UPPER LIMB MUSCLE STRENGTH AND ENDURANCE AS PREDICTORS OF SUCCESSFUL EXTUBATION IN MECHANICALLY VENTILATED PATIENTS: A PREDICTIVE CORRELATIONAL STUDY

by

CAROLINE RUBINE DE BEER

A research thesis submitted in fulfilment of the requirements for the degree Doctor of Philosophy in Physiotherapy (PhD)

Department of Physiotherapy

Faculty of Health Sciences

UNIVERSITY OF PRETORIA

Supervisor
Prof. A.J. van Rooijen

Co-supervisor
Prof. F. Paruk

April 2020

DECLARATION BY RESEARCHER

I declare that this study: "Upper limb muscle strength and endurance as predictors of successful extubation in mechanically ventilated patients: A predictive correlational study" is my own work. It has been submitted in fulfilment of the requirements for the degree Doctor of Philosophy in Physiotherapy (PhD Physiotherapy) to the University of Pretoria. It has not been submitted before for any other degree or examination at this or any other university.

9 April 2020

C.R. de Beer Date

DECLARATION BY LANGUAGE PRACTITIONER

I hereby declare that the thesis, *Upper limb muscle strength and endurance as predictors of successful extubation in mechanically ventilated patients: A predictive correlational study* by Caroline Rubine de Beer, for the fulfilment of the degree PhD in Physiotherapy, has been language edited by me.

After a career as editor-in-chief at a leading publishing house, I now work as a freelance text editor.

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Lambert Daniel Jacobs (BA Hons, MA, BD, MDiv) Date

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ABSTRACT

Mechanical ventilation temporarily replaces or supports breathing in the critically ill patient. Prolonged mechanical ventilation is associated with an increase in nosocomial infections, respiratory muscle weakness and intensive care unit acquired weakness (ICU-AW). Since the inception of mechanical ventilators, successful weaning and extubation failure has always been a challenge that physiotherapists, nurses and physicians grapple with. Due to the complexity of determining extubation readiness 10% to 20% of patients still fail extubation and therefore predictors for successful extubation are paramount. Different parameters including, rapid shallow breathing index (RSBI), partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2 ratio) and maximum inspiratory pressure (MIP) were used to predict extubation readiness, but none could be used in isolation. Failed extubation increases the intensive care unit (ICU) length of stay, the hospital length of stay, the financial costs and it decreases the patient's functional ability, muscle strength and health-related quality of life (HRQOL).

Early mobilisation and rehabilitation according to a patient centred program are essential to decrease the development of peripheral muscle weakness and respiratory muscle weakness. Previous research studies demonstrated associations between respiratory muscle weakness and peripheral muscle weakness as well as possible associations between successful extubation, exercise endurance and upper limb muscle strength respectively.

The aim of this study was to determine if upper limb muscle strength and exercise endurance can be used by physiotherapists as predictors of successful extubation in mechanically ventilated patients. The statistical objective of this study was to develop a prediction equation based on upper limb muscle strength and exercise endurance for outcome of extubation.

A total of 463 patients were recruited from the medical and trauma ICU's of a large Academic hospital. Fifty seven of these patients were eligible for testing. Peripheral and respiratory muscle strength was evaluated using the Oxford grading scale,

Medical Research Council score (MRC-score), handgrip dynamometer and MIP. Exercise endurance was tested while patients were riding the MOTOmed® letto2 cycle ergometer for six minutes with the upper limbs.

In an attempt to determine whether upper limb muscle strength and exercise endurance can predict successful extubation, a prediction equation was developed. Univariable logistic analysis was performed to identify the marginal significant and significant factors to be included in the multivariable logistic regression analysis to develop the final prediction equation. The predictive ability of the prediction equation was assessed using cross validation. Testing was based on a 0.05 level of significance. Data analysis employed STATA version 15.1 software.

The results demonstrated that the exercise endurance (time the patient rode actively) (P = 0.005), general body muscle strength (MRC-score: P = 0.007) and number of days ventilated (P = 0.005) were associated with successful extubation. The handgrip strength (P = 0.061), MIP (P = 0.095) and muscle strength of the sternocleidomastoid (P = 0.053) and trapezius muscles (P = 0.075) were marginally associated with successful extubation. The muscle strength of the deltoid (P = 0.273) and pectoralis major muscles (P = 0.327) were not significantly associated with successful extubation. Due to multicollinearity between muscle strength and exercise endurance, elimination of factors were done. The newly developed prediction equation only included the exercise endurance and the number of days ventilated as the other factors did not contribute to the predictive value of the equation. This newly developed prediction equation had a sensitivity of 81.82% and a specificity of 77.14% to predict successful extubation.

Conclusion: Exercise endurance can be used as predictor of successful extubation in mechanically ventilated patients when physiotherapists apply the newly developed prediction equation $\hat{y}$ = -1.0064 – (0.17 x active time) + (0.230 x ventilator days) and the value for $\hat{y}$ is less than or equal to -0.282. Theoretically the equation indicated that if the number of days the patient is ventilated decrease and the exercise endurance increase the risk to fail extubation will decrease. Clinically, successful extubation reduce the ICU length of stay, hospital length of stay and the development of ICU-AW. It increases the patients' functional level and HRQOL, therefore the findings of this study have the potential to impact positively on patient outcomes.

Keywords: Intensive care unit (ICU), prolonged mechanical ventilation, extubation failure, weaning from mechanical ventilation, predictors of successful extubation, upper limb muscle strength, measuring muscle strength, exercise endurance, cycle ergometer, health-related quality of life

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%VO_2R	Percentage of oxygen consumption reserve
6-MAT	Six-minute arm test
6MWT	Six-minute walk test
Ach	Acetylcholine
ARDS	Acute Respiratory Distress Syndrome
ATP	Adenosine Triphosphate
ATPase	Acetylcholinesterase
BNP	B-type natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
CINAHL	Cumulative Index to Nursing and Allied Health
COPD	Chronic Obstructive Pulmonary Disease
EMG	Electromyography
FRI	Fatigue Resistance Index
GCS	Glasgow Coma Scale
HR	Heart rate
HRQOL	Health-related quality of life
HRR	Heart rate reserve
ICF	The International Classification of functioning, Disability and Health
ICU	Intensive care unit
ICU-AW	ICU-acquired weakness
IPPV	Intermittent positive pressure ventilation
MEP	Maximum expiratory pressure
MIP	Maximum inspiratory pressure
MMT	Manual muscle testing
MRC-score	Medical Research Council score
$PaO_2/FioP_2$ ratio	Partial pressure of arterial oxygen to fraction of inspired oxygen ratio
PEEP	Positive end expiratory pressure
RASS	Richmond Agitation-Sedation Scale
RR	Respiratory rate

RSBI	Rapid shallow breathing index
SBT	Spontaneous breathing trial
SIRS	Systemic Inflammatory Response Syndrome
SpO_2	Peripheral oxygen saturation
TB	Tuberculosis
TwPdi	Trans-diaphragmatic pressure
VAP	Ventilator associated pneumonia
VC	Vital capacity
VIDD	Ventilator induced diaphragmatic dysfunction
VILI	Ventilator induced lung injury
VO_2max	Maximal oxygen uptake
VT	Tidal volume

ETHICAL CLEARANCE CERTIFICATE

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 03/14/2020.

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Faculty of Health Sciences Research Ethics Committee

28/09/2017

Approval Certificate
New Application

Ethics Reference No: 394/2017

Title: Upper limb muscle strength and endurance as predictors of successful extubation in mechanically ventilated patients: A predictive correlational study

Dear Miss Caroline de Beer

The **New Application** as supported by documents specified in your cover letter dated 20/09/2017 for your research received on the 20/09/2017, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 27/09/2017.

Please note the following about your ethics approval:

- Ethics Approval is valid for 2 years
- Please remember to use your protocol number (**394/2017**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:

- The ethics approval is conditional on the receipt of **6 monthly written Progress Reports**, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers; MBChB; MMed (Int); MPharMed,PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 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, Second Edition 2015 (Department of Health).

☎ 012 356 3084 deepeka.behari@up.ac.za / fhsethics@up.ac.za http://www.up.ac.za/healthethics
✉ Private Bag X323, Arcadia, 0007 - Tswelopele Building, Level 4, Room 60, Gezina, Pretoria

CHAPTER 1
INTRODUCTION

1.1 Background

Management of the critically ill patient is a complex process and involves a multidisciplinary approach which focuses primarily on life support. Mechanical ventilators temporarily offer essential support during recovery from acute respiratory failure.[1] Weaning off the ventilator and extubation can account for up to 40% of a patient's total time on mechanical ventilation.[2-8] Since the inception of mechanical ventilators, weaning success and extubation failure have been a challenge.[7] Sooner liberation of patients from the ventilator will have positive effects, but premature discontinuation of mechanical ventilation can compromise gas exchange and lead to problems with re-intubation.[8]

Patients are usually extubated after successfully completing the spontaneous breathing trial (SBT). However, 10% to 20% of those patients that complete the SBT successfully still fail extubation.[9-10] Failed extubation is associated with an increase in intensive care unit (ICU) length of stay, hospital length of stay, increased costs and an increase in mortality rate.[11-13] Failed extubation can be due to congestive cardiac failure, upper airway obstruction, neurological impairment, an ineffective cough with airway secretions or respiratory failure.[9] Respiratory failure usually occurs when the load on the diaphragm and accessory respiratory muscles (trapezius, sternocleidomastoid, scalene, pectoralis major muscles) exceed its capacity.[6] The integration of the respiratory, cardiovascular and neuromuscular systems is necessary to achieve maximum oxygen uptake to maintain exercise endurance.

Prolonged mechanical ventilation is detrimental to the human body and is associated with an increase in nosocomial infections, critical illness myopathy or polyneuropathy and respiratory muscle weakness.[1,11] The patient's function and health-related quality of life (HRQOL) is also decreased after prolonged mechanical ventilation.[1] Therefore it is important to determine the earliest time for extubation by assessing the patient's ability to breathe independently, determine their readiness for extubation and their risk for extubation failure.[14]

Several studies have been performed to evaluate parameters predicting successful extubation.[8,11,14,15-17] The conclusion was that, due to the complexity of successful extubation a combination of parameters was necessary to predict extubation success. Studied parameters included the fluid balance, pneumonia, amount of secretions, respiratory rate (RR), heart rate variability, tidal volume (VT), rapid shallow breathing index (RSBI), cough strength, partial pressure of arterial oxygen to fraction of inspired oxygen ratio ($PaO_2/FioP_2$ ratio), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), diaphragmatic dysfunction and handgrip strength.[8,11,14-17] These parameters represent the functional ability of the respiratory and cardiovascular systems. A study conducted by De Jonghe et al.[18] indicated that respiratory muscle weakness is associated with peripheral muscles weakness. Toosizadeh et al.[19] on the other hand concluded that upper extremity strength is associated with pulmonary function (MIP and MEP) and exercise endurance tested with the six-minute walking test (6MWT).

A pilot study by De Beer et al.[20] demonstrated that the muscle strength of the deltoid, sternocleidomastoid and trapezius muscles measured with the Oxford grading scale may possibly be associated with successful extubation.[20] During the same study exercise endurance tested with the MOTOmed® letto2 cycle ergometer indicated a trend of possible association with successful extubation.[20]

A physiotherapist plays an important role in managing the patient's respiratory system as well as musculoskeletal system. Regular evaluation of the muscle strength with the Medical Research Council score (MRC-score) or Oxford grading scale and exercise endurance with the six-minute arm test (6-MAT) will assist the physiotherapist in developing the most suitable patient centred rehabilitation program. Early mobilisation and rehabilitation are essential to decrease the development of intensive care unit acquired weakness (ICU-AW) and respiratory muscle weakness.[21] Physiotherapy exercises and mobilisation improve the muscle strength, range of motion, exercise endurance and functional level of the patient at ICU discharge.[15] The physiotherapist also has unique skills to assess and manage the secretions and lung function of the patient during and after ventilation. It is important that physiotherapists are involved and participate in the decision to extubate,[14] because physiotherapy driven weaning protocols are safe and decrease the weaning time.[22-23]

Keeping in mind the possible associations between the exercise endurance, muscle strength and successful extubation described in the pilot study[20] as well as the conclusion regarding the association between respiratory muscle strength and peripheral muscle strength,[18-19] the researcher asked the question whether physiotherapy can contribute to successful extubation by using upper limb muscle strength and exercise endurance as predictors.

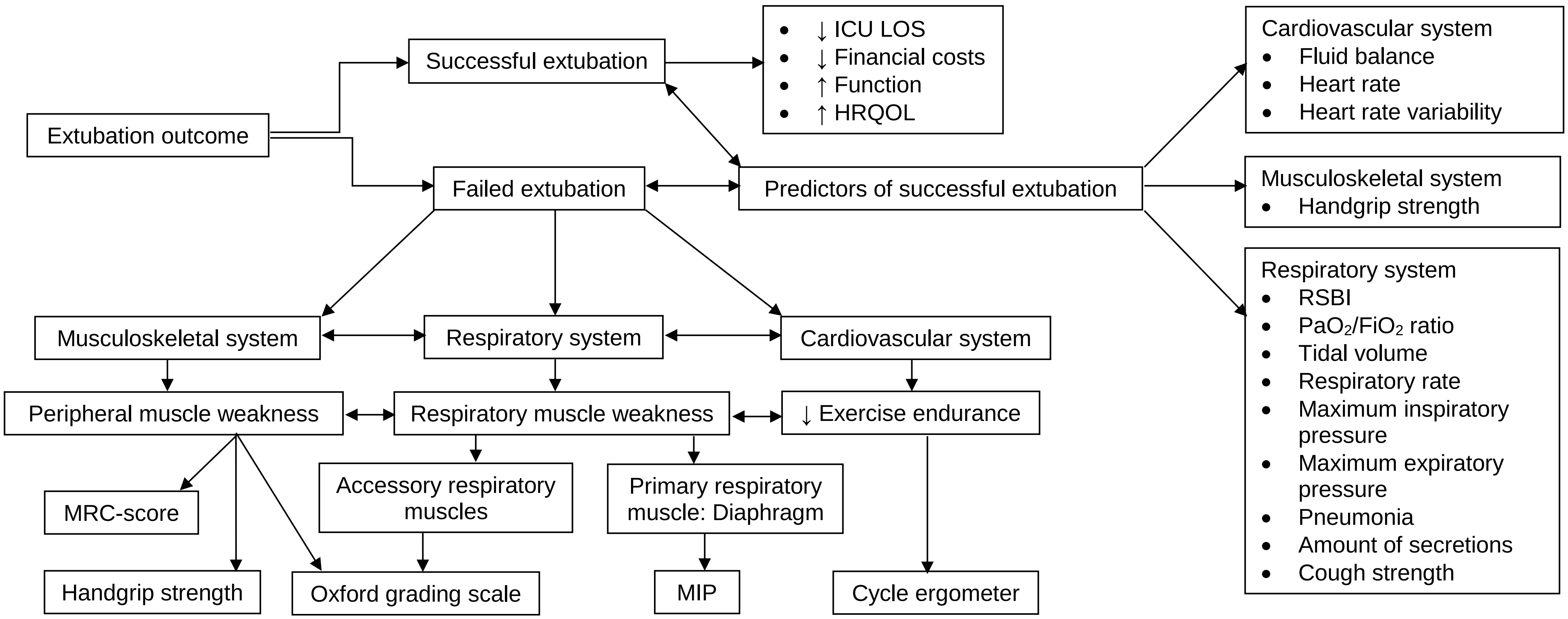
1.2 Problem statement and significance of the study

Effective and successful extubation of patients have several benefits for the patient, the health care team and the institution.[1,5] Successful weaning from mechanical ventilation is a challenge that physiotherapists, nursing staff and physicians are commonly faced with. Since the advent of the first mechanical ventilators, it has been acknowledged that weaning is not always predictable and successful.[7] Due to the complexity of determining extubation readiness, 10% to 20% of patients still fail extubation.[9-10,24-25] Failed extubation increases the ICU length of stay, the hospital length of stay and the financial expenses. Extubation failure is associated with decreased muscle strength, functional ability and HRQOL.[2,6,11]

Successful extubation is of utmost importance to prevent the detrimental effects caused by failed extubation. Determining the readiness of the patient for extubation is difficult, therefore predictors for successful extubation are paramount.

