Diaphragm Contractile Activity during Mechanical Ventilation

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

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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Date: March 2018

ABSTRACT

Introduction

Mechanical ventilation has been shown to have detrimental effects on the diaphragm, causing extubation failure. Diaphragm ultrasound has recently been investigated as a measurement technique that could identify diaphragm dysfunction in real-time. Investigation of diaphragm function and the impact thereof on patient outcome could inform us of the behaviour of the diaphragm muscle during mechanical ventilation.

Methods

A Scoping review was done to investigate the effect of mechanical ventilation on the diaphragm. Six databases were searched using a specific search strategy. Predefined inclusion criteria were used to identify papers suitable for the review. The primary investigator used a systematic process to identify suitable papers and extract data into an Excel spreadsheet. Data was used to inform the planning of the primary research study. A prospective observational cohort study was conducted to determine the effect of diaphragm contractile activity on extubation success in mechanically ventilated patients. Mechanically ventilated participants were recruited on admission to the intensive care unit. Sonographic measurements of the diaphragm were taken daily until extubation, and respiratory muscle strength measurements were taken within 24 hours of extubation. Diaphragm thickness (Tdi), diaphragm thickening fraction (DTF) and daily rate of change in both Tdi and DTF related to the previous day were calculated. Patient outcomes were reported by two variables: extubation outcome and duration of ventilation. Associations between diaphragm and inspiratory measurements were reported using Spearman's correlations, and between-group differences were analysed by means of Mann-Whitney U tests and ANOVA graphs. A p-value of <0.05 was used to indicate significance.

Results

Six hundred and thirty-seven articles were assessed for inclusion into the scoping review. Fifty-six papers were included in the review. Diaphragm assessment techniques, ventilation modes, cellular changes to the diaphragm and confounding factors were reported. Similar techniques were reported regarding diaphragm contractile activity and Tdi measurements, however results were contrasting, especially concerning patient outcome. Sixty-eight participants were included in the primary study. Fifty-four participants passed extubation. The mean age of the sample was 45.1 years (SD = 16.9). Neither age, gender, comorbidities, smoking nor alcohol use were different in success versus failed extubation groups. Baseline Tdi measurement was significantly higher in failed than successful extubation groups ($p=0.033$), and a significant moderately positive association was found between baseline Tdi and total duration of mechanical ventilation ($r=0.412$, $p<0.01$). Baseline DTF did not differ between failed and successful extubation groups ($p>0.05$). Baseline Tdi was not associated with maximal inspiratory pressure ($r=0.02$, $p=0.901$).

Conclusion

Several diaphragmatic assessment techniques exist, however there are discrepancies within the results reported. Ultrasonography proves to be an easy assessment technique to visualise the diaphragm in real-time. Furthermore, we conclude that in our population, thicker diaphragms at baseline may be more prone to an increased duration of mechanical ventilation and may be linked to extubation failure. Measuring diaphragm contractile activity during tidal breathing may not be a valid indicator of extubation readiness and further research should be done to prove its value in the critically ill population.

OPSOMMING

Inleiding
Meganiese ventilasie is bewys om nadelige effekte op die diafragma te hê, wat mislukte ekstubasie kan veroorsaak. Diafragma ultraklank is onlangs ondersoek as ‘n assesseringstegniek wat diafragma disfunksie in ware tyd kan identifiseer. Diafragma funksie en die impak daarvan op pasiënt uitkomste kan ons inlig oor die gedrag van die diafragma spier tydens meganiese ventilasie, en moet ondersoek word.

Metode
‘n Literatuur omvangsbepaling was gedoen om die effek van meganiese ventilasie op die diafragma te ondersoek. Ses databasisse was deursoek met ‘n spesifieke soektog strategie. Gedefinieerde insluitingskriteria was gebruik of gepaste artikels te identifiseer. Die primêre ondersoeker het ‘n sistematiese proses gevolg om sodoende gepaste artikels te identifiseer en data in ‘n Excel sigblad in te lees. Hierdie inligting was gebruik om die primêre studie te beplan. ‘n Voornemende waarnemings kohort studie was uitgevoer om the effek van diafragma kontraktiele aktiwiteit op ekstubasie sukses in meganies geventileerde pasiënte te bepaal. Meganies geventileerde deelnemers was gewerf tydens opname in die intensiewe sorg eenhede. Sonografiese metings van die diafragma was daagliks geneem tot in met ekstubasie, en respiratoriese krag metings was geneem binne 24 uur vanaf ekstubasie. Diafragma dikte (Tdi), diafragma verdikkingsfraksie (DTF) en daaglikse koers van verandering in diafragma dikte en verdikkingsfraksie in vergelyking met die vorige dag was bereken. Pasiënt uitkomste was deur twee veranderlikes voorgestel: ekstubasie uitkomste en duur van meganiese ventilasie. Assosiasies tussen diafragma en respiratoriese metings was gerapporteer deur “Spearman’s” korrelasies, en tussen-groep verskille was geanaliseer deur middel van “Mann-Whitney U” toetse en ANOVA grafieke. ‘n P-waarde van <0.05 was as statisties beduidend gestel.

Resultate
Ses-honderd-sewe-en-dertig artikels was geassesseer vir insluiting in die omvangsbepaling. Ses-en-vyftig artikels was ingesluit. Diafragma assesserings tegnieke, ventilasie metodes, molekulêre veranderinge in die diafragma en verwarrende faktore was gerapporteer. Eenderse tegnieke met betrekking tot diafragma kontraktiele aktiwiteit en dikte metings was berig, alhoewel resultate rondom pasiënt uitkomste verskil. Agt-en-sestig deelnemers was ingesluit in die primêre studie. Vier-en-vyftig deelnemers was suksesvol geëkstubeer. The gemiddelde ouderdom van die toetsgroep was 45.1 jaar (SD = 16.9). Nie ouderdom, geslag, mede-siektetoestande, rook of alkohol gebruik was verskillend tussen suksesvolle en mislukte ekstubasie groepe nie. Basislyn dikte metings was beduidend hoër in die mislukte ekstubasie groep ($p=0.033$). Basislyn DTF was nie verskillend tussen suksesvolle en mislukte ekstubasie groepe nie ($p>0.05$). ‘n Gemiddelde positiewe assosiasie was gevind tussen basislyn dikte en totale duur van meganiese ventilasie ($r=0.412$, $p<0.01$). Basislyn dikte was nie geassosieer met maksimale inspiratoriese druk nie ($r=0.02$, $p=0.901$).

Gevolgtrekking
Verskeie diafragmatiese assesseringstegnieke bestaan alhoewel daar verskille in die resultate gerapporteer is. Ultrasonografie is bewys om ‘n maklike assesseringstegniek te wees om die diafragma in ware tyd te visualiseer. Verder het ons gevind dat ‘n dikker diafragma by basislyn moontlik meer geneig is tot verlengde duur van meganiese ventilasie, en moontlik gekonnekteer kan word aan mislukte ekstubasie, in ons populasie. Deur diafragma kontraktiele aktiwiteit te meet gedurende gety asemhaling mag moontlik nie ‘n geldige aanwyser wees van ekstubasie gereedheid nie en verder navorsing word benodig om die waarde daarvan in ‘n kritieke populasie te bewys.

Dedication

Thank you to my husband, friends and family for their continuous support and understanding. Would not have done it without you.

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DEFINITION OF TERMS

APACHE II – A severity of disease classification system that groups patients according to their risk of death based on physiological data (1).

Diaphragm Thickening Fraction (DTF) – The percentage change in diaphragm thickness during inspiration (2). Can be used to assess diaphragmatic function and its contribution to respiratory workload (3).

Diaphragm excursion (EXdi) – The movement of the diaphragm (4).

Diaphragm Thickness (Tdi) – The thickness of the diaphragm muscle at end-expiration (at its thinnest) in the zone of apposition (5,6).

Electromyography (EMG) – The study of muscle activity by analysis of electromyographic signals (7).

Electrical activity of the diaphragm (EAdi) – Quantification of the activity of the diaphragm and the precise timing thereof (4).

Oesophageal pressure (Poes) – Pressure in the lower one third of the oesophagus (BENDITT), also a reflection of pleural pressure (4).

Extubation – The removal of tracheal tube (8).

Extubation failure / Non-successful extubation – If a patient requires reintubation, or dies within 48 hours after extubation (9).

Extubation readiness - When weaning is completed, thus the patient is awake and hemodynamically stable, with intact airway reflexes, and has manageable secretions (10).

Extubation success - The absence of ventilatory support during the first 48 hours after extubation (8).

Gastric pressure (Pgas) – Measure of abdominal strength (4).

Inspiratory muscle training (IMT) – The use of progressive resistance to provide loading to the inspiratory muscles to achieve a strengthening effect (11).

Maximal Inspiratory Pressure (PImax) – The maximum pressure generated in upper airway, during a voluntary inspiratory effort (4,7).

Maximal Expiratory Pressure (PEmax) – The maximum pressure generated in upper airway during a voluntary expiratory effort (4,7).

Residual Volume (RV) – Volume of air remaining in the lung after a maximal expiration (12).

Respiratory Failure – Inadequate oxygen delivery (13).

Tidal volume (TV) – Volume of air inhaled or exhaled during a single normal breath (12).

Total lung capacity (TLC) – Total volume of air in the lungs at the end of a maximal inspiration (12).

Transdiaphragmatic pressure (Pdi) – Voluntary measure of specific diaphragm strength (14).

Twitch airway pressure (PawTw) – Involunatry measure of pressure at airway opening (4).

Twitch endotracheal tube pressure (PettTw) – Noninvasive involuntary measure of pressure at opening of endotracheal tube (15).

Twitch gastric pressure (PgasTw) – Involuntary measure of abdominal muscle strength (4).

Twitch transdiaphragmatic pressure (PdiTw) – Involuntary measure of isolated diaphragm strength (14,16).

Twitch oesophageal pressure (poesTw) – Involuntary measure of oesophageal pressure (4,15).

Ventilator induced diaphragmatic dysfunction (VIDD) - A loss of the force-generating capacity of the diaphragm as result of the use of mechanical ventilation (17).

Weaning process – Slowly adjusting settings to remove the respiratory support when a patient under mechanical ventilation recovers his or her breathing capabilities (18).

Zone of apposition (ZOA) - The area of the chest wall where the abdominal contents reach the lower rib cage (6).

CHAPTER 1: INTRODUCTION

Mechanical ventilation is often used in the Intensive Care Unit (ICU) as a life-saving supportive treatment of respiratory failure, ensuring adequate ventilation and gas exchange (17,19,20). However, in the past decade much research has focused on the detrimental effects of mechanical ventilation on the diaphragm muscle (17,19–23). In this chapter we give a brief overview of diaphragm function and mechanical ventilation.

1.1 Mechanical ventilation and the diaphragm

Ventilator induced diaphragmatic dysfunction (VIDD) was first described by Vassilakopoulos & Petrof (3) as the loss of the force-generating capacity of the diaphragm muscle as a result of mechanical ventilation. With the diaphragm being the main respiratory muscle contributing to inspiration, any dysfunction of the diaphragm could impair the ability to ventilate and aerate optimally (24). The phenomenon of VIDD is as a result of mechanical ventilation unloading the diaphragm muscle, leading to atrophy and decreased contractility of the diaphragm muscle (17,20,21,24). Several factors and mechanisms exist in explaining the cause and extent of VIDD, namely cellular changes, duration of ventilation, ventilation mode and risk factors associated with mechanical ventilation.

Animal studies done at cellular level show a discrepancy between proteolysis and protein synthesis, resulting in a loss of protein within the muscle when skeletal muscles are inactive (25). This discrepancy results in changes in muscle structure and consequent impaired muscle function. Proteolysis initiates within 12 hours of controlled mechanical ventilation (25). This phenomenon was tested on rats by Hudson et al. (25) and they concluded that strategies to prevent the imbalance between protein synthesis and proteolysis could lead to better diaphragm functioning when mechanically ventilated. Furthermore, Hudson et al. (25) also revealed that choosing partial support ventilation over controlled mechanical ventilation could prevent the rate of proteolysis in the diaphragm muscle, ultimately improving diaphragm contractility and function. Human cellular studies have reported similar findings with regards to diaphragm wasting (26,27). A study done by Picard et al. (28) found that mechanical ventilation induced oxidative stress causing mitochondrial dysfunction, which leads to muscle fibre weakness and impaired contractility. Jaber et al. (29) found a decrease in cross-sectional length of diaphragm muscle fibres which also contributed to decreased contractility.

Research on the diaphragmatic force production during mechanical ventilation showed that increased time on the ventilator led to a decreased force produced by the diaphragm, which may correlate with VIDD (30). Schepens et al. (31) and Zambon et al. (32) stated that the length of mechanical ventilation can be associated with diaphragmatic atrophy. It has been found that mechanical ventilation can initiate thinning or develop a thinning process of the diaphragm over time, however the relationship between thinning and weaning requires further investigation (33). Zambon et al. (32) examined the effects of different modes of ventilation on diaphragm thickness (Tdi) and reports a decrease in Tdi of 1.5% in low pressure support ventilation daily, and a daily decrease of up to 7.5% in controlled mechanical ventilation, however this study had a small sample.

Research has found diaphragmatic dysfunction in both controlled and assisted mechanical ventilation, however the degree of dysfunction in different modes has to be investigated further (31). The triggering of ventilation in assisted mechanical ventilation modes may be

due to secondary breathing muscles activating and not necessarily the diaphragm, hence the possibility for VIDD in both controlled and assisted ventilation modes (31).

Medication is vital in the mechanically ventilated population. Often patients need medicated support to suppress restlessness, numb pain, control heart rate and blood pressure and fight infection etc. Although mostly beneficial, side-effects may be present. Neuromuscular blockers are often given to patients to reduce discomfort and inhibit respiratory movements (20). However, this can lead to contractile dysfunction of the musculature but has not yet been studied intensively in humans (20). Another medication often used is corticosteroids, especially in the presence of inflammation. Although this could be life-saving, it can also cause steroid-induced myopathy which can worsen VIDD (20). Conflicting results show that a high dose corticosteroids at the early stages of mechanical ventilation might be more beneficial than detrimental in rats, however this needs further investigation (24,34).

1.2 Monitoring Diaphragm function

Diaphragm function has been related to weaning outcome (17). More recently, studies have aimed at evaluating diaphragm function to predict extubation outcome (35–38). Diaphragm thickening fraction (DTF), measured by ultrasonography, represents both maximal and minimal Tdi of the diaphragm during a tidal breath and therefore reveals contractile activity of the diaphragm muscle, which in turn is related to function (2). Goligher et al. (38) found that contractile activity, when measured with DTF, was proportional to the Tdi of the diaphragm, thus the lower the contractile activity was, the thinner the diaphragm became over time, suggesting that Tdi is related to diaphragm function. Cut-off values have been proposed in order to identify possible successful extubation (35,37). A DTF of more than 30% has been reported to be indicative of successful extubation (35). Grosu et al. (33) has reported measuring daily Tdi at end-expiration in order to establish the rate of change in Tdi during mechanical ventilation, and found a daily decrease in Tdi of 6%. This confirms the ability of mechanical ventilation to induce atrophy in the diaphragm. The extent to which the Tdi of the diaphragm is related to function however needs further investigation.

Twitch transdiaphragmatic pressure (PdiTw) is the most accurate measure of diaphragm strength (4), but requires the insertion of balloon catheters into the stomach and oesophagus. Therefore, researchers have been investigating possible surrogate strength measures which could be used to quantify diaphragm strength less invasively. Dubé et al. (39) compared PdiTw to diaphragm function measures (Tdi and DTF) and found a strong correlation between DTF and PdiTw, however only under pressure support ventilation and not assist control ventilation.

1.3 Significance of the study

Mechanical ventilation plays a vital role in managing respiratory failure, however it could have unfavourable effects. Extubation failure increases hospital stay and costs, therefore better predictors of successful extubation are paramount. If diaphragm dysfunction can be identified and quantified earlier, strategies to prevent further atrophy and dysfunction can be implemented sooner. Furthermore, if extubation success can be predicted, as well as the trend of diaphragm contractile activity, a patient's readiness for weaning/extubation can be objectively assessed and managed accordingly. The rate of change in DTF and Tdi could also indicate whether further diaphragm strengthening or weakening could be anticipated. When we know the behaviour of diaphragm contractile activity during mechanical ventilation,

we could intervene early by means of inspiratory muscle training in order to optimise diaphragm function where necessary.

The purpose of this thesis was to investigate the Tdi and diaphragm contractile activity during mechanical ventilation, as well as respiratory strength and extubation outcome of critically ill patients who received mechanical ventilation.

1.4 Thesis outline

This thesis is presented in “Masters by Publication” format.

CHAPTER 1 provides an introduction to the study, background, significance of the study and thesis outline.

CHAPTER 2 is a scoping review on the effects of mechanical ventilation on the diaphragm muscle, and is used to inform the planning of the primary study.

CHAPTER 3 describes the primary study conducted as part of this thesis. A prospective, observational cohort study was conducted to determine the **effect of diaphragm contractile activity on extubation success.**

CHAPTER 4 is a general discussion of results and achievement of aims, together with limitations and future research ideas.

REFERENCES

ADDENDA relating to literature overview, ethical approval, pilot study and journal preparation.

CHAPTER 2: SCOPING REVIEW

The Effect of Mechanical Ventilation on the Diaphragm

2.1 OBJECTIVE

The objective of this scoping review is to examine the influence of mechanical ventilation and its different modes on the diaphragm muscle of critically ill patients. We aim to establish how the diaphragm is assessed and the outcome measures used, which ventilation modes have what effect on the diaphragm as well as any risk factors for diaphragm dysfunction.

2.1.1 QUESTION

What is the effect of Mechanical Ventilation on the Diaphragm in Critically Ill Patients?

2.1.2 KEY WORDS

Mechanical ventilation

Diaphragm

Critically Ill patients

2.2 BACKGROUND

Mechanical ventilation is widely used in the intensive care setting to support the respiratory system during disease or dysfunction, or when a person fails to adequately ventilate spontaneously. It has many benefits which include supplementation of gas exchange, reduced work of breathing, protection from respiratory muscle injury and ultimately improved alveolar ventilation (17,19,20). Yet, mechanical ventilation can lead to serious complications such as infection, injuries to the tracheobronchial tree, prolonged exposure to increased amounts of oxygen and diaphragm muscle wasting and contractile dysfunction (17,19,20,23,31). The latter is better known as ventilator-induced diaphragmatic dysfunction (VIDD), as stated by Vassilakopoulos and Petrof (17).

