MV and post-extubation between the groups that had either an increase or decrease in TF from day 1 to day 2 of MV (p = 0.94) (*Figure 3.3* – image B).

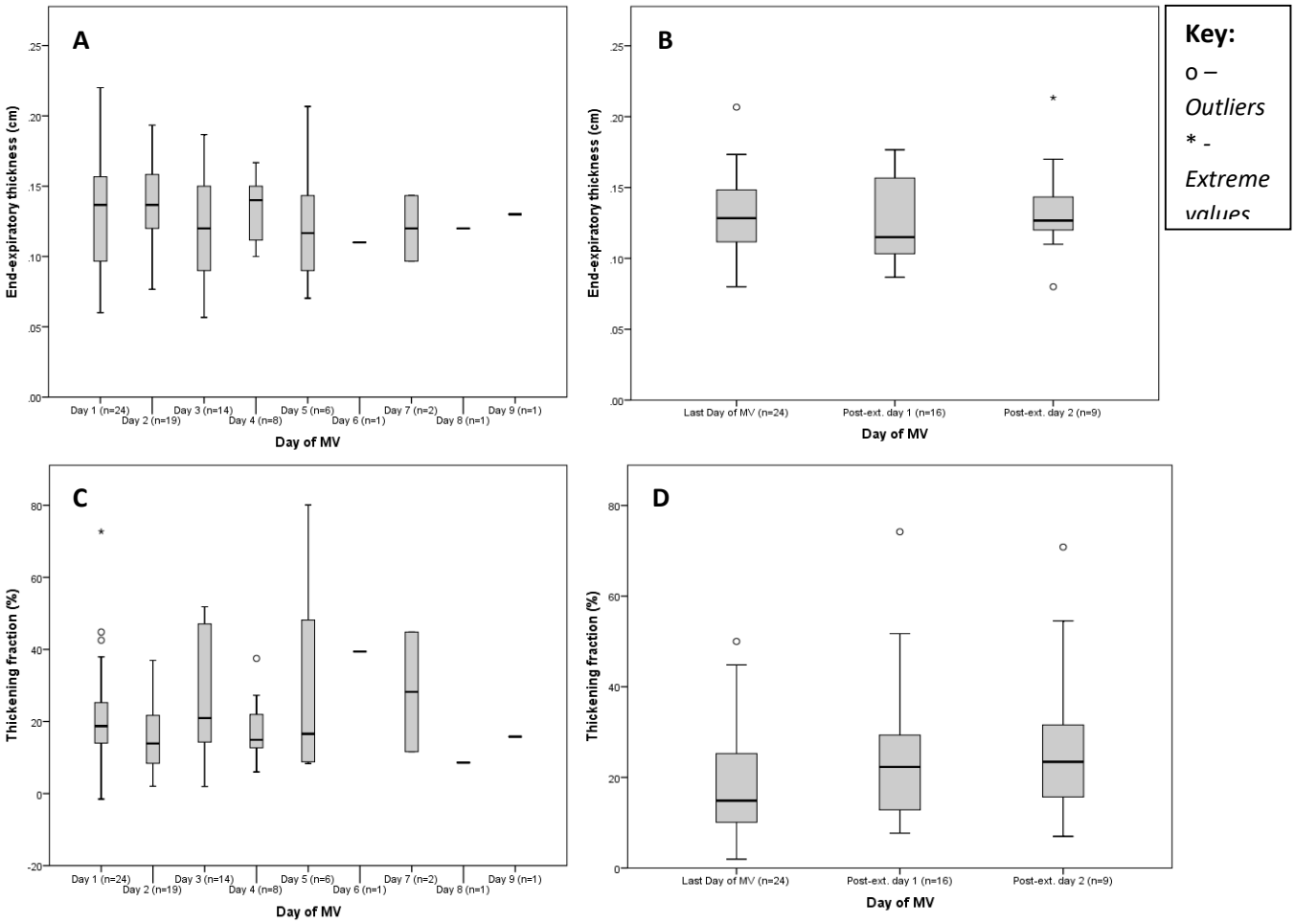

Figure 3.2 – Box and whisker plots of the medians and IQRs for measures of end-expiratory thickness and TF for the full duration of MV, the last day of MV and two days post-extubation for all participants

The mean differences and 95% confidence intervals for the respective days for end-expiratory diaphragm thickness were recorded in Table 3.2.

Table 3.2 - End-expiration thickness mean differences and 95% confidence intervals

	Day 1	**Day 2**	**Day 3**	**Last day**	**Post-ext. day 1**
Day 1					
Day 2	0.001 (-0.012 – 0.014)				
Day 3	-0.01 (-0.36 – 0.016)	-0.014 (-0.026 - 0.002)			
Last Day	-0.001 (-0.016 – 0.014)				
Post-ext. Day 1	0.001 (-0.02 – 0.022)	-0.000 (-0.026 – 0.026)	0.01 (-0.029 – 0.048)	0.000 (-0.027 – 0.028)	
Post-ext. Day 2	0.09 (-0.018 – 0.035)	-0.012 (-0.042 – 0.018)	-0.01 (-0.098 – 0.078)	-0.006 (-0.04 – 0.029)	0.009 (-0.015 – 0.033)

Diaphragm thickening fraction

During mechanical ventilation

TF ranged between -1.5% and 72.7% on the first three days of MV; *Figure 3.2* (Image C) charts these measures. There was a significant difference in TF on day 2 of MV between the patients that increased or decreased in TF within 48 hours of intubation (*p=0.006)*. (*Figure 3.3* – image C).

After mechanical ventilation

The TF ranged between 1.96% - 74.2% on the last day of MV and two days post-extubation, *Figure 3.2* (image D) charts all of these measures. Although the increase group had a higher TF post-extubation, it was no significant between groups (*Figure 3.3* – image D). Patients that were breathing above the set ventilator rate on day 1 of MV (n=14) had a significantly higher TF post-extubation than those not breathing above the set rate (n =10) (Addendum Q).

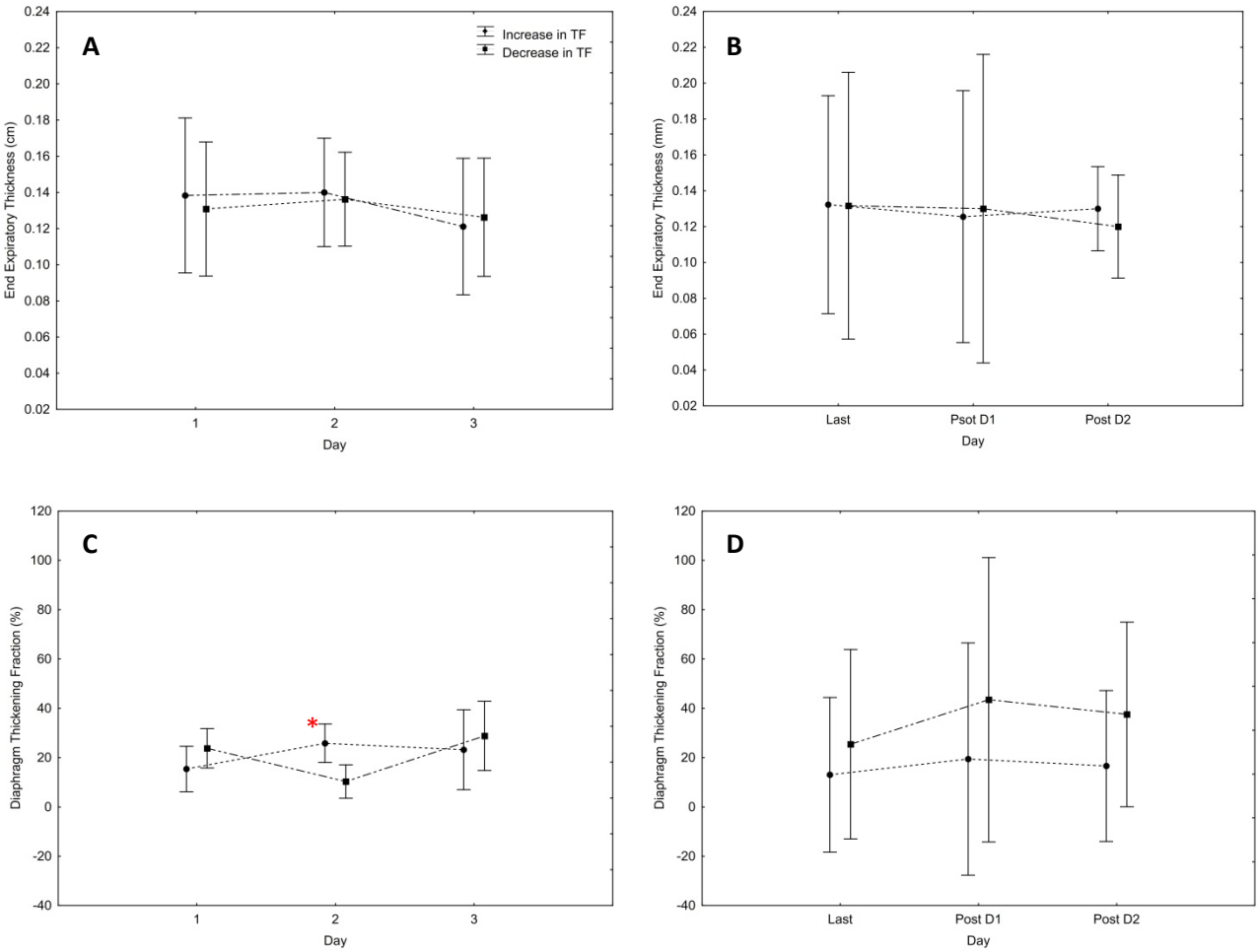

Figure 3.3 - Two-way ANOVA illustrating differences between patients who had an initial increase in diaphragm TF from day 1 to day 2 of MV through the course of MV, on the last day of MV and post-extubation. The TF between-group difference was significant at the point marked by (*) (p = 0.006).

The mean differences and 95% confidence intervals for the respective days for TF were recorded in Table 3.3.

Table 3.3 - Thickening Fraction mean differences and 95% confidence intervals

	Day 1	**Day 2**	**Day 3**	**Last day**	**Post-ext. day 1**
Day 1					
Day 2	-2.08 (-8.86 -4.70)				
Day 3	6.22 (-4.91 - 17.35)	9.42 (-2.07 - 20.91)			
Last Day	-2.35 (-10.45 - 5.75)				
Post-ext. Day 1	3.33 (-9.13 - 15.8)	6.59 (-8.66 - 21.83)	-1.41 (-24.5 - 21.68)	3.68 (-8.72 - 16.08)	
Post-ext. Day 2	7.90 (-8.11 - 23.92)	4.88 (-21.60 - 31.36)	13.56 (-23.52 - 50.65)	6.66 (-13.11 - 26.44)	-0.49 (-16.21 - 15.23)

EMG measures of diaphragm electrical activity

Daily measures of diaphragm electrical activity for all participants are charted in supplementary material (Addendum R).

During mechanical ventilation

Diaphragm activity measures ranged between 1.6 – 7.2µV on the first 3 days of MV (*Figure 3.4* - image A). There was a significant decrease in diaphragm activity from day 1 to day 3 of MV (p=0.007) (*Figure 3.4* –image A). *Figure 3.5* (image A) shows that the initial change in TF within 48 hours of intubation had no effect on diaphragm electrical activity over the first three days of MV.

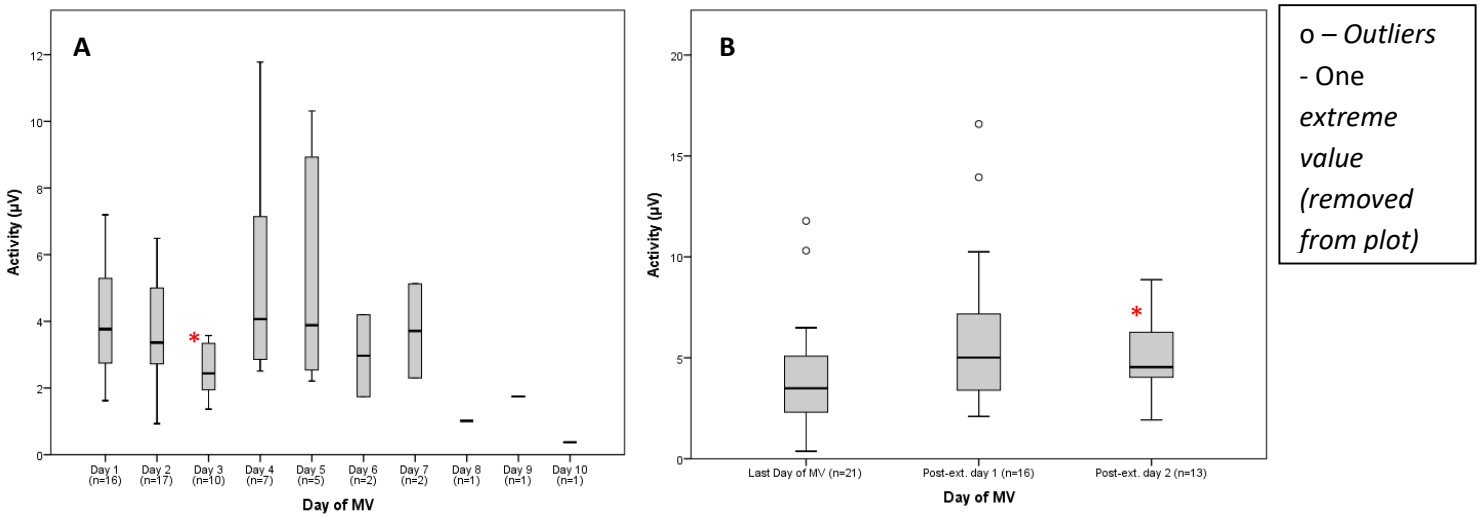

Figure 3.4 – Box and whisker plots for the medians and IQRs of diaphragm electrical activity measures for the full duration of MV, last day of MV and two days post-extubation for all participants.
Electrical activity decrease was significant from day 1 to day 3 at the point marked by (*) (p=0.007)
Electrical activity increase was significant from day 1 post-extubation and 2 post-extubation at the point marked by (*) (p = 0.008)

After mechanical ventilation

Last day of MV and post-extubation electrical activity measures ranged between 0.37 - 16.6µV. There was a significant increase in activity from day 1 post-extubation and 2 post-extubation (p = 0.008) (*Figure 3.4* –image B). *Figure 3.4* (image B) charts diaphragm electrical activity measures, one extreme value was removed from the plot (27.9µV). Differences in diaphragm activity between the groups that had an initial increase or decrease in TF within the first 48 hours of intubation were not significant (*Figure 3.5* - image B).