Several studies have demonstrated that different parameters (heart rate variability, RSBI, PaO_2/FiO_2 ratio, handgrip strength, VT, RR, MIP and MEP)[8,11,14] were used to predict extubation readiness. These studied parameters assess the functional ability of the cardiovascular and respiratory systems. Previous research studies concluded that extubation failure is due to a decrease in the pulmonary function which is not only correlating with respiratory muscle weakness but also with peripheral muscle weakness.[9,18-19] The lack of oxygen transport, ventilation limitation, fatigue and lack of peripheral muscle strength may be related to the decrease in exercise endurance in the body.[19]

With the literature in mind that respiratory muscle weakness is associated with peripheral muscle weakness which are related to decrease endurance, the researcher asked the question whether upper limb muscle strength and exercise endurance can predict successful extubation. The researcher could not find any literature other than the results of a pilot study conducted by De Beer et al.,[20] indicating a possible association between muscle strength, exercise endurance and successful extubation. Due to the lack of literature in this regard, it was decided to conduct a predictive study by developing a predictive equation to determine whether upper limb muscle strength and exercise endurance could be used as predictors of successful extubation in mechanically ventilated, critically ill patients. The following conceptual framework (Figure 1.1) has been developed in illustration of the problem statement.



Clinical observation

- Determining successful extubation is a challenge and predictors are paramount.
- 10% - 20% of patients still fail extubation with current predictors.
- Respiratory muscle strength (MIP) used to predict extubation outcome.
- Peripheral muscle strength is associated with respiratory muscle strength.
- Integration of the respiratory, cardiovascular and neuromuscular systems is necessary for attainment of maximum oxygen uptake (Exercise endurance).

Implication

- Respiratory muscle strength indicate extubation outcome and is associated with peripheral muscle strength → peripheral muscles strength might indicate extubation outcome.
- Integration of respiratory and musculoskeletal system indicate exercise endurance → exercise endurance might determine extubation outcome.

Gap in the literature

- Mostly only parameters from the respiratory system and cardiovascular system addressed as extubation predictors.
- Limited research regarding the influence of peripheral muscle strength and exercise endurance on extubation outcome.

Expected outcome

Upper limb muscle strength and exercise endurance can predict successful extubation.

Figure 1.1: Conceptual framework of the study

1.3 Research question

Can upper limb muscle strength and exercise endurance be used as predictors of successful extubation in mechanically ventilated critically ill patients?

1.4 Aim and objectives

1.4.1 Aim

To determine if successful extubation in mechanically ventilated critically ill patients can be predicted by using upper limb muscle strength and exercise endurance.

1.4.2 Primary objectives

1.4.2.1 To determine whether upper limb muscle strength (trapezius, deltoid, sternocleidomastoid and pectoralis major muscles) could predict successful extubation in mechanically ventilated patients who are critically ill.

1.4.2.2 To determine whether exercise endurance could predict successful extubation in mechanically ventilated patients who are critically ill.

1.4.3 Secondary objectives

1.4.3.1 To assess the association between the level of orientation using the Richmond Agitation-Sedation Scale (RASS) and successful extubation.

1.4.3.2 To assess the association between the MIP and successful extubation.

1.4.3.3 To assess the association between the RSBI and successful extubation.

1.4.3.4 To assess the association between the PaO_2/FiO_2 ratio and successful extubation.

1.4.3.5 To assess the association between the number of days ventilated and successful extubation.

1.4.3.6 To assess the association between muscle strength measured with the MRC-score and the exercise endurance measured with the MOTOmed® letto2 cycle ergometer in mechanically ventilated patients who are critically ill.

1.4.3.7 To assess the association between the handgrip strength measured with the handheld dynamometer and the exercise endurance measured with the MOTOmed® letto2 cycle ergometer.

1.5 Assumptions

The research study was only conducted in two ICU's of the Steve Biko Academic Hospital, Pretoria, South Africa. It was a single centre study. The researcher assumed that the nursing staff and medical doctors were performing the screening, SBT and extubation according to the unit protocols.

1.6 Delimitations

The study was only conducted in the Trauma / Surgery and Medical ICU's of the Steve Biko Academic Hospital. The Cardiothoracic ICU was excluded. Recruiting patients from a multicentre would assist with covering a wide spectrum of the critical care setting.

1.7 Terminology

Table 1.1: Concept clarification

Concept	**Description**	**Context of the study**
Failed extubation	Reintubation within 48 hours to 72 hours of extubation.[14]	Need for re-intubation within 48 hours to 72 hours after planned extubation.
Successful extubation	No need for re-intubation within 48 hours after extubation.[17,25]	No need for re-intubation within 48 hours to 72 hours after planned extubation.
Spontaneous breathing trial	Short duration trials to assess the patient's ability to breathe while receiving reduced ventilatory support before extubation.[8,11]	Testing a patient's readiness for extubation for 30 minutes.
Haemodynamic instability	Presence of active myocardial ischemia, vasopressor use or more than 20% decrease in HR, or blood pressure.[17,21]	Any changes of 20% of the baseline of HR, blood pressure or oxygen saturation.
Exercise endurance	An individual's ability to sustain high-intensity exercise for longer than four minutes.[20]	The period of time the patient could cycle independently on the MOTOmed® letto2 cycle ergometer using the upper limbs.
Health-related quality of life	Multidimensional concept that comprises every aspect of life, health and illness.[26]	Patient can function physically, emotionally and mentally independently.
Health care team	Multidisciplinary team consisting of nursing staff, physiotherapist and medical staff.[23]	Team work between the physicians, nursing staff and physiotherapists.
Peripheral muscles	Non-postural muscles with mainly phasic function, which usually contract on demand.[27]	Upper limb and lower limb muscles.
Critically ill	Patient who might experience multi-organ failure while medical treatment aims primarily to stabilize acute life-threatening disease in ICU.[28]	Patient in ICU with multi-organ failure.
Standard physiotherapy	Evidence based protocol care that addresses pulmonary dysfunction and promotes early mobility.[29]	Chest physiotherapy and rehabilitation (including mobilisation and active or passive upper limb and lower limb exercises).

1.8 Outline of thesis

Chapter 2: Literature review

The comprehensive review of current literature available regarding mechanical ventilation, prolonged mechanical ventilation, weaning and extubation failure, anatomy and physiology of the muscles, muscle strength testing and exercise endurance testing in ICU will be discussed in different sections in the next chapter. A critical analysis of available studies will be presented.

Chapter 3: Methodology

The methodology chapter will consist of a description of the research process including ethical considerations, data collection and data capturing. The inclusion and exclusion criteria for recruiting patients will be explained. The process for evaluating muscle strength with the Oxford grading scale, handheld dynamometer, MRC-score and MIP will be discussed. Measuring exercise endurance with the MOTOmed® letto2 cycle ergometer will also be explained.

Chapter 4: Results

The captured data were analysed and will be presented in tables and figures in chapter 4.

Chapter 5: Discussion

The findings of the current study will be discussed and compared with the results of previous studies. Limitations of the study will be discussed.

Chapter 6: Conclusion

The outcomes and clinical importance of the results for assessment of patients' readiness for extubation will be highlighted. Recommendations for future studies will be made.

CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

Physical function has been described as the physical abilities that allow functional independence.30[30] The International Classification of functioning, Disability and Health (ICF) was introduced in 2001 to provide a conceptual framework for describing physical function.[30] The ICF framework describes physical functioning as an interaction between the four basic components and domains including body functions and structures, activities and participation, environmental factors and personal factors. According to a scoping review conducted by Gonzalez-Seguel et al.[30] mobility and muscle function were the most frequent domains present in the physical function measurement tools for the intensive care unit (ICU). Muscle function was referred to as muscle strength and endurance of the peripheral and respiratory muscles.[30] The six-minute walking distance, Medical Research Council score (MRC-score), handgrip dynamometer and maximum inspiratory pressure (MIP) were described as assessment tools to evaluate the mobility, muscle strength and endurance in ICU.

The most recent literature regarding evaluation of upper limb muscle strength and endurance, mechanical ventilation and predictors of successful extubation in ICU was explored and documented in this chapter.

Critically ill patients in the ICU are monitored continuously to identify general wellness, any physiological changes or metabolic changes. These changes can cause organ dysfunction and can be life threatening. During the ICU stay, the patients' cardiovascular, respiratory, gastro-intestinal, urinary tract, central nervous and musculoskeletal systems are affected.

Care of critically ill patients in ICU includes mechanical ventilation to temporarily replace and support spontaneous breathing.[1] Prolonged mechanical ventilation is detrimental to the human body and can lead to respiratory and peripheral muscle weakness, decreased functional capacity and the development of nosocomial infections.[1,6,11] It is therefore important to wean a patient on mechanical ventilation as soon as possible since it can be a time-consuming process.[2] The weaning process commences immediately after a patient has been resuscitated and is haemodynamically stable. Although the aim of the medical team is to extubate a patient as soon as possible, a too aggressive weaning process and extubation, may lead to failed extubation.[11,23]

Failed extubation has been associated with increased hospital length of stay, ICU length of stay, financial expenditures and mortality rate.[6,9,11] Increased length of ICU stay causes the development of ICU-acquired weakness (ICU-AW).[4] A decrease in muscle strength and functional capacity leads to prolonged mechanical ventilation, extubation failure and prolonged rehabilitation.[1,11,31] ICU-AW affects the patient's functional status and health-related quality of life (HRQOL) for months and years after hospital discharge.[21] Early mobilisation and rehabilitation by the physiotherapist is essential to decrease the development of ICU-AW. Physiotherapy exercises and mobilisation improve the muscle strength, range of motion, exercise endurance and functional level of the patient at ICU discharge.[18,21] Due to the physiotherapist's unique skills to assess and manage the secretions and lung function of the patient during and after ventilation, it is important that they are involved and participate in the decision to extubate.[14]

Successful extubation is a very complex process. A variety of predictors, including rapid shallow breathing index (RSBI), MIP and heart rate variability had been tested to determine successful extubation.[8,11,15] None of these parameters could be singled out as a successful predictor of extubation.[17] Patients are usually extubated if the medical condition precipitating intubation is reversed or significantly improved, the patient is haemodynamically stable and the spontaneous breathing trial (SBT) is successful.[20] Although patients with the aforementioned prerequisites may demonstrate a successful SBT, some still fail extubation.[9] Successful extubation will decrease the physical rehabilitation time, ICU length of stay, hospital length of stay and will increase the patient's functional capacity and HRQOL. With this in mind the researcher reflected about how current physiotherapy treatment techniques could contribute to predicting successful extubation. The results of a pilot study conducted by De Beer et al.[20] demonstrated possible associations between successful extubation, exercise endurance and upper limb muscle strength respectively, suggesting a possible utility in this domain. De Beer et al.[20] concluded that incorporating muscle strength and endurance testing into weaning protocols and physiotherapy rehabilitation programmes might lead to greater extubation success.

Previous research studies have demonstrated an association between peripheral muscle strength and respiratory muscle strength.[18-19] With the available literature in mind - of a possible association between successful extubation, exercise endurance and upper limb muscles strength[20] as well as the association between peripheral muscle strength and respiratory muscle strength[18-19] - the research question was asked whether upper limb muscle strength and exercise endurance can be used as predictors of successful extubation in mechanically ventilated patients.

2.2 The literature search methodology

A scoping literature review[32] was conducted to identify the gap in the literature with regards to the research question whether upper limb muscle strength and exercise endurance can be used as predictors of successful extubation in mechanically ventilated patients. In order to identify gaps in the literature, the literature review aimed to address the following questions:

- For mechanically ventilated critically ill patients, what are the factors causing weaning and extubation failure during their ICU stay?
- Does prolonged mechanical ventilation influence extubation outcome in critically ill ventilated patients?

- For critically ill patients that are ventilated, how is successful extubation predicted during their ICU stay?
- Does prolonged mechanical ventilation and extubation failure influence respiratory muscle strength in critically ill patients?
- Does prolonged mechanical ventilation and extubation failure influence upper limb muscle strength in critically ill patients?
- Does prolonged mechanical ventilation and extubation failure influence exercise endurance in critically ill patients?
- For critically ill patients that are ventilated, how is respiratory muscle strength being evaluated?
- For critically ill patients that are ventilated, how is upper limb muscle strength being evaluated?
- For critically ill patients that are ventilated, how is exercise endurance being evaluated?

Search process for relevant studies

The researcher performed individual search strategies for the following databases: PubMed, OVID SP Medline, Cochrane Library and Cumulative Index to Nursing and Allied Health (CINAHL). The following keywords were used: mechanical ventilation, prolonged mechanical ventilation, intensive care unit, extubation failure, weaning from mechanical ventilation, muscle strength, exercise endurance, measuring muscle strength, measuring endurance, handgrip dynamometer, Medical Research Council score, cycle ergometer. Keywords were separated and combined by the words "AND" and "OR" during the literature review. Due to limited literature available and to determine the changes in practice over time, the researcher continued with the literature search until February 2018. The researcher also did manual tracking of articles from the reference lists.

Inclusion criteria and study selection

Studies that complied with the inclusion criteria as described in the next paragraph were included in the study analysis.

Quantitative studies (systematic reviews with meta-analysis, randomised control trials, cohort and cross-sectional studies) in full text articles, theses, dissertations and protocols were reviewed for inclusion. Trials with participants of any gender and race, older than 18 years and mechanically ventilated were included. Studies explaining the evaluation, intervention or outcome measures to determine the association between predictors of successful extubation, upper limb muscle strength, exercise endurance, mechanical ventilation, weaning and failed extubation were included. Filters applied during our study included English language and published dates from 1990 until February 2018.

Extraction of data

The data extraction process is explained in Figure 2.1.

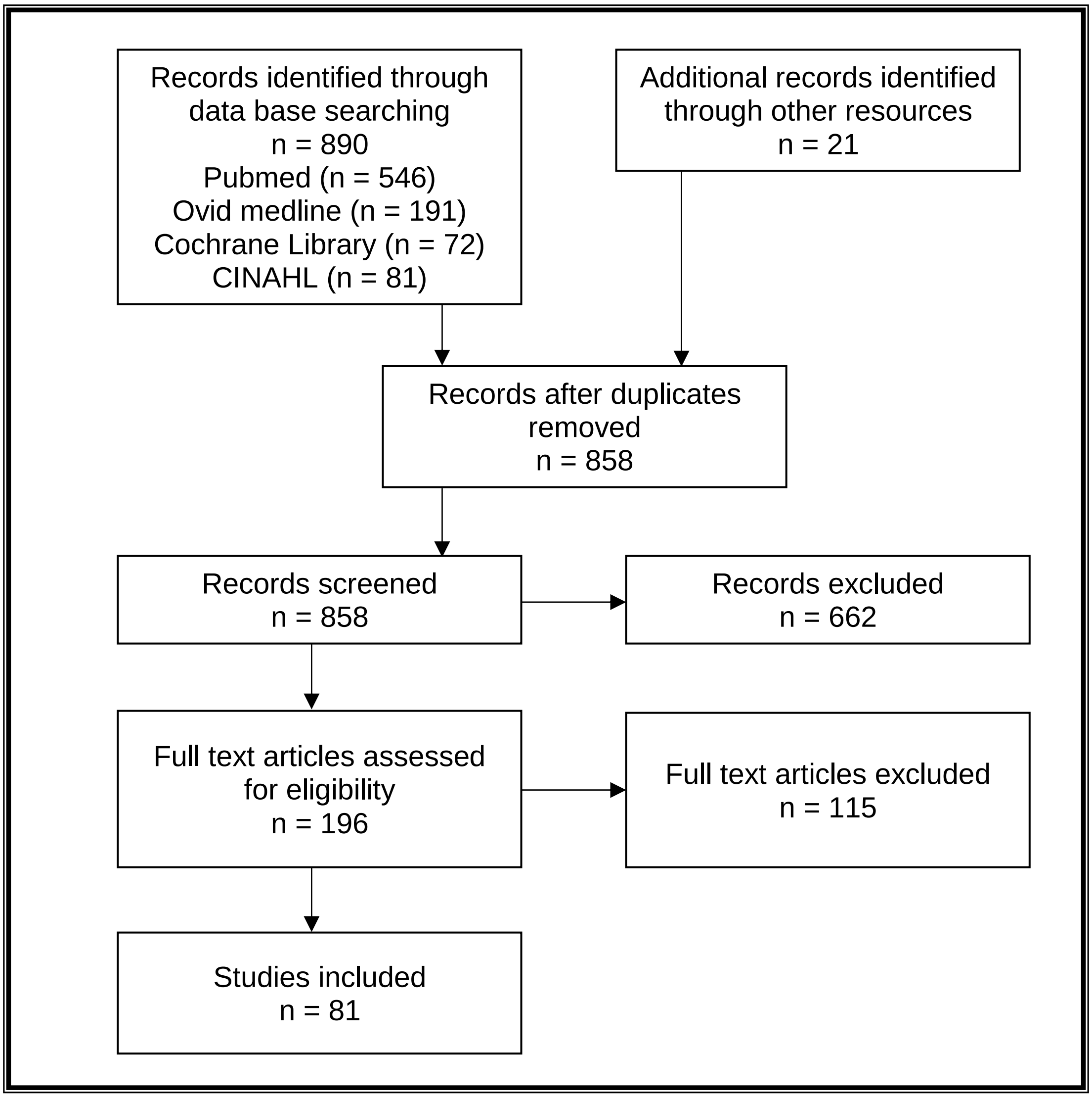


Figure 2.1: Flow diagram explaining the data extraction process

Analysis of the included literature are summarised in the tables attached in Appendix 1.