The diaphragm is the main respiratory muscle responsible for generating inspiratory pressure (24). Therefore, the functionality of the diaphragm is directly related to the ability to ventilate spontaneously. In healthy subjects, the diaphragm contracts to generate the necessary pressure in order to breathe spontaneously. Diaphragm effort is decreased during mechanical ventilation, depending on the mode used (22). Thus, mechanical ventilation has the ability to unload the diaphragm, which inactivates muscle contraction leading to atrophy and weakness (17,24).

Diaphragm dysfunction has been described as a possible contributor to weaning failure (17,20,40), and weaning failure has been associated with significant morbidity and mortality (8,41). Research, however, has shown that weaning failure is multifaceted and many confounding factors exist which could contribute to weaning failure (17,18,20,42). In current practice, weaning is mainly initiated by the treating clinician at his or her own discretion. Protocols for weaning readiness have been investigated with specific objective measures that can be used to assess weaning readiness (18). However, conflicting results exist as to whether these indices can predict successful weaning and whether these protocols can be generalised to any mechanically ventilated patient, regardless of the length of ventilation and other confounding risks (18,42). Examples of these objective weaning parameters include a

rapid shallow breathing index (RSBI), tidal volume and maximal inspiratory pressure (MIP) (8,43).

More recently, studies have been published on the measuring of diaphragm thickness (Tdi) or contractility of mechanically ventilated patients and subsequently predicting extubation success or failure, with the aim of providing a more direct and objective measure of diaphragm function (35–37). The use of ultrasonography is specifically highlighted in these studies, as it is a non-invasive and safe method to use with the added benefit of real-time imaging to be able to make decisions faster (33,35,37,44). However, the outcomes measured with ultrasonography need further validation as results published are contradictory (31,37,45).

Mechanical ventilation has evolved vastly with regards to different settings, modes and the combinations thereof. Controlled mechanical ventilation is shown to have the most detrimental effects on the diaphragm and is not commonly used in current practice anymore (17,46). However, it is unclear how much different modes affect the diaphragm and whether the duration of mode used contributes to ventilator induced diaphragmatic dysfunction. This once again highlights the multifaceted causes of weaning failure, as duration and mode might influence the outcome of mechanically ventilated patients.

Similarly, there are other confounding factors which may affect the diaphragm and cannot be overlooked. Examples of possible confounders include: underlying comorbidities, sedation, neuromuscular blocking agents and infection (20,41,47). The extent to which these confounders add to diaphragm dysfunction, if any, needs further investigation.

A scoping review was conducted to inform planning of the proposed main study investigating diaphragm contractile activity in mechanically ventilated patients. The aim of this scoping review was to determine the effect of mechanical ventilation on the diaphragm muscle of critically ill patients. The objectives of this scoping review were to describe different diaphragmatic assessment techniques and their specific outcome measures. Another objective was to describe whether different ventilation modes had different effects on the diaphragm and identify risk factors for diaphragm dysfunction.

2.3 MATERIALS and METHODS

2.3.1. Search strategy

A systematic literature search was conducted on six computerised databases including: Pubmed, Cinahl, PEDRO, Cochrane, Medline and Science Direct using a broad search strategy compiled by the primary investigator and faculty librarian (48). Initial search was done in March 2016 but an updated search was done in June 2017. Literature was searched from inception to June 2017. Key terms such as “mechanical ventilation”, “diaphragm muscle”, “critical illness”, “measure”, “ventilation mode” and “outcome” were used in different combinations. MeSH terms were used where applicable. All searches were limited to English articles, and additional limits were applied to each separate database. Refer to Addendum A for the detailed search strategies used.

2.3.2 Inclusion and exclusion criteria

Papers were included if they reported on:

i) All adults 18yrs and older
ii) Humans
iii) Invasive and non-invasive mechanical ventilation

Papers were excluded if the population specified included degenerative neuromuscular diseases. No papers reporting on healthy subjects were used, and all non-English papers were excluded. Reviews, editorials, summaries and randomised-controlled trials were excluded.

2.3.3 Study selection and Data extraction

One reviewer independently and systematically screened and evaluated the titles, abstracts and then full texts of all papers yielded through the search strategy for inclusion of potentially relevant articles. All full texts were accessed electronically. The same reviewer independently extracted all relevant data items from the included papers, using a Microsoft Excel spreadsheet. Data extracted included: year of publication, country of origin, outcome measures used, methodology and findings.

2.3.4. Analysis and Synthesis

Data were reported descriptively and summarised in different groups under the results section such as: assessment techniques and outcome measures, modes of ventilation, cellular findings and confounding risk factors. Data were discussed at the end of each respective section in order to identify the effect of mechanical ventilation on the diaphragm of critically ill patients.

2.4 RESULTS

The search strategy yielded a total of 637 titles. A total of 265 duplicates were removed. The remaining 372 titles were screened for inclusion and 129 titles were excluded. Out of the 243 abstracts screened, a total of 106 were excluded. 137 full texts were retrieved and assessed for inclusion, of which 81 were excluded. The total number of 56 publications were included in this review. Figure 2.1 shows the prisma flow diagram of article exclusion process.

2.4.1 Description of publications

Of the 56 publications included in this scoping review, 38 (67.9%) papers reported on the assessment of the diaphragm in mechanically ventilated patients (Tables 2.1-2.7), and the effect of different modes of ventilation on the diaphragm was described by 20 (35.7%) papers (Table 2.8). Only eight (14.2%) papers described the cellular changes in the diaphragm of mechanically ventilated patients (Table 2.9). Five (9%) papers looked at confounding/risk factors to diaphragm weakness and one (2%) paper described the effect of the tracheostomy tube size. Some of these papers described more than one variable and will be described under each different section. Table 2.1 shows a summary of the number of articles included in each subtopic.

Table 2.1: Summary of the number of articles included under each subheading of this literature overview

Sub-topic	Number of studies included
Assessment of diaphragm	38
Different modes of ventilation	20
Cellular changes in the diaphragm	8
Confounding/risk factors to diaphragm weakness	5
Effect of tracheostomy tube size	1

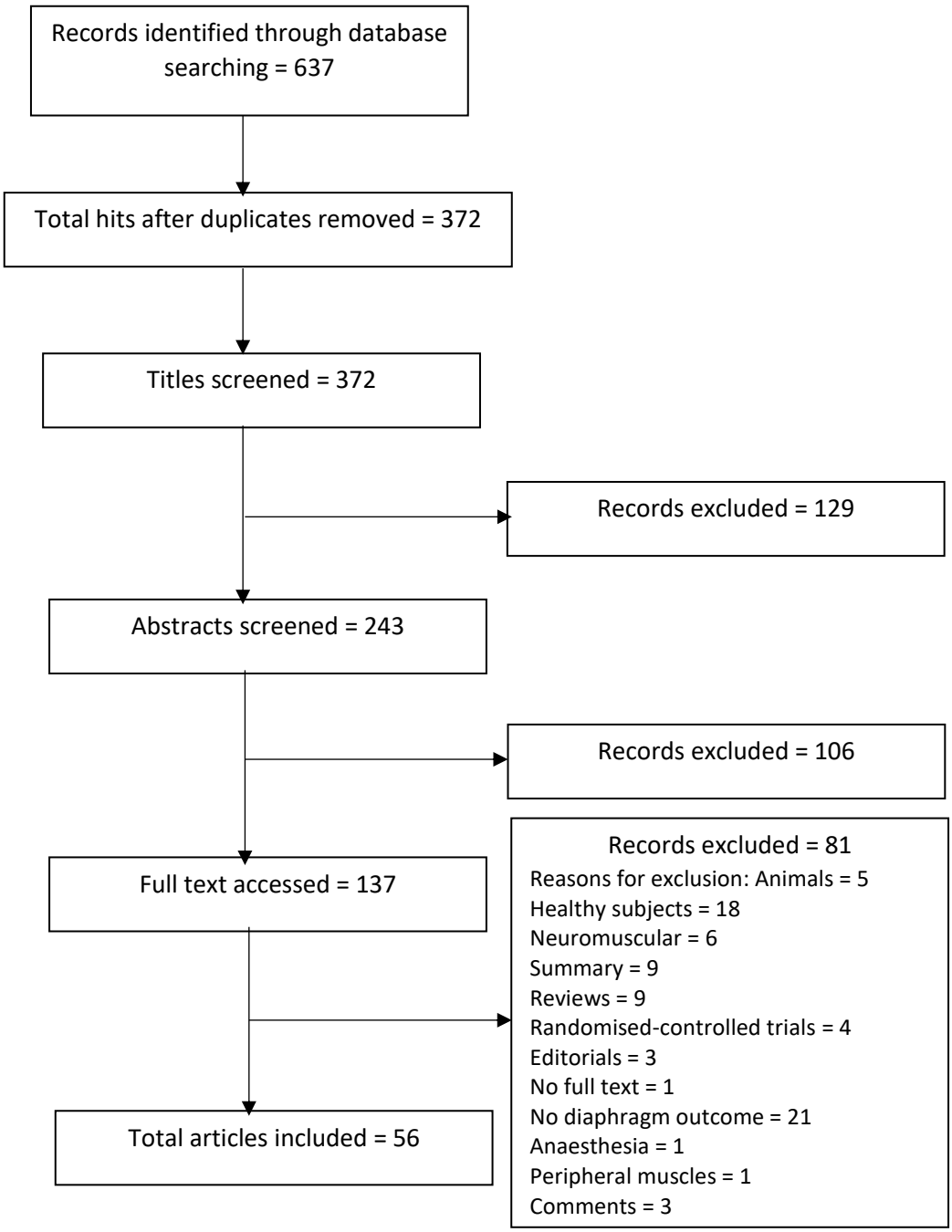

Figure 2.1: Prisma flow diagram of article exclusion process

2.4.2 Demographics of all included papers

Majority (37, 66%) papers were published in France (15 27%), Italy (12, 21%) and the United States of America (10, 18%) (Figure 2.2). The papers included in this scoping review were mostly published between 2010 and 2017. The earliest paper included in this review was published in 1985 (49). Figure 2.3 shows the precise number of papers per year of publication. It is evident that research on the diaphragm and mechanical ventilation is becoming increasingly popular, especially within the developed countries. These publications could reflect a difference in research agenda between developed and developing countries, as the latter might not be able to conduct these techniques due to

inaccessibility of resources and accurate monitoring. This could also impact clinical practice. The generalisability of these results should therefore be applied with caution.

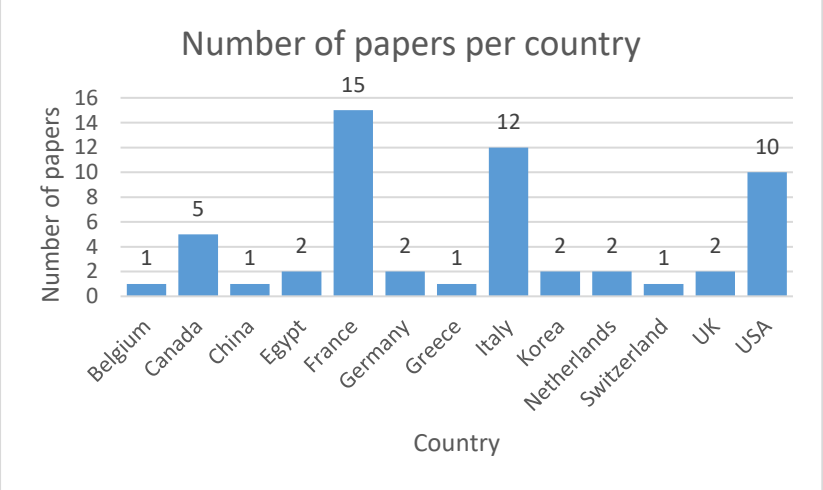

Figure 2.2: Number of papers included in this review from each country

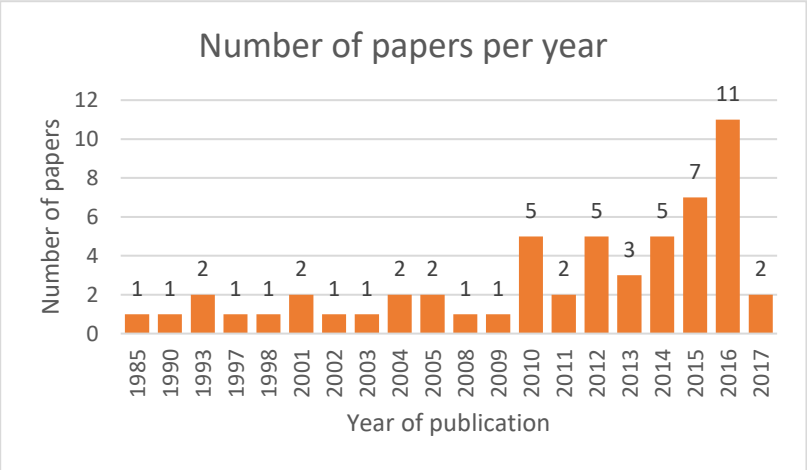

Figure 2.3: Number of papers published per year of publication

2.4.3 Diaphragm assessment and outcome measures

Papers reporting on the assessment of the diaphragm of critically ill mechanically ventilated patients were identified during the search. Multiple techniques of assessment have been described in the following paragraphs. The techniques mostly used to assess the diaphragm of mechanically ventilated patients include: ultrasonography (17, 45%), bilateral anterior magnetic stimulation (8, 21%), electrical activity of the diaphragm and diaphragm electromyography (6, 16%) and pressure measurements via balloon catheterisation (7, 18%). A single study used computed tomography (CT) to evaluate Tdi retrospectively (50). The methodology of each technique is described as the reproducibility is paramount in sound research. Furthermore, each technique is associated with different outcome measures depending on the specific variables measured. A detailed description of the methodology and outcome measures can be found below.

2.4.3.1. Ultrasonography method

Ultrasound has recently become a popular method of respiratory assessment. It can provide real-time visualisation of the lung and respiratory mechanics and assist with instant decision making. Reliability of diaphragm ultrasound measures have been established by a number of studies (2,3,44) and the feasibility thereof have been mentioned in almost all the ultrasonography studies, proving it to be a safe, non-invasive and easily accessible tool to assess the diaphragm of critically ill patients. Table 2.1 represents a summary of the ultrasound methodology.

The least common position used to measure the diaphragm was the seated position (45). Majority (5, 29%) papers measured diaphragm ultrasonography with participants in a 30˚ head up position (3,31,32,51,52) as opposed to a 45˚ head up position (2, 11%) (31,53). The supine position has also been described to measure the diaphragm with ultrasonography in three papers (18%) (54–56).

With regards to probe placement, the majority (15, 88%) of papers report better visualisation of the diaphragm on the right side, between either the eighth, ninth or tenth intercostal space, at the zone of apposition (2,3,31–33,35,38,39,44,51–54,56,57). Both the anterior-axillary and mid-axillary lines have been used for probe alignment, and many studies (7, 41%) suggest trying both alignments and using the one with the clearer image. It is however of note that most studies found clearer images with the probe aligned with the mid-axillary line. Refer to Table 2.1 for specific references to probe placements.

Both B-mode and M-mode ultrasound are equally popular in the measurement of the diaphragm. B-mode, also known as brightness mode, is the most basic mode and captures a two dimensional image of the structures below the probe, delivering greater definition of the diaphragm (58). M-mode, also known as motion mode, is a one-dimensional imaging mode often used to measure the diaphragm over time (especially measuring diaphragm excursion (36,56,57). Cohn et al (58) criticised the use of M-mode as one can easily mistake fluid between the parietal pleura and diaphragm as part of the diaphragm muscle. However it is still unknown whether either of these modes are more accurate in the assessment of Tdi and DTF.

Ultrasonography outcome measures

Multiple characteristics of the diaphragm muscle can be assessed by ultrasonography. The most common outcome measures described in the literature include: Tdi, DTF, diaphragm excursion and the rate of change (%) in either Tdi or DTF. Table 2.2 shows a summary of outcome measures used with ultrasonography.

Tdi, measured at either end-inspiration or end-expiration or both, is described in almost all (15, 88%) of the ultrasonography papers (2,3,31–33,35–39,44,51,53,54,57). The Tdi of the diaphragm is measured to determine diaphragmatic atrophy. At end-inspiration, the diaphragm is at its thickest, due to inspiration causing muscle contraction. At end-expiration, the diaphragm is at its thinnest as the muscle is relaxed.