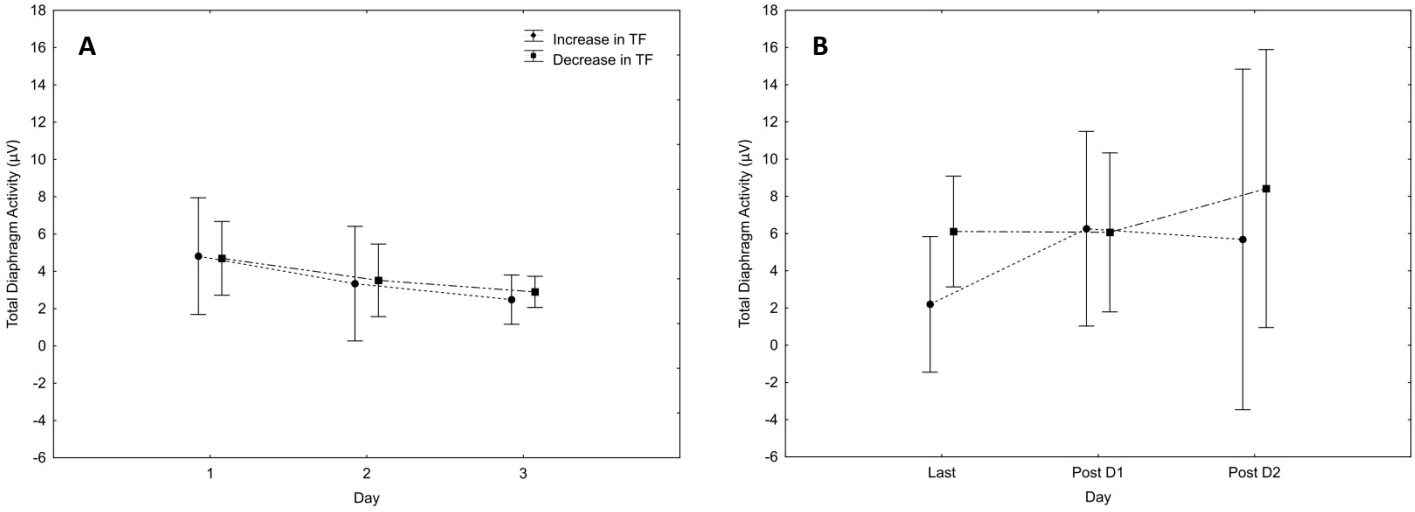

Figure 3.5 - Two-way ANOVA illustrating differences between patients who increased in diaphragm TF from day 1 to day 2 of MV through the course of MV, on the last day of MV and post-extubation

The mean differences and 95% confidence intervals for the respective days for diaphragm electrical activity were recorded in Table 3.4.

Table 3.4 - Diaphragm electrical activity mean differences and 95% confidence intervals

	Day 1	**Day 2**	**Day 3**	**Last day**	**Post-ext. day 1**
Day 1					
Day 2	-0.31 (-1.62 – 1.01)				
Day 3	-1.95 (-3.13 - 0.77)*	-0.64 (-1.63 – 0.36)			
Last Day	0.51 (-1.13 – 2.14)				
Post-ext. Day 1	1.46 (-1.38 – 4.3)	3.81 (1.21 – 6.41)**	4.49 (-0.05 – 9.04)	1.99 (-1.26 – 5.24)	
Post-ext. Day 2	0.82 (-1.51 – 3.16)	3.53 (-0.97 – 8.03)	5.33 (-3.25 – 13.92)	2.41 (-2.61 – 7.43)	1.01 (-1.61 – 3.63)

significant differences: p = 0.01; p=0.01***

Diaphragm function

Scatter plots of diaphragm TF and electrical activity, and diaphragm resting thickness and electrical activity show no significant relationship between these two variables on the last day of MV (p = 0.73; p = 0.80 respectively). A weak relationship between diaphragm resting thickness and electrical activity was found (Linear R^2=0.14, Spearman's r = -0.07), compared to TF and electrical activity which showed no relationship (Linear R^2=0.01, Spearman's r = -0.09) on the last day of MV (Addendum S).

Mechanical ventilation outcome

Scatter plots showed that larger increases or decreases in TF on the first day of MV were associated with increased MV duration (*Figure 3.6*); although there was no statistically significant correlation (Increase group: Spearman's r = 0.137; p = 0.726; Decrease group: Spearman's r = -0.491; p = 0.150).

There was no significant relationship between MV duration and diaphragm resting thickness or electrical activity on day 1 of MV in the TF increase and decrease groups (Spearman's r = -0.063; *p* = 0.771 and Spearman's r = -0.088; *p* = 0.75, respectively) (Addendum T).

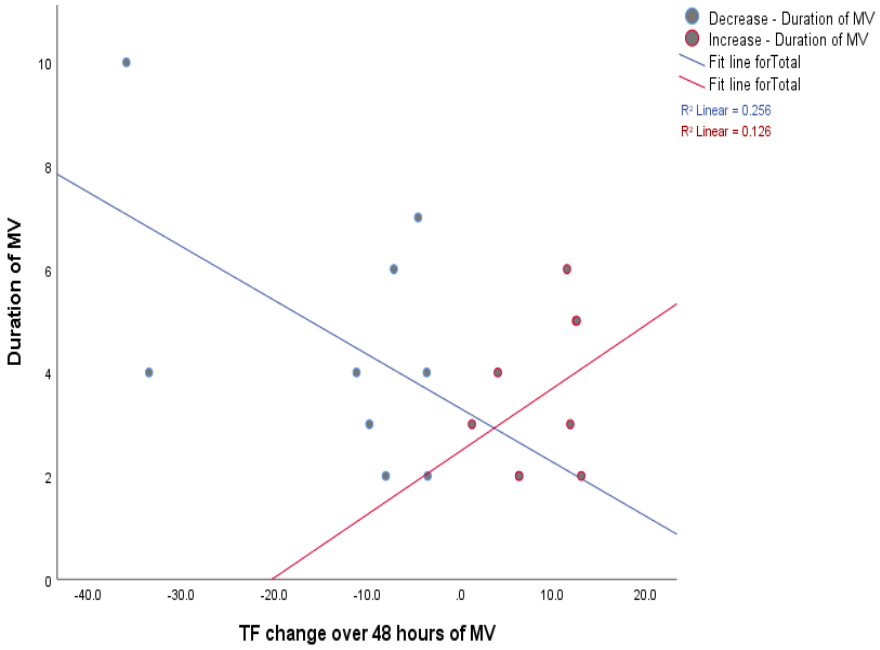

Figure 3.6 - Scatter plot of MV duration and TF increase/decrease over 48 hours of intubation

Discussion

The median duration of MV in our sample was three days, which is similar to another study which reported that average MV duration was four days (Wielenga *et al*., 2016). Morrow et al (2012), who reported on data in a South African PICU, reported a median MV duration of 6 days. There was characteristic variability in our sample, which could explain the median duration of MV being shorter than that of other studies; as duration of MV may differ between patients of varying age, diagnosis and MV mode (Wielenga *et al*., 2016). Studies by Blackwood et al (2013) and Farais et al (2004) reported that the most common diagnostic category requiring the need for MV are respiratory conditions; and Morrow et al (2012) identified pneumonia, gastroenteritis, sepsis and traumatic brain injury as the most common diagnoses requiring MV. In our study population, the largest diagnostic category was cardiac followed by gastrointestinal conditions; and only four participants with respiratory conditions were included; these results may have influenced by the exclusion of participants during recruitment. Our small sample size could also explain the difference in our sample characteristics compared to other studies.

Overall results of this study suggest that there is no identifiable pattern of change in diaphragm thickness or electrical activity over a period of MV in the paediatric population. TF measures could be split between two groups: those that had an increase in TF and those that had a decrease in TF from day 1 to day 2 of MV; where a significant difference could be identified on day 2 of MV. Measures of resting diaphragm thickness and electrical activity remained consistently within a narrow range for all participants; whereas TF measures remained in broader range. This suggests there may be a more variable change in inspiratory diaphragm activity over the period of MV. As expected, an increase in all measures of diaphragm function post-extubation was identified, as patients resumed independent breathing. These findings are consistent with results from a study by Emeriaud *et al.* (2014) who reported that electrical activity measured invasively, was lower in MV than in extubated children. This is expected as the intent of MV is to decrease the work of breathing (Emeriaud *et al.*, 2014), which would thus increase after extubation.

There is a lack of data in the healthy paediatric population for measures of diaphragm resting thickness and TF, thus we cannot compare our data to 'normal' or baseline measures. Diaphragm electrical activity in this study was found to be within a similar range to healthy participants from an unpublished study by A. Lupton-Smith (2014) (Addendum U).

There was a significant difference in TF from day 1 to day 2 of MV between the participants that had an initial increase or decrease in TF from day 1 to day 2 of MV. Neither diaphragm resting thickness nor electrical activity was significantly affected by these initial changes in TF in these two groups. A very weak relationship between electrical activity and TF was identified in this study, which could be why electrical activity was unaffected by changes in TF between these groups. The small sample size and lack of power in this study could account for the lack of significance obtained in these results. A stronger relationship between electrical activity and resting diaphragm thickness on the last day of MV was identified. This finding suggests that diaphragm electrical activity may be more affected by atrophy than by contractile activity. In our study, measures of diaphragm thickness at end-inspiration and end-expiration were used to obtain TF, therefore we did not assess the relationship between diaphragm thickness and TF.

The significantly lower TF recorded for patients that were not breathing above the set ventilator rate on day 1 of MV could be an indication that the patients that were more ventilator dependant from day 1 of MV also had less inspiratory diaphragm activity post-extubation; which may indicate weaker diaphragmatic contraction. However, in this study patients were only recorded as

spontaneously or non-spontaneously breathing during the time of measurement, and this cannot be generalised to how the patient was breathing for the rest of the day.

Although both a greater increase and decrease in TF was associated with longer duration of MV, there was a stronger relationship between TF decrease and increased MV duration on the first day on MV; however it was not significant. This is consistent with findings from Goligher et al (2015), who reported that both a decrease and an increase in diaphragm thickness are associated with diaphragm dysfunction mechanically ventilated adults.

The lack of a significant change in diaphragm function during MV that was reported in our study could also be due to the short duration of MV in the participants. Greater changes in diaphragm function may be found in long term or chronically ventilated patients, however more studies will need to be done in those populations.

Grosu *et al*. (2012) reported that in adults the relationship between diaphragm thickness and length in response to acute hyperinflation is unknown; the same is true in the paediatric population and will require further investigation. The presence of hyper- or hypo-inflation in our study sample was not recorded.

Limitations

This study had a small sample size. A larger sample size could allow for further sub-group analysis and increase the power to reach statistical significance.

Ideally all measures of diaphragm thickness would have been taken on a spontaneous breath, to obtain more accurate measurement of inspiratory diaphragm activity in the TF. In this study we were unable to coordinate our measurements with patient driven breaths, and were unable to determine whether the measured breath was patient or ventilator driven.

No associations could be made between extubation failure and diaphragm function in this study as all included participants were either successfully extubated or died before extubation.

Conclusion

Changes in diaphragm thickness and activity occur in paediatric patients over a period of MV, though there is no identifiable pattern of change. Diaphragm TF changes are more variable based on diaphragm inspiratory activity. Diaphragm function in the healthy paediatric population warrants further investigation for comparisons to be made with the mechanically ventilated population. More research in this area should be done in larger populations and should be used to identify if measures

of diaphragm function may be used to predict MV outcome in MV infants and children. This study has introduced novel data for future studies.

CHAPTER 4: OVERALL DISCUSSION, RECOMMENDATIONS AND CONCLUSIONS

Discussion

The aim of this thesis was to report on diaphragm function in mechanically ventilated infants and children. Our literature overview summarised current knowledge and identified gaps in the literature regarding consensus on weaning guidelines and extubation readiness testing in paediatric critical care. Our observational studies reported novel data on the reliability of diaphragmatic ultrasound (US) thickness measures, as well as reported on diaphragm function during mechanical ventilation (MV) in infants and children.

Diaphragm thickness in mechanically ventilated infants and children

This study was the first to evaluate the reliability of diaphragmatic US as a measure for diaphragm thickness in the paediatric population; results in this pilot study indicated excellent inter- and intra-rater reliability. These are novel findings and can be used to promote the use of US in the critically ill paediatric population to measure diaphragm thickness during MV. Diaphragmatic US can be used to measure the resting diaphragm thickness, which can be used to monitor diaphragm muscle atrophy, as well as the thickening fraction (TF) of the diaphragm, which gives an indication of the contractile activity of the diaphragm; data of which will provide valuable information about diaphragm structure and function, respectively.

There are currently no data on baseline diaphragm thickness in infants and children, and thus these measures cannot be compared to expected norms for this population; however this research shows that patients can be serially monitored to identify noteworthy changes in diaphragm thickness or contractile activity over the period of MV. Changes in thickness or contractile activity may be directly related to the unloading effect of MV on the diaphragm muscle or may be due to other confounding factors; which would require further investigation. Changes in diaphragm contractile activity, whether an increase or a decrease, may be associated with longer MV duration in this population. A stronger relationship between a decrease in contractile activity and MV duration was identified, however both an increase and a decrease in contractile activity was found to be related to increased MV duration; but more research is required to assess this relationship. To prevent prolonged MV duration, an effort needs to be made to monitor and prevent excessive changes in diaphragm contractile activity during MV in infant and children. Diaphragm atrophy, assessed by monitoring resting diaphragm thickness, may also be associated with poor outcomes; however no significant correlations were made between these variables in this study. Adult studies have associated diaphragm atrophy with poor MV outcomes, however the small sample size of participants and thus lack of power may be the reason why no significant relationships were identified in our study. More

research needs to be done to assess how US measures of diaphragm function can be related to MV outcome.

Diaphragm electrical activity in mechanically ventilated infants and children

To our knowledge, this is the first report on non-invasive measures of diaphragm electrical activity in mechanically ventilated infants and children. Surface electromyography (EMG) is a feasible and safe modality to use in this population, although we cannot report on the reliability of these measures in infants and children. Technical measurement errors obtained during data acquisition in our primary study required us to remove extreme values from our data analysis, which was a limitation. There may be value in comparing invasive and non-invasive measures of diaphragm electrical activity in the paediatric population for an assessment of the reliability of surface EMG to measure electrical diaphragm activity in this population. Surface EMG may be a more appropriate measure or a surrogate measure of diaphragm electrical activity for patients for whom invasive measures would be inappropriate, such as those that are non-invasively mechanically ventilated; however more research is required.

Diaphragm electrical activity measures seem to remain within a range for all participants and are comparable to data recorded in healthy participants from an unpublished study. This may indicate that although diaphragm electrical activity may fluctuate during MV, measures still remains within a normal range compared to healthy infants and children. Wolf *et al.* (2011) reported that higher electrical activity of the diaphragm, measured with invasive oesophageal electrodes, can be associated with patients who are more likely to pass an extubation readiness test in children. In our study, changes in diaphragm electrical activity were not found to be related to increased duration of MV, which may indicate that diaphragm electrical activity is not necessarily related to the force production of the muscle. The non-significant relationship identified could also be due to the small sample size and lack of power in this primary study. No associations could be made between diaphragm electrical activity and extubation readiness because no extubation readiness assessments were done in this study and none of our included participants failed extubation.

Suggestions for future research

Future research in this field should aim to assess the relationship between diaphragm function in infants and children and MV outcomes. Poor MV outcomes include prolonged MV duration, weaning difficulties and extubation failure. Research shows that paediatric patients that are more at risk for extubation failure are those of younger age (<2 years), on MV for a longer duration and are receiving sedation or analgesic medications (Fontela *et al.*, 2005). There may be value in sub-group analysis of the patients that have been identified as more at risk of developing extubation failure; however the small sample size in our study did not allow for sub-group analysis. A recommendation for future

studies would be to include a larger sample size which would allow for sub-group analysis of the at-risk populations to identify how diaphragm function and poor MV outcomes may be related in these at-risk groups.

There is a lack of reliable measures of extubation readiness in the paediatric population. Measures of diaphragm function may be a means by which extubation readiness can be tested. Our study did not identify how diaphragm function testing can be used as a test for extubation readiness, which would be a recommendation for future studies. Identification of patients at risk of extubation failure due to diaphragm dysfunction could allow for early intervention and preventative measures before an extubation attempt. Large changes in diaphragm function, out of the expected range for this population, may also give an indication of patients receiving excessive or insufficient MV support.