In order to address the research questions, the literature survey was conducted by dividing the literature under the following headings: mechanical ventilation, prolonged mechanical ventilation, weaning from mechanical ventilation and extubation failure, predictors of successful extubation, respiratory muscle strength, peripheral muscle strength, muscle testing, exercise endurance and electrolytes.

2.3 Mechanical ventilation

Mechanical ventilation dates back to 1664 when Robert Hooke applied the first mechanical ventilation to a dog.[33] He ventilated a dog via a tracheostomy using a pair of bellows.[33] In the mid-eighteenth century, mechanical ventilation of humans came into vogue.[33] Roberson et al.[34] described mechanical ventilation as the process of exchanging oxygen and carbon dioxide using a device. Mechanical ventilation temporarily replaces and or supports breathing in the critically ill patient.[1] It reduces the work of breathing and diaphragm activity.[24] Whilst mechanical ventilation can save a patient's life in ICU, it is also associated with numerous complications such as diaphragm weakness[35], ventilator-associated pneumonia (VAP), veno-thrombotic events, pressure ulcerations, gastritis and increased length of stay.[36-37] Different modes of ventilation (controlled ventilation, intermittent mandatory ventilation, and positive pressure ventilation) were developed during the centuries.[2] Intermittent mandatory ventilation is usually delivered in a synchronized manner with demand-valve circuitry.[2] However it increases the work of breathing and may contribute to the development of respiratory muscle fatigue.[2] Pressure support ventilation was developed in the 1980's.[2] It is commonly used to counteract the work of breathing imposed by endotracheal tubes and ventilator circuits.[2]

In 2004 a prospective international observational study conducted by Esteban et al.[38] investigated and compared the different modes of ventilation and ventilation strategies from a cohort study done in 1998. According to Esteban et al.[38] the use of non-invasive ventilation for acute respiratory failure and chronic obstructive pulmonary disease (COPD) patients were significantly higher in 2004 than in 1998. The researchers also found that patients with acute respiratory distress syndrome (ARDS) were ventilated with lower tidal volumes and inspiratory pressures.[38] Esteban et al.[38] mentioned that using SBTs with pressure support to evaluate extubation readiness increased from 1998 to 2004.[38] The findings by Esteban et al.[38] were supported in a review done by Jaber et al.[36] in 2011. Jaber et al.[36] supported the findings that controlled mechanical ventilation was associated with adverse effects on the diaphragmatic structure and function. A direct correlation was also made between the magnitude of diaphragmatic weakness and duration of mechanical ventilation.[36] Due to their results Jaber et al.[36] encouraged low levels of pressure support ventilation.

2.4 Prolonged mechanical ventilation

Although mechanical ventilation is necessary in the care of critically ill patients to temporarily replace and or support spontaneous breathing, prolonged mechanical ventilation is detrimental for the human body.[1] Prolonged mechanical ventilation has been defined by Chang et al.[24] as the need for mechanical ventilation for more than 48 hours. It is associated with the development of respiratory muscle weakness,[24] nosocomial infections and critical illness myopathy or polyneuropathy.[1] Prolonged mechanical ventilation is also associated with an increase in financial expenditures.[11] It also increases the ICU length of stay, hospital length of stay and mortality rate.[11]

Mechanical ventilation causes the development of symptoms such as pain, anxiety and sleep deprivation.[39] Unmanaged anxiety increases the work of breathing, fatigue and it causes prolonged weaning.[39] The anxious, depressed patient is demotivated to participate in rehabilitation. Rehabilitation of patients is important to prevent the decrease in functional status and HRQOL that is caused by prolonged mechanical ventilation.[1] Increased length of ICU stay is associated with the development of VAP[11], deep vein thrombosis, blood stream infections, gastrointestinal bleedings and ICU-AW.40[40] It has been demonstrated that ICU-AW is an independent predictor of prolonged mechanical ventilation.[41] Respiratory as well as peripheral muscle strength decrease after one week of mechanical ventilation.[41] A decrease in respiratory muscle strength was confirmed by Chang et al.[24] in a prospective study comprising of 20 subjects. They also reported that respiratory muscle endurance is reduced with longer periods of mechanical ventilation.[24]

2.5 Weaning from mechanical ventilation and extubation failure

There are different interpretations and definitions of the process of ventilator discontinuation / weaning.[7] A study by Porta et al.[42] in 2005 indicated that patients were considered successfully weaned when they are spontaneously breathing for more than 48 hours and none of the following are present: respiratory rate (RR) more than 35 breaths per minute, heart rate (HR) more than 145 beats per minute, major arrhythmias requiring intravenous drug therapy, systolic blood pressure (BP) more than 180 mmHg and anxiety or agitation.[42]

In their study Frutos-Vivar et al.[43] added the following as readiness-to-wean criteria: improvement in the condition that led to acute respiratory failure, alert and able to communicate, temperature < 38°C, no use of vasoactive drugs, PaO_2 > 60 mmHg, FiO_2 < 40% and positive end expiratory pressure (PEEP) ≤ 5 cmH_2O. In a multicentre, prospective study conducted by Peñuelas et al.[5] they also used the same parameters mentioned by Frutos-Vivar et al.[43] as standard criteria for weaning readiness. Peñuelas et al.[5] however added the partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2 ratio) > 200. Thille et al.[10] described the same weaning criteria mentioned by Frutos-Vivar et al.[43] and Peñuelas et al.[5] in their current review. Dos Santos Bien et al.[15] agreed with all the above mentioned researchers regarding the criteria for readiness to wean from mechanical ventilation.

Magalhães et al.[35] and Baptistella et al.[25] defined weaning as the gradual liberation from mechanical ventilation to spontaneous breathing, allowing the patient to breath without mechanical support. Consensus groups agree about the use of the term “weaning” to describe the process of ventilator discontinuation.[1,5]

Since the development of mechanical ventilation, weaning success and extubation failure has been a challenge.[7] The duration of weaning from mechanical ventilation comprises 40% of the patient’s stay in ICU.[2-5,7-8] The weaning process can be divided into three categories, simple, difficult and prolonged weaning.[5,9,44] Simple weaning includes patients who are extubated on the day of their first attempt of withdrawal from mechanical ventilation.[5,9-10,35,44] The difficult to wean patients are extubated within seven days of their first attempt of withdrawal.[5,9-10,35] The prolonged weaning patients are only extubated after seven days of their first withdrawal attempt.[5,9-10,35,44] Esteban et al.[2] reported in 1993 that patients weaned with daily SBTs have higher successful extubation rates than patients ventilated with intermittent mandatory ventilation or pressure support ventilation. According to Esteban et al.[2] the possible development of respiratory muscle fatigue during intermittent mandatory ventilation and the increase pressure to counteract the work of breathing imposed by the ventilator circuits might contribute to a decrease in the successful extubation rate. Factors such as sepsis, using corticosteroids, phrenic nerve injuries or critical illness polyneuropathy or myopathy contribute to weaning failure.[35]

Another important aspect of weaning is the decision as to when to initiate the weaning process. This is important because premature weaning can lead to aspiration, defective gas exchange, and losing the airway.[8] In contrast, delayed weaning is associated with developing complications such as VAP, ventilator induced lung injury (VILI) and ventilator induced diaphragmatic dysfunction (VIDD).[8] Weaning failure was defined by Frutos-Vivar et al.[43] as either the failure of an SBT or as the failure of extubation after a successful SBT. Frutos-Vivar et al.[43] reported that delayed weaning and premature extubation from mechanical ventilation were associated with an increase in mortality. This was supported by Peñuelas et al.[5] that patients with prolonged weaning demonstrated a higher mortality rate than patients who underwent simple weaning. Peñuelas et al.[5] added that duration of mechanical ventilation before the first weaning attempt was also associated with the weaning outcome.

Several research studies have been conducted on weaning failure. According to Carlucci et al.[3] approximately 15% of patients fail the first attempt of weaning. They found that repeated weaning failure was associated with an imbalance between the increased load on the respiratory system and the reduced capacity of the respiratory muscles and cardiovascular system.[3,45] A review by Doorduin et al.[46] concluded that weaning failure is largely due to an imbalance between the patient's ventilator needs and the respiratory capacity that is available. They are of the opinion that changing from positive inspiratory pressure during mechanical ventilation to negative airway pressure during spontaneous breathing is challenging for the patient's cardiac and respiratory physiological reserves.[46] Doorduin et al.[46] highlighted that weaning failure can be caused by cardiac dysfunction, cognitive dysfunction, endocrine and metabolic disorders, iatrogenic factors, impaired respiratory mechanics and respiratory muscle dysfunction. Martin et al.[45] conducted a single centre, single blind randomised control trial during which they evaluated the effect of inspiratory muscle training on 69 of the 129 recruited patients. They found that inspiratory muscle training increased the respiratory muscle strength by measuring MIP.[45] Martin et al.[45] also reported that respiratory muscle weakness was a greater contributor to weaning failure than respiratory fatigue.[45]

During a prospective observational study conducted by De Jonghe et al.[18] it was demonstrated that respiratory muscle as well as peripheral muscle weakness were associated with weaning failure in critically ill patients. In this multicentre study 324 patients were recruited from the medical and trauma ICU's in university hospitals.[18] Peripheral muscle strength was evaluated with the MRC-score and respiratory muscle strength was evaluated with the MIP, maximum expiratory pressure (MEP) and vital capacity (VC) when the patients were awake and orientated.[18] A patient was defined as awake if they scored 3/5 for the Five Point Questionnaire.[18] A total of 116 patients' data were evaluated during the study. The median (interquartile range) MRC-score, MIP, MEP and VC obtained were 41/60, 30 cmH_2O, 30 cmH_2O and 11.1 ml/kg respectively. The results demonstrated a significant correlation between MRC-score and MIP (*rho = 0.35*), MEP (*rho = 0.49*) and VC (*rho = 0.31*) respectively.[18] Univariate and multivariate analyses of the study demonstrated that low MIP, MEP and MRC-scores were independent predictors of delayed successful extubation.[18]

Patients are usually extubated after successful completion of the SBT, but 10% to 20% of these patients still fail extubation.[9-10,24-25] Failed extubation is defined as the need for re-intubation within 48 hours to 72 hours after planned extubation.[8-9,24,44] The time interval in the definition is not generally agreed upon and varies from hours to a week.[9] Extubation failure is mainly due to primary or secondary respiratory failure. Secondary respiratory failure can be due to upper airway obstruction after extubation, congestive cardiac failure, inability to clear airway secretions, haemodynamic instability and altered mental status.[13,44]

Risk factors for extubation failure include neurological disorders, abundant secretions, a weak cough, respiratory or cardiac diseases, delirium, inappropriately excessive positive fluid balance and patients older than 65 years of age.[9-10,12-13,24] A new onset of sepsis or surgical complications can also contribute to reintubation.[9] According to Thille et al.[9] reintubation is associated with developing a VAP and therefore leads to clinical deterioration of the patient. During a recent prospective observational study conducted by Piriyapatsom et al.[13], they found that patients with acute kidney injury, and lower oxygen saturation levels 24 hours prior to extubation were more prone to extubation failure.[13] Elevated blood urea nitrogen (BUN) levels, muscle weakness (< grade 3) and low haemoglobin levels were identified as independent predictors of re-intubation in the surgery ICU.[13] Reintubation usually has been found to be more common when patients meet at least one of the following criteria: decreased mental status, oxygen saturation (SpO_2) < 85%, despite the use of a high fraction of inspired oxygen, lack of improvement in signs of respiratory muscle fatigue, hypotension, systolic BP < 90 mmHg for > 30 min despite adequate volume loading and or use of vasopressors.[12,24] Extubation failure is associated with poor outcomes including an increase in the ICU length of stay and the mortality rate.[12-13] The mortality rate of patients who failed extubation is between 25% to 50%.[9-10] Prediction of successful weaning and extubation is therefore of utmost importance to avoid prolonged mechanical ventilation and to decrease the mortality rate.

2.6 Predictors of successful extubation

Weaning predictors are defined as parameters that are intended to help clinicians predict whether weaning attempts will be successful or not.[8] Baptistella et al.[25] described successful weaning as the passing of an SBT and successful extubation as completion of the SBT and no need for reintubation within 48 hours. The SBT is regarded as the gold standard to predict successful extubation world-wide for many years, although it has inherent limitations.[10,4747] The SBT is a safe, well-tolerated and easy to perform test.[16,43] It can be performed with a T-piece or ventilator with low-levels of pressure support.[7-10,35,48] A retrospective study done by Huang and Yu[16] at the National Taiwan University Hospital showed that the mode of SBT (T-piece or low levels of pressure support) did not have an effect on the extubation outcome. It is recommended that the SBT should be conducted for at least 30 minutes, but not longer than 120 minutes in adult patients.[7-8,11]

Cappati et al.[47] performed an observational, prospective, multicentre study to determine the interobserver agreement of the SBT between physicians and respiratory therapists. They determined a failed SBT when one of the following criteria was persistently present: RR > 35 b/min, SpO_2 < 88%, HR > 140 b/min, acute arrhythmia, systolic BP < 90 mmHg, facial signs of distress, increased accessory muscle activity, intense agitation or depressed level of consciousness.[47] The results of the study done by Cappati et al.[47] also demonstrated a moderate interobserver agreement for SBTs (*kappa* = 0.46 for physicians and *kappa* = 0.57 for respiratory therapists).[47] Different extubation decisions may be made depending on the therapist or physician observing the SBT.

Currently the challenge is that 10% to 20% of patients who successfully completed the SBT, still fail extubation.[43] The ability to predict extubation with certainty still eludes us. Over the years several predictors including RSBI, fluid balance, pneumonia, amount of secretions, cough strength, age, RR, MIP, MEP, VC, PaO_2/FiO_2 ratio and tidal volume (VT) have been investigated to determine successful extubation, but none in isolation can predict successful extubation and demonstrated high accuracy.[11,16-17] Evidently different researchers observed different findings and opinions regarding the successful prediction of extubation.

Frutos-Vivar et al.[43] conducted a multicentre international observational cohort study to assess prospective variables associated with reintubation. They recruited a heterogeneous group of 980 patients from 37 hospitals in eight countries from November 1999 till May 2002. The patients were screened daily for extubation readiness. The extubated patients were followed up for 24 hours to 48 hours post extubation.[43] According to Frutos-Vivar et al.[43] there were three variables that were associated with reintubation within 72 hours of extubation after successful completion of the SBT. These variables included a RSBI > 57 breaths/min/L, a positive fluid balance within 24 hours prior to extubation and pneumonia being the primary reason for initial intubation.[43] Frutos-Vivar et al.[43] also found that older patients were more prone to reintubation. The RSBI was described as an independent predictor for extubation failure by Frutos-Vivar et al.[43] (cited by Upadya et al.), however they found a RSBI value of > 100 breaths/min/L to be predictive of successful extubation.[43]

In the Frutos-Vivar et al.[43] cohort no echocardiographic monitoring was performed to ascertain whether the positive fluid balance was attributed to cardiac dysfunction. Cough strength, amount of secretions, level of consciousness and patient cooperation were not associated with extubation outcome in the cohort of Frutos-Vivar et al.[43] Contrary to the Frutos-Vivar et al.[43] findings, a prospective observational cohort study conducted by Mokhlesi et al.[48] showed with the use of a multivariable logistic regression model that moderate or copious amount of secretions (need for suctioning every 1-2 hours), a Glasgow Coma Scale (GCS) < 10 and pre-extubation hypercapnia ($PaCO_2$ > 44 mmHg) were independently predictive of extubation failure.

Huang and Yu[16] conducted a retrospective study recruiting 331 patients and analysed 119 patients' data. Patient's cough strength, breathing rate, minute ventilation, VT, RSBI, MIP, airway secretions, positive fluid balance and GCS were documented. They reported that ineffective coughing demonstrated a negative predictive value of 94%, a positive predictive value of 46% and a sensitivity and specificity of 85% and 71% respectively.[16] Cardiac dysfunction is one of the reasons for weaning failure. Latent left ventricular heart failure may be recognised when preload and or the afterload are increasing during the transition from pressure mechanical ventilation to spontaneous ventilation.[10] Thille et al.[10] suggested that age older than 65 years, an in-effective cough, neurological dysfunction and amount of secretions are factors associated with extubation failure. Extubation failure was demonstrated to be caused by upper airway obstruction in 7% to 20% of patients after extubation due to laryngeal oedema.[10] Failed extubation due to laryngeal oedema was however not associated with a poor prognosis.[10]

Findings in another clinical review conducted by Thille et al.[9] found that cough strength, patients older than 65 years and the amount of secretions are good predictors of extubation failure. They also mentioned that a positive fluid balance prior to extubation and high baseline levels of B-type natriuretic peptides (BNP) were risk factors associated with extubation failure as well.[9] Both reviews conducted by Thille et al.[9-10] were not systematic reviews, but only clinical reviews. Since then Doorduin et al.[46] reported in their clinical review that high BNP levels could diagnose weaning failure with a sensitivity of 76% and a specificity of 78% in mechanically ventilated patients. Doorduin et al.[46] also performed only a clinical review like Thille et al.[9-10] and not a systematic review.