Table 2.2: Summary of Ultrasonography method used in studies measuring diaphragm function

Study	Positioning				Probe placement						
	Seated	30˚ head up	45˚ head up	Supine	Right hemi-diaphragm	Left hemi-diaphragm	Intercostal space	Mid-axillary	Anterior axillary	Respiratory cycles	US mode
Ali & Mohamad (54)	N	N	N	Y	Y	N	8/9th	Y	Y	3	B-mode
DiNino et al. (35)	N	Y	N	N	Y	N	8-10th	Y	N	3-5	B-mode
Dres et al. (57)					Y	N	9/10th	Y	Y	3	M-mode
Dubé et al. (39)					Y	N	9/10th	Y	N	3	M-mode
Farghaly & Hasan (36)	N	Y	N	N			8/9th	Y	Y	3	B- & M-mode
Ferrari et al. (37)	N	N	Y	N			8/9th	Y	Y	3	B-mode
Francis, Hoffer & Reynolds (44)	N	N	N	Y	Y	N	8/9th	Y	N	3	B-mode
Goligher et al. (38)					Y	N	9/10th	Y	Y	Multiple	
Goligher et al. (2)					Y	Y	9/10th	Y	N	2	M-mode
Grosu et al. (33)	y	N	N	N	Y		ZOA	Y	N	3	B-mode
Kim et al. (56)	N	N	N	Y	Y	Y		Y (Left)	Y (Right)	6	M-mode
Lu et al. (53)	N	N	Y	N	Y		8/9th	Y	N	2	B-mode
Mariani et al. (52)	N	Y	N	N	Y	Y	8th	Y	N	3-4	B- & M-mode
Schepens et al. (31)	N	Y	Y	N	Y	N	8/9th	Y	N		B-mode
Umbrello et al. (51)	N	Y	N	N	Y	N	9th	Y	N	3	B- & M-mode
Vivier et al. (3)	N	Y	N	N	Y		9th	Y	Y	3	M-mode
Zambon et al. (32)	N	Y	N	N	Y	Y	8-10th	Y	Y	3	M-mode

Y= yes, N= No, Blank = not mentioned; ZOA – zone of apposition; US - ultrasound

Table 2.3: Summary of ultrasound outcome measures used when measuring diaphragm function

Study	Outcome measure							Results
	Diaphragm Thickness (Tdi)		Diaphragm Thickening fraction (DTF)		Excursion (EXdi)	Rate of change %		
	End-inspiration	End-expiration	Maximal breathing	Tidal breathing		Related to baseline	Related to previous day	
Ali & Mohamad (54)	Y	Y	N	Y	N	N	Y	- ↓ Tdi,DTF,EXdi associated with ↑ length of MV - Successful weaning = DTF > 30%
DiNino et al. (35)	Y	Y	N	Y	N	N	N	- Successful extubation = DTF ≥ 30%
Dres et al. (57)	Y	Y	N	Y	Y (Maximal breathing)	N	N	- Weaning failure = ↓ DTF, ↓ EXdi
Dubé et al. (39)	Y	Y	N	Y	N	N	N	- DTF < 29% = diaphragm dysfunction, ↑ length of MV, ↑ Mortality
Farghaly & Hasan (36)	Y	Y	N	Y	Y (Tidal breathing)	N	N	- DTF, Tdi & EXdi ↑ in successful extubation groups - Successful extubation = DTF ≥ 34.2%
Ferrari et al. (37)	Y	Y	Y	N	N	N	N	- Successful weaning = DTF > 36% - DTF ↑ in successful vs failed groups
Francis, Hoffer & Reynolds (44)	N	Y	N	N	N	N	Y	- ICC = interoperator & interobserver > 0.95 - ACV = Tdi ↓ 4.7% per day - PSV = Tdi↑ 1.5% per day
Goligher et al. (38)	Y	Y	Y	N	N	Y	N	- ↑ DTF = ↑ Tdi - Max DTF ↓ in bigger Tdi changes (↑ or ↓) - Max Tdi change in first week of MV
Goligher et al. (2)	Y	Y	N	Y	N	N	N	- Measurement of Right hemi diaphragm more feasible - DTF ↓ in MV vs normal subjects
Grosu et al. (33)	N	Y	N	Y	N	N	Y	- Tdi ↓ 6% per day - MV duration predicts ↓ Tdi
Kim et al. (56)	N	N	N	N	Y (Tidal breathing	N	N	- DD = ↑ duration of ventilation, ↑ weaning time
Lu et al. (53)	Y	Y	N	Y	N	N	N	- DTF <20% = ↑ length of MV

Mariani et al. (52)	N	N	N	N	Y (Tidal breathing)	N	N	- Diaphragm dysfunction = EXdi ≤ 11mm
Schepens et al. (31)	N	Y	Y	N	N	Y	N	- Tdi ↓ 10.9% per day - Atrophy associated with length of MV
Umbrello et al. (51)	Y	Y	N	Y	Y	N	N	- ↑ ventilator support = ↓ DTF
Vivier et al. (3)	Y	Y	Y	N	N	N	N	- ↑ Pressure support = ↓ DTF - ICC > 0.75 for DTF repeatability
Zambon et al. (32)	Y	Y	Y	N	N	N	Y	- Tdi ↓ 7.5% (CMV) - Tdi ↓ 5.3% (High PSV) - Tdi ↓ 1.5% (Low PSV) - Tdi ↑ 2.3% (CPAP)

Y= yes, N= No, Blank = not mentioned, Tdi = diaphragm thickness, DTF = diaphragm thickening fraction, EXdi = diaphragm excursion, MV = mechanical ventilation, ICC = intraclass correlation coefficient, ACV = assist control ventilation, PSV = pressure support ventilation, CMV = controlled mechanical ventilation, CPAP = continuous positive airway pressure, DD = diaphragm dysfunction

The rate of change in Tdi have been measured by several studies (6, 35%), with different results. Grosu et al. (33) were the first to quantify the rate of change in Tdi as an average of 6% decline daily. Francis, Hoffer & Reynolds (44) found a slightly lower rate of change in Tdi (4.7%) during assist control ventilation, however an increase in daily rate of change in Tdi of 1.5% was seen when pressure support ventilation was applied. This is in contrast with a study done by Zambon et al. (32) who found the Tdi of the diaphragm to decrease daily with pressure support ventilation, and only increase during the use of CPAP. Several studies (3, 17%) concluded that an increased length of mechanical ventilation was associated with a decrease in Tdi (31,45,54). Two methods for calculating rate of change have been described. The first method calculates rate of change in Tdi or DTF by relating each day's measurement to baseline (first measurement) (31,38). The second and more popular method calculates the rate of change by relating each measurement to the measurement of the previous day, and then calculating the mean (32,44,45,54).

DTF has been reported to describe the contractile activity of the diaphragm (3,31–33,35–39,51,53,54,57). DTF relates to the function of the diaphragm, as it takes into account both the Tdi at end-inspiration and end-expiration. Several studies have used DTF as a predictor of extubation outcome. The earliest paper reporting a cut-off value for successful extubation was by DiNino et al. (35), who found a DTF ≥ 30% to predict successful extubation. Farghaly & Hasan (36) found an even higher DTF of 34.2% or more to predict successful extubation. This is in keeping Dubé et al. (39) who found an association between an increased length of mechanical ventilation and a DTF of 29% or less. Two studies (12%) found a relationship between increasing ventilatory support and decreasing DTF (3,51). This could be explained by the fact that increasing support unloads the diaphragm, leading to a possible decrease in diaphragm contractile activity as the diaphragm is not working as hard to contract.

Diaphragm excursion has also been used to describe diaphragm dysfunction (36,51,52,57). An excursion of less than 11 mm has been said to indicate diaphragm dysfunction (52). Also, diaphragm excursion showed similar associations with length of mechanical ventilation as DTF and Tdi.

It is of note that both Tdi and DTF have been measured at different lung volumes (2,31,32,35–39,45,51,53,54,57). Tidal volume measurements represent quiet breathing and does not need patient cooperation. It is however influenced by mechanical ventilator triggering of breaths and pressures set by the clinicians. Breathing at maximal capacity (total lung capacity) however, relies on either maximal patient co-operation or electrical stimulation, with the latter being the gold standard technique for measurement of diaphragm strength, as discussed below. The importance of distinguishing between measurements done at different lung volumes will be discussed later.

2.4.3.2 Bilateral phrenic nerve stimulation method

The gold-standard measurement technique for diaphragm strength is by means of bilateral anterior magnetic phrenic nerve stimulation (4,39,59,60,16). Magnetic stimulation is safe and comfortable, and can be used in patients who are unable to cooperate (4,7). However, to quantify the diaphragm strength, balloon catheters need to be inserted to obtain gastric and oesophageal pressure to ultimately calculate twitch transdiaphragmatic pressure (discussed later). Table 2.3 contains a summary of phrenic nerve stimulation methodology.

All the studies (8, 100%) reporting on phrenic nerve stimulation placed participants in a semi-recumbent position, specifying either 30˚ or 45˚ head-up positions

(29,39,47,57,59,16,61,15). Measurements are made at end-expiration at an intensity of 100%. %. All studies reported standardised protocols in terms of ventilator settings and positioning.

The most common placement of the magnetic coils were at the level of cricoid cartilage immediately posterior to sternocleidomastoid muscle (29,39,57,16,15). Deviations from this placement included positioning the coils at cervical vertebrae levels 5-7 (59) and along the border of the sternocleidomastoid muscle (47). Table 2.3 shows a summary of the phrenic nerve stimulation methodology.

Bilateral phrenic nerve stimulation outcome measures

As mentioned earlier, phrenic nerve stimulation measures diaphragm strength by means of twitch transdiaphragmatic pressure (PdiTw), which is the difference between twitch gastric pressure (PgasTw) and twitch oesophageal pressure (PoesTw) obtained by insertion of balloon catheters (7). This proves to be a slightly more complex and invasive method of measuring diaphragm strength, although the most accurate. Table 2.4 shows the different pressures measured and results obtained when using phrenic nerve stimulation.

Twitch pressure measured at the endotracheal tube (PettTw) have been correlated with twitch transdiaphragmatic pressure (PdiTw) and could be used to estimate diaphragm strength in a less-invasive way (39,59). Interestingly, when Dubé et al. (39) compared phrenic nerve stimulation to diaphragm ultrasonography, he reported that PettTw and PdiTw were only associated with DTF when measured in pressure support ventilator mode, and not in assist control modes. In a paper published by Watson et al. (15), it is reported that twitch transdiaphragmatic pressure is not clearly associated with length of stay in the ICU. Supinski & Ann Callahan (61), however found a twitch trans diaphragmatic pressure of less than 10cmH_2O to be associated with increased length of mechanical ventilation as well as increased mortality.

Table 2.4: Summary of phrenic nerve stimulation methods used during diaphragm assessment

Study	Positioning				When measured		Stimuli		
	Seated	30˚ head up	45˚ head up	Supine	End inspiration	End expiration	Amount	Intensity	Location
Buscher et al. (59)	N	Y	Y	N	N	Y	8-10	100%	Cervical spine – C5-C7
Cattapan, Laghi & Tobin (16)	N	Y	N	N	N	Y	8-10	100%	Posterior border of sternocleidomastoid muscle at the level of cricoid cartilage
Dres et al. (57)	N	Y	N	N	N	Y	3	100%	Immediately posterior to sternocleidomastoid muscles at level of cricoid cartilage
Dube et al. (39)	N	Y	N	N	N	Y	3	100%	Immediately posterior to the sternocleidomastoid muscles at the level of the cricoid cartilage
Jaber et al. (29)	N	Y	N	N	N	Y	3	100%	Immediately posterior to sternocleidomastoid muscle at level of cricoid cartilage bilaterally
Supinski, Westgate & Callahan (61)	N	Y	N	N	N	Y	5	100%	Over phrenic nerves
Supinski & Callahan (47)	N	Y	N	N	N	Y	5	100%	Border of sternocleidomastoid muscle
Watson et al. (15)	N	N	Y	N	N	Y	3-5	100%	Anterolateral on either side of neck, lateral to the cricoid cartilage

Y= yes, N= No

Table 2.5: Phrenic nerve stimulation outcome measures and results reported when measuring diaphragm function

Study	**Outcome measure**					**Results**
	Twitch oesophageal pressure (PoesTw)	Twitch gastric pressure (PgasTw)	Twitch endotracheal tube pressure (PettTw)	Twitch airway pressure (PawTw)	Twitch trans diaphragmatic pressure (PdiTw)	
Buscher et al. (59)	Y	N	Y	N	Y	- PettTw lower in patients with weaning failure - PdiTw correlated with PettTw
Cattapan, Laghi & Tobin (16)	Y	N	N	Y	Y	- Good correlation between PawTw & PdiTw
Dres et al. (57)	N	N	Y	N	N	- Weaning failure = ↓ PettTw
Dube et al. (39)	N	N	Y	N	N	- PettTw associated with DTF (on PSV only) - Good correlation of PettTw to PdiTW and PoesTw
Jaber et al. (29)	N	N	Y	N	N	- PettTw ↓ in long term MV - Mean PettTw reduced by 32 ± 6% after 6 days
Supinski, Westgate & Callahan (61)	Y	Y	N	N	Y	- PdiTw < 10cmH2O = ↑ mortality & length of MV
Supinski & Callahan (47)	Y	Y	N	N	Y	- PdiTw small correlation with PImax - PdiTw & PImax correlates with mortality & length of MV
Watson et al. (15)	Y	Y	Y	N	Y	- PdiTw not clearly associated with length of ICU stay

Y= yes, N= No, Blank = not mentioned, PoesTw = Twitch oesophageal pressure, PgasTw = Twitch gastric pressure, PettTw = Twitch endotracheal tube pressure, PawTw = Twitch airway pressure, PdiTw = Twitch transdiaphragmatic pressure, PSV = pressure support ventilation, MV = Mechanical ventilation, ICU = intensive care unit, PImax = Maximal inspiratory pressure

2.4.3.3 Electrical activity of the diaphragm and electromyography methods

Diaphragm electromyography (EMGdi) measures the activation of action potentials along the diaphragm muscle and can be used to assess muscle contractility, and even diagnose neuromuscular dysfunction (4). Similarly, the electrical activity of the diaphragm (EAdi) records action potentials from the diaphragm and therefore assess whether the phrenic nerve is intact (62). Both studies reporting on diaphragm electromyography (EMGdi) positioned participants in the 30˚ head up and supine positions (63,64), however the latter also used the seated position for assessment of EMGdi. No positioning were specified in the EAdi studies. Table 2.5 refers to EMG and EAdi methodology as presented in the studies.

Diaphragm electromyography and electrical activity outcome measures

Electromyography (EMG) signals are analysed to detect muscle activity. Fratacci et al. (63) found no EMGdi signal when participants were connected to controlled mechanical ventilation. This could indicate the value of using partially assist ventilator modes as opposed to controlled modes. Walterspacher et al. (64) evaluated the effects of different positions on the diaphragm activity in difficult to wean tracheotomised patients, by means of EMGdi. They found the diaphragm to be most active during the supine and semi recumbent positions, compared to the seated position. The seated position could therefore be useful when the diaphragm is fatigued, however the effect on atrophy and contractility needs further investigation.

Beck et al. (62) found an association between increasing ventilator pressure and decreasing electrical activity of the diaphragm (EAdi), which once again indicates that increasing mechanical support might decrease the activity of the diaphragm. A study conducted by Bellani et al. (65) reported that the pressure develop by the respiratory muscles (Pmusc) is related to the electrical activity of the diaphragm (EAdi), and that the ratio of Pmusc/EAdi could estimate inspiratory effort. In contrast, a study published by the same author three years later found no correlation between the Pmusc/EAdi ratio and ventilator variables (66). It remains unclear whether EAdi is a valuable tool to assess diaphragm activity accurately. Table 2.6 shows the outcome measures used.

2.4.3.4 Pressure measurements methodology

Diaphragmatic strength can be measured by trans diaphragmatic pressure (Pdi), similarly to twitch transdiaphragmatic pressure obtained by phrenic nerve stimulation (4). The difference lies in that the patient needs to cooperate when measuring Pdi. Balloon catheters are inserted into the stomach and distal oesophagus and connected to pressure transducers (62). Transdiaphragmatic pressure is also calculated as the difference between gastric and oesophageal pressures, however no phrenic nerve stimulation is involved and measurements are taken at either tidal or maximal breathing (7). All patients were required to breathe spontaneously and were minimally sedated (3,49,51,62,63,65,67).

Pressure outcome measures

Table 2.7 shows a summary of pressure outcome measures. A decrease in transdiaphragmatic pressure has been associated with increased pressure support levels (62). This is in keeping with abovementioned results of higher ventilator pressures decreasing diaphragmatic activity. An interesting finding was reported by Chieveley-Williams et al. (67), comparing bladder pressure to

Table 2.6: Summary of diaphragm electromyography methods used to assess diaphragm function

Study	Positioning				When measured			Stimuli	
	Seated	30˚ head up	45˚ head up	Supine	End inspiration	End expiration	Maximal	Repeats	Location
Beck et al. (62)					N	Y	Y	Average for 2 min	Level of crural diaphragm
Bellani et al. (65)					Y	Y	N	2 every 10 min	Nasogastric tube with NAVA electrodes
Bellani et al. (66)					N	Y	N	3	
Fratacci et al. (63)	N	Y	N	Y	Y	Y	N	5	Diaphragmatic pleural surface
Muttini et al. (68)					Y	Y	Y	Average of 5 min	EAdi signal acquired from ventilator
Walterspacher et al. (64)	Y	Y	N	Y	Y	N	Y	3	Parasternal muscles & diaphragm

Y= yes, N= No, Blank = not mentioned, NAVA = neutrally adjusted ventilator assist, EAdi = Electrical activity of the diaphragm, min = minutes

Table 2.7: Electromyography studies: outcomes and results reported in diaphragmatic studies

Study	Outcome measure					Results
	Electrical activity of diaphragm (EAdi)	Diaphragm Electromyography (EMGdi)	Electromyography of parasternal muscles (EMGpara)	Pressure developed by respiratory muscles (Pmus)	Pressure developed by ribcage muscles (Prcm)	
Beck et al. (62)	Y	N	N	N	N	- ↑ Pressure support = ↓ EAdi
Bellani et al. (65)	Y	N	N	Y	Y	- Pmusc related to EAdi - Pmusc/EAdi = valuable estimation of inspiratory effort
Bellani et al. (66)	Y	N	N	Y	N	- Pmusc/EAdi not associated with ventilator variables or outcome
Fratacci et al. (63)	N	Y	N	N	N	- CMV = no costal EMGdi signal - No difference in EMGdi before & after epidural anaesthesia
Muttini et al. (68)	Y	N	N	N	N	EAdi peak & EAdi area under curve (P/I Index) = ↑ in weaning failures
Walterspacher et al. (64)	N	Y	Y	N	N	- Diaphragm most active during supine & semi recumbent position

Y= yes, N= no, EAdi = Electrical activity of diaphragm, EMGdi = Diaphragm Electromyography, EMGpara = Electromyography of parasternal muscles, Pmus = Pressure developed by respiratory muscles, Prcm = Pressure developed by ribcage muscles, CMV = controlled mechanical ventilation

Table 2.8: Pressure measurement outcomes and results (without stimulation) reported during diaphragm assessment

Study	**Outcome measure**					**Results**
	Oesophageal pressure (Poes)	Gastric pressure (Pgas)	Airway opening pressure (Pao)	Transdiaphragmatic pressure (Pdi)	Other (specified)	
Beck et al. (62)	Y	Y	Y	N		- ↑ Pressure support ↓ Pdi & EAdi
Bellani et al. (65)	Y	N	N	N	Pmus – pressure generated by respiratory muscles	Pmus related to electrical activity of diaphragm
Chieveley-Williams et al. (67)	Y	Y	Y	Y	Pblad – bladder pressure Pcvp – central venous pressure	- ∆Pblad correlates with ∆Pgas - ∆Poes correlates with ∆Pcvp - ∆Pcvp could show diaphragmatic activity
Fratacci et al. (63)	Y	Y	N	Y		- Pdi ↑ after epidural anaesthesia
Swartz & Marino (49)	Y	Y	N	Y	Pab – Abdominal pressure	- Pdi not ↓ at time of weaning
Umbrello et al. (51)	Y	Y	Y	Y	PTPdi – Diaphragm pressure-time-product PTPoes – Oesophageal pressure-time-product	- ↑ level of support = ↓ PTPdi, PTPoes
Vivier et al. (3)	Y	Y	N	Y	PTPdi – Diaphragm pressure-time-product	- ↑ level of support = ↓ PTPdi - PTPdi correlated with DTF

Y= yes, N= No, Poes = Oesophageal pressure, Pgas = Gastric pressure, Pao = Airway opening pressure, Pdi = Trans diaphragmatic pressure, Pmus = Pressure developed by respiratory muscles, Pblad = bladder pressure, Pcvp = central venous pressure, Pab = Abdominal pressure, PTPdi = Diaphragm pressure-time-product, PTPoes = Oesophageal pressure-time-product, EAdi = Electrical activity of the diaphragm

gastric pressure and central venous pressure to oesophageal pressure, and stating that central venous pressure might indicate diaphragm activity due to the similarity between the change in central venous pressure and change in oesophageal pressure. Change in central venous pressure was specifically evident during a reduction in pressure support, and could therefore be useful in detecting diaphragmatic contraction rapidly instead of inserting balloon catheters (67).