A study by Kurachek *et al*. (2003) on extubation failure in the paediatric intensive care unit (PICU), identified insufficient respiratory muscle strength in 40% of patients that had failed extubation and that these patients could have been identified before an extubation attempt (Kurachek *et al.*, 2003). Diaphragm strength and endurance are other important aspects of diaphragm function that may also be affected by MV and may also be necessary for successful weaning and extubation. In our study only diaphragm thickness and activity were assessed and more research needs to be done on other measures of diaphragm function in this population.

More studies should be done on diaphragm function both within the spontaneously breathing and mechanically ventilated population; to create a more comprehensive picture of diaphragm function in these paediatric populations and to allow for comparisons between these groups.

Research into diaphragm function of critically ill infants and children is still emerging and this data may be the beginning of research in this field. Novel data from this study on diaphragm function in the mechanically ventilated paediatric population should provide the basis for further research.

Conclusion

There is no current consensus on weaning guidelines, as well as no accurate predictor of extubation readiness in the paediatric population; and most current clinical practice is guided by findings from adult studies.

US can be used to reliably measure the thickness of the paediatric diaphragm during MV. Both US and surface EMG are feasible and safe to use in the critically ill paediatric population, although how these measures relate to MV outcome is unknown.

Diaphragm function in mechanically ventilated infants and children shows no clear pattern of change over time, however there is an expected range in which these measures can be found. How these ranges compare to measures of diaphragm function in healthy infants and children warrants further research.

Diaphragm function during MV in infants and children has not been sufficiently researched. There may be a relationship between changes in diaphragm contractile activity and increased MV duration in the paediatric population. No other relationships between diaphragm function and MV outcome have been made thus far.

Since this research is an introduction of new data in this field, these studies are descriptive in design; however they present novel data on paediatric diaphragm function during MV, providing a basis of further study.

References:

Anraku, M. and Shargall, Y. (2009) 'Surgical Conditions of the Diaphragm: Anatomy and Physiology', *Thoracic Surgery Clinics*. Elsevier Ltd, 19(4), pp. 419–429. doi: 10.1016/j.thorsurg.2009.08.002.

Baisch, S. D. *et al.* (2005) 'Extubation failure in pediatric intensive care incidence and outcomes.', *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*, 6(3), pp. 312–318. doi: 10.1097/01.PCC.0000161119.05076.91.

Baumeister, B. L. *et al.* (1997) 'Evaluation of predictors of weaning from mechanical ventilation in pediatric patients', *Pediatric Pulmonology*, 24(5), pp. 344–352. doi: 10.1002/(SICI)1099-0496(199711)24:5<344::AID-PPUL7>3.0.CO;2-I.

Bhat, P. *et al.* (2016) 'Prediction of infant extubation outcomes using the tension-time index', *Archives of Disease in Childhood - Fetal and Neonatal Edition*, pp. 1–5. doi: 10.1136/archdischild-2015-309264.

Blackwood, B. *et al.* (2013) 'Protocolized versus non-protocolized weaning for reducing the duration of invasive mechanical ventilation in critically ill paediatric patients : Cochrane systematic review Review information', *The Cochrane Library*, (11), pp. 1–36. doi: 10.1002/14651858.CD009082.

Blackwood, B. and Tume, L. (2015) 'The implausibility of "usual care" in an open system: sedation and weaning practices in Paediatric Intensive Care Units (PICUs) in the United Kingdom (UK).', *Trials*. Trials, 16(1), p. 325. doi: 10.1186/s13063-015-0846-3.

Bousso, A. *et al.* (2006) 'Evaluation of the dead space to tidal volume ratio as a predictor of extubation failure.', *Jornal de pediatria*, 82(5), pp. 347–353. doi: 10.2223/JPED.1520.

Chavez, A. *et al.* (2006) 'Spontaneous breathing trial predicts successful extubation in infants and children.', *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*, 7(4), pp. 324–328. doi: 10.1097/01.PCC.0000225001.92994.29.

Cheifetz, I. (2003) 'Invasive and non-invasive pediatric mechanical ventilation', *Respiratory care*, 48(4), pp. 442–453. Cicchetti, D. V (2001) 'The precision of reliability and validity estimates re-visited: distinguishing between clinical and statistical significance of sample size requirements.', *Journal of clinical and experimental neuropsychology*, 23(5), pp. 695–700. doi: 10.1076/jcen.23.5.695.1249.

Edmunds, S., Weiss, I. and Harrison, R. (2001) 'Extubation failure in a large pediatric ICU population', *Chest*, 119(3), pp. 897–900. doi: 10.1378/chest.119.3.897.

Emeriaud, G. *et al.* (2014) 'Evolution of inspiratory diaphragm activity in children over the course of the PICU stay', *Intensive Care Medicine*, 40(11), pp. 1718–1726. doi: 10.1007/s00134-014-3431-4.

Farias, J. *et al.* (2002) 'An evaluation of extubation failure predictors in mechanically ventilated infants and children', *Intensive Care Medicine*, 28(6), pp. 752–757. doi: 10.1007/s00134-002-1306-6.

Farias, J. A. *et al.* (1998) 'Weaning from mechanical ventilation in pediatric intensive care patients', *Intensive Care Medicine*, 24(10), pp. 1070–1075. doi: 10.1007/s001340050718.

Farias, J. A. *et al.* (2004) 'What is the daily practice of mechanical ventilation in pediatric intensive care units? A multicenter study', *Intensive Care Medicine*, 30(5), pp. 918–925. doi: 10.1007/s00134-004-2225-5.

Ferguson, L. P. *et al.* (2011) 'A spontaneous breathing trial with pressure support overestimates readiness for extubation in children.', *Pediatric critical care medicine*, 12(6), pp. e330-5. doi: 10.1097/PCC.0b013e3182231220.

Fontela, P. S. *et al.* (2005) 'Risk factors for extubation failure in mechanically ventilated pediatric patients.', *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*, 6(2), pp. 166–70. doi: 10.1097/01.PCC.0000154922.65189.48.

Foronda, F. K. *et al.* (2011) 'The impact of daily evaluation and spontaneous breathing test on the duration of pediatric mechanical ventilation: a randomized controlled trial', *Critical Care Medicine*, 39(11), pp. 2526–2533. doi: 10.1186/cc10193.

Gibson, G. J. *et al.* (2002) 'ATS/ERS Statement on respiratory muscle testing.', *American journal of respiratory and critical care medicine*, 166(4), pp. 518–624. doi: 10.1164/rccm.166.4.518.

Goligher, E. C. *et al.* (2015) 'Evolution of diaphragm thickness during mechanical ventilation: Impact of inspiratory effort', *American Journal of Respiratory and Critical Care Medicine*, 192(9), pp. 1080–1088. doi: 10.1164/rccm.201503-0620OC.

Grosu, H. B. *et al.* (2012) 'Diaphragm muscle thinning in patients who are mechanically ventilated', *Chest*. The American College of Chest Physicians, 142(6), pp. 1455–1460. doi: 10.1378/chest.11-1638.

Harikumar, G. *et al.* (2009) 'Tension-time index as a predictor of extubation outcome in ventilated children', *American Journal of Respiratory and Critical Care Medicine*, 180(10), pp. 982–988. doi: 10.1164/rccm.200811-1725OC.

Hutten, G.J. *et al*. (2008) 'Relative impact of respiratory muscle activity on tidal flow and end expiratory volume in healthy neonates', *Pediatric Pulmonology*. 43 (9),pp882-891. doi: 10.1002/ppul.20874

Hutten, G. J. *et al.* (2010) 'A literature review of the methodology of EMG recordings of the diaphragm', *Journal of Electromyography and Kinesiology*. 20(2), pp. 185–190. doi: 10.1016/j.jelekin.2009.02.008.

Johnston, C. *et al.* (2010) 'Risk factors for extubation failure in infants with severe acute bronchiolitis.', *Respiratory care*, pp. 328–333.

Johnston, C. and da Silva, P. S. L. (2012) 'Weaning and Extubation in Pediatrics', *Current Respiratory Medicine Reviews*, 8, pp. 68–78. doi: 10.2174/157339812798868852.

Jouvet, P. A. *et al.* (2007) 'Weaning children from mechanical ventilation with a computer-driven system (closed-loop protocol): A pilot study', *Pediatric Critical Care Medicine*, 8(5), pp. 425–432. doi: 10.1097/01.PCC.0000282157.77811.F9.

Keogh, S. (2004) 'Weaning from mechanical ventilation a national survey of Australian paediatric intensive care units', *Neonatal, Paediatric and Child Health Nursing,*7(3), pp. 13–19.

Keogh, S., Courtney, M. and Coyer, F. (2003) 'Weaning from ventilation in paediatric intensive care: An intervention study', *Intensive and Critical Care Nursing*, 19(4), pp. 186–197. doi: 10.1016/S0964-3397(03)00041-7.

Khan, N., Brown, A. and Venkataraman, S. T. (1996) 'Predictors of extubation success and failure in mechanically ventilated infants and children', *Critical Care Medicine*, 24(9), pp. 1568–1579.

Kurachek, S. C. *et al.* (2003) 'Extubation failure in pediatric intensive care: a multiple-center study of risk factors and outcomes.', *Critical care medicine*, 31(11), pp. 2657–2664. doi: 10.1097/01.CCM.0000094228.90557.85.

Laham, J. L., Breheny, P. J. and Rush, A. (2013) 'Do clinical parameters predict first planned extubation outcome in the pediatric intensive care unit?', *Journal of Intensive Care Medicine*, 30(2), pp. 89–96. doi: 10.1177/0885066613494338.

Levine, S. *et al.* (2008) 'Rapid Disuse Atrophy of Diaphragm Fibers in Mechanically Ventilated Humans', *The New England Journal of Medicine*, 358(13), pp. 1327–1335.

Maarsingh, E. J. W. *et al.* (2000) 'Respiratory muscle activity measured with a noninvasive EMG technique: technical aspects and reproducibility', *Jouranl of Applied Physiology, 88(6),* pp. 1955–1961.

Morrow, B. M. *et al.* (2012) 'Investigation into the effect of closed-system suctioning on the frequency of pediatric ventilator-associated pneumonia in a developing country*', *Pediatric Critical Care Medicine*, 13(1), pp. e25–e32. doi: 10.1097/PCC.0b013e31820ac0a2.

Newth, C. J. L. *et al.* (2009) 'Weaning and extubation readiness in pediatric patients*', *Pediatric Critical Care Medicine*, 10(1), pp. 1–11. doi: 10.1097/PCC.0b013e318193724d.

Noizet, O. *et al.* (2005) 'Does taking endurance into account improve the prediction of weaning outcome in mechanically ventilated children?', *Critical care*, 9(6), pp. R798-807. doi: 10.1186/cc3898.

Peters,M.D.J. *et al.* (2015) 'Guidance for conducting systematic scoping reviews', *International Journal of Evidence-Based Healthcare,* 13(3):141-146. doi: 10.1097/XEB.0000000000000050.

Petrof, B. J. and Hussain, S. N. (2016) 'Ventilator-induced diaphragmatic dysfunction', *Current Opinion in Critical Care*, 16(1), pp. 19–25. doi: 10.1097/MCC.0b013e328334b166.

Puthucheary, Z. A. *et al.* (2013) 'Acute Skeletal Muscle Wasting in Critical Illness', 310(15), pp. 1591–1600. doi: 10.1001/jama.2013.278481.

Randolph, A. G. *et al.* (2002) 'Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial.', *JAMA: The journal of the American Medical Association*, 288(20), pp. 2561–8. doi: 10.1001/jama.288.20.2561.

Restrepo, R. D. *et al.* (2004) 'Protocol-driven ventilator management in children: comparison to nonprotocol care.', *Journal of intensive care medicine*, 19(5), pp. 274–284. doi: 10.1177/0885066604267646.

Rose, L. *et al.* (2015) 'Automated versus non-automated weaning for reducing the duration of mechanical ventilation for critically ill adults and children', *The Cochrane database of systematic reviews*, 6, pp. 1–12. doi: DOI 10.1186/s13054-015-0755-6.

Saikia, B., Kumar, N. and Sreenivas, V. (2015) 'Prediction of extubation failure in newborns, infants and children: brief report of a prospective (blinded) cohort study at a tertiary care paediatric centre in India', *SpringerPlus*. Springer International Publishing, 4(1), p. 827. doi: 10.1186/s40064-015-1607-1.

Santschi, M. *et al.* (2007) 'Acceptable respiratory physiologic limits for children during weaning from mechanical ventilation', *Intensive Care Medicine*, 33(2), pp. 319–325. doi: 10.1007/s00134-006-0414-0.

Sarwal, A., Walker, F. O. and Cartwright, M. S. (2013) 'Neuromuscular ultrasound for evaluation of the diaphragm', *Muscle and Nerve*, 47(3), pp. 319–329. doi: 10.1002/mus.23671.

Schepens, T. *et al.* (2015) 'The course of diaphragm atrophy in ventilated patients assessed with ultrasound: a longitudinal cohort study', *Critical Care*. 19(1), p. 422. doi: 10.1186/s13054-015-1141-0.

Schindler, M. B. (2005) 'Prediction of ventilation weaning outcome: children are not little adults.', *Critical care* , 9(6), pp. 651–652. doi: 10.1186/cc3950.

Siren, P. M. A. and Siren, M. J. (2011) 'Critical diaphragm failure in sudden infant death syndrome', *Upsala Journal of Medical Sciences*, 116(2), pp. 115–123. doi: 10.3109/03009734.2010.548011.

Thiagarajan, R. R. *et al.* (1999) 'Predictors of Successful Extubation in Children', *American Journal of Respiratory and Critical Care Medicine*, 160, pp. 1562–1566.

Turner, D. A. and Arnold, J. H. (2007) 'Insights in pediatric ventilation: timing of intubation, ventilatory strategies, and weaning', *Current Opinion in Critical Care*, 13(1), pp. 57–63. doi: 10.1097/MCC.0b013e32801297f9.

Vassilakopoulos, T. and Petrof, B. J. (2004) 'A stimulating approach to ventilator-induced diaphragmatic dysfunction', *American Journal of Respiratory and Critical Care Medicine*, 195(3), pp. 281–282. doi: 10.1164/rccm.201608-1619ED.

Venkataraman, S., Khan, N. and Brown, A. (2000) 'Validation of predictors of extubation success and failure in mechanically ventilated infants and children.', *Critical care medicine*, 28(8), pp. 2991–2996. doi: 10.1097/00003246-200008000-00051.

Verhagen, A. P. *et al.* (1998) 'The Delphi List : A Criteria List for Quality Assessment of Randomized Clinical Trials for Conducting Systematic Reviews Developed by Delphi Consensus', 51(12), pp. 1235–1241.

Wielenga, J. *et al.* (2016) 'Protocolized versus non-protocolized weaning for reducing the duration of invasive mechanical ventilation in critically ill newborn infants (Review)', *The Cochrane Library*, (3), pp. 1–18. doi: 10.1002/14651858.CD009082.

Wolf, G. K. *et al.* (2011) 'Electrical activity of the diaphragm during extubation readiness testing in critically ill children', *Pediatric Critical Care Medicine*, 12(6), pp. e220–e224. doi: 10.1097/PCC.0b013e3181fe28fc.