A systematic review and meta-analysis performed by Wang et al.[49] in 2014 concurred with Frutos-Vivar et al.[43] that pneumonia is a predictor of extubation failure. Wang et al.[49] indicated that atelectasis, thick secretions, no intact gag reflex, inability to follow commands, low GCS and longer than 24 hour mechanical ventilation were predictors of extubation failure in neurocritical patients. According to Wang et al.[49], the nine studies included in the meta-analysis indicated that gender, secretion volume, RSBI, minute ventilation, VT, PaO_2/FiO_2 ratio and coughing with suctioning were not important as extubation predictors in neurocritical patients.

An observational multicentre cohort study conducted by Seely et al.[11] found that heart rate variability and respiratory rate variability are significantly associated with extubation failure. The researchers recruited 721 patients, but after exclusions only 434 results were analysed. During the study carbon dioxide monitors were attached to the ventilator circuits of recruited patients.[11] The carbon dioxide and electrocardiogram readings were documented 30 minutes prior, during and 30 minutes after the SBT.[11] Seely et al.[11] concluded in the study that failed extubation is due to the inability of the cardiorespiratory system to tolerate the increased workload. Seely et al.[11] also supported the findings by Frutos-Vivar et al.[43] that positive fluid balance, a history of pneumonia and elevated RSBI were factors independently increasing the risk of extubation failure.

The findings by Frutos-Vivar et al.[43] and Seely et al.[11] were also supported by Liu et al.[17] in 2015 after they conducted a prospective, validation cohort study in 10 Chinese ICU's to validate the modified three-factor model. Liu et al.[17] reported that a three-factor model consisting of RSBI measurement, occlusion airway pressure measurement, mental status, cough strength and secretions could predict extubation. The results demonstrated that the three-factor modified model has a sensitivity of 93.4%, specificity of 80.3% and diagnostic accuracy of 91.1%.[17] During the study, patients performed an SBT for 60 minutes.[17] The RSBI was calculated at one minute of SBT, 30 minutes of SBT and 60 minutes of SBT. The product of the airway occlusion pressure and RSBI were also calculated at the same intervals.[17] When the patient passed the SBT, the patient was extubated if they had an adequate mental status, ability to cough and expectorate secretions. The modified three-factor model outperformed the use of single predictors alone to predict extubation success.[17]

World-wide the RSBI and MIP are used as predictors of successful weaning and extubation, but their predictive accuracy has not been investigated.[15] Dos Santos Bien et al.[15] demonstrated in a prospective, cross-sectional study that the RSBI and MIP were good predictors of weaning success, but the MIP had greater accuracy than the RSBI. During the study the MIP was evaluated while the patient was on pressure support ventilation.[15] The RSBI was calculated when the SBT was conducted for 30 minutes.[15] Over a two year period, 195 patients were recruited from the adult ICU. The successfully extubated patients showed a higher mean GCS and MIP and a lower mean RSBI, duration of ventilation and APACHE score.[15] The results demonstrated that the MIP had a greater sensitivity (*0.93*) and specificity (*0.95*) than the RSBI (*0.84; 0.91*) respectively. The results also demonstrated no difference in the PaO_2/FiO_2 ratio between the successfully and unsuccessfully extubated patients.[15]

The results from a prospective observational study conducted by Thille et al.[12] in 2015 supported previous results from studies conducted by Mokhlesi et al.[48], Huang and Yu[16] and Thille et al.[9-10] with regards to predictors of successful extubation. In the most recent study, Thille et al.[12] concluded that an ineffective cough, severe systolic left ventricular dysfunction and mechanical ventilation for more than seven days were strong predictors of extubation failure. During this study, 225 patients were included and evaluated for muscle strength of the four limbs, cough strength, amount of secretions and cardiac function.[12] The results showed that extubation failure exceeded 30% in patients with ICU-AW, ineffective cough and severe systolic left ventricular dysfunction.[12] The patients with an ineffective cough had a lower MRC-score than those with an effective cough.[12] The researchers indicated that according to their results, cough strength was a stronger predictor than peripheral muscle strength.[12] Due to these results, Thille et al.[12] recommended that extubation in patients with strong coughs, should not be delayed due to weakness in the limbs.[12]

A retrospective, observational study conducted by Lai et al.[50] in 2016 also identified that age, gender, disease severity, GCS, RSBI, MIP, MEP and a cuff leak test were associated with extubation failure. During the study 6 583 patients were included in the analysis and 6.1% failed extubation.[50] The results demonstrated that a cuff leak test = 2+, MEP > 55 cmH_2O and RSBI < 68 breaths/min/ml were independent predictors of successful extubation.[50] The three predictors represented upper airway patency, cough strength and respiratory capability.[50]

Zein et al.[8] conducted an educational review on ventilator weaning and SBTs in 2016 and stated that all possible predictors were indicators of the breathing and respiratory function of the patients. During their discussion, Zein et al.[8] were of the opinion that heart rate variability, sleep quality, handgrip strength, diaphragmatic dysfunction and oxidative stress markers were weaning predictors. A systematic review conducted by Baptistella et al.[25] in 2018 identified the RSBI, MIP, age, RR, number of days ventilated, VT, cough strength and PaO_2/FiO_2 ratio as some of the 56 predictors of successful extubation. During the review of 43 articles, the RSBI was the most studied and relied parameter to determine successful extubation.[25]

A clinical review done by Magalhães et al.[35] also investigated the RSBI and MIP as predictors of successful extubation. They investigated different predictors including the RSBI, MIP, measurement of diaphragm function, airway occlusion pressure, Tension-time index of the diaphragm and compliance / rate / oxygenation / pressure (CROP) index.[35] The RSBI is a physiological index and an accurate predictor (RSBI < 105) to predict extubation success. According to Magalhães et al.[35] MIP is described as the maximal negative pressure generated for at least one second during a maximal inspiratory effort from residual volume during a forced inspiratory manoeuvre against a closed airway. A MIP measurement > -30 cmH_2O has a high sensitivity (97%), but low specificity (64%) in predicting successful weaning.[35] Despite extensive research in the domain of weaning from mechanical ventilation, weaning is a complex process and the ability to predict its success with certainty remains poor. Unfortunately, none of the predictors can be used in isolation and even combined their overall predictive accuracy remains unacceptably low. Depending on the clinical scenario, clinicians and therapists often choose specific predictive tools to try and improve the ability to predict the success of extubation.

2.7 Respiratory muscles

Successful extubation can be determined by the strength and function of the respiratory muscles.[1,4] Breathing is an essential life-sustaining activity and requires the contraction of the respiratory muscles.[51] It is coordinated by the respiratory motor control system consisting of the brain, brainstem, spinal cord and peripheral nerves.[51] Respiratory muscles are skeletal muscles contracting during inspiration and expiration.[51] Expiration is a passive process.[51] Respiratory muscles are classified as the inspiratory muscles and the accessory muscles. The dome shaped diaphragm is the most important muscle for inspiration.[51-52] Grosu et al.[53] described the diaphragm as a three layered structure superficial to the liver. The three layers consist of a muscular layer, diaphragmatic peritoneum and the diaphragmatic pleura. The muscular layer consist of slow twitch and fast twitch muscle fibres.[53] During inspiration the muscle fibres shorten, causing an increase in the thoracic cavity and displacement of the abdominal contents.[51] The diaphragm is innervated by the phrenic nerves which arise from the cervical spinal nerve roots C3-C5.[51]

The sternocleidomastoid and upper fibres of trapezius muscles are part of the accessory inspiratory muscles. The accessory muscles contract when the ventilator demands are higher than normal.[51] Bilateral sternocleidomastoid muscles assist during forced breathing to elevate the ribs.[54] The trapezius muscle is part of the extrinsic muscles of the posterior thorax which assist with stabilisation of the scapula to the thorax.[54] The trapezius muscle also assists in stabilising the neck for the sternocleidomastoid muscle to function optimally during stressful respiration.[54] The sternocleidomastoid and trapezius muscles are innervated by the spinal accessory nerve (Cranial Nerve XI) and spinal roots of the cervical spinal nerves (C2-C4).[51]

Terson de Paleville et al.[51] explained in their literature review, that the electromyography (EMG) activity of the sternocleidomastoid muscle showed a strong linear correlation with the MIP ($R^2 = 0.97$) and trapezius a nonlinear correlation ($R^2 = 0.50$) (cited Yokoba et al).[51]

The pectoralis major and latissimus dorsi muscles can contract during forced expiratory tasks.[51] EMG activities of the pectoralis major and latissimus dorsi muscles showed a correlation with the peak expiratory flow.[51] Pectoral muscle atrophy and diaphragm atrophy were present in 29% and 48% of patients respectively after five days of mechanical ventilation.[33] Pectoral muscle atrophy was more prominent in patients treated with steroids whereas diaphragm atrophy was especially seen in patients diagnosed with organ failure and septic shock.[33]

Respiratory muscle weakness with special reference to the diaphragm is described in the literature as the main reason for weaning failure.[1,4,55] A literature review on the multi-causal entity of respiratory muscle dysfunction in critically ill patients by Diaz et al.[6] revealed that factors associated with respiratory muscle dysfunction include age, metabolic status, duration of ventilation, mode of ventilation and nutritional status.[6] They reported that comorbidities and the use of pharmacological treatment including glucocorticoids and neuro-muscular blocking agents were also associated with respiratory muscle dysfunction.[6] Although respiratory muscle dysfunction has a multi-causal origin, proteolysis and or a reduction in protein synthesis is the primary mechanism for respiratory muscle dysfunction and diaphragm atrophy. The diaphragm is the primary respiratory muscle that is affected by mechanical ventilation.[6] Due to the limited mobility of the diaphragm during mechanical ventilation, it promotes the early onset of respiratory muscle dysfunction.[6]

According to Chang et al.[24] respiratory muscle weakness could be due to central or peripheral fatigue of the respiratory muscles. Central fatigue is described as a reduction in the voluntary contraction force due to the reduced central nervous system output.[24] Peripheral fatigue occurs due to injury to the contractile component of the respiratory muscle.[24] Chang et al.[24] concluded that it is not known whether prolonged mechanical ventilation is a cause of inspiratory muscle fatigue or a result, but the presence of inspiratory muscle fatigue may increase the risk of respiratory pump failure.[24] More recently, Schellekens et al.[55] supported Chang et al.[24] by reporting that phrenic nerve neuropathy could cause a reduced force respiratory output. Contractile dysfunction of the respiratory muscles could be due to the loss of muscle mass and or dysfunction of the contractile proteins.[55] Respiratory muscle weakness was caused by an increased load due to elevated elastic and resistive forces of the respiratory system.[55]

Respiratory muscle weakness has been shown to be associated with the development of VAP, increased ICU length of stay and hospital length of stay.[55] VIDD has been described and defined as a loss of diaphragmatic force-generating capacity and diaphragm atrophy specifically related to the use of mechanical ventilation.[1,4,53,55-56] VIDD has been previously diagnosed in several animal studies.[36] Berger et al.[57] reported in a literature review that diaphragmatic dysfunction contributed to difficult weaning or even weaning failure. VIDD is mostly observed after periods of controlled mechanical ventilation.[57] Assisted ventilation modes reduce the negative effect on the diaphragm.[57] Animal model studies have demonstrated that muscle fibre atrophy and muscle fibre remodelling are the most prominent changes during VIDD.

According to Levine et al.[58] atrophy of the diaphragmatic myofibres of the rat was visible after 18 hours of mechanical ventilation. By performing diaphragmatic muscle biopsies they demonstrated that atrophy of the human diaphragm is present within 18 hours to 69 hours of diaphragmatic inactivity and mechanical ventilation.[58] The slow-twitch as well as fast-twitch fibres were affected.[58]

The findings from the longitudinal observational study conducted by Grosu et al.[53] agree with previous animal studies. Grosu et al.[53] demonstrated that diaphragm atrophy starts within 48 hours after initiation of mechanical ventilation. During the study seven patients were recruited for daily assessment of diaphragm thickness.[53] Patients were evaluated from day one of intubation up until the day of extubation. The diaphragm thickness was evaluated with the M-Turbo ultrasound system in two-dimensional B-mode.[53] Diaphragm thickness was defined as the distance from the middle of the diaphragmatic pleura to the middle of the peritoneal pleura, to the nearest 0.1 mm.[53] The results showed that the diaphragm thickness decreased with an average of 6% per day on mechanical ventilation.[53]

The magnitude of diaphragmatic weakness has been shown to correlate directly with the duration of mechanical ventilation.[36] Hermans et al.[4] found that the trans-diaphragmatic pressure (TwPdi) in patients decreased with the increase in ventilation days. Trans-diaphragmatic pressure monitoring is a non-volitional measure of respiratory muscle strength. A limitation of measuring TwPdi is that the procedure is sophisticated, fairly invasive and requires a patient to be haemodynamically stable.[4,57] Hermans et al.[4] also demonstrated that TwPdi worsened during a control mode of ventilation compared with a pressure support mode of ventilation. Patients on intermittent positive pressure ventilation (IPPV) showed a lesser reduction in TwPdi than with control ventilation.[4] The combination of pressure support ventilation and PEEP may unload the diaphragm during mechanical ventilation and therefore subject it to changes in myofibre length.[1] This can lead to diaphragm atrophy.[1]

Supinski and Callahan[59] reported that a strong relationship is present between the presence of an infection and diaphragm weakness. They evaluated the TwPdi in response to bilateral anterior magnetic stimulation of the phrenic nerve in 57 patients in the medical ICU.[59] The median TwPdi for patients with and without infection were 5.5 cmH_20 and 13.0 cmH_2O respectively.[59] Supinski and Callahan[59] also reported that the incidence of death was 49% in patients with a TwPdi lower than 10 cmH_2O.[59] They finally reported that the relationship between diaphragm strength and duration of mechanical ventilation was curvilinear, the duration of mechanical ventilation increased whilst the TwPdi decreased.[59]

Prolonged mechanical ventilation is a contributing factor to a patient's respiratory pump decline.[35] Vassilakopoulos[60] reported in an editorial that controlled mechanical ventilation decreased the diaphragm myofibrillar force generation. This was caused by decreased myosin cross-bridge kinetics and myofibrillar protein levels.[60] Diaphragm weakness could be due to sepsis, multi-organ failure, inflammation, electrolyte disturbances and hyperinflation.[60]

The rapid proteolysis that occurs in peripheral skeletal muscles is also present in the diaphragm. Inspiratory muscle weakness is confirmed with a reduction in MIP.[61] Peripheral muscle weakness is detectable early after ICU admission.[61] The proteolysis of the peripheral muscles as well as the diaphragm, complicate illness and affect recovery. In a prospective observational study conducted by Bissett et al.[61] they discovered that patients with a low MIP score has a low fatigue resistance but there was no significant correlation between the MIP and functional scores. During the study 43 patients were recruited from a single tertiary medical / surgical ICU.[61] The MIP and Fatigue Resistance Index (FRI) were evaluated in combination with the perceived exertion and global function. The results provided by Bissett et al.[61] show that inspiratory muscle endurance is often impaired in ICU patients. Bissett et al.[61] also found that an increase in duration of mechanical ventilation was not associated with lower FRI scores.[61] These results are in stark contrast with Chang et al.[24] who found that FRI is negatively correlated with the duration of ventilation.[61] The difference in results between Chang et al.[24] and Bissett et al.[61] is due to different ventilation modes being used. Chang et al.[24] used predominantly control modes of ventilation and Bissett et al.[61] used pressure support ventilation. Bissett et al.[61] concluded that inspiratory muscle endurance is reduced after mechanical ventilation, but inspiratory muscle weakness is not associated with dysfunction or perceived exertion following successful weaning.