2.4.3.5 Discussion of diaphragm assessment and outcome measures

Diaphragm strength, contractility and function can be measured with invasive and non-invasive techniques. Ultrasonography has been deemed an easily accessible, reproducible and safe measurement technique to identify diaphragm dysfunction. It is apparent that the best location to measure the diaphragm is on the right side, in the zone of apposition between the eighth to tenth rib spaces, in the mid-axillary line. With the specific location described in detail, we can easily reproduce measures and make assumptions from the data. In order to compare values between subjects, the technique used must be as reproducible and precise as possible. Therefore, ultrasonography proves to be an easy technique to use in diaphragm assessment.

Decreasing values of both Tdi and DTF have been shown to identify diaphragm dysfunction in mechanically ventilated patients. Lower Tdi and DTF values were associated with higher mortality rates as well as weaning failure (31,36,39,45,53,54,57).

The rate of change in Tdi or DTF has also been shown to predict atrophy in the diaphragm muscle. Schepens et al. (31) found a daily decrease in Tdi as much as 10.9%, almost double the value first reported by Grosu et al. (33). However, Francis, Hoffer & Reynolds (44) reported the possibility that thicker diaphragms may atrophy faster, as shortened skeletal muscles are associated with faster atrophy when inactive, but this needs further investigation. Although it is suspected that diaphragm atrophy is associated with diaphragm strength, it cannot be concluded yet. Goligher et al. (38) found that both increased and decreased Tdi were associated with a lower value of maximal DTF, as compared to the group who had no change in Tdi. This is dependent on patient cooperation, and often critically ill patients struggle to reach a breath at total lung capacity due to sedation, fatigue and airway resistance, to name a few. Thus, DTF could be an indicator of diaphragm function, but care must be taken to assure patients are cooperating optimally.

The gold standard for measuring diaphragm strength is twitch transdiaphragmatic pressure (PdiTw). Due to its invasive nature, many studies have compared PdiTw to other possible strength measures in order to find an alternate measure that is easier to do and less invasive. No specific alternate measurement has been identified to be equally as accurate as PdiTw, however good correlations were found with twitch airway pressure and twitch endotracheal tube pressure, respectively (39,59,16). Maximal inspiratory pressure and PdiTw showed a moderate correlation (61). Thus, maximal inspiratory pressure might be useful to assess diaphragm dysfunction, although maybe not very accurately. This could be attributed to the fact that maximal inspiratory pressure measures inspiratory strength as a whole, and not the diaphragm exclusively, as compared to PdiTw.

No association was found between PdiTw and Tdi although PdiTw and DTF were associated. As mentioned above, maximal DTF has been used to measure diaphragm function, whereas Tdi relates more to atrophy. Therefore, with PdiTw being a measure of diaphragm strength and showing an association with DTF, we could argue that DTF is a

better outcome measure to use in terms of detecting diaphragm dysfunction. Further research is needed to determine whether this is true.

Diaphragm electromyography (EMGdi) can be used to detect the pattern of diaphragmatic activity (4). Using EMGdi, we could detect which positions activate the diaphragm more as well as the effect of the ventilator mode used on the activity of the diaphragm. Literature shows the seated position eliciting the least amount of diaphragmatic activity. In terms of diaphragm fatigue, this could be helpful. However, ventilator induced diaphragmatic dysfunction supports the notion of losing diaphragm strength due to inactivity, leading to dysfunction and weaning failure. Care must be taken to carefully select which patients should receive muscle resting and which should receive muscle activation, and whether these positions have an effect on diaphragm strength needs to be investigated. Electrical activity of the diaphragm can be used to evaluate the action potentials within the diaphragm muscle, and test the integrity of the phrenic nerves (4), however contrasting results exist whether it is a useful tool to identify diaphragm dysfunction. Being a non-volitional measure, it could possibly assist in describing the effect of early mechanical ventilator settings in sedated or comatose patients, but this needs further research.

Transdiaphragmatic pressure measured without phrenic nerve stimulation has also been reported as a useful measure of diaphragm strength. The biggest disadvantage of this technique however is that it needs patient co-operation (7). The method used is similar to the phrenic nerve stimulation method, where it entails the insertion of balloon catheters into the stomach and oesophagus and measuring the gastric and oesophageal pressures, only without the phrenic nerve stimulation. Being another invasive method, researchers have found central venous pressure as a possible substitute to assess the diaphragm strength. Due to the volitional and invasive nature of this method, it does not seem like the best method to assess diaphragm strength, especially if other techniques have been shown to measure the diaphragm non-invasively and accurately. However, it remains a traditional technique that can be useful when balloon catheters are in situ and when phrenic nerve stimulation is unavailable.

Majority of ultrasonography measures of Tdi and DTF showed decreased values as the length of mechanical ventilation increases. It is still unknown whether diaphragm strength is related to Tdi or contractile activity. This identified a gap in the literature investigating substitute respiratory strength measurements and the need for further comparison of methods, especially in the critically ill population.

2.4.4 Ventilation modes

Various modes of mechanical ventilation and their effect on the diaphragm muscle has been described in 20 (36%) publications. Modes included controlled mechanical ventilation (CMV), assist-control ventilation (ACV), pressure support ventilation (PSV), proportional assist ventilation (PAV), positive- and negative pressure ventilation (PPV & NPV), continuous positive airway pressure (CPAP) and neurally adjusted ventilator assist (NAVA). Table 2.8 shows a summary of the studies reporting on the effect of different ventilation modes on the diaphragm.

Majority papers (10, 50%) compared NAVA mode to PSV (69–78) and only one paper (5%) looked at NAVA mode exclusively (79). Contrasting results have been reported with regards to the effect of NAVA on the diaphragm muscle. One similarity was that NAVA reduces patient-ventilator asynchrony (72,76,78,80).

Table 2.9: Different Ventilation modes investigating diaphragm function and their respective results

Study	Ventilation modes investigated											Results
	NIV	Invasive	CMV	ACV	PSV	PAV	PPV	NPV	CPAP	NAVA	SV	
Akoumianaki et al. (69)		✓			✓	✓				✓		Inspiratory effort ↑ with NAVA & PSV, ↓ with PAV
Ali & Mohamad (54)		✓	✓			✓						Early switch from CMV to PAV = reversal of VIDD
Belman et al. (81)	✓						✓	✓				↓ Pdi and EMGdi during PPV
Brander et al. (79)										✓		↑ NAVA unloads respiratory muscles
Carteaux et al. (73)		✓			✓					✓		↑ level of assistance = ↓ respiratory effort
Cecchini et al. (70)		✓			✓					✓		↑ Diaphragm contribution to inspiratory effort in NAVA
Coisel et al. (71)					✓					✓		EAdi lower with NAVA than PSV
Colombo et al. (72)		✓			✓					✓		NAVA improves patient-ventilator interaction
Demoule et al. (80)		✓								✓		NAVA ↓ patient-ventilator asynchrony
Di Mussi et al. (75)		✓			✓					✓		NAVA improves diaphragm efficiency
Fratacci et al. (63)		✓	✓								✓	Diaphragm shortening less with SV than with CMV
Girault et al. (82)	✓			✓							✓	ACV ↓ EMGdi to 36% of control value
Hilbert et al. (83)		✓	✓		✓							Optimal level with no diaphragm stress = 70% of PIP
Nava et al. (84)	✓				✓							↓ Diaphragm activity at PSV of 10 & 20 cmH2O
Poggi et al. (85)	✓				✓	✓						PAV & PSV unloads diaphragm in COPD during SB & AE
Prinianakis et al. (86)	✓				✓							PTPdi ↓ with all pressurisation rates, not ↓ with SB
Schmidt et al. (76)		✓			✓					✓		NAVA ↑ breathing pattern variability, EAdi unchanged
Schmidt et al. (77)		✓			✓					✓		Similar EAdi and PIP for all modes
Terzi et al. (78)		✓			✓					✓		NAVA ↓ patient-ventilator asynchrony
Zambon et al. (32)		✓	✓		✓				✓			Ventilator support predictive of diaphragm atrophy rate

NIV = non-invasive ventilation, CMV = controlled mechanical ventilation, ACV = assist control ventilation, PSV = pressure support ventilation, PAV = proportional assist ventilation, PPV = positive pressure ventilation, NPV = negative pressure ventilation, CPAP = continuous positive airway pressure, NAVA = neutrally adjust ventilator assist, SV = spontaneous ventilation, VIDD = ventilator induced diaphragmatic dysfunction, Pdi = trans diaphragmatic pressure, EMGdi = diaphragm electromyography, EAdi = electrical activity of the diaphragm, PIP = positive inspiratory pressure, COPD = chronic obstructive pulmonary disease, SB = spontaneous breathing, AE = arm elevation test

Furthermore, Akoumianaki et al. (69) reported an increase in inspiratory effort with NAVA, whereas Coisel et al. (71) found lower electrical activity of the diaphragm when using NAVA ventilation. Both Brander et al. (79) and Carteaux et al. (73) found higher levels of NAVA to decrease the effort of respiratory muscles. Interestingly, Cecchini et al. (70) reported that the diaphragm contributes more to the inspiratory effort during NAVA as opposed to PSV. It is unclear whether NAVA contributes to diaphragm atrophy and needs further evaluation.

Higher levels of pressure support was associated with decreased diaphragm activity (32,84). This is in keeping with previously mentioned studies showing an increase in ventilator support associated with diaphragm dysfunction. Controlled mechanical ventilation has become an unpopular ventilation mode in critically ill patients. Research has shown that controlled mechanical ventilation has the worst effect on the diaphragm in terms of Tdi and function (32,54,63).

2.4.4.1 Discussion of ventilation modes

NAVA is a new mechanical ventilation mode that delivers ventilator support guided by the electrical activity of the diaphragm. Thus far we have realised that the diaphragm is influenced by many factors around mechanical ventilation, whether it is length of ventilation, mode, support or positioning. When the diaphragm guides mechanical ventilation by means of electrical activity, it might alleviate the detrimental effects of mechanical ventilation. However, with this mode being new still, further research is needed in order to confirm its benefits.

It is evident that controlled mechanical ventilation should be avoided as far as possible in order to maintain diaphragm function. Increasing support leads to decreased diaphragm activity and therefore might lead to atrophy. Interestingly, no studies reporting on synchronised intermittent mandatory ventilation (SIMV) have been found. This mode of ventilation synchronises spontaneous breaths with ventilator triggered (mandatory) breaths (87). These mandatory breaths are pre-set. SIMV is commonly used in the South African intensive care units, and therefore further research is needed to identify whether SIMV has the same, if any, effects on the diaphragm.

Several of these modes are being implemented in order to prevent diaphragm muscle fatigue, especially NAVA and high pressure support ventilation. This drive towards muscle-protective ventilation may need further justification as research have shown that diaphragm atrophy is linked to diaphragm inactivity. Therefore, by sparing the diaphragm in order to prevent fatigue, we might be concomitantly causing atrophy in the diaphragm. Further research must be done to establish a ventilation protocol to prevent atrophy as well as fatigue.

2.4.5 Cellular changes

Cellular changes of the diaphragm muscle of mechanically ventilated humans have been studied in eight papers (14%) and forms the foundation of ventilator induced diaphragmatic dysfunction (VIDD). Factors investigated include the effect of oxidative stress in diaphragm dysfunction, the contractility of diaphragm muscle fibres exposed to mechanical ventilation, the myofibrillar force generation of the diaphragm muscle and lastly the proteolytic system involved in the diaphragm muscle of a mechanically ventilated patient. Table 2.9 provides a summary of each study and their results.

Oxidative stress has been labelled as the root of diaphragm dysfunction (88). Several pathways have been identified causing oxidative stress in the diaphragm. An activated JAK-STAT pathway has been demonstrated to induce oxidative stress in the human diaphragm (89). Oxidative stress plays a role in mitochondrial damage and impairs the ability of tissues to regenerate (27,88,89). Another mediator of the intrinsic apoptotic pathway causing oxidative stress was identified by Tang et al. (88), namely Bim, which is a mediator of cell death. Picard et al. (28) found that mitochondria in the mechanically ventilated diaphragm are dysfunctional and leads to impaired biogenesis, meaning the mitochondria are unable to grow and divide further.

2.4.5.1 Discussion of cellular changes

Mechanical ventilation has been shown to activate pathways leading to oxidative stress (26,27,29,88). Oxidative stress disrupts cellular function, especially the mitochondria, which in turn leads to a loss of energy producing cells needed for diaphragm functioning. This, in conjunction with decreased cross-sectional area and decreased myofibrillar force leads to diaphragm dysfunction (26,27,29,30,90).

Although literature on the cellular changes in the diaphragm of mechanically ventilated patients are scarce, the foundation of ventilator induced diaphragm dysfunction has been established. Further research is needed to quantify the extent of the effects of different modes and settings on the ventilated diaphragm.

2.4.6 Confounding / Risk factors for VIDD

Critical illness is multifaceted and mechanical ventilation is only one adjunct used to treat the critically ill population. Certain factors such as infection, inflammation, duration of mechanical ventilation and ventilation settings could increase the risk of developing diaphragm dysfunction, and certain factors such as high blood pressure, thrombosis, cardiac instability and multi-organ failure may be independent of the diaphragm however still fatal (38,39,47). Possible confounding factors identified include infection, duration of mechanical ventilation and tracheostomy tube size. Goliger et al. (38) noted that thicker diaphragms may be due to systemic inflammation and that inflammation may cause diaphragm dysfunction (31,38,39,47,53,54,91).

Infection has been associated with diaphragm dysfunction (47) but blood urea nitrogen (BUN), albumin and glucose has not been correlated with diaphragm dysfunction. Increased BUN can possibly show increased levels of protein catabolism, which in turn may show muscle breakdown (92). Albumin is a protein and is important for restoring tissue, and transport of hormones and medicine and low albumin levels may also indicate malnutrition, infection or inflammatory process activation (93). Both higher BUN levels and lower serum albumin levels have been associated with weaning failure (92,93). Hyperglycaemia may be involved in mitochondrial dysfunction which may impact diaphragm function (94). However, Supinski et al. (47) found no association between diaphragmatic dysfunction and BUN, albumin and glucose, only with infection. This is important to note, as infection is very common in the intensive care unit and could be the underlying reason for diaphragm dysfunction as opposed to ventilation mode or duration of ventilation. Also, this is alarming as several patients are diagnosed with infection a few days before receiving mechanical ventilation, which might indicate diaphragm dysfunction at baseline (first day of mechanical ventilation) already.

Valentini et al. (91) studied the effect of different sized tracheostomy tubes on diaphragm effort and concluded that smaller diameter tubes increased the work of breathing of the diaphragm and might reduce the patient's ability to wean successfully. When the diaphragm fatigues easily, the patient will need increased ventilator support in order to give the diaphragm a rest. If the diaphragm is fatigued and the patient is expected to breathe spontaneously, they might experience respiratory distress as the diaphragm is overexerted and cannot control respiration. Clinicians should therefore take notice of the different tube sizes (tracheostomy and endotracheal) in order to eliminate the unnecessary load on the diaphragm.

Table 2.10: Summary of cellular changes in the diaphragm of mechanically ventilated patients

Study	Factors tested	Results
Hooijman et al. (90)	Contractility of sarcomeres	- Muscle fibres of control and case subjects did not differ in sarcomere length - Cross-sectional area of slow- and fast-twitch diaphragm muscle fibres of MV not different from controls - Contractility of diaphragm muscle fibres not different between MV and control subjects
Hooijman et al. (27)	Diaphragm muscle fibre Ubiquitin–proteasome pathway	- Slow- and fast-twitch diaphragm muscle fibres = ± 25% smaller cross-sectional area (compared to control subjects) and ↓ contractile force - Ubiquitin–proteasome pathway were up-regulated - Diaphragm muscle fibres of critically ill patients display atrophy and severe contractile weakness
Hussain et al. (26)	Autophagy-lysosome pathway	- CMV activates both autophagy and proteasomal protein degradation pathways - Triggered by oxidative stress and mediated through activation of the FOXO1 transcription factor
Hussain et al. (95)	Myofibrillar force generation Myofilament protein level	- Prolonged CMV ↓ active and passive diaphragm myofibrillar force generation - Mediated by impaired myosin cross-bridge kinetics and decreased myofibrillar protein levels
Jaber et al. (29)	Diaphragm biopsies Ubiquitin Nuclear factor-kB Calpains	- Longer periods of MV were associated with = ↑ ultrastructural fibre injury, ↓ cross-sectional area, ↑ ubiquitinated proteins, ↑ expression of p65 nuclear factor-kB, ↑ levels of calcium-activated proteases calpain-1, -2, and -3
Picard et al. (28)	Mitochondrial function Mitochondrial gene expression	- Mitochondrial function disrupted in MV diaphragms due to metabolic substrate oversupply - Impaired mitochondrial biogenesis & DNA damage
Tang et al. (88)	Myonuclear DNA fragmentation Caspase 9	- Fos/FoxO1/Stat3-Bim intrinsic apoptotic pathway identified = central to oxidative stress in the development of VIDD - MV down-regulates mitochondrial gene expression = induce oxidative stress
Tang et al. (89)	JAK–STAT pathway	- JAK–STAT activation critical in regulating oxidative stress = central to pathogenesis of VIDD

MV = mechanical ventilation, CMV = controlled mechanical ventilation, VIDD = ventilator induced diaphragmatic dysfunction

2.5 CONCLUSION OF SCOPING REVIEW

The aim of this scoping review was to determine the effects of mechanical ventilation on the diaphragm muscle of critically ill patients. Ventilator induced diaphragmatic dysfunction (VIDD) has become an increasing popular topic in research, evidently shown in this review.

We conclude that ultrasound is a relatively new tool that can be used for real-time assessment of diaphragm function in the critically ill population. Further research is needed to substantiate the validity of DTF as a measure of diaphragm function, as compared to the gold standard twitch transdiaphragmatic pressure. Maximal inspiratory pressure also shows a moderate correlation to twitch transdiaphragmatic pressure, which could give clinicians an indication of respiratory strength, albeit crude. Electromyography is also useful to assess the electrical activity of the diaphragm, although further research needs to establish the accuracy and accessibility thereof.