Addendum A: Search Results - Literature overview

Search terms:

1. "paediatrics" OR "pediatrics" OR "child" OR "children"
2. "mechanical ventilation" OR "Respiration, artificial"
3. "causes" OR "underlying reasons"
4. "weaning" OR "ventilator weaning" OR "respirator weaning" OR "mechanical ventilator weaning"
5. "extubation failure" OR "extubation success" OR "airway extubation OR success"

Pubmed

Duplicates: 15 (eliminated after total hits)

Search Terms	Total hits	Eliminated titles	Eliminated Abstracts	Eliminated Full text	Included
Pediatrics AND Ventilator Weaning	41	22	1	6	2
Paediatrics AND mechanical ventilation	246	241	2	1	0
Pediatrics AND Airway Extubation	79	65	6	1	4
Total	366	328	9	8	6

PEDro

Duplicates: 43 (eliminated after total hits)

Search Terms	Total hits	Eliminated titles	Eliminated Abstracts	Eliminated Full text	Included
Pediatrics AND Ventilator Weaning	49	18	3	1	2
Paediatrics AND mechanical ventilation	125	108	0	0	1
Pediatrics AND Airway Extubation	36	30	4	0	0
Total	210	156	7	1	3

Scopus

Duplicates: 41 (eliminated after total hits)

Search Terms	Total hits	Eliminated titles	Eliminated Abstracts	Eliminated Full text	Included
Pediatrics AND Ventilator Weaning	292	250	14	5	17
Paediatrics AND mechanical ventilation	38	17	4	3	1
Pediatrics AND Airway Extubation	182	158	2	0	0
Total	512	425	20	8	18

Cinahl

Duplicates: 25(eliminated after total hits)

Search Terms	Total hits	Eliminated titles	Eliminated Abstracts	Eliminated Full text	Included
Pediatrics AND Ventilator Weaning	149	125	1	2	2
Paediatrics AND mechanical ventilation	2	1	0	0	0
Pediatrics AND Airway Extubation	31	14	8	1	3
Total	182	140	9	3	5

Cochrane Library

Duplicates: 5 (eliminated after total hits)

Search Terms	Total hits	Eliminated titles	Eliminated Abstracts	Eliminated Full text	Included
Pediatrics AND Ventilator Weaning	7	6	0	0	0
Paediatrics AND mechanical ventilation	65	60	1	0	0
Pediatrics AND Airway Extubation	7	5	2	0	0
Total	79	71	3	0	0

Total articles included into review: 32

Addendum B: Summary of included systematic reviews

Author	Country	Total studies included	Population			Invasively MV patients	Primary objective	Main findings
			Neonates	Infants/children	Adults			
Newth *et al,* 2009	USA	15		X	X	X	Describe current weaning practice	• No reliable methods for assessing readiness to wean and predicting extubation outcome are evident in paediatric literature
Wielenga *et al,* 2016	Amsterdam	0	X			X	Efficacy of protocolised vs non-protocolised weaning	• No data on weaning protocols in neonates • Research required
Blackwood *et al,* 2013	UK	3		X		X	Efficacy of protocolised vs non-protocolised weaning	• Limited evidence that weaning protocols reduce MV duration • Inadequate research on whether shorter duration of MV is beneficial or harmful to children
Rose *et al*, 2015	Canada	21		X	X	X	Automated vs non-automated systems effect on reducing weaning duration	• Automated systems may result in clinically meaningful reduced durations of weaning, MV and ICU stay

United States of America (USA), United Kingdom (UK), mechanical ventilation (MV), intensive care unit (ICU)

Addendum C: Summary of included intervention studies

Author	Country	Type of study	Population type (age range)	Sample size	Intervention	Control	Primary outcomes				Main Findings
							Extubation Outcome	Duration of MV	Duration of weaning	Length of stay	
Randolph *et al,* 2002	USA	Randomised Controlled Trial	Neonate Paediatric Adolescent (0-17 yrs)	182	PSV weaning protocol VSV weaning protocol	No protocol	X		X		Weaning protocols do not significantly decrease duration of weaning from MV (p=0.75) or impact EF rates (p=0.44)
Foronda *et al,* 2011	Brazil	Randomised Controlled Trial	Paediatric Adolescent (28 days - 15 yrs)	294	Weaning protocol (2 h SBT)	Standard weaning protocol	X	X			Daily assessment of readiness to wean combined with a SBT reduces the duration of MV (p=0.01), without increasing EF rate
Jouvet et al, 2007	France	Prospective interventional study	Paediatric Adolescent (1-17yrs)	20	Weaning using pressure support	Historical – clinician guided weaning		X			A closed-loop protocol was used to successfully

					mode by a closed-loop computerized protocol						wean children from MV. No statistically significant difference in duration of weaning compared to clinician driven weaning was found (p=0.33).
Keogh, Courtney and Coyer, 2003	Australia	Quasi-experimental	Neonate Paediatric Adolescent (0-16 yrs)	220	Weaning guidelines	Standard care – weaning outcomes	X	X	X	X	The use of weaning guidelines may prolong MV time, however quality indicators (weaning outcome/rate of reintubation) are improved. Longer term ventilated patients would benefit more from weaning guidelines

United States of America (USA), pressure support ventilation (PSV), volume support ventilation (VSV), mechanical ventilation (MV), spontaneous breathing trial (SBT), extubation failure (EF)

Addendum D: Summary of included observational studies

Author	Country	Type of study	No. of participants	Age of participants	Primary Outcome Measures	Primary Objectives	Main Findings
Farais et al, 2004	Costa Rica, Spain, Greece, Panama, UK, USA	Prospective cohort	36 medical surgical PICUs	1 months - 15 years	Weaning process	To describe the daily practice of MV and it's outcome in PICUs	1 in 3 patients that are admitted to PICU require MV. ARF is the most common reason for MV. 85% survival rate after MV for more than 12 h.
Keogh, 2004	Australia	Survey	7 PICUs	-	Weaning process	To describe the management of weaning from mechanical ventilation, unit activity, patient admission and staff profile characteristics	Weaning processes are inconsistent across Australian PICUs.
Johnson and da Silva, 2010	Brazil	Prospective observational study	40	1–12 months	Extubation outcome	To evaluate demographic characteristics, MV parameters, blood gas values and ventilator indexes as predictors of extubation failure in infants with severe acute bronchiolitis	Lower minute volume and lower maximal inspiratory pressure may be useful parameters to predict infants that at risk for EF
Edmunds, Weiss and Harrison, 2001	USA	Retrospective chart review	548	Mean age: 52.4 months (SD ± 61.4 months)	Extubation outcome	To establish baseline rate of extubation failure/success and to identify characteristics that increase the risk for extubation failure.	Overall failure rate of planned extubations was 4.9%. Younger patients and those on MV for longer were more at risk for EF.
Saikia, Kumar and Sreenivas, 2015	India	Prospective observational study	92	>12 years old	Extubation outcome	To determine the factors associated with EF and to facilitate prediction of EF	Paediatric EF may be multifactorial and disease specific. The

							measurement of respiratory effort and SBT could be vital in deciding re-intubation.
Harikumar et al, 2009	UK	Prospective observational study	80	0.15 – 16 years old	Extubation outcome	To evaluate the performance of a non-invasive assessment of TTI, the respiratory muscle tension time index (TTmus), by comparison to that of the diaphragm tension time index (TTdi) and other predictors of extubation outcome in ventilated children.	Invasive and non-invasive measurements of TTI may provide accurate prediction of extubation outcome in mechanically ventilated children.
Santschi et al, 2007	Canada	Survey	97 intensivists (49 PICUs)	-	Weaning process	To characterize the physiological limits considered appropriate during weaning from mechanical ventilation in children	Accepted weaning limits are broad. Thinking on weaning children from MV should be consolidated before guidelines can be created and initiated in PICU.
Ferguson et al, 2011	USA	Retrospective chart review	538	<19 years	Extubation outcome	To evaluate the performance of an extubation readiness test based on a spontaneous breathing trial using pressure support.	An ERT based on a SBT with pressure support adjusted according to ETT size overestimates a child's ability to breathe independently. Objective data from ERT may be useful to identify patients who may benefit from planned extubation to

							non-invasive ventilation.
Laham, Breheny and Rush, 2015	USA	Prospective observational study	319	0-20years	Extubation outcome	To evaluate the practice of determining extubation readiness based on physician judgment of pre-extubation ventilator settings, blood gas analysis, and other factors affecting extubation outcome	Determining extubation readiness by weaning to low ventilator settings may not be justified during short-term ventilation. Gradual weaning of ventilator settings may unnecessarily prolong MV.
Baisch et al, 2005	USA	Prospective observational study	3,193	Mean age: 37 months	Extubation outcome	To evaluate the hypotheses that children requiring re-intubation are at an increased risk of prolonged hospitalizations, congenital heart disease, and death	Failed extubations lead to longer ventilator times, PICU stays, and hospitalizations, and increases tracheostomy rate.
Kurachek et al, 2003	USA	Prospective observational study	2,794	0-18 years	Extubation outcome	To determine a contemporary failed extubation rate, risk factors, and consequences of extubation failure in paediatric intensive care units	Determining the precise moment of extubation readiness requires further study.
Thiagarajan et al, 1999	USA	Prospective observational study	472	0 -5 years	Extubation outcome	To study factors associated with extubation success and to evaluate the usefulness of	Patients that failed extubation had higher RSBIs and a lower CROP index. Children that

						the RSBI and the CROP index in children	failed extubation showed signs of respiratory dysfunction. The RSBI and CROP index are useful to predict extubation success in paediatrics.
Fontela et al, 2005	Brazil	Prospective observational study	124	1- 3 months	Extubation outcome	To describe the incidence of extubation failure and its associated risk factors among mechanically ventilated children.	EF occurred more so among: younger infants, those receiving prolonged MV support, receiving intravenous sedation, on CPAP, had impaired oxygenation, and those requiring inotropic therapy
Blackwood and Tume, 2015	UK	interview/survey	23 PICUs	-	Weaning process	To describe PICU context, 'usual' practice in sedation and weaning from mechanical ventilation, and factors affecting implementation	There were a lack of protocols in place to guide staff in patient assessment and management in terms of sedation and MV weaning
Venkataraman, Khan and Brown, 2000	USA	Prospective, descriptive study.	312	1 – 5 years old	Extubation outcome	To validate predictors of extubation success and failure in mechanically ventilated infants and children by using bedside measures of respiratory function.	Bedside respiratory function measures can assist in prediction of extubation success or failure in paediatric patients. Adult extubation indices cannot reliably predict extubation success or failure in paediatrics.

Khan, Brown and Venkataraman, 1996	USA	Prospective collection of data	213	< or = 37 weeks gestation	Extubation outcome	To predict extubation success and failure in mechanically ventilated infants and children using bedside measures of respiratory function.	Integrated indices are poor predictors of extubation success and failure in infants and children. Children fail extubation due to poor respiratory effort, increased load on the respiratory muscles and a decreased inspiratory drive.
Baumeister et al, 1997	USA	Observational study	47 patients	3-22 years	Extubation outcome	To evaluate the RSBI and the CROP index in predicting extubation outcome in a paediatric mechanically ventilated population.	The modified CROP index and modified RSBI are useful in predicting EF in paediatric patients.
Farais et al, 1998	Argentina	Prospective observational study	84 infants/children	Median age: 7.5 months	Extubation outcome	To evaluate the accuracy of weaning indices in predicting weaning failure.	75% of paediatric patients on MV can be successfully weaned after a SBT, lasting 2 h
Farais et al, 2002	Spain	Prospective observational study	418	1m – 15 years	Extubation outcome	To assess traditional weaning indices and their efficacy in predicting extubation failure.	Respiratory parameters are poor predictors of EF in children who have passed a SBT. The accuracy of the weaning indices does not improve when they are re-measured immediately before extubation.
Wolf et al, 2011	USA	Prospective observational study	20 patients	1 month - 18 years	Extubation outcome	To assess the electrical activity of the diaphragm muscle	Patients who have higher diaphragmatic activity in relation to tidal volume

						during ERT.	may have better preserved diaphragmatic function and thus a better chance of passing the ERT. Electrical activity of the diaphragm also may be a useful adjunct to assess neuromuscular drive in ventilated children.
Bousso et al, 2006	Brazil	Prospective observational study	86 children	mean age: 16.8 months	Extubation outcome	To evaluate the ratio of dead space to tidal volume (VD/VT) as an accurate predictor of extubation failure in MV children.	In a paediatric population receiving MV due to a variety of etiologies, the VD/ VT ratio was unable to predict the populations at risk of EF or of re-intubation
Chavez, dela Cruz and Zaritsky, 2006	USA	Prospective observational study	70 patients	1 month - 18 years	Extubation outcome	To assess efficacy of a spontaneous breathing trial using a flow-inflating bag in predicting extubation success.	A 15-min flow-inflating bag SBT represents a practical and reliable bedside test that has 95% sensitivity for predicting extubation success in paediatric patients
Bhat et al, 2016	UK	Prospective observational study	60 infants	23-42 weeks	Extubation outcome	to determine whether TTdi or TTmus predicted extubation outcome and performed better than other measures of respiratory function or clinical data	Assessment of TTdi and TTmus cannot be recommended for use in routine clinical practice to predict extubation success

Restrepo et al, 2004	USA	Retrospective observational study	187 patients	0.5-252 months	Weaning and MV duration	To assess ventilator weaning time, overall ventilator and time to spontaneous breathing with use of a ventilator management protocol compared to standard non-protocol-based care in a PICU.	Use of an institution-specific VMP developed by a multidisciplinary team was associated with reduced weaning time and time to spontaneous breathing

United Kingdom (UK), United States of America (USA), paediatric intensive care unit (PICU), mechanical ventilation (MV), acute respiratory failure (ARF), extubation failure (EF),spontaneous breathing trial (SBT), tension-time index (TTi), respiratory muscle tension-time index (TTmus),diaphragm tension-time index (TTdi), endo-tracheal tube (ETT), rapid shallow breathing index (RSBI),dynamic compliance, respiratory rate, oxygenation, maximum inspiratory pressure (CROP), continuous positive airway pressure (CPAP), ratio of dead space to tidal volume (VD/VT ratio),ventilator management program (VMP), extubation readiness test (ERT)

Addendum E: Ethical Clearance (Stellenbosch University)

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Approval Notice
Response to Modifications- (New Application)

04-Jul-2016
Terhart, Maxine MN

Ethics Reference #: S16/05/087

Title: **Mechanical ventilation and diaphragm function in mechanically ventilated infants and young children. An explorative study.**

Dear Miss Maxine Terhart,

The **Response to Modifications** - ***(New Application)*** received on **24-Jun-2016**, was reviewed by members of **Health Research Ethics Committee 2** via Expedited review procedures on **04-Jul-2016** and was approved.
Please note the following information about your approved research protocol:

Protocol Approval Period: **04-Jul-2016 -03-Jul-2017**

Please remember to use your **protocol number** (**S16/05/087**) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:
Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.
Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel:

Addendum F: Ethical Clearance (University of Cape Town)

Form FHS006: Protocol Amendment

HREC office use only (FWA00001637; IRB00001938)

☑ Approved ☑ Type of review: Expedited ☐ Full committee

This serves as notification that all changes and documentation described below are approved.

Signature Chairperson of the HREC: [signature] Date: 29/8/16

Note: All major amendments must include a brief PI Synopsis just lying the changes for the amendment. Please note that incomplete amendment submissions will not be reviewed.

Comments from the HREC to the Principal Investigator:

Thank you for your letter received 25/8/16

Note: The approval of this protocol amendment does not grant annual approval. Please complete the FHS015 / FHS017 form for annual approval at least one month before study expiration.