An observational study conducted by Walterspacher et al.[62] evaluated nine patients to assess the acute effects on neural respiratory drive when weaning patients in three different positions. The positions were described as supine (0°), semi-recumbent (30°) and sitting upright (80°).[62] Each position was maintained for 10 minutes with mechanical ventilation and five minutes with spontaneous breathing.[62] At the end of the spontaneous breathing period, the patients' maximal voluntary muscle activation was evaluated while they were performing two maximal ventilation maneuvers.[62] Walterspacher et al.[62] hypothesised that there is no difference in respiratory muscle activity of the diaphragm between sitting and lying supine while breathing spontaneously. The study demonstrated that the diaphragm is the most active respiratory muscle during mechanical ventilation and spontaneous breathing.[62] The sitting position reduced the neural respiratory drive to the diaphragm during spontaneous breathing.[62] This demonstrates that sitting causes a reduction of the load on the respiratory muscles and actively imposes load on the diaphragm to activate the main respiratory muscle during the weaning process.[62] Therefore, sitting is the favoured position when performing an SBT.[62]

An observational study conducted by Dres et al.[63] explored the prevalence and coexistence of limb muscle weakness and respiratory muscle weakness in mechanically ventilated patients. During the study they screened 330 patients and 76 patients were consequently enrolled.[63] After the first SBT, 21% of the patients had ICU-AW and respiratory muscle weakness, 63% had only diaphragm dysfunction and 34% had only ICU-AW.[63] The results demonstrated that diaphragm weakness was associated with difficult weaning, prolonged weaning, increased duration of mechanical ventilation, ICU length of stay, hospital length of stay and mortality. ICU-AW was associated with increased duration of mechanical ventilation and hospital length of stay.[63] The researchers concluded that diaphragm weakness was twofold higher than the prevalence of ICU-AW. They found only a small overlap between diaphragm weakness and ICU-AW.[63]

Supinski et al.[56] also agreed in their review that diaphragm weakness was present twice as often as limb weakness. Results showed that 60% to 80% of mechanically ventilated patients suffered from diaphragm weakness.[56] Diaphragm weakness was associated with prolonged mechanical ventilation and difficult weaning. According to Dres et al.[63] and Supinski et al.[56] weaning success was influenced by diaphragm weakness and not ICU-AW. According to the above literature, respiratory muscle weakness is prevalent in more than 60% of mechanically ventilated patients.[56,63] Increased length of ICU stay, weaning failure and ICU-AW are associated with respiratory muscle weakness. ICU-AW influences respiratory muscle strength as well as peripheral muscle strength.

2.8 Peripheral muscles

The human body consists of three types of muscle tissue, including cardiac, smooth and skeletal muscles. The bony skeleton is covered by the skeletal muscles.[54] These muscle fibres account for 40% of the body mass. They are the longest muscle cells with striations and can be controlled voluntarily.[54] The cardiac muscle tissue covers the heart. These muscle fibres are striated and involuntarily controlled.[54] The smooth muscle fibres are present in the walls of the visceral organs, including the stomach, bladder and respiratory passages.[54] The smooth muscle fibres force the fluids and substances through internal body channels. These fibres are non-striated and under involuntary control.

Muscles consist of several individual muscle fibres. The muscle fibres are constituted of myofibrils (sarcomeres) that are composed of bundles of myofilaments.[54] The myofilaments (contractile unit) are divided into the thin (actin) and thick (myosin) filaments.[54] The myosin filament is divided into the thick tail and the head area. The heads of the filament contain actin, adenosine triphosphate (ATP) binding sites and acetylcholinesterase (ATPase) enzymes. Each muscle fibre with the sarcolemma, sarcoplasm, mitochondria and nuclei is covered by the endomysium (Figure 2.2). The group of fibres (fascicle) is covered by the perimysium.[54]

The whole muscle is covered by the epimysium. All these layers are constituted of connective tissue.[54] These connective tissue sheaths are continuous with one another. If the muscle contracts, the sheaths are also pulling to force the bone to move.[54] The muscles are surrounded by arteries, veins and nerves.

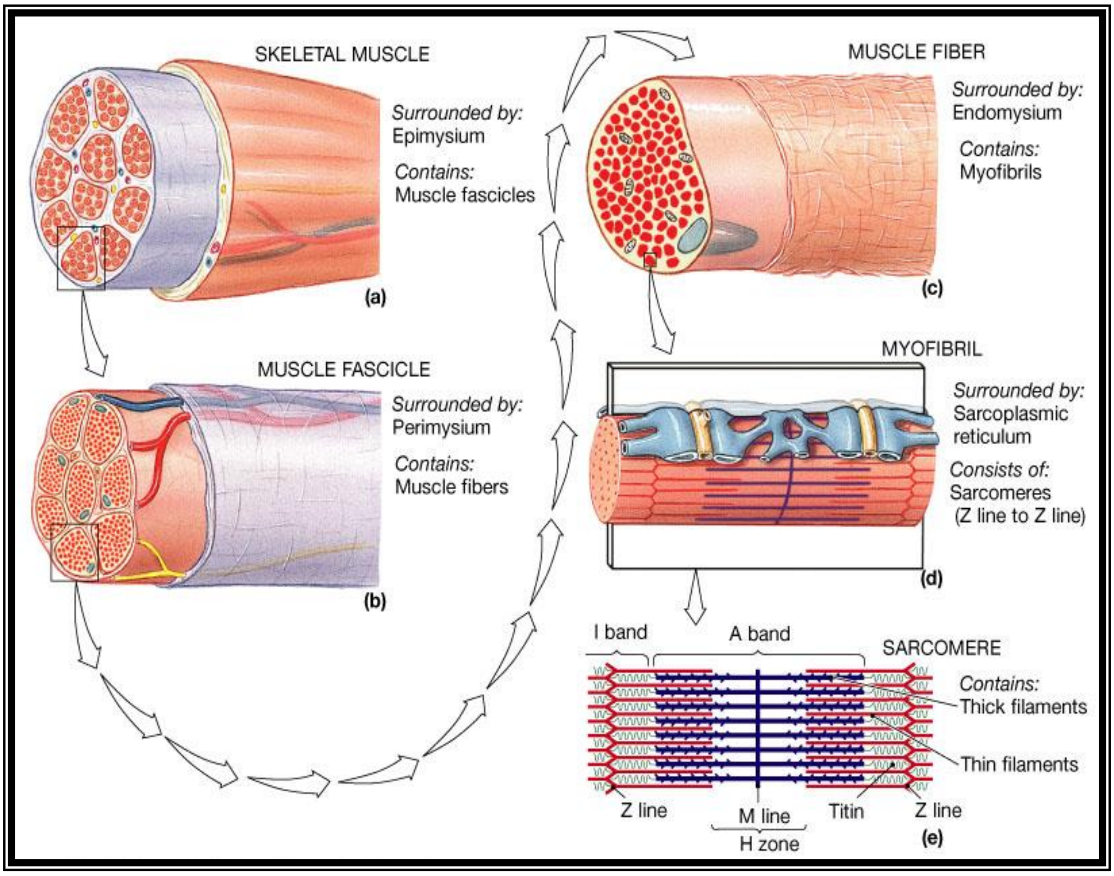


Figure 2.2: Anatomy of skeletal muscle[64]

A muscle contraction was described in 1954 by Hugh Huxley according to the sliding filament theory.[54] The theory states that during a contraction the thin filaments slide past the thick ones and therefore the actin and myosin filaments overlap to a greater degree.[54] The heads of the myosin bind to the thin actin filaments.[54] When the muscle is relaxed, the thin and the thick filaments only overlap slightly.[54] The muscle fibres are stimulated by the nervous system to start with the cross bridge attachment and detachment.[54]

The true functional unit of the neuromuscular system is the motor unit. A motor unit consists of an alpha motor neuron of the somatic nervous system. The motor neuron originates at the anterior horn of the spinal cord and all the muscle fibres it supplies[54] (Figure 2.3).

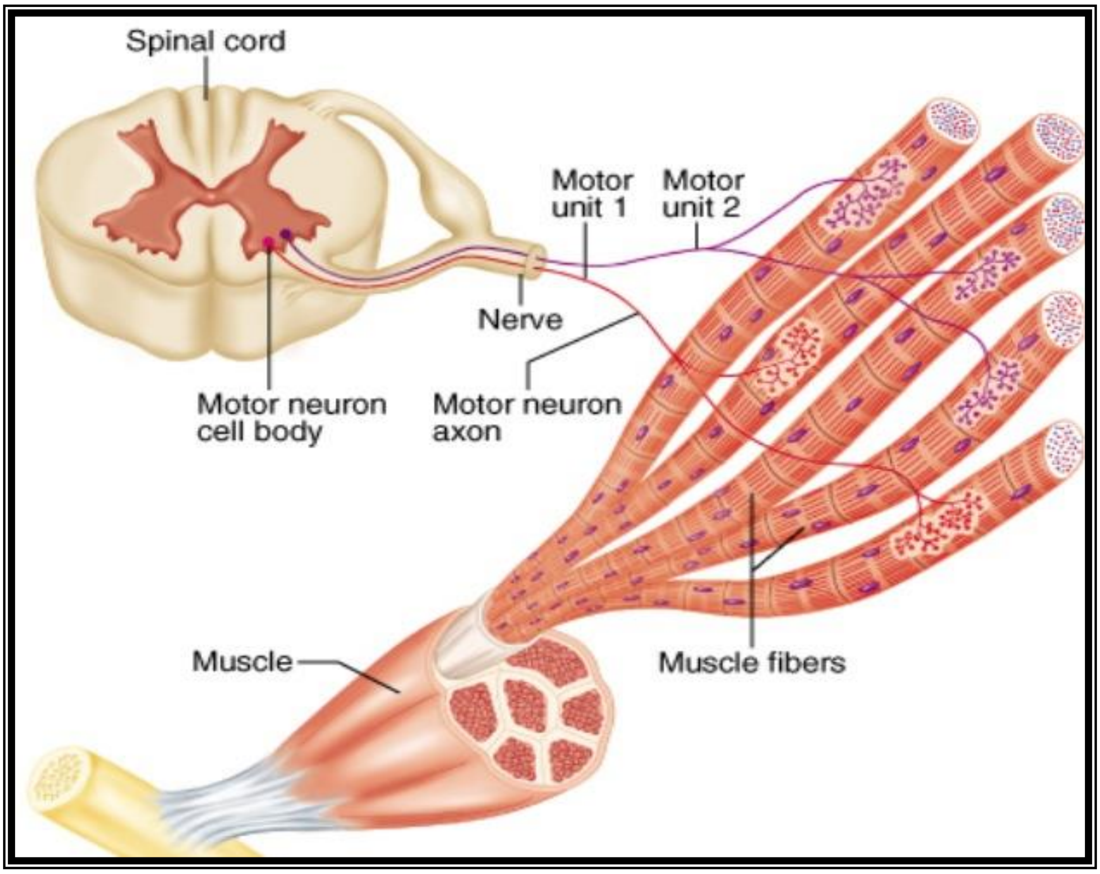


Figure 2.3: Motor unit[64]

The size of a motor unit gives an indication of how fine the control of movement will be.[54] Fine control muscles have small motor units and large, weight bearing muscles have large motor units.[54] Small motor units usually consists of slow twitch muscle fibres. The large motor units consists of faster, more powerful muscle fibres.[54] Motor units can change in size in response to demands as well as converting from one type to another. This plasticity of motor units allows for adaptation to different functional demands.[54] A neuromuscular junction is formed by the axon and a single muscle fibre when it enters the muscle.[54] Each muscle fibre has only one neuromuscular junction. The neuromuscular junction is formed by the motor end plate (part of the muscle fibre's sarcolemma) and the axonal ending with the synaptic vesicles.[54] The synaptic vesicles contain mitochondria and the neurotransmitter acetylcholine (Ach).[54]

Each muscle fibre receives a stimulus in the form of an action potential. Calcium flows from the sarcoplasmic reticulum into the extracellular fluid.[54] Ach is released into the synaptic cleft due to the presence of the calcium in the axon terminal.[54] The Ach attaches to the Ach receptors on the sarcolemma and results in the opening of the sodium and potassium channels.[54] An end plate potential is produced when more sodium enters the cell than potassium leaving the cell. After the Ach was bounded to the receptors, it is been broken down by ATPase into acetic acid and choline. The destruction of Ach prevents continuous muscle fibre contractions.[54]

Skeletal muscles can be classified according to the speed of contraction into the slow muscle fibres (Type I) and the fast muscle fibres (Type II).[54] The slow Type I fibres have a low maximum velocity of shortening and the fast Type II fibres have a high velocity of shortening. The difference in speed of these fibres reflects how fast their myosin ATPase split ATP (metabolism of the muscle).[54] The slow and fast twitch classification of muscle fibres is based on metabolic pathways that are either aerobic (oxidative) or anaerobic (glycolytic).[54] Aerobic respiration occurs in the mitochondria. It requires oxygen and involves chemical reactions to break the fuel molecules and release the energy to make ATP.[54] During the aerobic respiration the glucose and oxygen are broken down into carbon dioxide, water and ATP molecules.

The fibres that rely on the oxygen-using aerobic pathways for ATP generation are the oxidative fibres.[54] Anaerobic respiration is when the glucose is broken down into pyruvic acid and ATP. This process happens in the presence and absence of oxygen, but it is not using oxygen.[54] A muscle cell will form ATP by aerobic reactions as long as it has enough oxygen. If ATP demands are within the capacity of the aerobic pathway, light to moderate activity can continue for several hours.[54] If the exercise demands are exceeding the ability of the muscle cells to carry out the necessary reactions, glycolysis will contribute to more of the ATP generated.[54] Aerobic endurance is described as the length of time a muscle can continue to contract while supported by mitochondrial activities.[54] Anaerobic endurance is the length of time muscular contraction can continue to be supported by glycolysis and the energy reserves of ATP.[54] Fast muscle fibre groups (fast glycolytic fibres) appear white and slow muscle fibre groups (slow oxidative fibres) appear red.[54]

The redness is due to high amounts of myoglobin and a high capillary content. The greater myoglobin and capillary content in the red muscles contributes to the greater oxidative capacity of the muscles.[54] The blood flow increases in proportion to the metabolic activity when muscles become active.[54]

The force generated by a muscle contraction is dependent on the size and number of the muscle fibres, the time and frequency of stimulation[52] and the speed of the cross-bridge cycling.[54] Skeletal muscles that are not regularly stimulated by motor neurons lose muscle tone and mass. The muscle fibres become smaller and weaker and the muscle atrophies.[54]

Development of limb muscle weakness, as a result of muscle atrophy, is a clinical feature of critical illness.[51,65-66] ICU-AW is defined as severe generalised muscle weakness developing during the course of an ICU admission in the critically ill patient.[67-69] Patients develop ICU-AW due to muscle inactivity, hyperglycaemia, sepsis and the use of corticosteroids and neuromuscular blocking agents.[21,40] A prevalence of 25% to 58% of ICU-AW in patients mechanically ventilated for at least four to seven days is reported upon.[34,65,68-69] Muscle atrophy is the greatest during the first two to three weeks in ICU.[21,34,68] Most studies demonstrate that the reduction in muscle strength is due to myopathic changes in the form of muscle necrosis or myosin loss and muscle atrophy.[40] Muscle atrophy is due to increased proteolysis and a decrease in protein synthesis.[69] The function of the remaining muscle proteins may be impaired by enhanced oxidation and dephosphorylation.[70] Inflammation and oxidative stress are the major drivers of the impairment.[70]

Bittner et al.[52] indicated that the muscle fibre area decreased by 2% to 4% per day in ICU. Parry and Puthucheary[68] indicated that muscle mass reduced by 5.2% within the first two weeks. Turton et al.[71] demonstrated in an observational study that although the elbow flexor compartment did not show any changes in muscle thickness, the vastus lateralis muscle changed in thickness and structure within five days of ICU stay. The elbow flexor compartment did not show any changes on day five or day 10 of ICU stay.[71] Muscle thickness was measured with B-mode ultrasound.[71] Turton et al.[71] are of the opinion that muscles surrounding non-weight bearing joints were less susceptible to wasting than muscles surrounding weight bearing joints.

Kawahara et al.[72] reported that skeletal muscle mass decreased by 1% to 1.5% per day on bed rest and 4% to 5% after one week of bed rest. The results of the prospective observational study conducted by Kawahara et al.[72] demonstrated that muscle atrophy is observed 72 hours post ICU admission. They evaluated the muscle circumference at five different sites in the upper and lower limbs.[72] The sites included the midpoint of the upper limb between the acromion and the olecranon, the maximum diameter of the triceps surae and then 5cm, 10cm and 15cm above the superior pole of the patella.[72] Muscle circumference of 41 patients were measured on the day of admission, 72 hours and 144 hours post admission.[72] Results reflected greater atrophy in the lower limbs than upper limbs of the ADL-independent patients.[72] These results support the findings of Turton et al.[71] that muscles surrounding non-weight bearing joints are less susceptible to wasting than muscles surrounding weight bearing joints.