With regards to ventilation mode, we identified some studies leaning toward muscle-protective ventilation rather than lung-protective ventilation, as several studies show lower diaphragm contractile activity when pressure support is applied, however recent studies link lower diaphragm contractile activity to an increase length of mechanical ventilation and even increased mortality rate. Therefore, further investigation as to which modes of ventilation, outcome measures and risk factors accurately predict diaphragm function is needed.

Limited research is available on the cellular basis of VIDD, particularly in humans. It has been highlighted that oxidative stress is present in VIDD, and treatment towards reversing oxidative stress may be of benefit to patients with VIDD although further research is needed to confirm this statement. The ability to identify diaphragm dysfunction earlier should be paramount in future critically ill research.

This literature overview has some limitations. We limited inclusion to only human studies, which evidently shows that more research is necessary to be able to draw conclusions. Referring to animal research might reveal more detail. Another limitation is that we did not review any literature done on healthy subjects, therefore we cannot compare baseline values for healthy subjects with those of the critically ill population.

Recommendations for future research include the investigation of feasible surrogate respiratory strength measurements, as well as further investigation into possible risk factors and effects of confounders on length of mechanical ventilation, weaning indices and outcome measurements.

CHAPTER 3: RESEARCH MANUSCRIPT

The Effect of Diaphragm Contractile Activity on Extubation Success

This chapter will be prepared as a manuscript for submission to *Critical Care Medicine* under the title **"The Effect of Diaphragm Contractile Activity on Extubation Success".**

3.1 Introduction

Prolonged mechanical ventilation impairs diaphragmatic contractile function (34,40,96). Diaphragm dysfunction associated with mechanical ventilation is known as ventilator induced diaphragmatic dysfunction (VIDD), and has been defined as a loss of the force-generating capacity of the diaphragm as result of the use of mechanical ventilation (17). Gayan-Ramirez (40) confirmed diaphragm dysfunction in humans, emphasising this contractile impairment leads to diaphragmatic muscle atrophy. A study done by Levine et al. (97) showed that as little as 18 hours of mechanical ventilation induced atrophy of the diaphragm muscle in humans. The mechanisms behind diaphragm dysfunction remain uncertain due to the various effects of confounding factors in intensive care unit (ICU) illness (22). Some of the possible mechanisms for diaphragm dysfunction include: 1.) mitochondrial dysfunction; 2.) reduction in myofibrillar protein concentration; 3.) abnormalities of contractile or cytoskeletal proteins; and 4.) impairment in calcium handling (i.e. E-C coupling) in the diaphragm (34).

Diaphragm dysfunction is associated with difficult weaning from mechanical ventilation (17,20,21). Although the diaphragm is not always the sole reason for difficult weaning, it is often the major contributor especially where prolonged mechanical ventilation was needed (30). Weaning failure is a fairly common occurrence with an estimated prevalence of 31% (8). Strategies to reduce weaning failure and increase extubation success are thus paramount. Currently, clinicians are responsible for initiating the weaning process. Several subjective and objective markers have been proposed to indicate weaning readiness. These include: adequate cough, resolution of acute disease phase, clinical stability, adequate oxygenation, adequate pulmonary function and adequate mental function (or stable neurological patients) (8,35,37). However, none of the above-mentioned parameters take into account diaphragm contractile activity or strength. The only indicative measure of inspiratory (and therefore diaphragm) strength used is maximal inspiratory pressure, but this includes all muscles involved in inspiration and not the diaphragm in isolation. By assessing the diaphragm directly, one might obtain a better and more objective assessment of the diaphragm's condition.

The gold standard for measuring diaphragm strength (transdiaphragmatic twitch pressure (PdiTw)) is by the use of bilateral anterolateral magnetic phrenic nerve stimulation (4,7,98,14). Measuring PdiTw is highly invasive and not feasible in all Intensive Care Units (7)**.** Diaphragmatic ultrasound has been investigated as a new and possible surrogate measure of diaphragm function, specifically diaphragm contractile activity by means of DTF (35–37).

The diaphragm can easily be measured with the use of ultrasound, with the added benefit of ultrasound being safe, non-invasive and widely available in the ICU (31,33,35–37,44,14). Ultrasound does not require co-operation of the patient, and can be performed at any stage of mechanical ventilation in order to diagnose diaphragmatic dysfunction or even indicate readiness to wean (99,100). Goligher, Laghi, et al. (2), as well as Zambon et al. (32), found the measurement of the right hemidiaphragm

thickness feasible in a mechanically ventilated population. Zambon et al. (32) reported on the reproducibility of ultrasound imaging (intraclass correlation coefficients and 95% CI's) and found a 0.98 (0.93-0.99) intra-observer reproducibility and 0.97 (0.88-0.99) inter-observer reproducibility.

Diaphragm ultrasound shows potential of being a useful tool in diagnosing VIDD and measuring diaphragm contractile activity non-invasively. Recently, multiple studies have investigated the use of ultrasonography as a valuable predictor of extubation success (35–37). In a study done by Ferrari et al. (37), a DTF of more than 36% during a spontaneous breathing trial was found to be linked to successful weaning, but DiNino et al. (35) found an even lower DTF of 30% to be indicative of successful weaning. Both of these studies however measured the DTF once-off as soon as a spontaneous breathing trial was started and not prior to extubation (35,37).

Inspiratory muscle strength is used in current practice to identify weaning readiness (8,14,101). Inspiratory muscle strength could be decreased due to diaphragm dysfunction, as the diaphragm is one of the primary respiratory muscles (20,21,80). Inspiratory muscle strength is measured by means of maximal inspiratory pressure (MIP), which is the maximum pressure generated at the airway opening, during a voluntary inspiratory effort (7,102,103). Caruso et al. (60) found a decreased MIP in an estimated 40% of mechanically ventilated patients. For many years, MIP has been part of the criteria for weaning readiness, with a measurement equal to or less than -30 cmH_20 as an indicator for possible successful weaning (43). Maximal expiratory pressure (MEP) measures expiratory muscle strength during a forced expiration (4). Supinski et al. (61) compared twitch trans diaphragmatic pressure (PdiTw) to MIP in the critically ill population and found a moderate correlation (r^2 =0.373, $p < 0.001$), but stated that either MIP or PdiTw should be used individually according to the outcome needed. Thus, MIP may be adequate when measuring inspiratory strength as a whole, as this will form baseline data for the use of inspiratory muscle training in the critically ill population.

It is evident that mechanical ventilation could have detrimental effects on the diaphragm muscle. The extent to which the diaphragm function is affected and the impact thereof on patient outcome requires further research. The aim of the study was to compare the diaphragm contractile activity and respiratory muscle strength with patient outcomes, and determining if any relationship exists. A secondary aim was to describe the change in the contractile activity of the diaphragm during the course of mechanical ventilation, until extubation, and determine any possible correlations with inspiratory strength post-extubation. Furthermore, the effect of confounding factors on the DTF and/or strength measures have been investigated.

3.2 Materials and Methods

3.2.1 Study Setting

The study was carried out in the medical and surgical intensive care units at a tertiary hospital in the Western Cape, South Africa. This study was conducted from March 2017 to August 2017.

3.2.2 Study design

The study is a prospective observational cohort study, as the outcome (extubation success/failure) was measured dichotomously, after exposure over time (mechanical ventilation).

3.2.3 Ethical consideration

Ethical permission was granted by the Institutional Health Research Ethics Committee (Ethics no: S16/09/173) (ADDENDUM B). Institutional permission was granted by the Chief Executive Officer of the hospital (ADDENDUM C). Proxy consent was obtained from the unit's Intensivist prior to data collection where appropriate. As soon as the participant was awake and alert, they were interviewed and the study was explained, where after informed consent was signed (ADDENDUM D). The Richmond-Agitation-Sedation-Scale was used to determine the level of sedation in order to establish whether patients were awake and alert. Patients were asked questions regarding orientation to time and place (mostly close-ended due to intubation) to determine whether they were awake and alert. Examples of questions include: "Do you know where you are?", "Are you at home?", "Is it morning?" "Can you hear me?" "Is your name ____?". The researcher also discussed the patient's level of alertness with the treating doctor or nursing staff. If the participant was unable to sign informed consent, the possible participant's family was contacted for informed consent in order to participate in the study. Only participants who signed informed consent's data was included. Only the researcher obtained consent throughout the study.

3.2.4 Sample

All patients nursed in the ICUs were screened daily by the researcher. Participants were considered for the study if they were
- mechanically ventilated (Invasive) when admitted to ICU (within 24 hours of admission)
- Newly intubated and mechanically ventilated for less than 24 hours
- 18 years and older

Participants were excluded if presented with a
- history of degenerative neuromuscular disease and/or diaphragm injury on admission;
- condition deemed inappropriate by Intensivist (i.e specific surgical contraindications to changing position or where the intensivist planned to extubate within the next hour);
- spinal cord lesion at level C5 or above

Participants were also excluded if measurements were infeasible due to
- dressings/wounds that may obscure ultrasound measurement site;
- morbidly obese (approximate distance from skin to ribcage > 5cm) as body size may influence the thickness of the diaphragm

3.2.5 Study procedure and data collection

Intra-rater reliability (ICC agreement = 0.95) and interrater reliability (ICC agreement = 0.74) was established for ultrasound DTF measurements during a pilot study prior to commencement of the main study. For the respiratory measurements (MIP and MEP), intra-rater reliability yielded an ICC agreement of 0.96 and interrater reliability ICC agreement was 0.97 (ADDENDUM E). Demographical data, dates of admission and

intubation, ventilation modes, comorbidities and blood results were collected daily for each participant. Patients received standard daily care specific to their unit. This included standard nursing and daily physiotherapy (as requested by the treating doctor). The researcher did not record whether and what physiotherapy was done and the decision to extubate remained the treating doctor's choice. No medication history prior to admission was collected.

Diaphragm ultrasonography

Participants were positioned in a semi-recumbent position. The head of the bed was elevated to 30˚ (32). The diaphragm was assessed with Ultrasound in B-mode, using a 5-12 MHz linear probe at a frequency of 31Hz (Samsung Medison MySonoU6, Samsung Company, Seoul, Korea) within 24 hours of admission to the ICU. The probe was placed on the right, perpendicular to the chest wall, in the mid-axillary or anterior-axillary line, in the intercostal spaces between the eighth, ninth or tenth ribs depending where the clearest image appeared (37,38). Images of the diaphragm were recorded in loops of three full tidal volume breathing cycles, from inspiration to expiration, and stored for later measure by the primary investigator or research assistant.

Of the three breaths measured, the researcher carefully inspected the loop to capture three points of end-inspiration and three points of end-expiration. On each of these images, we measured the diaphragm at three random points along the image of the diaphragm (5) and calculated the average for that single image. Thus, three end-inspiration images each had an average measurement, and three end-expiration images had an average measurement. Then, the average of those three images was calculated to reach a value for both end-inspiration and end-expiration for that specific day. A variation of less than 10% between the highest and lowest measure were regarded as good reliability. These values were then inserted into the DTF formula

$$\frac{(\text{Tdi end-inspiration} - \text{Tdi end-expiration})}{(\text{Tdi end-expiration})} \times 100 = \ \%$$

The end-expiration values were used for Tdi as this is where the diaphragm is at its thinnest during tidal breathing.

Participants were stratified into three groups as some of the participants in this hospital was transferred from a distant hospital already intubated and mechanically ventilated for some time. Because we did not know what would happen to the diaphragm daily and whether the biggest change (if any) happens in the first 24, 48 or 72 hours, we decided to stratify the participants into different groups. The serial group consisted of participants who had been mechanically ventilated for less than 24 hours on admission to the unit, and were measured daily, until extubation, with the last measurement within 24 hours after extubation. The once-off group consisted of participants who had been mechanically ventilated for longer than 24 hours on admission to the unit and were measured once-off at admission and again within 24 hours after extubation. The delayed group consisted of participants who had been mechanically ventilated for longer than 24 hours on admission to the unit, but were measured daily until extubation. This group was introduced due to a lack of participants admitted to the unit before 24 hours of mechanical ventilation has passed. Table 3.1 shows the different groups with their respective measurements. The first measurement taken will be referred to as the baseline measurement.

Table 3.1: Stratified groups of participants

Group	Number of participants	Measurements taken
Serial	37	Daily measurements from baseline to extubation/death
Delayed	8	Daily measurements from baseline to extubation/death
Once-off	23	Baseline measurement and measurement post-extubation

Maximal Inspiratory and Expiratory Pressure

MIP and MEP were measured via the MicroRPM (CareFusion, California, USA) (Image (104)) according to ATS/ERS standards (4). Measurements were taken within 24 hours post-extubation, by the primary investigator or research assistant. Participants were positioned in a 30˚ head-up position (61). The mouth piece (containing a bacterial filter) was placed in the participant's mouth via a bacterial filter. The participant was asked to take a deep breath in (maximal effort) and then exhale, and repeated three times. Participants rested two minutes between breaths. After inhalation, the participant was asked to exhale as much as they can (maximal effort), for another three breaths. Three readings of MIP and MEP were recorded, respectively, and the highest value for inspiration and expiration used for analysis. Participants were encouraged to take maximal breaths during all attempts, as no practice breaths were allowed due to the possibility of fatigue A variation of less than 10% between the two highest MIP values were regarded as good quality.

Image 3.1: MicroRPM device

Outcome

Extubation success or failure

Participants were followed up for 48 hours after extubation in order to establish extubation success or failure. If a participant was re-intubated or died (during the study or within 48 hours after extubation), they were deemed to have failed extubation. If none of the above was true, they had been successfully extubated.

Duration of mechanical ventilation

The number of hours was noted since intubation until extubation, and described as the duration of mechanical ventilation.

Data was collected and managed using REDCap electronic capturing sheets (ADDENDUM F) hosted at Stellenbosch University (105).

Risk profile

A risk profile was setup in order to group confounding factors into three distinct categories namely baseline risk, management risk and patient-specific risk groups. These risk categories were incorporated into the data analysis to reflect the potential impact of the confounding factors on diaphragm contractile activity and Tdi, as well as extubation outcome. "Baseline" risk category included once off measures collected on

admission (32,80,106,107), “management” risk category, included factors that could possibly be influenced by the participant’s medical management (21,38). These factors were collected daily; and the risk was based on values falling outside of the normal ranges during ICU stay. “Patient-specific” category included factors reflecting the participant’s reaction to their condition/disease/management (47). These values were also collected daily, however participants scored a maximum of 1 if the values were out of normal range at any given time during the data collection. Table 3.2 shows the different risk groups and the calculation of overall risk.

Table 3.2: Calculation of risk profile

Risk groups	Score	Total per group	Group risk	Overall risk
Baseline risk profile	**Yes = 1, No =0**			HIGH risk = ≥ 3 High group risk factors MEDIUM risk = 2 High group risk factors LOW risk = ≤ 1 High group risk factors
Presence of one or more co-morbidity		/5	≥ 3 = HIGH ≤ 2 = LOW	
Smoking (ever)				
Alcohol				
Age > 60				
Gender = Female				
Management risk profile	**Yes = 1, No =0**			
Days intubated ≥ 4		/4	≥ 2 =HIGH ≤ 1 = LOW	
HGT > 5.8 mmol/L				
RASS < -2 , > 2				
Corticosteroids used				
Patient-specific risk profile	**Yes = 1, No =0**			
Lactate > 1.8 mmol/L		/3	≥ 2 = HIGH ≤ 1 = LOW	
Creatinine F > 90 µmol/L M > 120 µmol/L				
Infection*				

*Infection criteria: WCC > 12, CRP > 8 mg/L, Pyrexia > 38˚C = any 2 out of 3 present (108)

Risk profiles were only calculated for the serial participants who had more than two ventilated measurements, as we cannot comment on the management and patient-specific risk profiles of the participants who had only one mechanically ventilated measure.

Scoring: If participants scored three or more out of five for the baseline category, they were regarded as “high” risk, otherwise they scored a “low” risk. If participants scored two or more for the management and patient-specific categories respectively, they were scored as “high” risk, otherwise “low” risk. Patients were categorised into overall high, medium or low risk categories. This scoring was based on consensus within the research team involved in this study, consisting of a pulmonologist, two highly qualified physiotherapists and the primary researcher.

Rate of change groups

Daily rate of change was calculated by comparing each measurement (Tdi or DTF) to the previous day for all the participants who had more than two ultrasound assessments (serial and delayed participants), and calculating the average for the total amount of days ventilated (32). Each measurement were compared to the specific participant’s own previous measurement, to establish a rate of change of Tdi and DTF compared to oneself. This was important to eliminate the possibility of body size or gender influencing the diaphragm thickness. Participants were grouped according to their rate of change in Tdi or DTF. Three groups were established. The cut-off values for these three groups

were as follows: a mean decrease in Tdi or DTF of more than 10% (decrease group), between a mean decrease or increase of 10% (no change group) and more than 10% increase in the mean rate of change (increase group). Groups were categorized according to their mean rate of change in Tdi or DTF for the duration of mechanical ventilation. Grouping method was similar to the groups chosen by Goligher et al. (38) and Schepens et al. (31).

3.2.6 Statistical analysis

IBM SPSS version 25 (New York, United States of America) was used to analyse the data, in consultation with a statistician. A p value <0.05 was considered as statistically signficant. Tdi and DTF values were checked for normality of distribution using Shapiro-Wilks tests. Normally distributed data were presented as means and standard deviations and non-normally distributed data were presented as medians and interquartile ranges. Non-parametric Mann-Whitney tests were used to compare median Tdi/DTF values between the success and failure groups as well as with length of mechanical ventilation, if data was non-normally distributed. Correlation between Tdi/DTF values and strength measurements (MIP) were assessed using Spearman's correlation analysis if non-normally distributed, and Pearson's correlations if normally distributed. Diaphragm measures, strength measures and duration of ventilation were compared between risk profiles and rate of change groups using Kruskal-Wallis H tests. Risk profiles and rate of change groups were compared using Chi-square tests or Fisher exact tests depending on expected cell counts. When a significant result was found, post-hoc pairwise comparisons were done to establish where the significance lay and a P-value was calculated with a Bonferroni correction to set statistical significance at p <0.02. Risk profiles and rate of change groups were plotted on ANOVA graphs to visualise change over time, and post-hoc analysis was done with Wilcoxon-signed rank tests to establish where significance lies. Strength of associations were categorised according to the following: weak correlations were defined as r= 0.00 to < 0.3, moderate correlations were defined as r= 0.30 to < 0.50 and strong correlations were defined as r ≥ 0.50 (109).