Principal Investigator to complete the following:

1. Protocol Information

Date when submitting this form			
HREC REF Number	178/2013		
Protocol title	The effect of mechanical ventilation on diaphragm function in infants and children.		
Protocol number (if applicable)	4		
Principal Investigator	A/Prof Bronda Mcmaw		
Department / Office Internal Mail Address	5th floor ICH Building Klipfontein Road Rondebosch		
1.1 Is this a major or a minor amendment? (see FHS001 for guidance) Minor: tick box; Major: tick box		☐ Major	✓ Minor
1.2 Does this protocol receive US Federal funding?		☐ Yes	✓ No
1.3 If the amendment is a major amendment and receives US Federal funding, does the amendment require full committee approval?		☐ Yes	✓ No

Addendum G: Informed consent form

University of Stellenbosch

and

University of Cape Town

Division of Physiotherapy

Effect of mechanical ventilation on diaphragm function in mechanically ventilated infants and children. An explorative study.

Reference number:

Principle Investigator: Maxine Terhart

Address: Francie Van Zijl Dr, Tygerberg Hospital

Cape Town

7505

Contact Number: 021 938 9111

You are being invited to take part in a research project for a Masters degree. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the Health Research Ethics Committee at Stellenbosch University and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

Your child is currently being mechanically ventilated by a machine to help his/her breathing. We are performing a study to find out how well the breathing muscles are working in children of the ICU while the machine helps them. We would like to find out how strong the breathing muscle is and if it is working the way that it is supposed to. We would also like to see if this changes over time.

How will we do this?

To do this, we will place five (5) small stickers (electrodes) on your child's skin around their chest in line with their nipples. We will need to take off your child's clothes so we can see their chest. Your child will not feel any discomfort or pain during this procedure. This shows which muscles are working on a computer. We will keep this information on the computer. We will use Electromyography (sEMG) to see which muscles are working. We will also take pictures of their breathing muscle using ultrasonography (US). We will do this while your child lies on their back. This should take about 2 minutes. If your child becomes upset during the measurements we will stop. We will take these readings once a day while the machine is helping your child breathe. We will also take readings for two (2) days after your child is off the machine. If your child lies still it may take less time and if they wriggle around it may take longer. If your child becomes upset during the measurements we will stop.

We will also ask you a few questions about your baby/child's birth and medical history or we will get this information from their hospital folder, with your permission. If we find anything wrong in your child's breathing muscles while the measurements are being taken, we will send your child to their doctor so that they get the right medicine or care.

Who will take part in the study?

We are hoping to look at a number of different babies in the PICU. We will be looking at babies and children between the ages of 0 to 6 years old who are getting help from the machine to breathe.

What are the risks? (Can anything go wrong?)

There is nothing that we know of that can go wrong with sEMG or US. Your child will not feel uncomfortable or any pain while the measurements are taken. No radiation is involved (it is not like an X-Ray).

How can this benefit my child?

This study will help us understand how the diaphragm works while your child is being helped by the machine. The measurements and results obtained from this study will improve the understanding of how the machine affects the diaphragm which could help future patients, and may not directly benefit your child at present. There is no payment for taking part in this study.

Is what we find kept private?

No one will know that the information comes from your child (it is confidential). None of the children's names will be in the article if it is written.

What will happen in the unlikely event of some form of injury occurring as a direct result of your taking part in this research study?

It is very unlikely; however, all the patients that take part in this study are covered by the insurance of the University of Stellenbosch, should any adverse event occur.

Contact Information of Researchers

If you have any problems or questions, you may contact the investigators (ANON) at the following number 021 658 5074 or Health Research Ethics Committee of Stellenbosch at 021 938 9207. You may choose not to allow your child to take part in this study; this decision will not affect the care of your child in any way. You may also stop child from taking part in this study at any time, without giving reasons. You will receive a copy of this information and consent form for your own records.

Declaration by legal guardian/parent of participant

By signing below, I …….. agree to allow my baby/child take part in a research study entitled: "Mechanical ventilation and diaphragm function in mechanically ventilated infants and children. An explorative study."

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and neither me nor my child has been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.
-

Signed at *(place)* ..... on *(date)* …….. 2016.

....

Signature of legal guardian/parent participant **Signature of witness**

Declaration by investigator

I *(name)* …… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. *(If an interpreter is used then the interpreter must sign the declaration below.*
-

Signed at *(place)* ..... on *(date)* ……..…….. 2016.

…….. ……..

Signature of investigator **Signature of witness**

Declaration by interpreter

I *(name)* …… declare that:

- I assisted the investigator *(name)* ……. to explain the information in this document to *(name of participant)* …….. using the language medium of Afrikaans/Xhosa.
- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) ..... on *(date)* ……..……..2016

…….. ……..

Signature of interpreter **Signature of witness**

Addendum H: Data capture sheet (baseline)

University of Stellenbosch

Department of Physiotherapy

Changes in diaphragm thickness and activity in mechanically ventilated infants and children. An explorative study.

Data collection sheet

Demographics and Medical history

Patient identifier:

Date:

Date of Birth: Age:

Gender:

Weight (kg):

Height (cm):

Spontaneous breaths YES NO (circle)

Birth History:

NVD	C/S	Gestational age at birth:	Complications at birth:	APGARS:

Admission diagnosis:
Medical History and comorbidities:

_____
_____ _____

Surgical History:

_____
_____ _____

Current/Chronic Medication:

_____
_____

Development:

_____
_____ _____

Addendum I: Daily data capture sheet (Daily)

University of Stellenbosch

Department of Physiotherapy

Changes in diaphragm thickness and activity in mechanically ventilated infants and children. An explorative study.

Ventilator settings, US and sEMG measurements

Patient identifier:

Day of MV (date)						
Mode						
RR (vent/pt)						
PIP						
PEEP						
TV						
FiO2						
HR						
MAP						
SaO2						

ABG's:

Date						
Time						
pH						
PaO2						
PaCO2						
BE						
HCO3-						
FiO2						

Medication

Date							
Sedation (Y/N)							
Type of sedation and dosage							
Muscle paralysis (Y/N)							
Spontaneous breaths (Number)							

sEMG

Date						
Diaphragm activity						

US

Date						
Thickness at endexpiration						
Thickness at endinspiration						
Thickening fraction						

Extubation date: _____

Failure to extubate: YES NO (circle one)

If yes: Invasive non-invasive (circle one) Date:_____

PICU outcome:

Discharged home General ward Deceased Not extubated

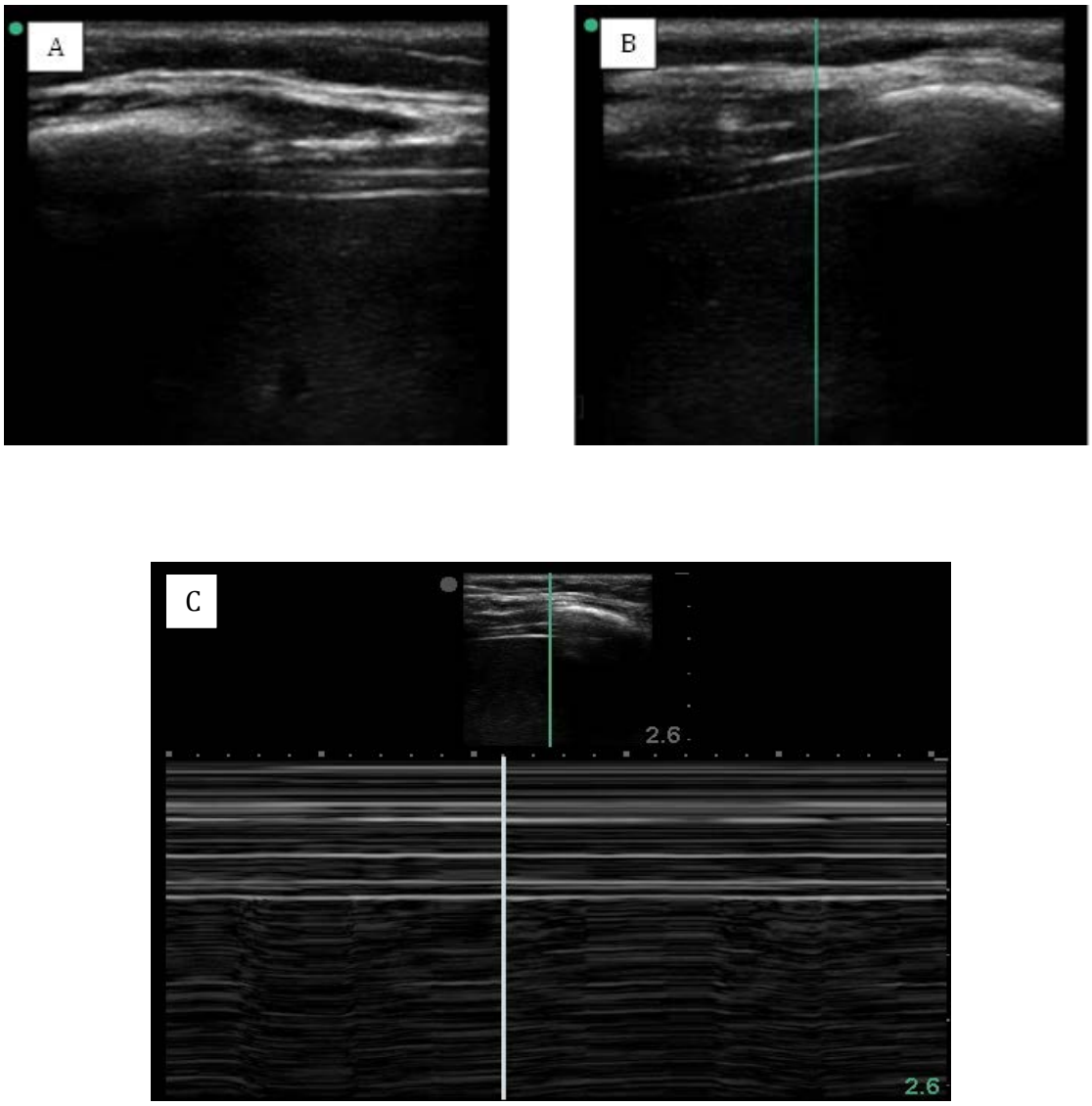
Any adverse events:

_____

_____

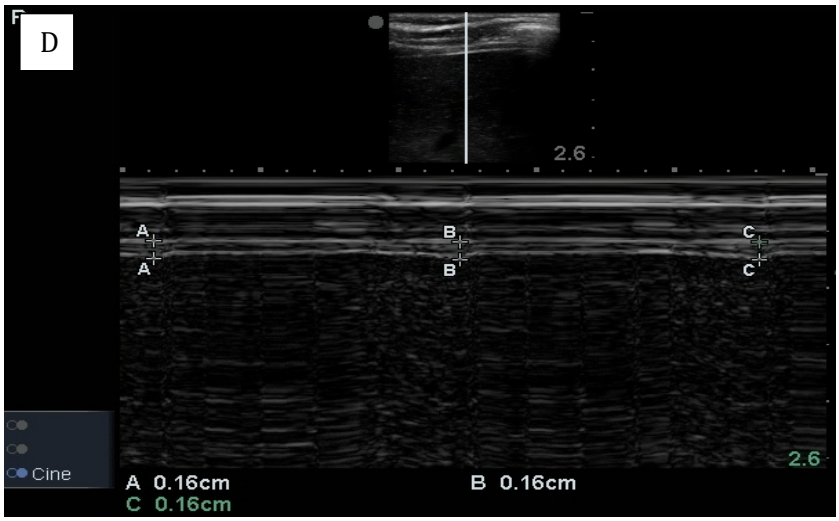
_____

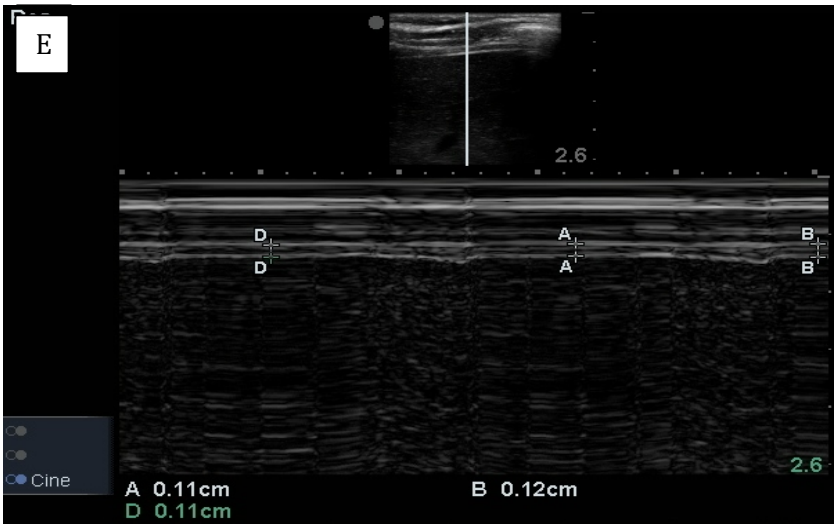
Addendum J: Ultrasound Methodology (diaphragm identification)



(Images A-C): Ultrasound methodology used to measure diaphragm thickness. A – Identification of diaphragm using B-mode; B: M-mode line (green) used to create a cine loop; C: M-mode cine loop recording of consecutive breaths

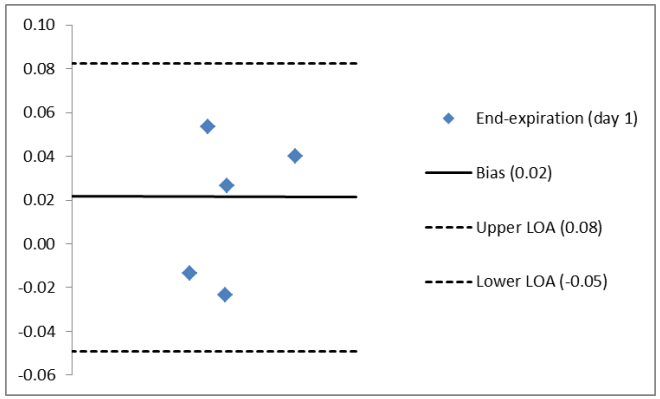
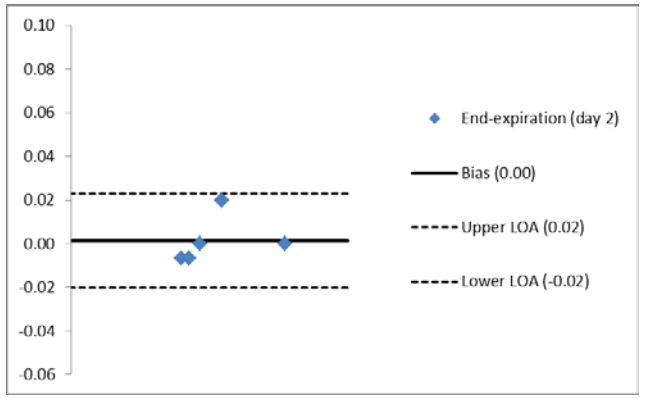
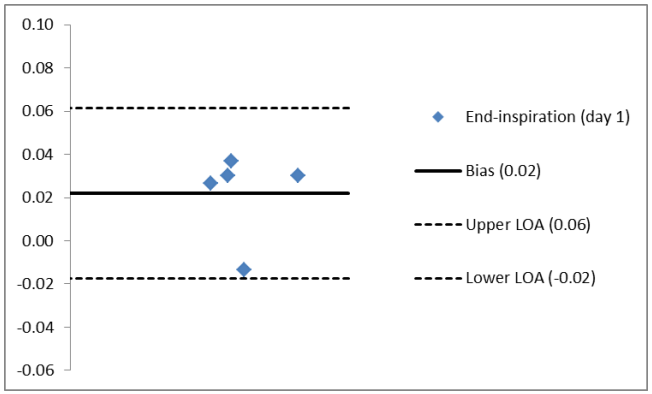
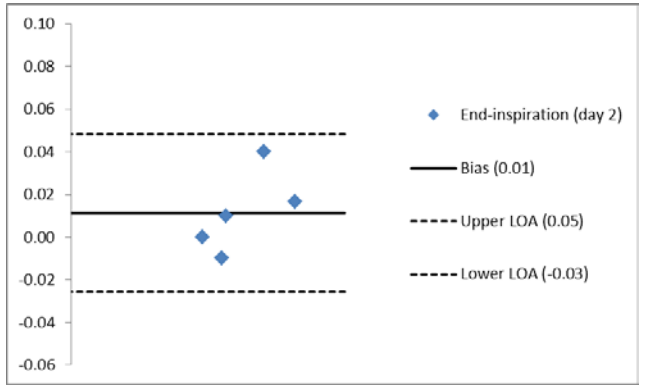
Addendum K: Ultrasound Methodology (diaphragm measurement)





(Images D and E): D: Freeze-frame of M-mode cine loop and measurements of end-inspiration; E: Freeze-frame of M-mode Cine loop and measurements of end-expiration

Addendum L: Bland-Altman plots (Inter-rater reliability)

	Day 1	Day 2
End - expiration		
End - inspiration		

Bland-Altman plots for inter-rater reliability for measurements taken on day one and day two.