Muscle weakness and fatigue may compromise the patient's functional status and HRQOL. Muscle weakness is described by Bittner et al.[52] as the loss of strength and power. They described fatigue as an exercise-induced decrease in the capacity to generate and maintain force or power over time.[52] Tzanis et al.[73] hypothesised that ICU-AW affect respiratory muscles as well as peripheral muscles, resulting in reduced inspiratory pressure. The aim of their study was to investigate whether MIP would be a surrogate parameter for assessment of ICU-AW.[73] The MIP measurement and MRC-score of 33 of the 74 recruited patients showed a significant correlation (r = 0.68).[73] The results from Tzanis et al.[73] demonstrated that patients with a MIP < 36 cmH_20 were diagnosed with ICU-AW. Tzanis et al.[73] support the findings of De Jonghe et al.[18] that ICU-AW is affecting the respiratory muscles as well as peripheral muscles and therefore contributes to increase in ICU stay and prolonged mechanical ventilation and weaning. Hermans and Van den Berghe[69] also supported Tzanis et al.[73] that peripheral and respiratory muscles are affected by ICU-AW. The researchers reported that the incidence of ICU-AW is associated with the ventilated days.[69]

Hermans and Van den Berghe[69] indicated in their clinical review that 26% to 65% of patients ventilated for five to seven days respectively were diagnosed with ICU-AW. Among the patients ventilated for > 10 days, 67% were diagnosed with ICU-AW.[69] ICU-AW was still present at discharge in 36% of patients who suffered from ARDS during their ICU stay.[69]

A longitudinal prospective cohort study conducted of 156 patients by Dinglas et al.[74] also showed that 38% of patients surviving ARDS, had decrease muscle strength at hospital discharge. ARDS patients were associated with worse survival over a five year follow up.[74] The findings of Dinglas et al.[74] concur with previous work indicating that patients surviving ICU demonstrate functional limitations for more than one year after discharge from hospital.[52,75-76] A descriptive, correlational study conducted by Chlan et al.[77] demonstrated that older, female patients ventilated for more than seven days have a reduction in peripheral muscle strength. Since the patients were awake and cooperative, Chlan et al.[77] tested daily the peripheral muscle strength with the handgrip dynamometer.[77]

ICU-AW is characterised by flaccid weakness of the limbs.[69] The weakness is generally more pronounced in the proximal muscles of the limb than in the distal muscles of the limb.[69] Risk factors for the development of ICU-AW include sepsis, systemic inflammatory response syndrome (SIRS), multiple organ failure, prolonged duration of mechanical ventilation, ICU length of stay, hyperglycaemia, immobilisation and age.[68-69]

Diagnosis of ICU-AW may be done by electrophysiological testing or muscle strength testing with the MRC-score.[68-69] Evaluation of handgrip strength has also been recommended.[68] Using electrophysiological testing is limited by cost, availability and its time-consuming nature.[68-69,78] An MRC-score < 48/60 is considered to be indicative of ICU-AW.[65,67] Diagnosing ICU-AW with the MRC-score requires an awake and cooperative patient.[73] A limitation in diagnosing ICU-AW with the MRC-score is that not all ICU patients are always awake and cooperative in the early days of admission to ICU. ICU-AW is associated with a poor outcome including prolonged mechanical ventilation, increased length of hospital stay, decrease in functional status, the need for rehabilitation after discharge and an increase in mortality rate.[66-67,73]

Early detection of ICU-AW and precautionary treatment including early mobilisation can reduce the risk factors and contribute to a better outcome. In a prospective observational study done by Wieske et al.[79] a prediction model for early prediction of ICU-AW was developed. During the study 212 patients were analysed. The MRC-score was used to evaluate muscle strength when the patients were regarded as awake and cooperative (Richmond Agitation-Sedation Scale between -1 and +1).[79] High lactate levels, treatment with any aminoglycoside and age had been described as the predictors in the prediction model.[79]

A prospective single blinded study conducted by Yosef-Brauner et al.[28] demonstrated statistically significant improvement in the MRC-score, handgrip strength and MIP measurements in patients who received rehabilitation physiotherapy. They evaluated the peripheral and respiratory muscle strength in 18 patients with the MRC-score, handgrip dynamometer and MIP.[28] The control group received daily physiotherapy and the intervention group received the same physiotherapy twice daily. The intervention group showed within 72 hours from the first assessment an improvement in the measurements.[28]

Increased length of ICU stay, respiratory muscle weakness and peripheral muscle weakness are associated with development of ICU-AW. Early physiotherapy treatment for ICU-AW weakness had shown positive results in improving respiratory and peripheral muscle strength.

2.9 Testing muscle strength in the ICU

Generalised muscle weakness related to critical illness is a common complication in the ICU.[80] Muscle strength is an important measure to evaluate or predict early mobilisation and rehabilitation in ventilated patients.[34] Testing muscle strength in ICU is done by volitional and non-volitional methods.[65] Non-volitional methods are not universally available and require deep sedation.[76]

Non-volitional methods include electrical and magnetic neuromuscular twitch stimulation.[65] These tests are independent of the adequacy and motivation of the patient.[65] Volitional muscle testing includes manual muscle testing (MMT) techniques or handgrip dynamometry.[40,76] Testing muscle strength with volitional methods requires awake and cooperative patients.[34,40,80]

Richmond Agitation-Sedation Scale

Patients are regarded as awake and cooperative when completing three out of five questions (*here after referred to as 3/5*) of the five point questionnaire as described by De Jonghe et al.[18] A Richmond Agitation-Sedation Scale (RASS) of “-1” to “+1” is regarded as sufficient for muscle strength testing in ICU.[40,80] A pilot study also indicated that a RASS of “-1” to “+1” and 3/5 for the questionnaire are satisfactory for muscle strength testing in ICU.[20]

The RASS is a 10-point scale that was developed by a collaborative effort with a multidisciplinary team consisting of nurses, doctors and pharmacists.[81-82] The RASS consists of four levels of anxiety or agitation, one level of a calm and alert state and five levels of sedation (Table 2.1).[81-82]

Table 2.1: Description of the Richmond Agitation-Sedation Scale[81-82]

Score	Descriptor	Characteristics
+4	Combative	Overtly combative or violent; immediate danger to staff.
+3	Very agitated	Pulls on or removes tubes or catheters or has aggressive behaviour towards staff.
+2	Agitated	Frequent non-purposeful movement or patient ventilator dyssynchrony.
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous.
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening with eye contact to voice.
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice.
-3	Moderate sedation	Any movement (but no eye contact) to voice.
-4	Deep sedation	No response to voice, but any movement to physical stimulation.
-5	Unarousable	No response to voice or physical stimulation.

According to Sessler et al.[81] the RASS had a high inter-rater reliability and validity (*kappa* = 0.73, *r* = 0.78) to determine level of cooperation than the visual analog scale or Ramsay sedation scale. The researchers recruited 192 patients during the study in the Virginia Hospital. The results obtained by Sessler et al.[81] were supported by Ely et al.[82] who also demonstrated a high inter-rater reliability and validity of the RASS. An awake and cooperative patient is needed to perform manual muscle testing.

Manual muscle testing

Manual muscle testing has been peer-reviewed since 1915.[83] It has been described by Cuthbert and Goodheart[83] as both an art and a science. According to the literature review conducted by Cuthbert and Goodheart[83] MMT has a high reliability and validity when testing protocols are followed. The testing protocols include factors of proper positioning, consistent timing and pressure.[83] Manual muscle testing was introduced in 1932 by Robert W. Lovett, MD.[84] He used gravity as resistance. Lovett[84] initially described the grading and testing of muscle strength as per Table 2.2.[84]

Table 2.2: Key indicators to muscle grading and testing as described by Lovett[84]

Grade	Description
Gone	No contraction felt.
Trace	Muscle can be felt to tighten but cannot produce movement.
Poor	Produces movement with gravity eliminated but cannot function against gravity.
Fair	Can raise the part against gravity.
Good	Can raise the part against outside resistance as well as against gravity.
Normal	Can overcome a greater amount of resistance than a good muscle.

The Oxford grading scale was implemented to use numbers instead of words to describe the change in muscle strength during research (Table 2.3).[84] The Oxford grading scale evaluates the muscle strength of individual muscles and not muscle groups like the MRC-score.[84] A grading according to the Oxford grading scale is dependent on the range of motion, the ability of the muscle to contract against gravity or the ability to contract against manual resistance.

Table 2.3: Description of the Oxford grading scale[84]

Grade	Description
0	No contraction, no twitch.
1	Palpable contraction, but no movement.
2	Full range of movement with gravity excluded, no resistance.
3	Full range of movement against gravity, but no resistance.
4	Full range of movement against gravity and resistance, but not necessarily functional.
5	Full range of movement against gravity with full functional resistance. Repeat movement for 10 repetitions.

The MRC-score was implemented in the ICU for diagnosing ICU-AW. The MRC-score evaluates the muscle strength of six muscle groups bilateral. In a prospective study conducted by Hough et al.[67] they determined that MMT could not be performed to most patients in the ICU. According to Hough et al.[67] the reduced awareness of patients prohibited the evaluation and use of MMT.[67] Hough et al.[67] evaluated 30 patients in a single centre study.

The patient's muscle strength was evaluated with the MRC-score when the patient could answer 3/5 questions as described by De Jonghe et al.[18] Hough et al.[67] are of the opinion that the MRC-score is a reliable and feasible tool to use in an outpatient department, but due to decrease awareness not in the ICU setting. On the other hand Hermans et al.[78] determined a high interobserver agreement for the MRC-score in the ICU. They evaluated 75 patients with the MRC-score when the patients could cooperate and respond to five questions as described by De Jonghe et al.[18] During the study, Hermans et al.[78] calculated the MRC-score by extrapolation of the value of the contralateral side if the one side could not be tested due to peripheral / central nervous lesions, orthopaedic reasons or amputations.[78] The study demonstrated a high reproducibility with *ICC* = 0.95.[78]

Vanpee et al.[65,85] support Hermans et al.[78] that the MRC-score is a reliable method to evaluate muscle strength in ICU. A systematic review by Vanpee et al.[65] mentions that muscle testing can be influenced by factors such as awareness, cooperation, motivation, testing procedures and the patients' position. Vanpee et al.[65] agree with Cuthbert and Goodheart's[83] opinion that standardised testing positions are important to ensure reliability of muscle testing. Standardisation includes the positioning of the patient, the limb position, joint angle, contraction time and verbal encouragement.[65] Various researchers are of the opinion that the MRC-score has limited sensitivity for evaluating MRC-grades four and five of the six muscle groups.[34,40,65,69,78,86]

Muscle strength can be evaluated with the MRC-score, handgrip dynamometry or the MIP in ICU.[34] Roberson et al.[34] recommended that a combination of the MIP, MRC-score and handgrip strength is used to quantify patient's muscle strength in ICU.

Handgrip strength

Ali et al.[80] conducted a multicentre study to determine whether handgrip strength measured with handgrip dynamometry would provide a concise measure of global (overall muscle) strength. They have screened 3 475 subjects but only 174 were included.[80] The patients' muscle strength was tested with the MRC-score and the handgrip with a handgrip dynamometer.[80] The results showed that the mortality rate increased as the average muscle strength and handgrip strength decreased. Ali et al.[80] also demonstrated that the handgrip dynamometry could be an alternative to the comprehensive MRC-score examination. The researchers determined that a value of < 7 kg and < 11 kg was indicative of ICU-AW for females and males respectively.

According to a prospective observational study conducted by Lee et al.[76] handgrip dynamometry is not associated with a change in the mortality rate, length of stay or number of days ventilated. Lee et al.[76] hypothesised that MMT and handgrip strength measurements may be associated as dependant variables of the length of stay and ventilated days. They used the RASS and De Jonghe's[18] five point questionnaire to determine if a patient was awake and cooperative for MMT and handgrip dynamometry.[76] The MRC-score and handgrip dynamometer were used over a 10 week period to evaluate the muscle strength of 95 patients.[76] The MMT results showed that muscle strength with the MRC-score was independently associated with mortality rate (P < 0.04), days ventilated (P < 0.01), ICU length of stay (P < 0.002) and hospital length of stay (P < 0.001) respectively.[76] When the muscle strength increased, the mortality rate decreased. The difference in results between Ali et al.[80] and Lee et al.[76] with the same handgrip dynamometer may be due to population differences of the study groups. Medical patients with a high level of illness were evaluated by Ali et al.[80] and surgical patients with a lower level of illness were evaluated by Lee et al.[76]

In a cross-sectional, observational study, conducted by Vanpee et al.[85] the interobserver reliability for the handheld dynamometer was very good (ICC = 0.91 – 0.96) for muscles with a muscle strength less than MRC-grade three.[85] Handheld dynamometry has been designed to assess maximal isometric limb muscle strength objectively.[85] During the study, Vanpee et al.[85] evaluated 39 critically ill patients in the medical and surgical ICU. The maximal voluntary isometric muscle strength of the upper limbs and lower limbs (four muscle groups) was tested with the handheld dynamometer.[85]

High inter-rater reliability figures for handgrip dynamometry were also determined by Hermans et al.[78] with a ICC = 0.93 (right) and ICC = 0.97 (left) and Parry et al.[86] (ICC = 0.88 - 0.97). During the studies 46 and 29 patients were respectively evaluated.[78,86] In both studies patients from the surgery and medical ICU's were positioned with their elbows in 90° flexion while testing the grip strength with the Jamar handgrip dynamometer.[76,86] Parry et al.[86] also demonstrated that handgrip dynamometry has a high sensitivity (0.88) and specificity (0.80) for diagnosing ICU-AW. Handgrip dynamometry is a reliable, simple, quick tool to assess muscle strength in daily practices.[86] It can be used as a surrogate for global strength measurement.[80,86]

In an observational cohort study done by Samosawala et al.[40] the upper limb and lower limb muscle strength was tested with handheld dynamometry.

Samosawala et al.[40] determined that proximal muscle strength in a limb decreased more than distal muscle strength, therefore the quadriceps muscle force capacity decreased more than the plantar flexors. A reduction of 10% to 13% in the muscle strength of 78 patients was observed between day three and day seven of their ICU stay.[40] The researchers demonstrated that measuring muscle strength with a dynamometer objectively measured a reduction in force capacity.[40] This indicates that a dynamometer can be proposed as an important alternative to manual muscle testing in a routine physiotherapy assessment.

A literature review conducted by Roberts et al.[87] demonstrated that the Jamar handgrip dynamometer is the instrument that is most widely used to evaluate handgrip strength. The small, portable dynamometer can read the force in kilograms and pounds.[87] Patients are usually tested with the hand span positioned in the second position of the handgrip dynamometer. The studies showed that if patients were positioned sitting, shoulders adducted (arm-by-side) and neutrally rotated (mid-point between medial and lateral rotation), elbow 90° flexion, forearm in neutral and the wrist in 0° to 30° flexion, the best reading for grip strength is obtained.[87] Measuring handgrip strength with the handgrip dynamometer has good to excellent (r = 0.80) test-retest reproducibility and excellent (r = 0.98) inter-rater reliability.[87]

The reliability and validity of the maximum handgrip strength and their relation to the distance walk with the six-minute walking test (6MWT) were determined in a test-retest study by Reuter et al.[88] These researchers supported Ali et al.[80] by mentioning that handgrip strength was not only indicating hand skeletal muscle strength, but was also an index of overall muscle strength and endurance. Reuter et al.[88] tested 16 subjects during the test-retest study. The subjects' handgrip strength was tested with the handgrip dynamometer and the endurance with the 6MWT on three different occasions. Subjects were positioned in a sitting position with shoulders adducted (arm-by-side), elbows 90° flexion and forearms resting on the arm of the chair. The best of three handgrip readings was documented.[88] The excellent test-retest reliability (ICC > 0.9) results of the study indicated that maximal handgrip strength was an indicator of the patient's status and progression. It was also predictive of the exercise capacity.[88] The researchers were of the opinion that the handgrip strength measurement could be used in the assessment of endurance where patients were not able to ride the bicycle or perform the 6MWT.[88]

A prospective study conducted by Cottereau et al.[89] found that handgrip strength was associated with difficult or prolonged weaning but not with extubation outcome. Cottereau et al.[89] described testing the handgrip strength with a handgrip dynamometer as a quick, non-invasive and easy to perform test. During the study patients who were regarded as ready to be weaned according to their unit protocol were evaluated for the handgrip strength just before the SBT was commenced.[89] The best of three readings were documented. The researchers accepted the values for defining ICU-AW as described by Ali et al.[80] The results by Cottereau et al.[89] showed that handgrip strength had a 0.76 sensitivity and 0.69 specificity for identifying difficult or prolonged weaning at a cut off of 11 kg.