3.3 RESULTS

3.3.1 Demographics

One hundred and twenty participants were screened for inclusion. 85 participants passed the inclusion criteria and were recruited for the study. Seventeen participants were excluded due to: 1. Early extubation before 24hours of mechanical ventilation (n=8); 2. Refused consent (n=2) and 3. Less than two ultrasound measurements were taken (n=7). Figure 3.1 shows the flow of data collection.

A total 68 participants (39 males, 57%) were included in the final data analysis for the study. The mean age for the sample was 45.1 years (SD = 16.9). No statistical difference was found between serial and delayed groups and their baseline Tdi or DTF (p=.144, p=.942 respectively). A summary of the participant's baseline characteristics can be seen in Table 3.3.

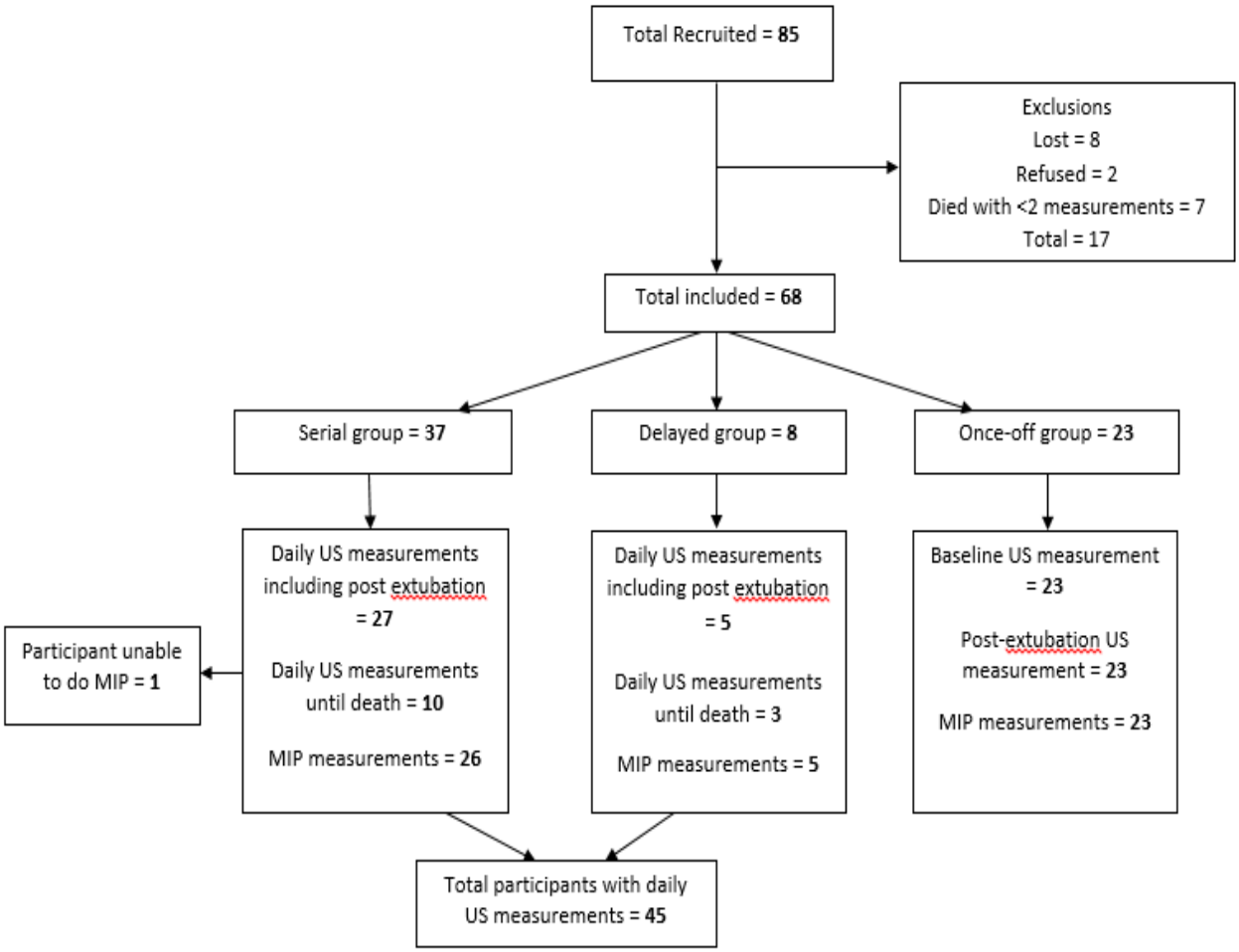

Figure 3.1: Consort flow diagram of data groups and data collection

A total of 14 participants died during the data collection period. Of these 14 participants, 13 (92.9%) died before extubation. Only one participant was deemed to have failed extubation due to re-intubation within 48 hours after extubation. The reason for re-intubation was due to a drop in saturation and hyperventilation. This participant died the following day.

There were no differences found between the proportions of participants in thickness groups and age, gender, presence of comorbidities, smoking or alcohol use ($p>0.05$). Neither age, gender, smoking history, alcohol use nor presence of comorbidities were different in successful versus failed extubation groups ($p>0.05$).

The number (n,%) of participants allocated to the rate of change in Tdi groups were as follows: decreased thickness (9, 20%), no-change (22, 48.9%) and increased thickness (14, 31.1%). The rate of change in DTF groups consisted of the following number (n,%) of participants: decreased thickness (10, 22.2%), no-change (17, 37.8%) and increased thickness (18, 40%).

Table 3.3: Summary of baseline characteristics collected from sample

Demographics		
Gender	Male (%) Female (%)	39 (57.4) 29 (42.6)
Initial admission hospital	Study Hospital (%) Other (%)	46 (67.6) 22 (32.4)
Admission diagnosis	Trauma (%) Surgery (%) Medical (%)	12 (17.6) 20 (29.4) 36 (52.9)
Sepsis	Yes (%) No (%)	10 (14.7) 58 (85.3)
Smoking	Ever (%)	44 (64.7)
Alcohol use	Yes (%)	18 (26.5)
Drug use	Yes (%)	8 (11.8)
Ventilation mode	BiPAP (%) PC SIMV (%) VC SIMV (%) CPAP (%) Other (%)	27 (39.7) 24 (35.3) 0 (0) 15 (22.1) 2 (2.9)
Median duration of mechanical ventilation (whole sample)	Days (range)	4 (1-29)
Median duration of MV on first day of admission (once-off and delayed groups)	Hours (range)	36.1(27.5-48)
Medication used at any time during study	Sedation (%) Corticosteroids (%) NMBA (%)	26 (38) 14 (21) 0 (0)
Extubation success	Yes (%) No (%)	54 (79) 14 (21)
Risk groups	High (%) Medium (%) Low (%)	7 (15.6) 14 (31.1) 24 (53.3)

BiPAP – Bilevel positive airway pressure; PC SIMV – Pressure controlled synchronized intermittent mandatory ventilation; VC SIMV – Volume controlled synchronized intermittent mandatory ventilation; CPAP – Continuous positive airway pressure; NMBA – Neuromuscular blocking agent

3.3.2 Diaphragm function measurements and respiratory muscle strength

The median (IQR) baseline Tdi was 1.47mm (1.17-1.86). The Tdi mean (SD) rate of change related to the previous day was 3.92% (18.38). The median (IQR) DTF at baseline was 24.64% (17.95-33.58). The median (IQR) for the rate of change in DTF related to the previous day was 6.67% (-7.10– 22.26). The median maximal inspiratory pressure (IQR) was 20.50 cmH_2O (11.75-38.25 cmH_2O) and median maximal expiratory pressure (IQR) was 27.50 cmH_2O (19.75-45.25 cmH_2O). Table 3.4 refers to these values.

Table 3.4: Summary of diaphragm and strength measurement medians and interquartile ranges for the complete sample

Variables	Value
Diaphragm thickening fraction %	
Median baseline measurement (IQR)	24.64 (17.95 – 33.58)
Median last measurement before extubation/death (IQR)	24.56 (16.40 – 36.27)
Median post-extubation measurement (IQR)	24.67 (18.67 – 36.73)
Median daily rate of change (%) from previous day (IQR)	6.67 (-7.10 – 22.62)
Diaphragm thickness (mm)	
Median baseline measurement (IQR)	1.47 (1.17 – 1.86)
Median last measurement before extubation/death (IQR)	1.51 (1.32 – 1.93)
Median post-extubation measurement (IQR)	1.41 (1.20 – 1.85)
*Mean daily rate of change (%) from previous day (SD)	3.92 (18.38)
Respiratory muscle strength (cmH_2O)	
Median MIP (IQR)	-20.50 (-11.75 - -38.25)
Median MEP (IQR)	27.50 (19.75 – 45.25)

DTF= diaphragm thickening fraction, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure
*Normally distributed = mean and SD reported

During the first three ventilated days, the group of participants who had a decreased rate of Tdi more than 10% showed a significantly higher baseline Tdi as compared to the no change and increased Tdi groups ($p<0.01$) (Figure 3.2). The decreased thickness group also showed a significant decrease in Tdi between the first and second day of mechanical ventilation ($p<0.01$) (Figure 3.2).

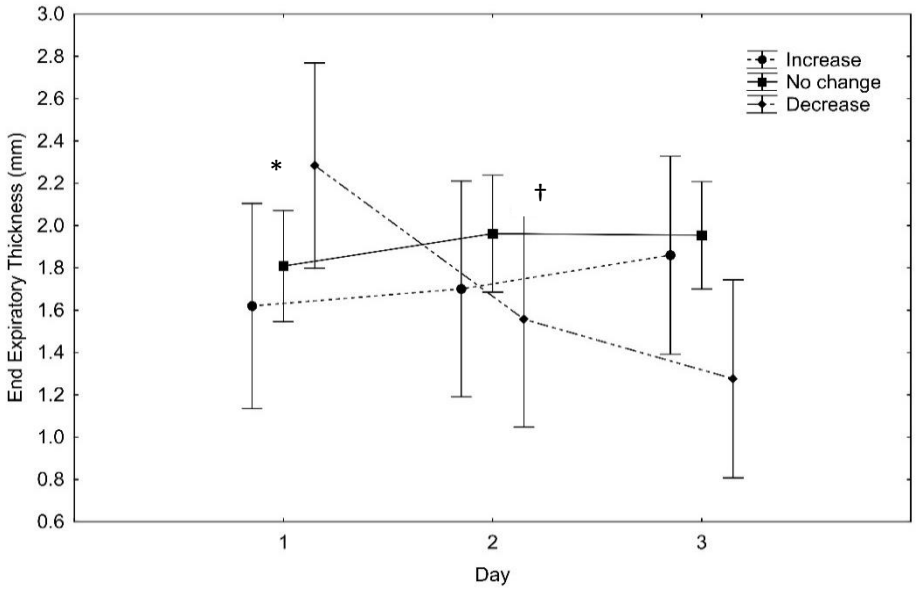

Figure 3.2: Difference in end expiratory thickness between rate of change thickness groups over the first three days of mechanical ventilation ($p<0.01$).
* $p<0.01$ between decrease change group and no change and increase change groups, respectively, on first day
† $p<0.01$ between Days 1 and 2 in the decrease change group

Furthermore, we found a significant decrease in Tdi between the baseline and last measurement for the decrease group (p<0.01) (Figure 3.3). Correspondingly, the decrease group had a significantly lower Tdi post-extubation as compared to their baseline Tdi (p=0.03) (Figure 3.3). There were no significant between group differences for the first, last and post-extubation Tdi measurements (p>0.05).

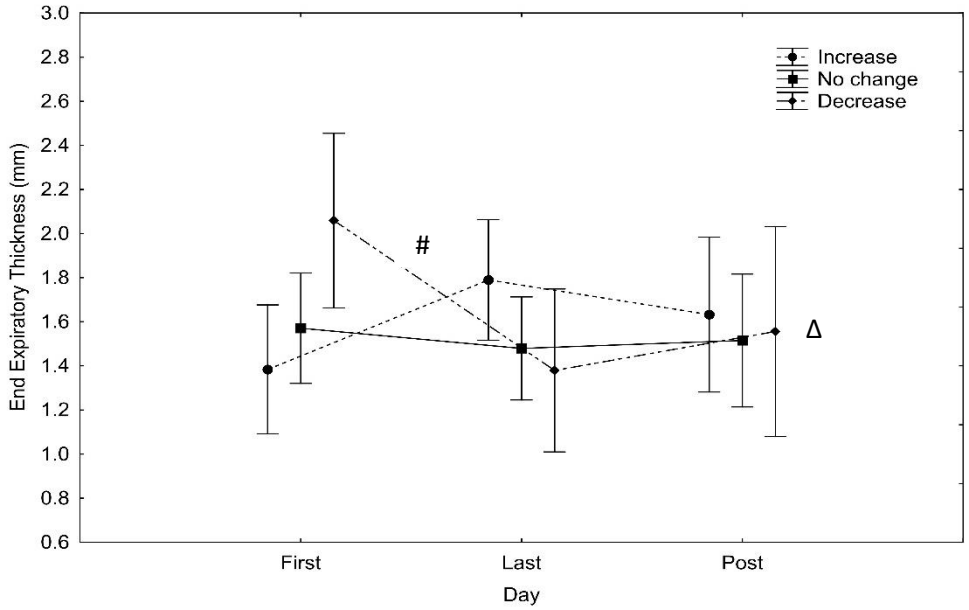

Figure 3.3: Difference in thickness between rate of change thickness groups at first, last and post-extubation measurements (P<0.01)
# p<0.01 between baseline and last measurement in decrease thickness group
Δ p=0.03 between baseline and post-extubation measurement in decrease thickness group

3.3.3 Measures related to extubation outcome

The baseline Tdi measurement was significantly higher in failed than successful extubation groups (p=0.033). Interestingly, there was no difference between the first DTF of failed and successful extubation groups (p>0.05), nor between the rate of change in Tdi of the failed and successful groups (p>0.05). Similarly, no significant difference could be found for the last intubated Tdi and DTF measurements between success and failure groups (p>0.05). We found no statistical significant differences in the proportion of participants of low, medium and high risk groups between success and failure groups, $p > 0.02$ (Bonferroni correction).

3.3.4 Measures related to duration of ventilation

A significant moderately positive association was found between baseline Tdi and total duration of mechanical ventilation (r=0.412, p<0.01) (Figure 3.4). The last intubated Tdi measurement was also significantly correlated with the duration of mechanical ventilation, with a moderate strength of r= 0.357 (p=0.016). It is of note that both the first and last intubated DTF value showed no association to the length of mechanical ventilation (p>0.05). The rate of change in Tdi showed a small negative correlation with duration of mechanical ventilation (r= -0.246). The relationship however did not reach significance (p>0.05). The duration of mechanical ventilation was significantly higher in the high risk group as compared to low risk group (p=0.028).

Inspiratory strength measurements showed no significant correlation with duration of mechanical ventilation (r=-0.116, p>0.05). When we compared duration of mechanical ventilation to extubation outcome, we found no significant difference between success and failure groups (p>0.05).

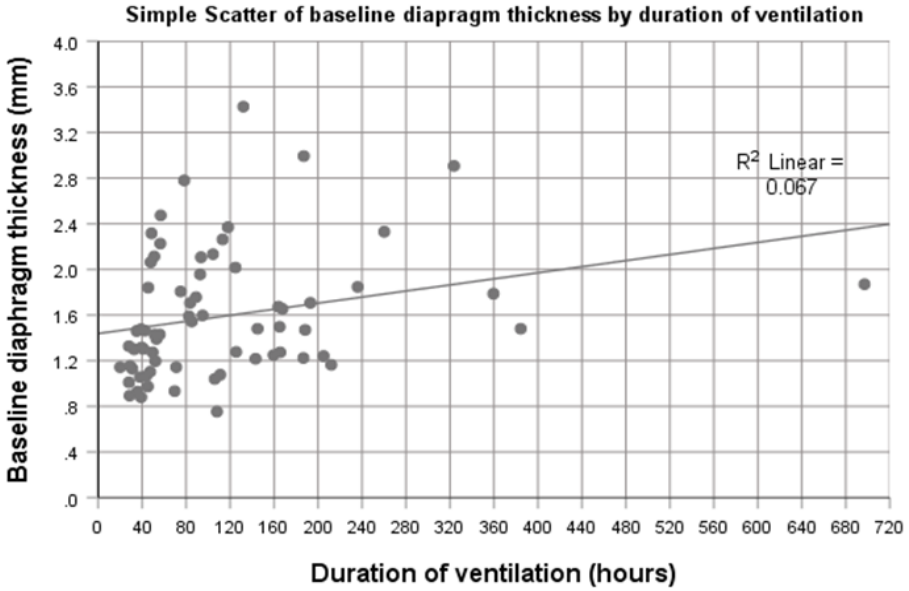

Figure 3.4: Scatterplot of baseline thickness by duration of ventilation

3.3.5 Diaphragm function associations

Small non-significant correlations were found between baseline DTF and maximal inspiratory pressure (r=0.17, p>0.05) and last Tdi before extubation and maximal inspiratory pressure (r=0.26, p>0.05). Interestingly, no association was seen between the baseline Tdi and MIP (r=0.02, p>0.05), nor the rate of change in Tdi or DTF and MIP (r=0.03, p>0.05, and r= -0.03, p>0.05, respectively). Results are shown in table 3.5. Distributions of MIP were not significantly different between the decrease, no change and increase Tdi groups (p>0.05). Post-extubation Tdi and DTF did not show any association with MIP (p>0.05).

Table 3.5: Spearman's correlations between diaphragm measurements and maximal inspiratory pressure

Interval	Spearman's Correlation (n)	p-value
Baseline DTF & MIP	0.17 (54)	.221
Last DTF & MIP	-0.04 (31)	.846
Post-extubation DTF & MIP	-0.02 (54)	.867
*Daily rate of change in DTF from previous day	-0.03 (31)	.862
Baseline Tdi & MIP	0.02 (54)	.901
Last Tdi & MIP	0.26 (31)	.162
Post-extubation Tdi & MIP	0.06 (54)	.694
*Daily rate of change in Tdi from previous day	0.03 (31)	.882

DTF = diaphragm thickening fraction, MIP = maximal inspiratory pressure, Tdi = diaphragm thickness (end-expiration) *Data transformed –Pearson's correlations done

3.4 DISCUSSION OF PRIMARY STUDY RESULTS

In this study we found, firstly, a thicker diaphragm at baseline was associated with an increased duration of mechanical ventilation, higher risk profile, and higher possibility of extubation failure. Secondly, DTF, measured at tidal breathing, may not be a good predictor of outcome as compared to end-expiratory Tdi, and must be interpreted with caution.