Addendum M: Bland-Altman plots (intra-rater reliability)

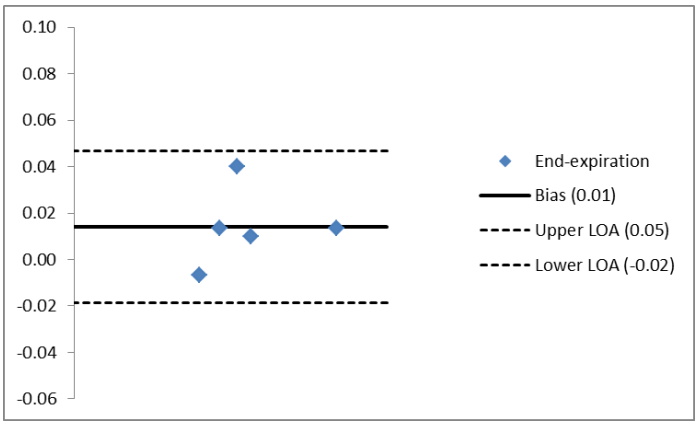
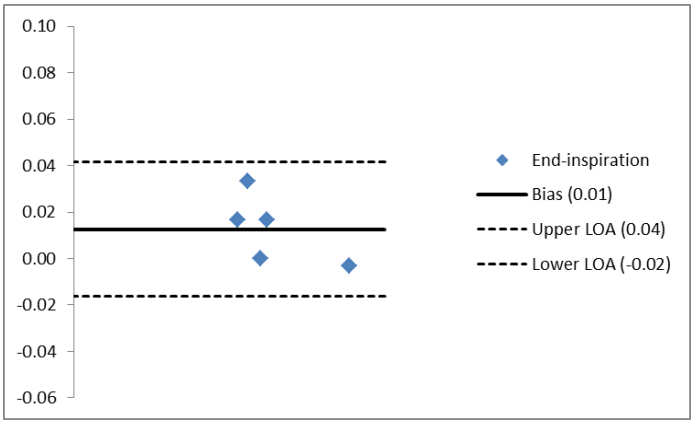
End – expiration	
End – inspiration	

Figure 2.3: Bland-Altman plots for intra-rater reliability

Addendum N: Electromyography Methodology

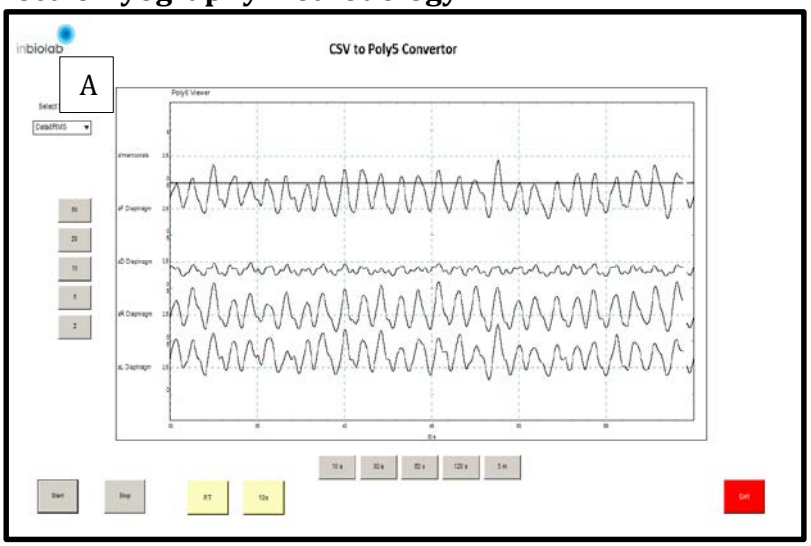


Image A: ***Raw data files processed using Inbiolab software***

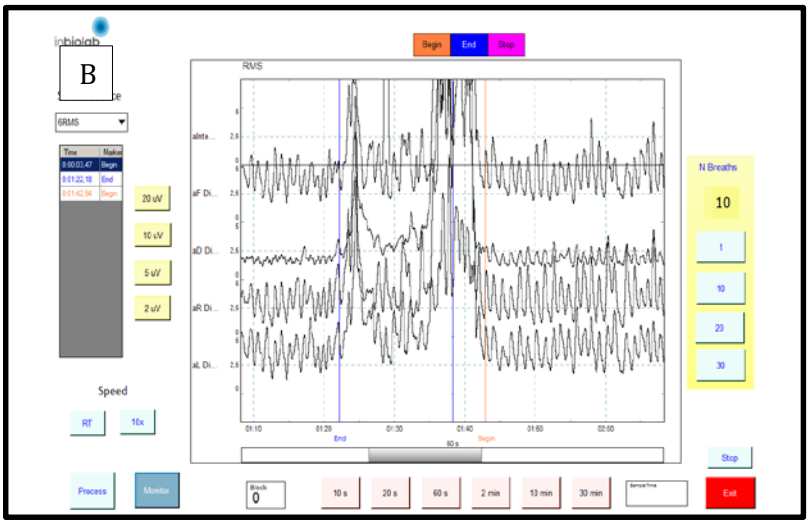


Image B: ***Areas of excessive movement by the patient are identified and removed before final analysis***

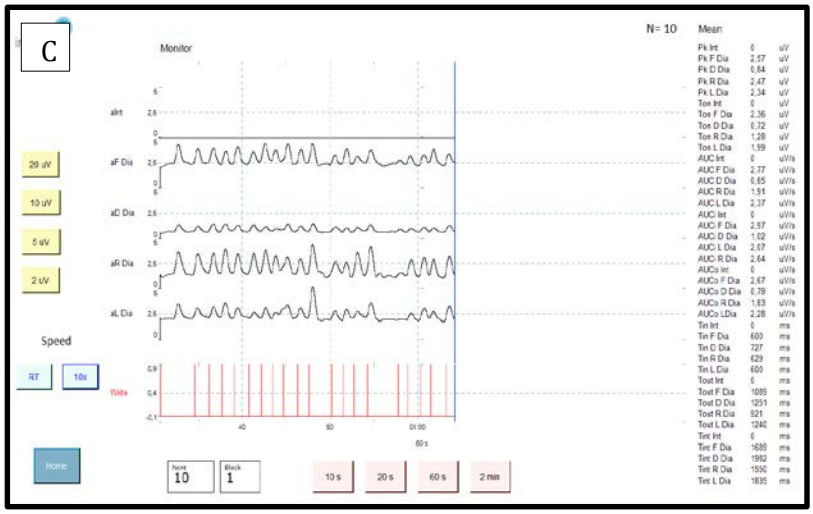
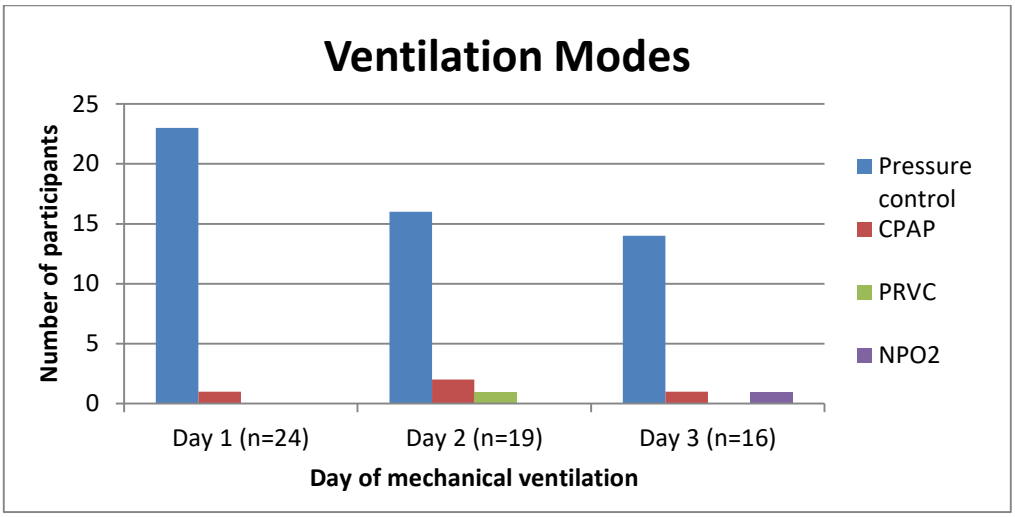
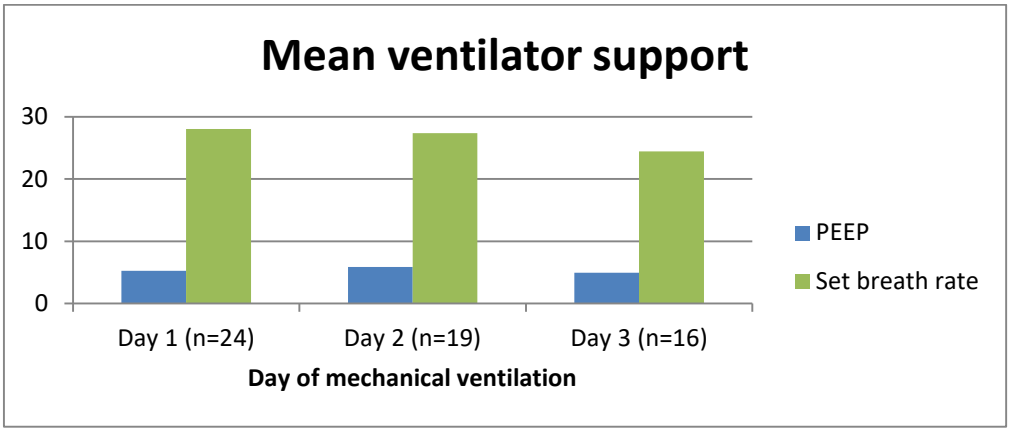


Image C: ***sEMG data are processed and a csv results file is created with the final data***

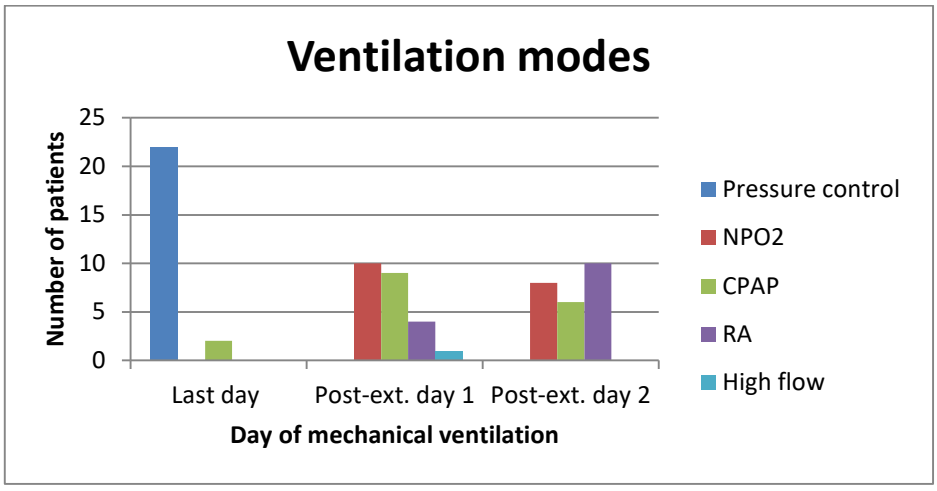
Addendum O: Modes of ventilation and ventilatory support received



Ventilator modes over the first three days and the last day of MV

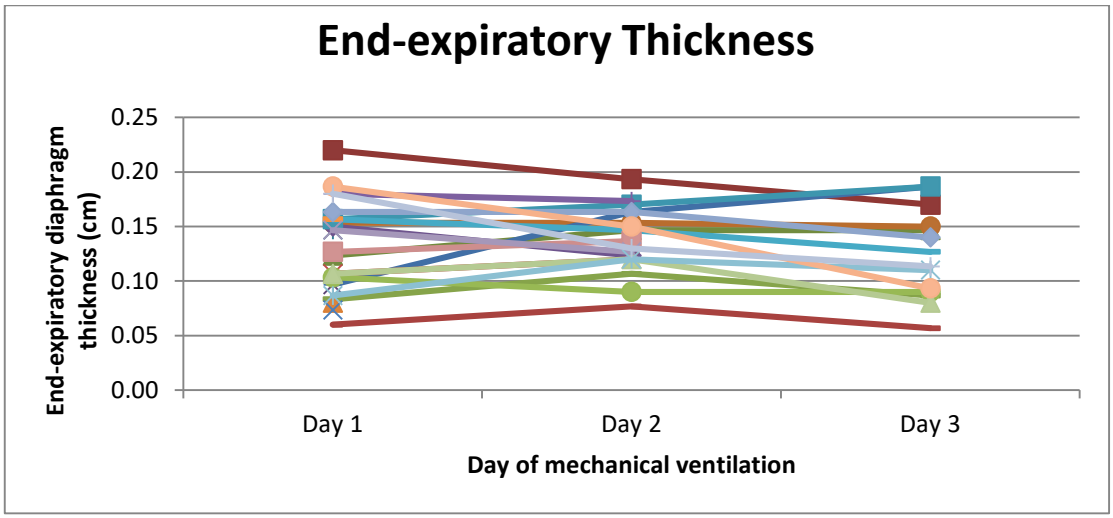


Mean ventilator support for the first three days and the last day of MV

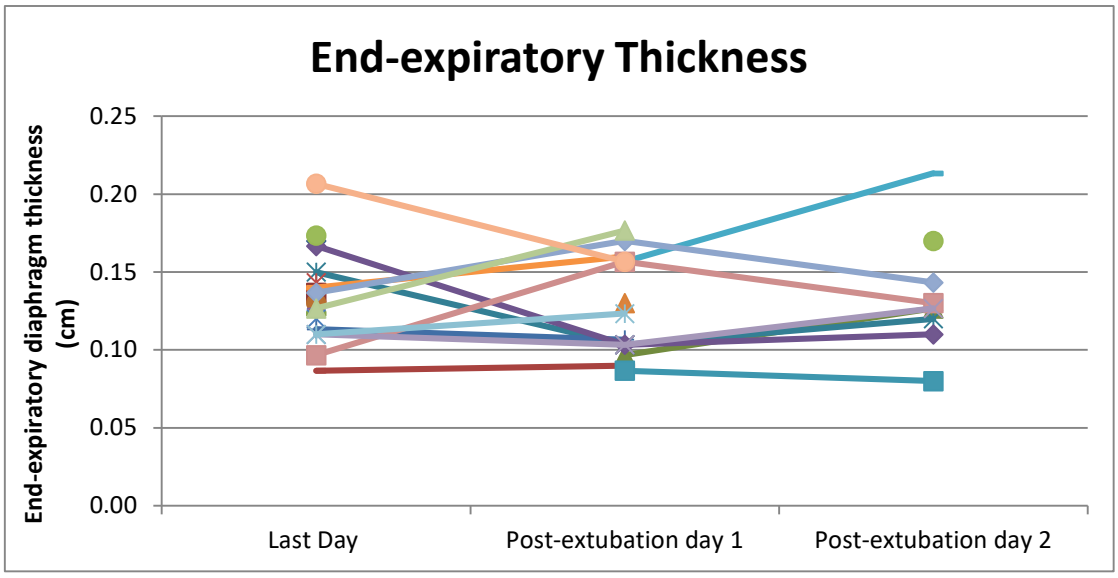


Ventilation modes on the last day of MV, day 1 post-extubation and day 2 post-extubation