In an observational study conducted by Efstathiou et al.[90] the results demonstrated a strong association (r = 0.76) between handgrip strength and MIP. During the study, the handgrip strength of 24 subjects was evaluated with a hydraulic gauge and the MIP with a handheld device.[90] The best of three readings was documented. The results of the study conducted by Efstathiou et al.[90] support the findings of Cottereau et al.[89] that handgrip strength is a functional prognostic indicator for evaluating the respiratory system.

Maximum inspiratory pressure

Respiratory muscle strength is usually evaluated with MIP and MEP.[46,55,69-70] The MIP reflects the combined force generating capacity of the inspiratory muscles during a quasi-static contraction.[90] MIP can be measured while the patient is connected to the ventilator or with a handheld pressure monitoring device.[70] Patients have to be awake and cooperative when MIP is measured with the handheld pressure monitoring device.[55,70] An MIP > 30 cmH_2O is associated with a shorter time to successful extubation.[46] Measuring the MIP can be influenced by the existence of upper airway obstruction or a submaximal effort.[90]

In 2015 Sommers et al.[91] developed an evidence-based protocol for assessment and treatment of the ICU patient. During their study they concluded that the MRC-score and handgrip dynamometer is the known methods for evaluation of muscle strength in ICU. Sommers et al.[91] did not focus on the assessment of the exercise endurance or the respiratory system. A systematic literature review comprising of nine articles conducted by Roberson et al.[34] indicates that peripheral and respiratory muscle strength can be evaluated with the MRC-score, handgrip dynamometer and MIP respectively. Although limitations are present in using the measurements individually, a combination of the measurements will quantify a patient's muscle strength.[34] Early detection of respiratory and peripheral muscle weakness can contribute to early mobilisation and improvement of physical function of the patient.

2.10 Exercise endurance and MOTOmed® letto2 cycle ergometer

Exercise endurance is associated with an increase in the maximal oxygen uptake (VO_2max).[92] It represents the greatest amount of oxygen a person can use to produce ATP aerobically on a per minute basis.[92] The maximum oxygen uptake usually occurs during high intensity dynamic exercise involving a large part of total muscle mass.[93] This high intensity exercise and maximum oxygen uptake can cause a physiological stress that elicit a cardiovascular or respiratory abnormality not present at rest.[93] The capacity to sustain exercise at high percentage of VO_2max is influenced by capillary density, enzymes and muscle fibre types.[92] An increase in the cardiac output during exercise cause an increase in oxygen uptake by the working muscles as well as increase of blood flow to the lungs.[94] Integration of the respiratory, cardiovascular and neuromuscular systems is necessary for attainment of VO_2max.[92] VO_2max serves as a standard to compare performance estimates of aerobic capacity and endurance fitness.[92] Large muscle groups are activated with sufficient intensity and duration to engage maximal aerobic energy transfer during VO_2max testing.[92] Fixed submaximal testing reach steady-state within three to five minutes after the onset of exercise.[93] During submaximal exercises, the oxygen uptake, HR and pulmonary ventilation are much higher in the upper limbs than the lower limbs due to the smaller muscle mass and vasculature of the arms that offer greater resistance to blood flow than the larger mass and vasculature of the legs.[92] Arm exercises require greater cardiovascular output due to the increased work requirement of the myocardium.[92,95]

In 1957 Karvonen et al., cited by Swain and Franklin,[96] reported that an intensity of at least 70% of the difference between the maximal and resting HR is necessary to improve cardiovascular endurance.[96] This difference between the maximal and resting HR is described as the heart rate reserve (HRR). In 1998 the American College of Sports Medicine suggested to use the percentage of oxygen consumption reserve ($\%VO_2R$) as an indicator for exercise intensity.[96] The results of the study conducted by Swain and Franklin[96] indicated that the fitness level has a minimal effect on the relationship between $\%HR_{max}$ and $\%VO_2R$. The authors determined the $\%VO_2R$ according to the following formula: $\%VO_2R = 1.667(\%HR_{max}) – 70\%$. $\%HR_{max}$ was calculated by dividing the exercise HR by the mean maximal HR.[96]

Maximum HR can be determined by the following formula: $HR_{max} = 220\text{-age}$. Swain and Franklin[96] also determined that training intensities of 30% or more of VO_2R improve aerobic capacity. This level of training can be considered the minimal effective intensity for the low fitness subjects.[96] No testing was done with less than 30% of VO_2R on healthy subjects. Swain and Franklin[96] suggested further research to evaluate lower training intensities. According to Balady et al.[94] light intensity exercises should be 40% of the HRR and resting HR.

Testing exercise endurance in ICU is not always reliable and according to Skinner et al.[66] there is no “gold standard” measurement for exercise endurance in the critically ill population. Exercise endurance of cardiorespiratory patients are generally tested in the outpatient department or ward with the six-step exercise test, ten-meter walk test, three-minute step test, treadmill test, timed up and go test, six-minute arm test (6-MAT) and 6MWT.[97] The 6MWT is used to test the capacity of a patient to walk as far as possible for six minutes.[98] It assesses submaximal exercise capacity and functional activity. Contraindications for the 6MWT include patients with unstable angina and acute myocardial insufficiency.[98] Factors that can influence the results of the 6MWT include body weight, age and mental health. The prospective, cross-sectional study done by Dourado et al.[98] demonstrated that thoracic muscle strength as well as handgrip strength are predictors of the six-minute walking distance in COPD patients. According to them upper limb muscle strength influences walking distance.[98]

A cross sectional study conducted by Toosizadeh et al.[19] also supports the findings of Dourado et al.[98] that upper limb muscle strength is a predictor of 6MWT. Toosizadeh et al.[19] evaluated the upper-extremity function test to assess for functional capacity. According to Toosizadeh et al.[19] the 6MWT cannot be performed by all patients and therefore an alternative functional capacity measurement is necessary. Results showed a strong correlation between the elbow moment and 6MWT (r = 0.44 – 0.62). The elbow moment represented the maximum moment imposed on the elbow while performing the repetitive elbow flexion task.[19] The elbow moment also showed a strong correlation with the grip strength (r = 0.51 – 0.67).[19] Toosizadeh et al.[19] concluded that upper extremity strength was associated with pulmonary function (MIP and MEP) and 6MWT.

Dourado et al.[98] as well as Porta et al.[42] are of the opinion that the influence of thoracic muscle strength on endurance (6MWT) might be explained by the large number of accessory muscles involved in performing the lateral pull down exercise. The muscles activated during the exercise included the latissimus dorsi, pectoralis major, trapezius, rhomboids and biceps muscles.[98] The latissimus dorsi, pectoralis major and trapezius muscles can adapt an accessory respiratory function when the primary respiratory muscles are weak and not meeting the ventilatory needs. Toosizadeh et al.[19] is of the opinion that decrease pulmonary function is not only correlating with weak respiratory muscles but also with weak peripheral muscles. The lack of oxygen transport, ventilation limitation, fatigue and lack of peripheral muscle strength may be related to the decrease endurance.[19] According to an evidence-based management algorithm developed by Hanekom et al.[99] an exercise program for the ICU patient need to target the trunk and extremities. The exercise program need to focus on strengthening and exercise endurance.[99]

Critically ill patients are usually not able to perform the 6MWT, but rather the 6-MAT when evaluating endurance. The reliability (*ICC* = 0.92) and validity (*r* = 0.92) of the 6-MAT were determined in a test-retest study conducted on 30 spinal cord injury patients in a rehabilitation unit.[95] The test was conducted for six minutes although physiological responses are typically seen after two to three minutes of exercise. The six minutes elicited steady state exercise, yet it did not fatigue the patient.[95] Patients rode the Monark Rehab trainer for six minutes with the upper limbs. The patients were in a seated position with the Monark Rehab trainer at their shoulder level.[95] The Monark Rehab trainer is a standard cycle ergometer commonly found in rehabilitation settings.[95] Hol et al.[95] demonstrated that the concurrent validity of the 6-MAT for assessing cardiovascular fitness in spinal cord injury patients is excellent. Hol et al.[95] suggested that the 6-MAT be used in future as a clinical tool in determining cardiovascular fitness.[95]

Developing submaximal tests is challenging because the workload needed to achieve this, elicits an aerobic response in all patients but not at a level of maximal test causing fatigue in untrained individuals. A study conducted by Bulthuis et al.[100] in 2010 also indicated the reliability and validity of the arm crank ergometer to determine aerobic capacity during submaximal exercise. During the cross over study they recruited 30 subjects.[100] The subjects were asked to ride the cycle ergometer for six minutes with a constant frequency of rotation. The resting HR was measured before the exercise.[100] The ICC of 0.64 indicates the reliability and validity for using the arm crank ergometer to determine exercise endurance.[100] During the study the HR was relatively low with a minimal 60% of the age-related maximum HR. This study however only used healthy subjects and not critically ill patients.

Upper limb strengthening exercises with a cycle ergometer increase patients' upper limb muscle strength, endurance and it decreases perceived dyspnoea at rest.[42] These findings were described in a prospective randomised trial conducted by Porta et al.[42] in patients weaned from mechanical ventilation. Porta et al.[42] screened 228 patients, but only 66 met the inclusion criteria. Patients had to ride the cycle ergometer for 20 min daily for 15 consecutive days.[42] Every day the resistance was increased by an additional 2.5 W. Porta et al.[42] also demonstrated that upper limb exercises yield greater improvement in the MIP. This may be explained by the increase in hyperinflation that leads to a shift from predominantly the diaphragm to the accessory inspiratory muscles that include muscles from the shoulder girdle.[42]

Riding a cycle ergometer for five minutes in a case series of 38 patients, demonstrated a small increase in HR (3%) and RR (20%).[75] Patients in the respiratory ICU had to actively pedal the cycle ergometer for five minutes at their own pace. The patients were asked to ride as fast as possible but also to maintain the same pace for the five minutes.[75] Activities like sitting, standing and walking increased the HR in critically ill patients by 10%.[75] This small increase in HR (3%) and RR (20%) when riding the cycle ergometer, supports the impression that a cycle ergometer is a safe and feasible instrument to use in the ICU. After riding the cycle ergometer, a high patient satisfaction for using the cycle ergometer as treatment modality in ICU has been reported.[75]

The safety and feasibility of using the MOTOmed® letto2 cycle ergometer in ICU were also reported by Burtin et al.[21] and Pires-Neto et al.[101] respectively. Pires-Neto et al.[101] evaluated in a case series whether any haemodynamic, respiratory or metabolic changes are present while riding a cycle ergometer within 24 hours after ICU admission. They recruited 19 sedated patients to perform passive cycling exercise for 20 minutes. There were no haemodynamic, respiratory or metabolic changes observed during the study. Kho et al.[102] tested 12 safety aspects in a retrospective study. The results showed only one incident of unsafeness (dislodging a femoral catheter) from 541 cycling sessions.[102] During the study, 688 patients' data were screened but only 181 were cycling and included in the data analysis.[102]

In a randomised control trial conducted by Burtin et al.[21] they recruited 90 medical and surgical ICU patients. All the patients received daily physiotherapy that included respiratory therapy and mobilisation.[21] The treatment group received an additional 20 minute exercise program with the MOTOmed® letto2 cycle ergometer.[21] The 20 minute exercise was at an individually adjusted intensity level. The six-minute walking distance, isometric quadriceps force and functional status of all patients were evaluated.[21] The study demonstrated that early exercise training improved the quadriceps force, functional status and exercise capacity of patients.[21]

The randomised clinical trial conducted by Dos Santos Machado et al.[31] supported the findings of Burtin et al.[21] that muscle strength improves with early cycle ergometer exercises. Machado et al.[31] found that peripheral muscle strength improves when passively exercising with the MOTOmed® letto2 cycle.[31] The passive exercises did not influence the duration of mechanical ventilation or length of hospital stay. During the seven months, 49 patients were recruited. Patients were randomised into the control group who received daily physiotherapy and the interventional group who received conventional physiotherapy together with 20 minutes of passive cycling with the MOTOmed® letto2 cycle ergometer.[31] Patients' peripheral muscle strength was evaluated with the MRC-score on the first day the patient was awake and responsive and on the last day before discharge from ICU.[31]

A randomised control trial conducted by Eggmann et al.[103] concluded that combined endurance and resistance training did not improve functional capacity compared to standard mobilisation programs. Hundred and fifteen (115) patients were randomised to either a control group receiving standard physiotherapy or an experimental group receiving early endurance and resistance training.[103] The control group received respiratory therapy, active and passive exercises and early mobilisation. The experimental group performed resistance training with weights and endurance training with a 20 minute ride on the MOTOmed® letto2, cycle ergometer.[103] The endurance training with the MOTOmed® letto2 cycle ergometer did improve their mental health six months after critical care discharge.[103]

The MOTOmed® letto2 cycle ergometer is an exercise machine used for rehabilitation purposes to improve the muscle strength and endurance of critically ill patients in the ICU. It enhances short term recovery and increases functional status at hospital discharge.[21] Patients can ride the MOTOmed® letto2 cycle ergometer with the upper limbs or the lower limbs. Different exercise programs can be followed during treatment. Patients can participate in passive (the machine is moving the pedals), active (the patient is pushing the pedals) or resistant (patient is pushing the pedals against resistance) cycle exercises. Different readings including the passive or active riding time, passive or active distance covered, speed, energy usage, resistance and amount of spasms can be monitored and analysed after the treatment session.

The MOTOmed® letto2 cycle ergometer is a mobile instrument. Logistically it should be easy to perform the exercise endurance testing with the MOTOmed® letto2 cycle ergometer. Results from the studies done by Porta et al.[42], Hol et al.[95] and Bulthuis et al.[100] with an arm ergometer, support the hypothesis that exercise endurance can be tested with a cycle ergometer in the ICU. Using the Monark Rehab trainer as described by above mentioned studies, might be difficult in the ICU, due to patients not being able to sit independently in front of the ergometer and riding at shoulder level. The MOTOmed® letto2 cycle ergometer is an adjustable cycle ergometer which can be adapted in height to the bed, while the patient is sitting or lying in bed. Using the MOTOmed® letto2 cycle ergometer to test exercise endurance in the ICU should be inexpensive and simple to administer.

2.11 Electrolytes

The human body consists of different elements that contribute to the total body weight and influence the metabolic function of the body. These elements include sodium, potassium, calcium, phosphate and magnesium. Magnesium is a cofactor for several enzymes.[54] Calcium, potassium and sodium play important roles in muscle contraction.[54] A decrease in the excitability of the sarcolemma can contribute to muscle fatigue.

During exercise, potassium leaves the muscle cell into the extracellular fluid while sodium enters the cell.[104] According to Hilbert et al.[104] (citing Street et al.) a decrease in potassium release reduces muscle excitability.[104] Phosphate is the source of high-energy phosphate bonds of ATP and is an integral component of proteins.[105] Hypophosphatemia is associated with a decrease in diaphragmatic muscle strength and an increase in weaning failure.[105] In a single centre prospective observational study done by Demirjian et al.[105] they concluded that hypophosphatemia is associated with an increase in prolonged respiratory failure. There was no association between hypophosphatemia and 28-day mortality.[105]

2.12 Conclusion

The aim of the literature review was to determine the gap in the literature with regards to testing of upper limb muscle strength and exercise endurance as predictors of successful extubation. This section summarise the findings of the following questions:

- For mechanically ventilated critically ill patients, what are the factors causing weaning and extubation failure during their ICU stay?

  After an in depth study of the literature the researcher concluded that factors such as neurological disorders, delirium, sepsis, the use of corticosteroids, amount of secretions, a weak cough or ICU-AW contribute to weaning and extubation failure.

- Does prolonged mechanical ventilation influence extubation outcome in critically ill ventilated patients?
- Does prolonged mechanical ventilation and extubation failure influence respiratory muscle strength in critically ill patients?
- Does prolonged mechanical ventilation and extubation failure influence upper limb muscle strength in critically ill patients?
- Does prolonged mechanical ventilation and extubation failure influence exercise endurance in critically ill patients?

Prolonged mechanical ventilation has a negative effect on the peripheral muscle strength, respiratory muscle strength and exercise endurance and may result in potential complications. A decrease in pulmonary function is not only correlating with weak respiratory muscles but also with weak peripheral muscles. The risk for developing diaphragm weakness, respiratory muscle weakness and critical illness myopathy / polyneuropathy increased with prolonged mechanical ventilation and extubation failure. The patient's highest functional level and HRQOL after ICU discharge are also compromised due to muscle weakness and lack of exercise endurance. Ventilation limitations, a lack of oxygen transport, fatigue and peripheral muscle weakness are related to a decrease in endurance.

Early mobilisation and rehabilitation play an important role in prevention of the development of ICU-AW and respiratory muscle weakness. To develop the most suitable rehabilitation program and to determine the effectiveness of the rehabilitation program in ICU, the physiotherapist had to regularly evaluate the patient's muscle strength and exercise endurance according to the ICF framework.