Several recent studies have investigated the use of diaphragm ultrasonography to assess the strength or function of the diaphragm, and compared these values to outcome (31,32,35–39,45,110). Goligher et al. (38) found that changes in Tdi occur mainly during the first week of mechanical ventilation and also reported that both an increase and decrease in Tdi were related to diaphragm dysfunction. Diaphragm atrophy has been studied in mechanically ventilated patients, with Grosu et al. (33) reporting a 6% daily decrease in diaphragm muscle, however this study had a small sample size (n=7). The average duration of ventilation was four days, which is similar to our study. Schepens et al. (31) reported a larger daily decrease of 10.9% and reported the rate of decrease is associated with length of mechanical ventilation. Schepens et al. (31) reported a mean duration of mechanical ventilation of eight days, which is not comparable to our mean duration of four days. Although our results did not yield a positive correlation between the rate of change in Tdi or DTF and length of mechanical ventilation, we did find a significant association between baseline Tdi and length of mechanical ventilation. Interestingly, we found a median increase in daily rate of change in Tdi of 4% as opposed to the decrease found by Grosu et al. (33) and Schepens et al. (31), which could be attributed to the fact that both the latter studies used controlled ventilator modes whereas our participants did not receive controlled modes of ventilation. It is possible that the longer participants are exposed to controlled mechanical ventilation, the higher the decrease in Tdi as evidently shown by Schepens et al. (31). Also, disease severity may play an important role here, as often controlled mechanical ventilation modes are used in higher severity of diseases. We did not report on disease severity but it could be that participants in our units were not as severely ill as the participant in the former two studies, which could possibly influence Tdi. It is important to note that the mean age of the study by Schepens et al. (31) was 67 years, which is more than 20 years older than our mean age in our study population. This could have also attributed to the difference in results.

Interestingly, a thicker diaphragm at baseline as well as before extubation/death was associated with longer mechanical ventilation and extubation failure. Also, the group showing a decrease in rate of change of more than 10% showed a significantly thicker diaphragm at baseline, and a significant decrease in Tdi from baseline to second, last and post-extubation measurement. Grosu et al. (110) reported similar results where a thinner baseline Tdi was associated with a higher chance of extubation success. This is in contrast with the findings of Farghaly & Hasan (36), who found a higher Tdi to be associated with extubation success. These results however could not be generalised to the entire ICU population as only patients with pulmonary diseases were included in their study. Francis, Hoffer & Reynolds (44) reported the possibility that a passively shortened diaphragm muscle may atrophy faster, similarly to skeletal muscles wasting when shortened. Positive end-expiratory pressure (PEEP) increases lung volumes, and could cause passive shortening of the diaphragm (44,100). Arguably, any increase in functional residual capacity could place the diaphragm in a passively shortened position (100). Thus, further investigation into lung mechanics and ventilator settings might be of

clinical importance. DTF has been investigated to be the measure of diaphragm contractile activity (2,35–37). DTF is hypothesised to be a more valuable indicator of diaphragm function as it measures the contractile activity of the muscle instead of Tdi alone (2). However, we found no association between DTF and extubation outcome, length of mechanical ventilation, or difference between DTF values of participants with different risk profiles. This probes the question of reliability towards DTF as measure of diaphragm function and predictor of outcome. DiNino et al. (35) reported a DTF ≥ 30% to be a predictor of extubation success, however our median DTF before extubation was less 25% and yet was not associated with extubation failure.

In our study, Tdi was a better predictor of outcome. DTF, being a fraction of Tdi at maximal inspiration and expiration during tidal breathing, could be influenced by inspiratory effort, respiratory rate, lung volume and pressure, and possibly lung pathology (2,38). Whereas Tdi at end-expiration could be a more reliable measure as less factors may affect end-expiratory Tdi. The variation between the highest and lowest measurement per breath for both end-inspiration and end-expiration was 7%, which shows good reliability of these measurements. We measured DTF during tidal breathing, which does not represent the maximal contractile activity of the diaphragm muscle. Maximal DTF might be a better measure to indicate contractile activity and its association with MIP. This warrants further investigation into physical factors affecting DTF and the influence thereof. Our current practice in the intensive care unit attempts to avoid controlled ventilation modes and give the least necessary amount of sedation, which is different to the known literature who describes using controlled modes of ventilation. With the mean duration of ventilation being as short as four days, our mean age being only 45.1 years and our high extubation success rate, it could be noted that our intensive care protocols may be regarded as of good quality. However, without the disease severity scores this cannot be confirmed and it may be limited to our study population.

We found a small non-significant correlation between maximal inspiratory pressure (MIP) and baseline DTF, as well as last Tdi, and no difference between MIP and rate of change in Tdi groups. This could be due to three reasons: MIP assesses the inspiratory strength as a whole, including intercostal and accessory muscles aiding inspiration; secondly, MIP is a measure of maximal breathing effort, whereas DTF and Tdi was measured at tidal breathing and lastly, patient co-operation is a major determinant of accurate MIP measurements. We measured MIP within 24 hours after participants were extubated in order to be able to correlate findings with Tdi and DTF measured post-extuabtion. During this timeframe, participants could still be semi-sedated or tired, adding to the possibility of sub-maximal inspiratory efforts. Our MIP measurements showed a variation of 16% between the two highest values, which indicate that MIP measurements might not have been true maximal efforts. We limited MIP to three attempts, to eliminate to chance of fatigue. Specific protocols or instructions might be of clinical use to ensure maximal efforts during MIP measurements. Supinski, Westgate & Callahan (61) reported a correlation between MIP with trans diaphragmatic twitch pressure, and although finding a moderate correlation, it was highlighted that MIP must be done properly and patient effort must be noted.

Taking into consideration the complexity of an ICU population, with different diseases, comorbidities, medical management protocols and reaction towards different multidisciplinary treatments, we cannot exclude the effect of confounding factors attributing to study results (111). In our study, we collected data of possible confounding

factors daily. We developed a risk profile in order to identify the associations between outcomes and risk factors more comprehensively. In our study, we could not find any significant baseline confounding factors associated with extubation failure. We did, however, find that high risk patients were associated with having a significantly longer duration of mechanical ventilation, which could provide clinical use in identifying participants at risk for diaphragm dysfunction according to the risk profiles described in this study. We recognise that this risk profile has not been validated, therefore it should be interpreted with caution, however we thought this is a novel way of categorising many factors related to the complexity of the critically ill population. Future studies should investigate the validity and reliability of such a scoring system.

This project was done to identify patients that could be at risk of respiratory muscle weakness/dysfunction and therefore candidates for targeted rehabilitation, using an easy, non-invasive and readily available tool. This is clinically very relevant for us physiotherapists, who often focus on early-intervention strategies to improve patient outcomes. This study generates new hypotheses such as Tdi possibly being a better indicator of diaphragm function, and that thicker diaphragms may be more prone to longer duration of MV, atrophy and extubation failure, but these hypotheses should be investigated in sufficiently powered studies. Taking into consideration that our population differs from the current existing literature, it is important to establish whether diaphragm dysfunction is a problem and whether early intervention would be beneficial. As this was not an intervention study, we did not look at treatment techniques and the outcomes of patients who received physiotherapy vs those who did not, however the results from this study could form a baseline for future intervention studies looking at the effect of physiotherapy on diaphragm function. Current literature on inspiratory muscle training (IMT) and its effectiveness has inconclusive results and if we can identify patients who need IMT sooner, we may be able to improve clinical outcomes. This however needs further investigation, and our study may provide a baseline on which IMT intervention studies can build in order to identify and treat diaphragm dysfunction sooner and more effectively.

The present study has some limitations in such that we did not record ventilator settings during mechanical ventilation. As reported earlier, different levels of pressure support may have different effects of diaphragm function. We did take note of ventilation modes used and whether patients had any spontaneous breaths during the 24hours that preceded each measurement. As we measured participants once daily, the recording of pressure support once a day may not yield accurate results in terms of the pressure support given to the specific patient throughout the day. Secondly, we did not look at diaphragm muscle endurance, which could possibly be decreased in diaphragm dysfunction. As cellular studies have found a decrease in the cross-section of slow and fast twitch fibers, it could be possible that the diaphragm fatigues with mechanical ventilation (27). This might have an effect on the endurance of the diaphragm, leading to diaphragm dysfunction. Thirdly, we did not collect disease severity (APACHE II) scores for each participant. Disease severity may affect diaphragm function. Lastly, participants were not allowed any practice breaths when measuring MIP and MEP, to avoid fatigue. This could however have caused submaximal breaths as they may have not understood the concept clearly, which may potentially impact the interpretation of the results.

Future research should investigate the effect of lung mechanics on Tdi and DTF to establish whether lung volumes or pressures have an influence on Tdi and contractile activity.

3.5 CONCLUSION OF PRIMARY STUDY

Neither Tdi, DTF nor the rate of change in Tdi were strongly correlated with inspiratory strength measures in our population. Duration of mechanical ventilation was positively associated with an increased baseline Tdi. Furthermore, an increased baseline Tdi is linked to extubation failure in our population.

CHAPTER 4: GENERAL DISCUSSION

The aim of this thesis was to investigate the Tdi and diaphragm contractile activity during mechanical ventilation, as well as respiratory strength and extubation outcome of critically ill patients who received mechanical ventilation. Proof exists of the negative effect of mechanical ventilation on the diaphragm muscle, however the extent and mechanisms behind this dysfunction show conflicting results. A Scoping review investigating the effects of mechanical ventilation on the diaphragm muscle was conducted. Different diaphragm assessment techniques and the effects of different ventilation modes were discussed. Ventilation modes and duration of mechanical ventilation described in published papers in the scoping review differ from the current practice in our units. Ultrasonography, being a relatively new measure of diaphragm function, has not been studied in our units. These different protocols and measurement techniques, together with contrasting results found during the literature overview, informed the planning of the primary study which looked further at the effect of diaphragm contractile activity on extubation success. The aim of the primary study was to compare the diaphragm contractile activity and respiratory muscle strength with patient outcomes and determining if any relationship exists. A secondary aim was to describe the change in the contractile activity of the diaphragm during the course of mechanical ventilation, until extubation, and determine any possible correlations with inspiratory strength post-extubation. Furthermore, the effect of confounding factors on diaphragm function have been investigated.

4.1 Current understanding of literature

The effect of mechanical ventilation on the diaphragm muscle have been investigated from as early as 1985, however a major surge in research was noted in the last decade. Most papers were published in developed countries, which could be due to diaphragm assessment not being feasible in resource-scarce areas. Multiple papers have reported on the assessment of diaphragm function by means of ultrasonography, with all favouring this method due to its easy and non-invasive use (32,36–39). No standardised protocol has been developed in terms of diaphragm ultrasonography, however consensus on probe placement is evident. Outcome measures used for ultrasonography still remains highly variable. It has been established that DTF could be indicative of diaphragm function, as it measures the contractile activity of the diaphragm muscle (35–37). Cut-off DTF values have been proposed to indicate possible successful extubation, however these values were higher than our median DTF before extubation. This could be due to previous studies reporting on controlled ventilation modes where our units did not use any controlled modes of ventilation. Whether DTF or Tdi are surrogate measures of diaphragm strength remains unclear.

Prolonged mechanical ventilation has been associated with diaphragm dysfunction, although literature exists showing the biggest decrease in Tdi occurs within the first week of mechanical ventilation (38). Our findings support this statement as we found a significant decrease in Tdi between the first two days in the group of participants who showed a mean decrease in rate of change of Tdi. We also found a link between an increased baseline Tdi and extubation failure in our population.

4.2 Achievement of study aims

The first aim of the primary study was to compare diaphragm contractile activity and respiratory muscle strength with patient outcome to determine if any relationship exists. This aim was achieved in Chapter 3. We concluded that Tdi may be a better predictor of extubation outcome than DTF in our context, and that an increased baseline Tdi may be linked to extubation failure. We also concluded that a thicker diaphragm at baseline was associated with a longer duration of ventilation. This was in contrast with current literature reporting thinner diaphragms associated with increased duration of ventilation, but could be due to a passively shortened diaphragm being more prone to atrophy similarly to skeletal muscles. Our second aim was to describe the change in diaphragm contractile activity of the diaphragm, during the course of mechanical ventilation and determine any possible correlations with respiratory strength measurements. We found no significant correlation between the rate of change in DTF and maximal inspiratory measures, as well as no correlation between the change in Tdi and maximal inspiratory pressure. Our last aim investigated the relationship of possible confounding factors to the diaphragm contractile activity and respiratory strength measurements. We developed a risk profile to categorise participants according to their probable risk for diaphragm dysfunction, as discussed in Chapter 3. We reported no statistical differences in proportions of patients in low, medium and high risk categories between successful and non-successful extubated groups. We found that participants classified as high risk were ventilated significantly longer than the low risk group. Neither age, gender, smoking nor alcohol history was associated with success or failure groups.

4.3 Limitations

- The Scoping review was conducted by the primary investigator alone and therefore inclusion and exclusion of articles could have been misinterpreted;
- MIP was only repeated with three breaths, to avoid fatigue. Possible submaximal efforts could have been recorded;
- MIP is a measure of the inspiratory pressure as a whole, and not solely diaphragm inspiratory pressure;
- We did not collect severity of illness scores (APACHE) which affects external validity of the study. It will be difficult for other researchers to interpret our findings within the context of their populations;
- We did not record ventilator settings during mechanical ventilation therefore we cannot comment on the effects of different settings of the ventilator on diaphragm function;
- We did not look at diaphragm muscle endurance, which could possibly be decreased in diaphragm dysfunction;
- Our participants had a relatively short duration of ventilation, which could indicate good clinical practice, however results might not be generalisable to the difficult-to-wean population.

4.4 Future research

- The effect of different lung mechanics including lung volumes and positive end-expiratory pressure on diaphragm contractile activity and Tdi should be investigated to establish whether it has an effect on diaphragm function;

- Investigate whether DTF could indicate diaphragm endurance and whether diaphragm endurance has an effect on the contractile activity of the diaphragm;
- Diaphragm contractile activity should be measured during maximal breaths when compared to maximal inspiratory pressure, to see if a better relationship exists;
- The assessment of diaphragm contractile activity in difficult to wean patients or patients who have been mechanically ventilated for longer should be investigated.

4.5 Take home message

- Tdi may predict patient outcome better than DTF;
- A thicker diaphragm at baseline may be linked to extubation failure;
- A thicker diaphragm at baseline may indicate longer duration of ventilation;
- DTF relies on patient breathing effort and may be influenced by lung volumes and pressures delivered mechanically;
- Ultrasound is an easy, safe and non-invasive way to assess the diaphragm of critically ill patients;
- Ultrasound protocols must be described in detail to ensure reproducibility, stating the probe frequency, mode used, probe placement, and positioning of the patient.

4.6 Final conclusion

Thicker diaphragms at baseline may be more prone to prolonged mechanical ventilation and may be linked to extubation failure. Diaphragm contractile activity measured with ultrasound during tidal breathing may not be indicative of extubation readiness and should be interpreted with caution. The use of ultrasound shows value for future research in diaphragm dysfunction of critically ill patients and should be further investigated to be able to identify and prevent diaphragm dysfunction earlier. The data included in this thesis can be used to inform the planning of future studies.

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ADDENDA

ADDENDUM A: Search strategy for literature overview

PUBMED

Filters: Humans; English; Adult: 19+ years

SEARCH	Hits
1. Search ((("Respiration, Artificial"[Mesh] AND Humans[Mesh] AND English[lang] AND adult[MeSH])) AND ("Critical Illness"[Mesh] AND Humans[Mesh] AND English[lang] AND adult[MeSH])) AND ((diaphragm muscle) AND Humans[Mesh] AND English[lang] AND adult[MeSH])	20
2. ("Respiration, Artificial"[Mesh]) AND (diaphragm muscle) AND (Measur*)	137
3. (("Respiration, Artificial"[Mesh]) AND (diaphragm muscle)) AND (ventilation mode)	30
4. ("Respiration, Artificial"[Mesh]) AND (diaphragm muscle) AND (outcomes)	12
5. (((diaphragm structure)) AND "Respiration, Artificial"[Mesh]) AND "Critical Illness"[Mesh]	23
TOTAL	**222**

CINAHL

Narrow by Language: - English, all adult

SEARCH	Hits
(MH "Respiration, Artificial") AND (diaphragm muscle)	11
(MH "Respiration, Artificial") AND (diaphragm muscle) AND measur*	8
(MH "Respiration, Artificial") AND (diaphragm muscle) AND (ventilation mode)	2
(MH "Respiration, Artificial") AND (diaphragm structure)	1
TOTAL	**22**

MEDLINE

English AND all adult: 19+ years

SEARCH	Hits
(MH "Respiration, Artificial") AND (diaphragm muscle)	16
(MH "Respiration, Artificial") AND (diaphragm muscle) AND measur*	6
(MH "Respiration, Artificial") AND (diaphragm muscle) AND outcomes	3
(MH "Respiration, Artificial") AND (diaphragm structure)	7
TOTAL	**32**

SCIENCE DIRECT

Limited to: Medicine and Dentistry, Neuroscience, Nursing and Health Professions, Pharmacology, Toxicology and Pharmaceutical Science)

SEARCH	Hits
(Mechanical ventilation) AND Humans AND (Critical Illness) AND (diaphragm muscle) AND English	47
(Mechanical ventilation) AND Humans AND (diaphragm muscle) AND measure AND English	98
(Mechanical ventilation) AND Humans AND (diaphragm structure) AND English	88
TOTAL	**233**

COCHRANE

SEARCH	Hits
"mechanical ventilation" and diaphragm and adults not children	40
"mechanical ventilation" and diaphragm and adults not children AND measure	5
"mechanical ventilation" and diaphragm structure and adults not children	4
TOTAL	**49**

PEDRO

SEARCH	Hits
Diaphragm AND ventilation	42
Diaphragm structure	3
Diaphragm muscle	34
TOTAL	**79**

TOTALS

DATABASE	Total hits
Pubmed	222
Cinahl	22
Medline	32
Science Direct	233
Cochrane	49
Pedro	79
TOTAL	**637**

ADDENDUM B: Ethical approval letter

UNIVERSITEIT·STELLENBOSCH·UNIVERSITY
jou kennisvennoot • your knowledge partner

Approval Notice
Response to Modifications- (New Application)

10-Nov-2016
Brouwer, Lindie LE

Ethics Reference #: S16/09/173
Title: The Effect of Diaphragm Contractile Activity on Extubation Success

Dear Mrs Lindie Brouwer,

The **Response to Modifications** - ***(New Application)*** received on **17-Oct-2016**, was reviewed by members of **Health Research Ethics Committee 2** via Expedited review procedures on **10-Nov-2016** and was approved.
Please note the following information about your approved research protocol:

Protocol Approval Period: **10-Nov-2016 -09-Nov-2017**

Please remember to use your **protocol number** (**S16/09/173**) 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: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics

We wish you the best as you conduct your research.
For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at .