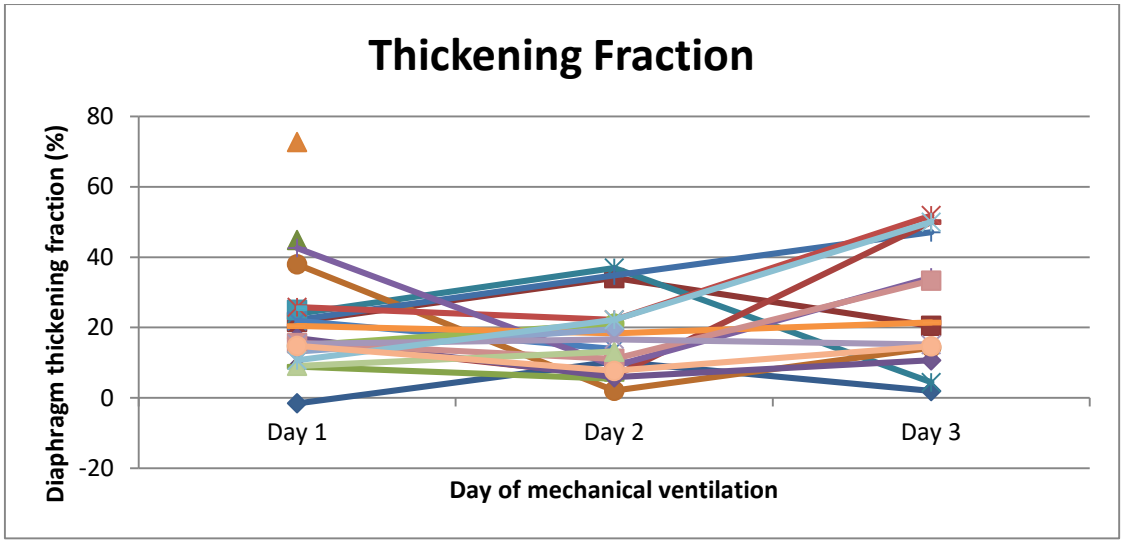
Addendum P: Ultrasound measures of diaphragm thickness



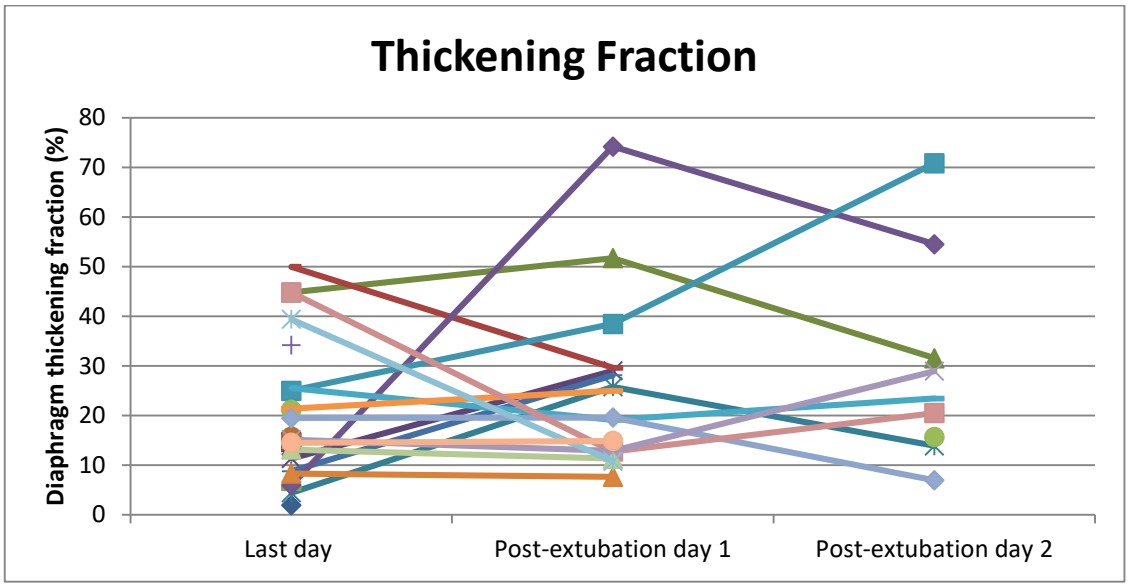
End-expiratory thickness measures for all participants for the first three days of MV



End-expiratory thickness measures for all participants for the last day of MV, post-extubation day 1 and post-extubation day 2



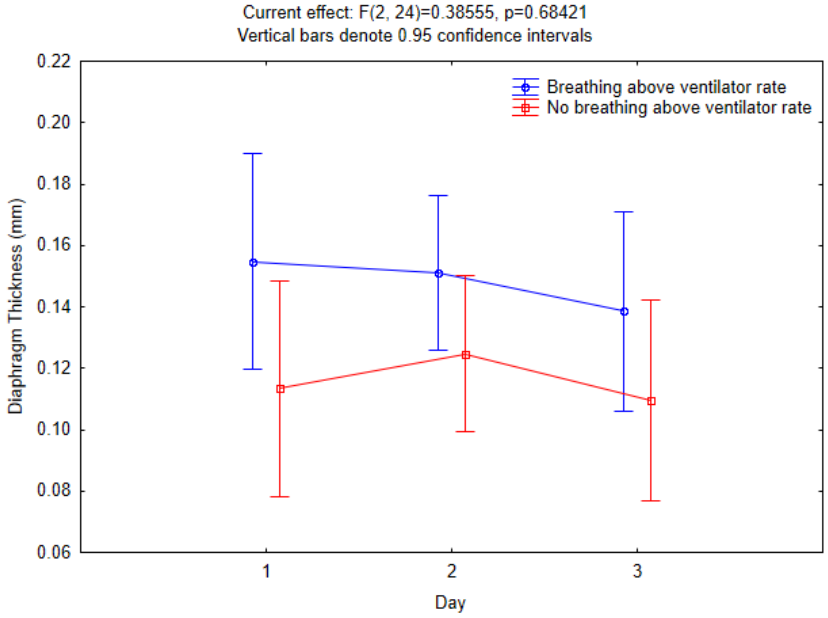
Thickening fraction for all participants for the first three days of MV



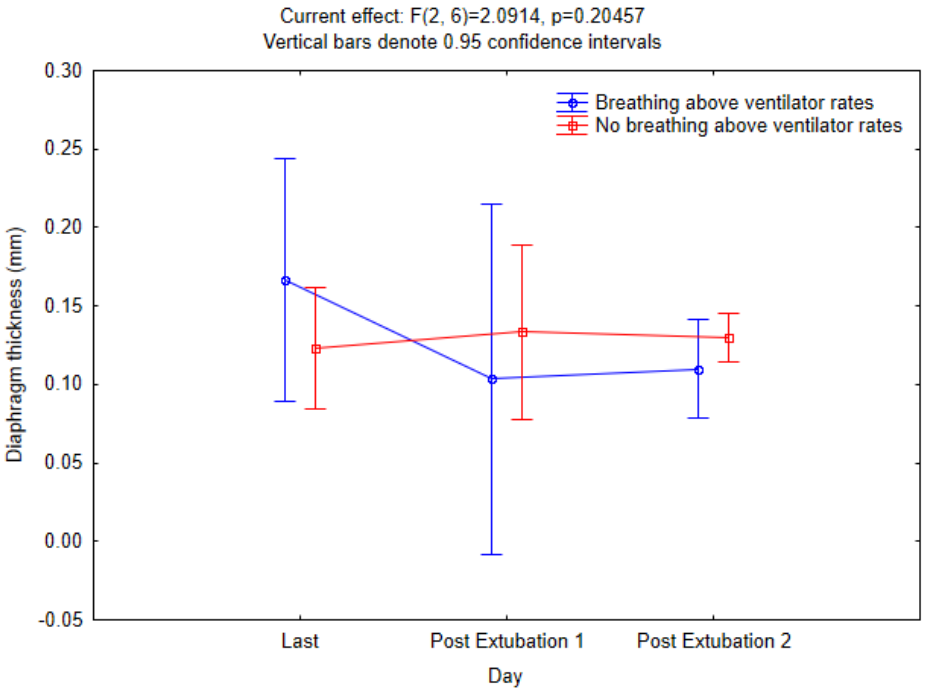
Diaphragm TF for all participants for the last day of MV, post-extubation day 1 and post-extubation day 2

Addendum Q: ANOVAs of groups breathing above or below set ventilator rate

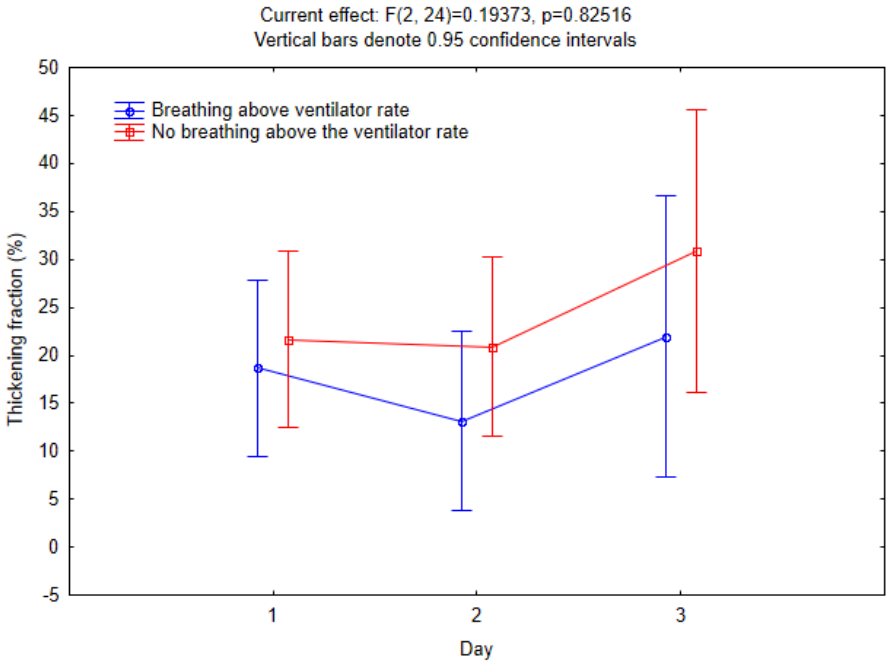
Grouping: patients identified as breathing above the set rate on day 1 of MV and those not breathing above the set ventilator rate on day 1 of MV.



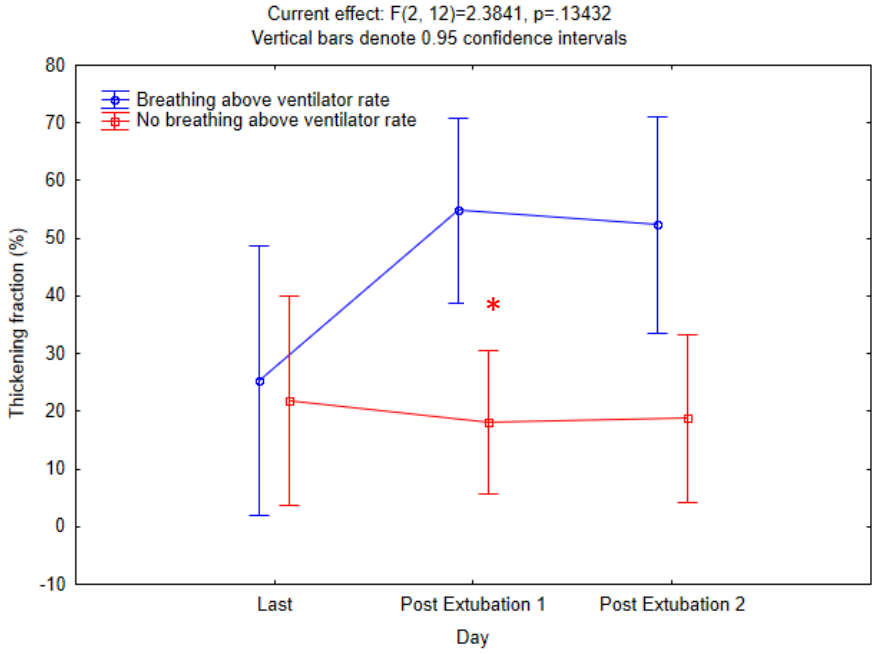
Two-way ANOVA illustrating differences between patients who on day 1 of MV were breathing above the set breath rate and those who were not and end-expiratory diaphragm thickness on day 1, day 2 and day 3 of MV



Two-way ANOVA illustrating differences between patients who on day 1 of MV were breathing above the set breath rate and those who were not and end-expiratory diaphragm thickness on the last day of MV, day 1 post-extubation and day 2 post-extubation

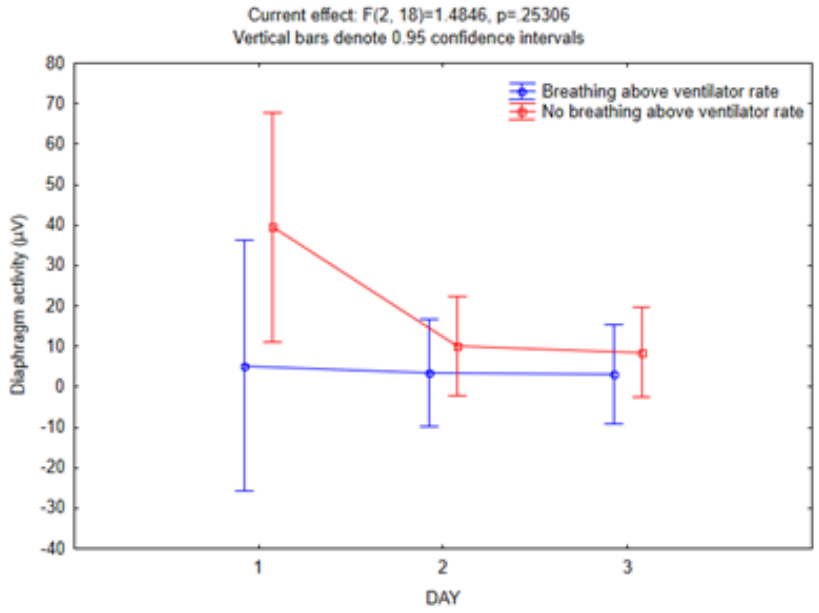


Two-way ANOVA illustrating differences between patients who on day 1 of MV were breathing above the set breath rate and those who were not and the diaphragm TF on day 1, day 2 and day 3 of MV