Included Documents:
Protocol.pdf
Declaration Prof S Hanekom.pdf
Protocol Synopsis.pdf
CV C Koegelenberg.pdf
CV S Hanekom.pdf
Declaration C Koegelenberg.pdf
Application form signature page.pdf
Declaration A Lupton-Smith.pdf
20161018 MOD Cover letter
20161018 MOD HREC Mods letter
Declaration L Brouwer.pdf
Application form.pdf
Checklist.pdf
CV A Lupton-Smith.pdf
CV L Brouwer.pdf
20161018 MOD Protocol

Sincerely,

Francis Masiye
HREC Coordinator
Health Research Ethics Committee 2

ADDENDUM C: Institutional approval letter

Western Cape Government
Health

TYGERBERG HOSPITAL
REFERENCES: Research Projects
ENQUIRIES: Dr GG Marinus
TELEPHONE NO.:021 938 5752

Ethics References: S16/09/173

TITLE: The Effect of Diaphragm Contractile Activity on Extubation Success.

Dear Mrs L Brouwer

PERMISSION TO CONDUCT YOUR RESEARCH AT TYGERBERG HOSPITAL

1. In accordance with the Provincial Research Policy and Tygerberg Hospital Notice No 40/2009, permission is hereby granted for you to conduct the above-mentioned research here at Tygerberg Hospital.

2. Researchers, in accessing Provincial Health Facilities, are expressing consent to provide the National Health Research Department with an electronic copy of the final feedback within six months of completion of research. This can be submitted to the Provincial Research Co-Ordinator (Health.Research@westerncape.gov.za)

3. Please take note of the comments of Head of Physiotherapy.

4. It is expected that the Head of each ICU is consulted prior to the commencement of the study to ensure this project does not cause delays on extubation of patient and putting further pressure on ICU bed availability.

DR GG MARINUS
MANAGER: MEDICAL SERVICES [RESEARCH CO-ORDINATOR]

DR D ERASMUS
CHIEF EXECUTIVE OFFICER

Date: 6 February 2017

Administration Building, Francie van Zijl Avenue, Parow, 7500
Tel: +27 21 938 5752 Fax: +27 21 938 4680
Private Bag X3, Tygerberg, 7505
www.capegateway.gov.za

TYGERBERG HOSPITAL

Ethics Reference: S16/09/173

Title: The Effect of Diaphragm Contractile Activity on Extubation Success.

BY 

An authorized representative of Tygerberg Hospital

NAME Dr DS Erasmus

TITLE CEO

DATE 6 February 2017

ADDENDUM D: Informed consent letter

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT:

The Effect of Diaphragm Contractile Activity on Extubation Success

REFERENCE NUMBER:

PRINCIPAL INVESTIGATOR: Mrs. Lindie Brouwer

ADDRESS: Division Physiotherapy, Faculty of Interdisciplinary Health Sciences, University of Stellenbosch, Tygerberg Campus, Western Cape

CONTACT NUMBER: 0725770876

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or physiotherapist 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.

What is this research study all about?

- *Aim*

  This study will look at how well the main breathing muscle (diaphragm) is of people that are connected to a machine that helps you breathe (mechanical ventilated).This study aims to find out if measuring the diaphragm muscle during breathing by taking pictures with ultrasound can help see whether you will be able to breathe without the machine.

- *Setting*

  This study will take place at the Medical (A5) and Surgical (A1) intensive care units at Tygerberg Academic Hospital. We hope to recruit 83 participants to be part of the study.

- *Procedure*

  Background information, including age, gender, diagnosis, date of intubation, ventilation modes, number of days intubated, medication, ventilation settings, vital signs and blood results will be collected by the researcher. Your bed will be elevated to 30˚. The researcher will find your right eight to tenth rib spaces and place the ultrasound probe with ultrasound gel in these spaces, in order to see the diaphragm clearly. Ultrasound pictures will be taken whilst you breathe in and out for three breaths. These ultrasound measurements will be done daily until you are extubated. You will not feel any pain when the researcher take these pictures.

  After extubation, the researcher will assess your breathing muscle strength with a machine you place in your mouth. You will be asked to take as deep as possible breath and blow out again as hard as possible. You will rest for two minutes, where after the researcher will repeat the action. This will be done three times to find the best value of your breathing muscle strength. We will follow you up 48 hours after the pipe was taken out to see how you are doing. These measurements are risk-free and done routinely in the ICU.

  The nursing staff and doctors will be available in case of any adverse reaction like shortness of breath, decrease or increase of blood pressure, pain, discomfort, increased heart rate and loss of consciousness.

Why have you been invited to participate?

- Often patients get so weak that they struggle to breathe on their own. This study will look at possible predictors of extubation success (the ability to breathe without mechanical support for 48 hours after being taken off the machine) in order to identify if you are strong enough to breathe on your own. This study will also show us what happens to the breathing muscle thickness during mechanical ventilation. These findings can help us to identify ways to improve the strength and function of the diaphragm to prevent weakness and long stays in the ICU.

What will your responsibilities be?

- You as participant will be asked to stay relaxed and report any pain or discomfort. During the ultrasound measurements you will have to lie still and breathe normally. When the strength measurements are done, you will be required to stay calm, and take as deep breathe as possible in order to obtain accurate values. There after you will be able to rest and recover. You will be asked to sign informed consent to participate in the study. You will be able to withdraw from the study at any time.

Will you benefit from taking part in this research?

- You will not benefit directly from this study, but future patients may benefit from the results. This results will pave the way for future studies aiming at strengthening the respiratory muscles in order to prevent weakness due to mechanical ventilation.

Are there in risks involved in your taking part in this research?

- There are no risks involved in the ultrasound measurements. With regards to the strength measurements prior to being extubated, you might experience shortness of breath however this is uncommon. When we reach this stage you will have been on low mechanical settings and should be able to cope without support. If there are any signs of distress or discomfort, you will be reattached to the ventilator and a doctor will be notified. These measurements are done as part of routine and are mainly risk-free.

If you do not agree to take part, what alternatives do you have?

- Standard care will continue as per normal, for all patients. This study does not involve treatment.

Who will have access to your medical records?

- All data collected will be kept confidential and saved on the researcher's computer with password protection. Only the researcher, research assistant and statistician will have access to the data. Once data has been imported to an Excel spreadsheet, you will be assigned a number and your name will be kept anonymous. The results will be published in a thesis or publication where all the data will remain anonymous. Members of the Ethical committee may need to inspect research records for auditing purposes.

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

- In the rare event of any injury occurring during this study, the team of health professionals in the ward will act immediately as needed. You as participant are covered by the insurance of the University of Stellenbosch.

Will you be paid to take part in this study and are there any costs involved?

- You will not be paid to take part in the study and the study will be of no cost to you.

Is there anything else that you should know or do?

- You can contact Lindie Brouwer at tel 0725770876 if you have any further questions or encounter any problems.
- You can contact the Health Research Ethics Committee at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study researcher.
- You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I ……..…….. agree to take part in a research study entitled The Effect of Diaphragm Contractile Activity on Extubation Success.

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 I have not 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 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*) ……...…….. 2005.

....
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*) ……...……..

....
Signature of interpreter **Signature of witness**

ADDENDUM E: Pilot study

Pilot Study

This pilot study was conducted before the commencement of the study.

Objectives:

- To determine the intra-rater reliability of the ultrasound measurements and respiratory strength measurements
- To determine the interrater reliability of the ultrasound measurements and respiratory strength measurements
- To determine the time taken to complete one full assessment of ultrasound and daily data collection

Method:

Setting: This pilot study was conducted in Tygerberg Academic Hospital.

Ethical considerations: All participants provided informed consent

Sample: Sample of convenience was used. Seven participants was included for ultrasound measures and five participants was included for respiratory measurements.

Measurements:

Ultrasound

Procedure: Seven intubated participants were screened in the Medical ICU of Tygerberg Hospital, and included in this pilot study. Study information and procedure was explained and informed consent obtained. Participants were positioned in a 30˚ semi-recumbent position. The diaphragm was assessed with Ultrasound in B-mode, using a 7-10 MHz linear probe (Samsung Medison MySonoU6, Samsung Company, Seoul, Korea). The probe was placed on the right, perpendicular to the chest wall, in the mid-axillary line, in the intercostal spaces between the eighth, ninth or tenth ribs depending where the clearest image appeared. Images of the diaphragm was recorded in loops of three full tidal volume breathing cycles, from inspiration to expiration. The primary investigator (PI) first recorded three consecutive breaths, where after the research assistant (RA) recorded three consecutive breaths on the same participant.

Diaphragm thickening fraction (DTF): Three measurements of diaphragm thickness was recorded on each of the inspiration and expiration breaths. This was done in order to obtain an average measurement per breath, due to limited literature stating exact location of measurement on an image of the diaphragm. The three consecutive breath measurements were then averaged again in order to calculate the DTF for that specific participant.

Intra-rater reliability: The PI repeated the procedure twice on each participant in order to establish intra-rater reliability of the separate ultrasound measurements. The exact same positioning was used with the exact same Ultrasound machine and settings. A five minute rest was given between measurements. Results are shown in table 1.

Inter-rater reliability: The DTF measurements of the seven participants taken by the PI was compared to the RAs seven measurements in order to establish interrater reliability. The same positioning, equipment and setting was used. Participants had a five minute break between measurements. Refer to table 1 for the results of the measurements.

Table 1: DTF measurements of PI and RA

PI - DTF 1	PI - DTF 2	RA - DTF 1	RA - DTF 2
115.12	85.47	88.20	78.86
128.68	132.87	105.40	91.42
48.76	46.13	102.79	83.60
58.26	49.71	42.22	38.39
24.50	23.81	22.15	24.97
51.27	49.65	35.44	34.39
59.24	56.58	61.32	57.46

*PI – Primary investigator: RA – research assistant; DTF – diaphragm thickening fraction

Test-retest: A test-retest reliability was done by the PI, measuring the same participant three times in five minute intervals. This was done to establish if the PI is able to replicate the same measurements on the same participant at two separate instances.

Respiratory strength measurements

Procedure: Five normal participants were recruited and screened at an abdominal clinic at Tygerberg hospital. The procedure was explained and information provided regarding the pilot study. Informed consent was obtained from all the participants. Participants were seated in an upright position on a chair. Maximal inspiratory strength (PImax) and maximal expiratory strength (PEmax) was measured via the Micro RPM (CareFusion, USA). The Micro RPM device was placed in the participant's mouth via a bacterial filter. The participant was asked to take a deep breath (maximal effort) and then exhale. This was repeated three times with two minute rest periods in between breaths. PImax values were recorded. The participant was then asked to exhale as much as they can (maximal effort), for another three breaths. The PEmax was also noted. The highest value out of the three breaths were used for analysis.

Intra-rater reliability: Each participant was measured twice by the PI and twice by the research assistant, with a five minute rest in between. Values of each participant was compared to themselves (separately for the PI and research assistant) in order to establish intra-rater reliability. The exact same procedure, equipment and instructions was followed. Refer to table 2.

Inter-rater reliability: The values obtained by the PI was compared to the values obtained by the research assistant for the same five participants, in order to establish inter-rater reliability. Table 2 shows the values obtained.

Table 2: Respiratory strength measurements of the PI and RA

PI – MIP 1	PI – MIP 2	PI – MEP 1	PI – MEP 2	RA – MIP 1	RA –MIP 2	RA – MIP 1	RA –MIP 2
-42	-52	42	42	-48	-60	41	52
-113	-120	94	96	-113	-136	100	96
-86	-94	63	82	-90	-92	82	77
-21	-21	54	48	-24	-20	55	52
-88	-85	70	67	-91	-94	66	67

*PI – Primary investigator; RA – research assistant: MIP – maximal inspiratory pressure; MEP – maximal expiratory pressure

Duration of ultrasound measurements:

Procedure: Time was taken from the start of data collection from the files of a single participant to the end of an ultrasound measurement to establish the total time needed daily per participant in order to obtain data and ultrasound measurements.

Data analysis

Intraclass correlation coefficients (ICC) were used in order to establish intra- and interrater reliability. Absolute agreement with a 95% confidence interval were selected. An ICC value > 0.75 was regarded as excellent reliability.

Results

Seven participants were included in the ultrasound leg of the pilot study. Intra-rater (0.95) and interrater (0.74) reliability was established. Test-retest reliability was also calculated for the ultrasound measurements (0.90). For the respiratory measurements, Intra-rater reliability yielded an agreement of 0.96 and interrater reliability was 0.97. The time taken to conduct one participant's data collection was 12 minutes.

Discussion

Excellent intraclass coefficients were yielded in all the reliability tests except the ultrasound interrater reliability test. This could be due to participants not having one breath the same as before and therefore each breath is different on its own. Coughing, anxiety, sleepiness, fatigue, medication and various other factors could contribute to different inspiratory and expiratory efforts. Therefore we can accept and account for a good instead of an excellent intraclass coefficient.

Conclusion

The procedure used in this pilot study for measuring ultrasound as well as respiratory strength proves to be reliable and can be used to successfully and consistently measure diaphragm thickening and maximal inspiratory and expiratory pressures.

ADDENDUM F: Data collection sheets

Demographics

Record ID	_____
Consent obtained	☐ Intensivist ☐ Patient ☐ Family member
First Name	_____
Surname	_____
ID/Passport number	_____
Folder number	_____
Address	_____
Contact number	_____
Alternative contact number	_____
Alternative contact number	_____
Date of Birth (D-M-Y)	_____
Date of assessment (D-M-Y)	_____
Age (years)	_____
Gender	○ Male ○ Female
Employed before admission	○ Yes ○ No
Date of admission to TBH (D-M-Y)	_____
Date of admission to TBH ICU	_____
Was the patient transferred from another hospital	○ Yes ○ No
Name of preceding hospital	_____
Date of admission to preceding hospital (D-M-Y)	_____
Date and time of Intubation (D-M-Y)	_____

Past Med Hx

Co-morbidities	☐ Hypertension ☐ Diabetes ☐ COPD ☐ Asthma ☐ Past TB ☐ RVD ☐ CVA ☐ Other
Date of CVA (year)	_____
Side of hemiplegia	_____
If other, please specify	_____
Smoking history	○ Current ○ Ex-smoker ○ Never ○ Unknown
Illicit drug use	○ Yes ○ No ○ Unknown
Name(s) of drugs used	_____ ((separate with comma))
ETOH abuse	○ Yes ○ No ○ Unknown

Current Med Hx

Admission diagnosis
○ Trauma ○ Surgery
○ Medical ○ Other

If Trauma, what was diagnosed?
☐ Upper limb fractures
☐ Lower limb fractures
☐ Spinal fractures
☐ Rib fractures
☐ Abdominal trauma
☐ Head injury
☐ Other

If Surgical, what was diagnosed?
☐ Neurosurgery
☐ Abdominal surgery
☐ Vascular surgery
☐ Plastic surgery
☐ Other

If Medical, what was diagnosed?
☐ Overdose
☐ Asthma
☐ COPD
☐ Cardiac arrest
☐ Pneumonia
☐ Other

If other, specify
_____

Bloods taken on admission to TBH ○ Yes ○ No

Date of bloods (D-M-Y) _____

CRP (if available) _____

HGT _____

Lactate _____

Creatinine _____

Comments
_____

Daily Assessment

Date and time of assessment (D-M-Y) _____

Is the patient extubated? ○ Yes ○ No

Date and time of extubation _____

Number of hours intubated _____

Number of hours currently intubated _____
(Ignore if extubated)

Is the patient for serial or once-off measurements? ○ Serial ○ Once-off

Mode of ventilation
○ BiPap
○ PC SIMV
○ VC SIMV
○ CPAP
○ Other

If other, please specify _____

Has the patient had spontaneous breaths in the preceding 24 hours? ○ Yes ○ No

Pyrexia in preceding 24 hours ○ Yes ○ No

Highest recorded temperature in preceding 24 hours _____

Blood results available (in the last 24 hours) ○ Yes ○ No

Date of bloods (D-M-Y) _____

CRP (if available) _____

HGT _____

Lactate _____

Creatinine _____

White Cell Count _____

Is the patient sedated ○ Yes ○ No

Sedatives used (name, dose) _____
(If more than one, separate with ;)

Has the patient received NMBA? ○ Yes ○ No

When was the last NMBA administered
○ Continuous infusion
○ 12 hours ago
○ 24 hours ago
○ >24 hours ago

Is the patient receiving corticosteriods? ○ Yes ○ No

If yes, please specify name and dosage _____

Richmond Agitation and Sedation Scale (RASS)
○ 4
○ 3
○ 2
○ 1
○ 0
○ -1
○ -2
○ -3
○ -4
○ -5
(Combative+4; Very agitated+3; Agitated+2; Restless+1; Alert and calm0; Drowsy-1; Light sedation-2; Moderate sedation-3; Deep sedation-4; Unarousable sedation)

Comments _____

Diaph Us

Date	_____
Diaphragm thickness during inspiration on first breath (mm)	_____
Diaphragm thickness during inspiration on second breath (mm)	_____
Diaphragm thickness during inspiration on third breath (mm)	_____
Average diaphragm thickness during inspiration (mm)	_____
Diaphragm thickness during expiration on first breath (mm)	_____
Diaphragm thickness during expiration on second breath (mm)	_____
Diaphragm thickness during expiration on third breath (mm)	_____
Average diaphragm thickness during expiration (mm)	_____
Diaphragm thickening fraction	_____

Extubation

Date and time of assessment	_____
Hours extubated	_____
First MIP	_____
Second MIP	_____
Third MIP	_____
Best maximal inspiratory pressure	_____
First MEP	_____
Second MEP	_____
Third MEP	_____
Best maximal expiratory pressure	_____
Was the patient successfully extubated	◯ Yes ◯ No
Reason for failed extubation	_____
Adverse events	_____

Addendum G: Pre-admission comorbidities of the whole sample

Comorbidity	**n(%)**
Hypertension	23(33.8)
Diabetes	11(16.2)
COPD	5(7.4)
Asthma	4(5.9)
Past TB	11(16.2)
RVD	9(13.2)
Antiphospholipid syndrome	1(1.5)
High Cholesterol	4(5.9)
Current PTB on Rx	1(1.5)
Epilepsy	1(1.5)
GERD	1(1.5)
Gout	2(2.9)
Microscopic polyangitis	1(1.5)
Renal transplant	1(1.5)