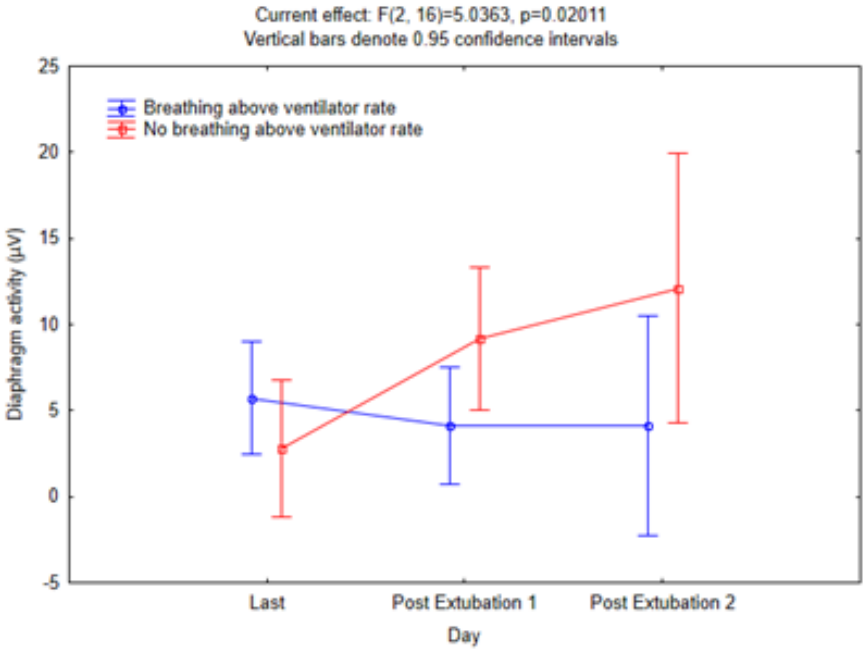


Two-way ANOVA illustrating differences between patients who on day 1 of MV were breathing above the set breath rate and those who were not and the diaphragm TF on the last day of MV, day 1 post-extubation and day 2 post-extubation

Significant difference between groups at point marked (*)

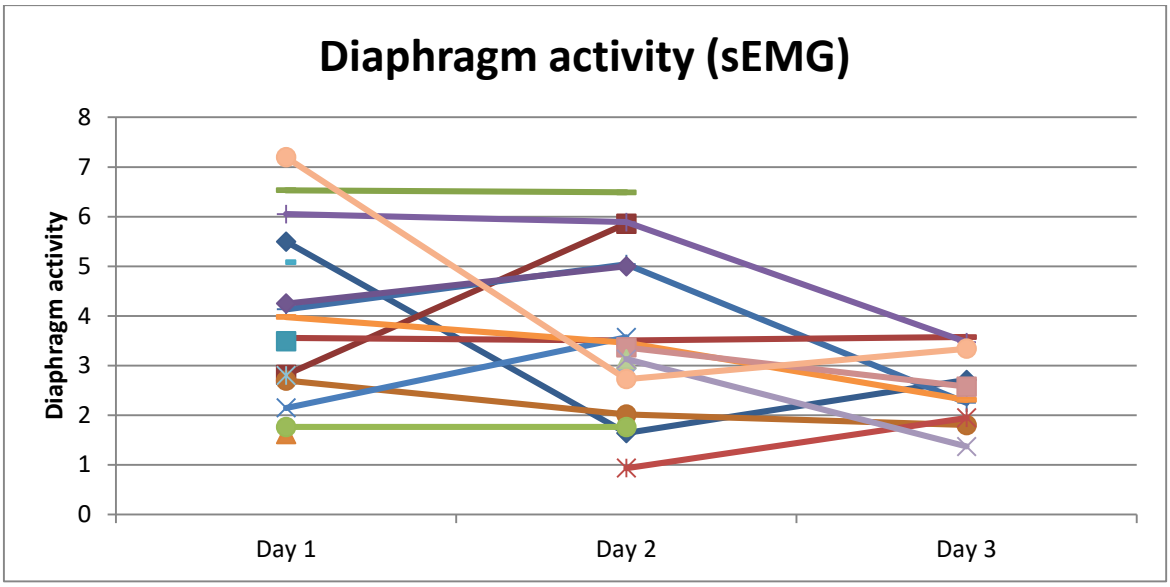


Two-way ANOVA illustrating differences between patients who on day 1 of MV were breathing above the set breath rate and those who were not and diaphragm activity on day 1, day 2 and day 3 of MV

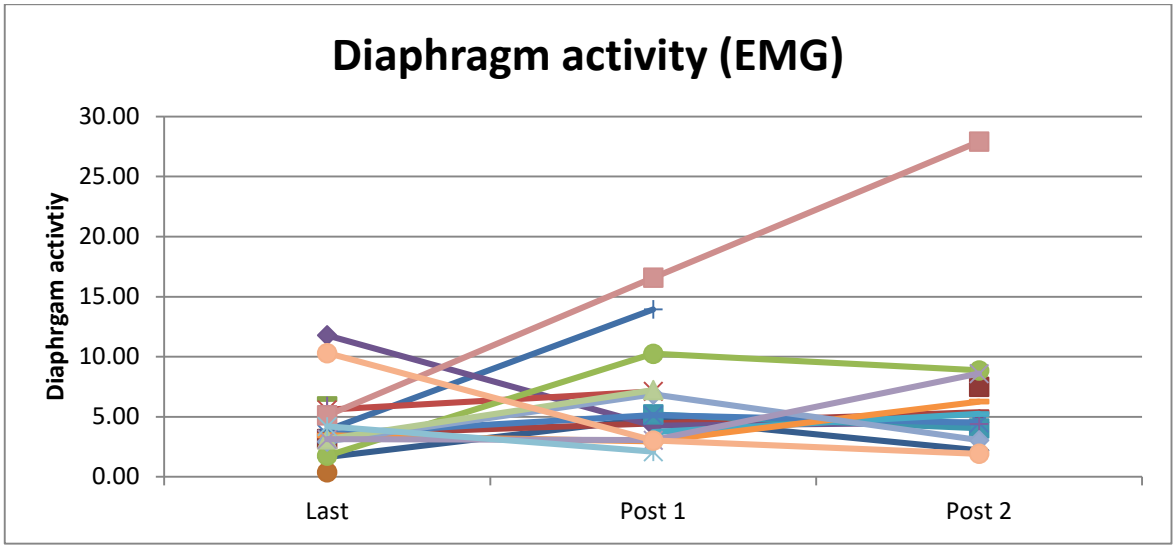


Two-way ANOVA illustrating differences between patients who on day 1 of MV were breathing above the set breath rate and those who were not and diaphragm activity on the last day of MV, day 1 post-extubation and day 2 post-extubation

Addendum R: Electromyography measures of diaphragm electrical activity

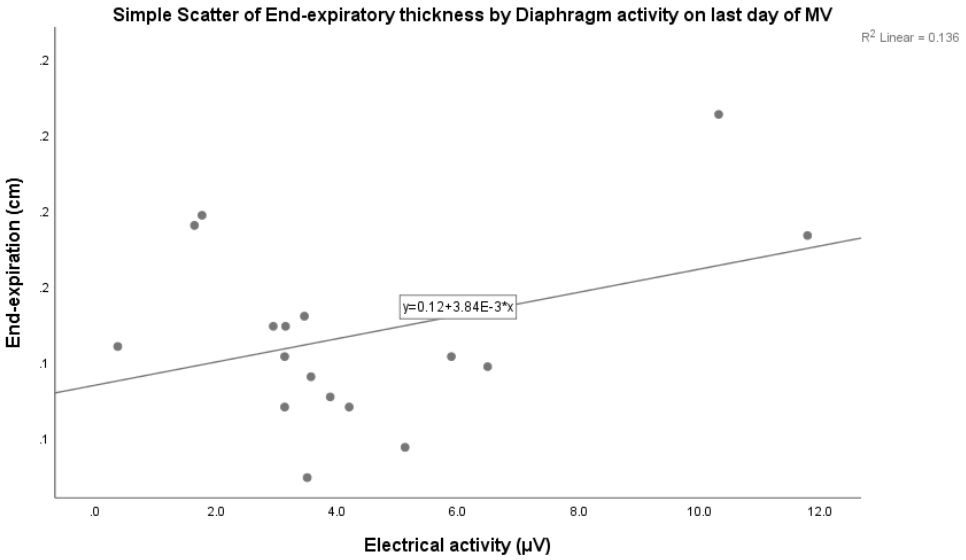


Diaphragm activity measures for all participants for the first three days of MV

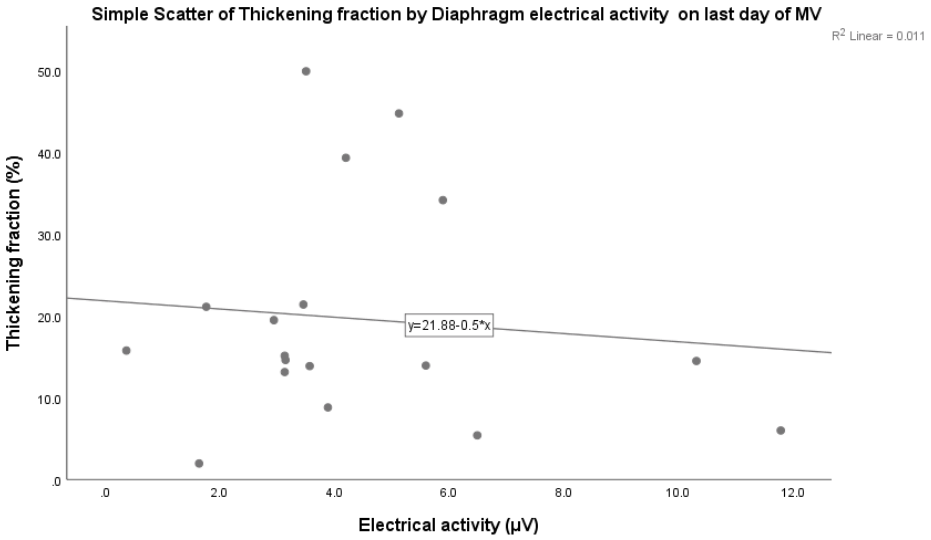


Diaphragm activity measures for all participants for the last day of MV and two days post-extubation

Addendum S: Relationship between diaphragm thickness and electrical activity

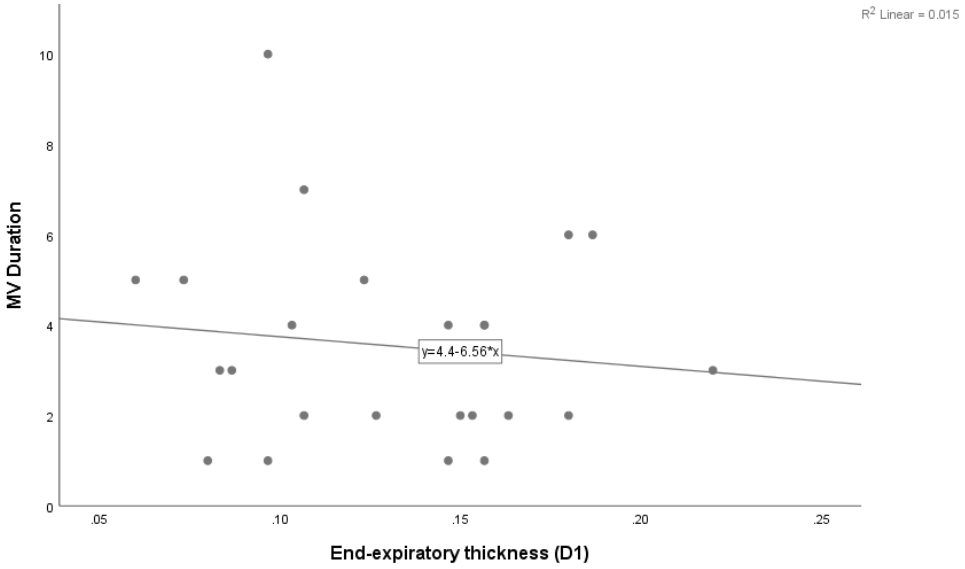


Scatter plot illustrating the relationship between diaphragm resting thickness and electrical activity for the last day of MV

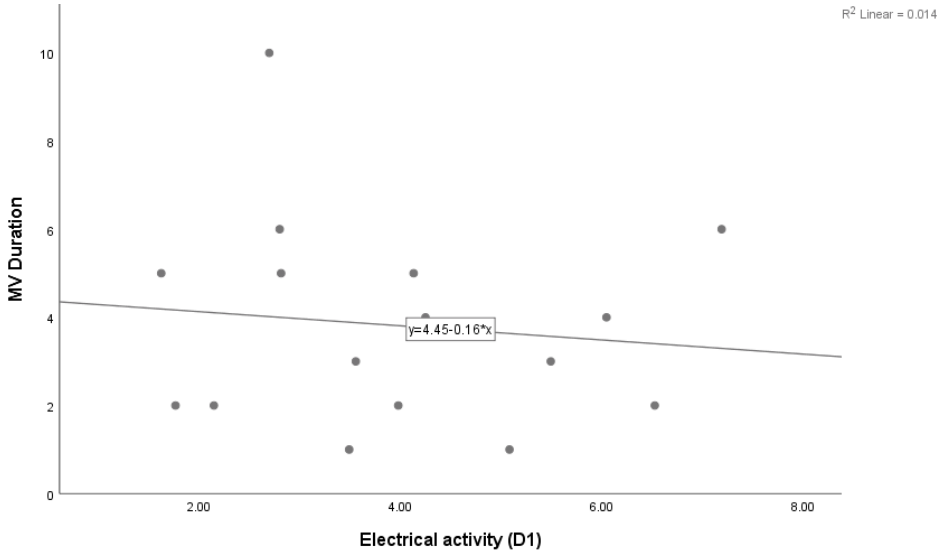


Scatter plot illustrating the relationship between diaphragm TF and electrical activity for the last day of MV

Addendum T: Relationship between diaphragm function and mechanical ventilation duration



Scatter plot of MV duration and end-expiratory thickness on day 1 of MV



Scatter plot of MV duration and diaphragm electrical activity on day 1 of MV

Addendum U: Unpublished data (EMG)

Unpublished data by A. Lupton-Smith – Diaphragm activity in healthy and mechanically ventilated infants and children:

Diaphragm activity in healthy children

	Mean (SD) (n=5)	**p-value**
Supine	3.78 (0.74)	0.65

Diaphragm in healthy children (side lying)

	Left side-lying (n=10)	**Right side-lying (n=10)**	**p-value**
Left hemi-diaphragm	2.35 (1.49 – 3.09)	2.28 (1.82 – 3.28)	0.85
Right hemi-diaphragm	2.03 (1.54 – 3.36)	2.88 (1.91 – 3.49)	0.36

Diaphragm activity in mechanically ventilated children (side lying)

	Left side-lying	**Right side-lying**	**p-value**
Left hemi-diaphragm	8.82 (6.53 – 11.95)	7.98 (6.04 – 11.44)	0.50
Right hemi-diaphragm	9.41 (6.74 – 12.07)	12.16 (5.19 – 18. 66)	0.23