- For critically ill patients that are ventilated, how is upper limb muscle strength being evaluated?
- For critically ill patients that are ventilated, how is respiratory muscle strength being evaluated?

Literature revealed that MMT with the MRC-score and handgrip dynamometry are the used methods to determine muscle strength in ICU. Although the MRC-score is the preferred method for evaluation of general muscle strength in ICU, it is not suitable to use for assessment of individual muscles. The MRC-score only evaluates the strength of 12 muscle groups and not individual muscles. The Oxford grading scale is a valid and reliable tool to use for manual muscle testing of individual muscles in the upper limbs. Respiratory muscle strength is determined by MIP and MEP measurements.

After in depth perusal of the literature the researcher decided to use the MRC-score for evaluation of the patient's general body muscle strength. The Oxford grading scale will be used to evaluate the muscle strength of the deltoid, sternocleidomastoid, trapezius and pectoralis major muscles. The individual muscle strength might give an indication whether these muscles will be able to assist the primary respiratory muscle (diaphragm) during increased work of breathing after extubation. The trapezius, sternocleidomastoid and pectoralis major muscles are part of the accessory respiratory muscles that assist with breathing when the patient's ventilatory needs increase. Figure 2.4 is a schematic summary of the theoretical framework explaining the selected muscles. The handgrip dynamometer and MIP will be used to evaluate the handgrip strength and respiratory muscle strength respectively.

Complication of Mechanical ventilation

- Decrease in respiratory muscle strength.
- Decrease in peripheral muscle strength.
- Decrease in exercise endurance.

Decrease respiratory muscle strength

- Diaphragm is primary respiratory muscle affected and consists of slow & fast twitch muscle fibres.

Accessory respiratory muscles will be activated

- Sternocleidomastoid → Elevate ribs during strenuous breathing.
- Trapezius → Stabilise the neck for sternocleidomastoid to function.
- Pectoralis major → assist with coughing.

Hypothesis

- If accessory muscles (sternocleidomastoid and trapezius muscles) have the strength to support the diaphragm, patients can maintain the respiratory needs after extubation.
- If pectoralis major muscle has the strength it can support the coughing which in literature is a predictor of successful extubation → clear the chest and assist with secretion management that is also a predictor of successful extubation.
- All these muscles need the exercise endurance to maintain the level of function.

Literature

- Muscles around weight bearing joints consists usually of fast twitching muscle fibres with large motor units that will atrophy faster than muscles around non-weight bearing joints.
- Muscles around non-weight bearing joints consists usually of slow twitch muscle fibres and atrophy slower than muscles around weight bearing joints.
- Sternocleidomastoid and pectoralis major muscles consists of fast twitching muscle fibres and might atrophy faster.
- Lack of oxygen transport, fatigue, ventilation limitation and peripheral muscle weakness relate to decrease endurance.

Figure 2.4: Schematic summary explaining the selected muscles

- For critically ill patients that are ventilated, how is exercise endurance being evaluated?

Exercise endurance of cardiorespiratory patients is usually tested in the ward and outpatient department with a variety of tests, including ten-meter walk test, three-minute step test, treadmill test, timed up and go test, 6-MAT and 6MWT. In the literature the 6MWT is the preferred method for assessment of exercise endurance. Critically ill patients are not able to perform the 6MWT, but will rather be able to perform the submaximal 6-MAT. Research showed that exercise endurance was tested with the 6-MAT using a cycle ergometer in spinal cord injured patients. Due to the gap in the literature regarding the assessment of exercise endurance in critically ill patients in the ICU, the researcher decided to use the 6-MAT with a cycle ergometer to assess exercise endurance.

- For critically ill patients that are ventilated, how is successful extubation predicted during their ICU stay?

Determining successful weaning and extubation is a complex process. Several predictors including RSBI, VT, MIP, MEP, cough strength, amount of secretions, level of consciousness, positive fluid balance and days ventilated have been evaluated to determine successful extubation, but none of the parameters can be used in isolation. Prediction of successful extubation will assist with reducing the number of ventilated days, the length of ICU stay, hospital stay and it will increase the patient's HRQOL. The current available predictors is an indication of the ability of the cardiovascular and respiratory systems to function after extubation.

Due to current evidence indicating that prolonged mechanical ventilation is associated with a decrease in the pulmonary function that correlates not only with respiratory muscle weakness but also with peripheral muscle weakness the question arises whether factors from the musculoskeletal system can be used as predictors for successful extubation. The results of the literature review showed that several studies were conducted on predictors of successful extubation, but none of these tested the combination of upper limb strength and exercise endurance as possible predictors of successful extubation. This gap in the literature led to the research question as to whether upper limb muscle strength and exercise endurance can predict successful extubation in mechanically ventilated critically ill patients.

The process to determine whether upper limb muscle strength and exercise endurance can predict successful extubation will be described in the next chapter.

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CHAPTER 3
METHODS

The research process from recruitment to participation as well as the study design, setting and ethical considerations will be discussed in this chapter.

3.1 Study design

The research study was a predictive correlational study.[106] A correlational research design can be relational (leading to correlation analysis) and predictive (leading to regression analysis).[107] A correlational (relational) research design is used in those cases when there is an interest to identify the existence, strength and direction of relationships between two variables. The correlational predictive design is used in those cases when there is an interest to identify predictive relationship between the predictor and the outcome/criterion variable.[107] The predictive correlational design required the development of a theory-based mathematical hypothesis proposing variables expected to effectively predicting the dependent variable (successful extubation).[106] Regression analysis was done to test the hypothesis. The extubation outcome along with demographic variables, clinical variables and other possible covariates were recorded.

3.2 Setting

The study was conducted from February 2018 to September 2019 in a tertiary care environment. Patients were recruited from the Surgery / Trauma and Medical intensive care units (ICU) of the Steve Biko Academic Hospital, Pretoria, South Africa. Critically ill ventilated patients that were haemodynamically stable participated in the study. On average a total of 14 patients were ventilated daily between the two ICU's.

3.3 Study population

All patients that were considered for the first time for extubation by the health care team according to the standard unit protocols (Table 3.1), were evaluated daily (Monday to Sunday) by the researcher to determine if they complied with the inclusion criteria. Patients who were ventilated for three or more days were included in the study, because according to Grosu et al.[53] and Levine et al.[58], diaphragm weakness presents within 48 hours to 69 hours of mechanical ventilation. All patients recruited in the study received standard physiotherapy treatment. The treatment included chest physiotherapy and rehabilitation (mobilisation and active or passive upper limb and lower limb exercises).

Table 3.1: Standard unit protocol for extubation

- Reversal of underlying cause of intubation
- Haemodynamic stability: HR < 140 b/min, Hb > 7 g/dl-1, T < 38.5˚C, no or minimal vasopressor or inotropes
- CPAP, PEEP ≤ 8 cmH_2O, FiO_2 ≤ 40%, SpO_2 ≥ 85%, pH ≥ 7.35, PaO_2/FiO_2 > 200
- Adequate cough strength
- No neuromuscular blocking agents

In preparation for the study the researcher practised the manual muscle strength testing (Oxford grading scale – *ICC* = 0.63 – 0.98)[83] techniques for muscle strength (deltoid, sternocleidomastoid, trapezius and pectoralis major) on models to ensure her own accuracy and patient safety with regards to handling the lines and tubes. The researcher also practised testing the handgrip strength with the handgrip dynamometer. Vanpee et al.[65] and Reuter et al.[88] confirmed the reliability of manual muscle strength testing (weighted kappa = 0.80 – 0.96) and the handgrip dynamometer (*ICC* > 0.9) respectively.

The characteristics of the sample group were stipulated in the inclusion and exclusion criteria.

3.3.1 Inclusion criteria

- Patients who were 18 years and older.
- Patients who were mechanically ventilated for three or more days.
- Patients who understood English.
- Patients who were awake, alert and responded to give appropriate informed consent (Appendix 2).
- Patients who met the safety and weaning criteria as described in previous studies:
  - Condition precipitating mechanical ventilation reversed[15]
  - Awake and co-operative: RASS "-1, 0, 1"
  - 3/5 for the five point questionnaire[18,91]
  - Did not receive a muscle relaxant[8]
  - No sedatives in the past 12 hours
  - Absence of fever < 38ºC[8,15,91]
  - Respiratory
    - Mode of ventilation: PS ventilation
    - PEEP ≤ 8 cmH_2O[15,91]
    - PaO_2/FiO_2 ratio > 150[15]
    - No significant respiratory acidosis pH ≥ 7.35[8]
    - SpO_2 ≥ 90%[8,91]
    - RSBI = fR/VT ≤ 105 breaths/min/L[8,15]
    - FiO_2 ≤ 40%[8,15,91]
  - Cardiovascular
    - Minimal inotropes (<5 μg/kg/minute dopamine)[8,15]
    - Heart rate ≤ 140 b/min[8]
    - Systolic blood pressure ≥ 90 mmHg[8,15]
    - Haemoglobin ≥ 8 g/dL[8]
  - Protected airway
    - Minimal and moderate secretions[8] (patients only suctioned four hourly according to unit protocol).
    - Strong cough to tracheal stimulation.[8]
    - Positive cuff test (>110 ml or 130 ml cuff-leak volume).[9]

3.3.2 Exclusion criteria

- Known upper airway obstruction.
- Morbid obesity[108-109] – BMI > 35 kg/m^{2}.
- Patient with a primary or previously diagnosed neuromuscular disorder (eg. Guillain-Barré syndrome, Myastenia gravis or motor neuron disease).[11,15]
- Patients with primary cardiomyopathy or arterial fibrillation.[11,91]
- Patients with psychiatric disorders or severe agitation.
- Patients with acute asthma attack.
- Inability to perform manual muscle testing technique due to spinal cord injury, bilateral amputations, bilateral fractures, soft tissue injuries, burns or dressings limiting the testing of the muscle strength.
- Patients with "do not resuscitate" status.
- Death before first spontaneous breathing trial (SBT).

3.4 Ethical considerations

Ethical approval was obtained from the Research Ethics Committee, Faculty of Health Sciences, University of Pretoria in 2017 (number 394/2017). The chief executive officer of the hospital as well as the consultants in charge of the different ICU's gave written consent before the study was conducted in the Steve Biko Academic Hospital.

Immediately after determining the suitability of the patient according to the inclusion and exclusion criteria, the researcher initiated the informed consent process (Appendix 2). The researcher informed the patients that a study would be conducted to determine how strong the patients' arm muscles and lungs were before removal of the breathing tube. The researcher explained that participation in the study entailed that the patient had to lift up their shoulders to the ears, bend their neck forward, put their chin on their collar bone, lift up their arms to the side and push the arm towards the opposite hip. The patient also had to bend and straighten their knees and hips. They had to squeeze the handgrip dynamometer and rode the bicycle (MOTOmed® letto2 cycle ergometer) with their arms for six minutes. All these tests were conducted while they were sitting or lying in bed. The researcher tested how strong their lungs were when they breathe in deeply for three times. Patients were informed that the only possible discomfort involved, would be a sense of tiredness in the patient's arms after the exercise. There were no foreseeable risks involved in the study. The study did not provide financial benefit to the patients. The results of this study might benefit patients in the future. The patient's participation lasted approximately 45 minutes per session. Only one session was required.

Patients were also informed that participation or withdrawal of the study would not influence their daily physiotherapy treatment. All information obtained in this study would be regarded as confidential and results would be published in such a manner that the patient remains anonymous. Patients received a study number and no personal information was disclosed. Patients gave either written consent or by nodding the head or showing with the thumb when they could not write. The verbal consent was witnessed by a professional nurse in charge of the unit. Only patients who gave consent were part of the study. There was no conflict of interest.

3.5 Data collection

The demographic and clinical characteristic information, muscle strength, exercise endurance and maximum inspiratory pressure (MIP) data were collected by the principle researcher (hereafter referred to as the researcher). All relevant research data were documented as described in Appendix 3. Quality control was done by a second researcher (supervisor) by means of spot checks of transferring data to the spreadsheet. The flow of the data collection process is presented in Figure 3.1.

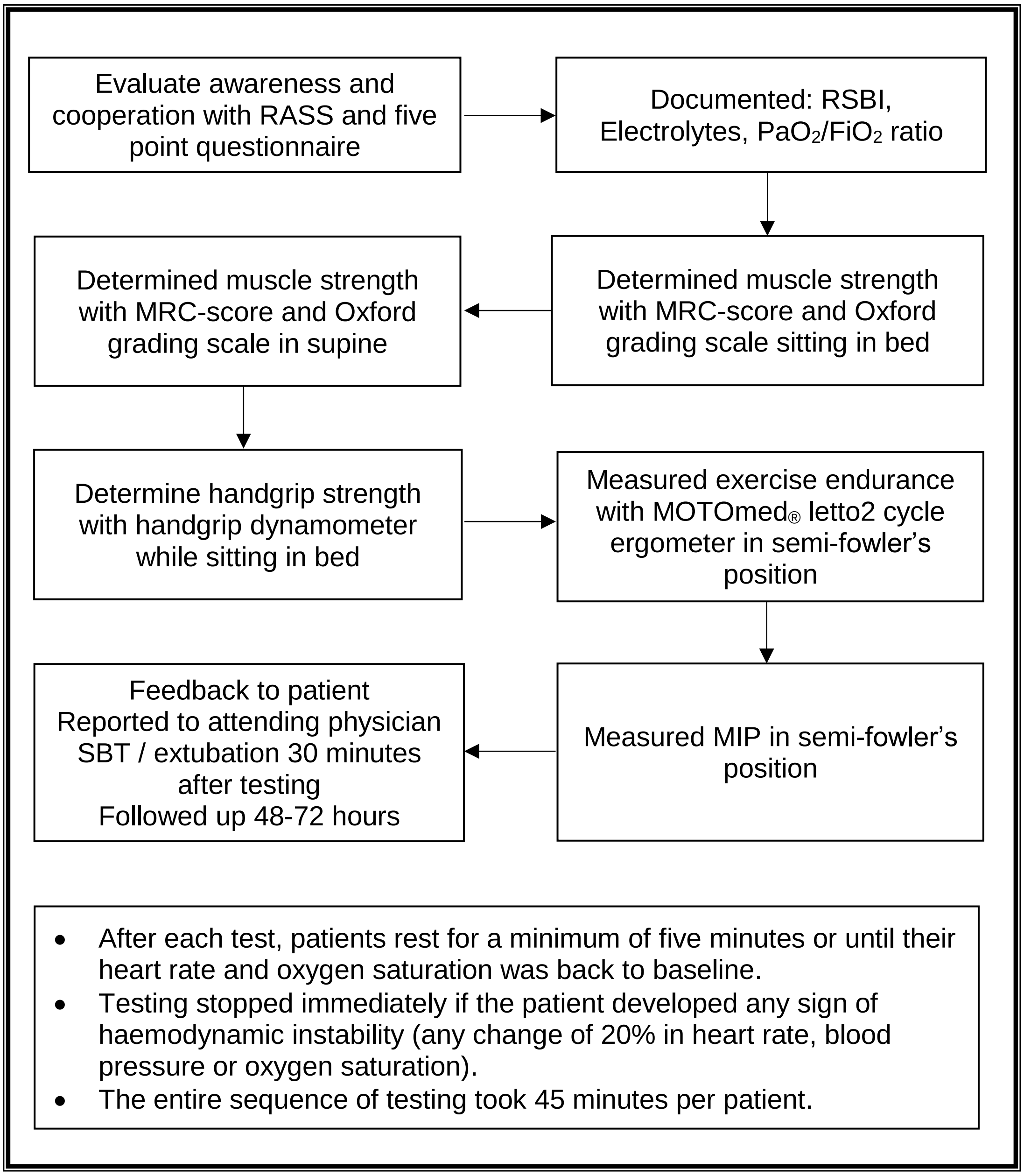

Figure 3.1: Flow diagram indicating the research process of the study

Patients considered for extubation by the health care team were evaluated daily by the researcher for awareness and orientation, using the Richmond Agitation-Sedation scale (RASS) and five point questionnaire. The RASS (Table 3.2) is a validated tool to determine if a patient is awake and orientated in ICU.[81] It is a 10 point scale with moderate to high inter-rater reliability and validity (kappa = 0.66-0.89) in ICU.[81]

Table 3.2: Description of the Richmond Agitation-Sedation scale[81]

Score	Descriptor	Characteristics
+4	Combative	Overtly combative or violent; immediate danger to staff.
+3	Very agitated	Pulls on or removes tubes or catheters or has aggressive behaviour towards staff.
+2	Agitated	Frequent non-purposeful movement or patient ventilator dyssynchrony.
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous.
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening with eye contact to voice.
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice.
-3	Moderate sedation	Any movement (but no eye contact) to voice.
-4	Deep sedation	No response to voice, but any movement to physical stimulation.
-5	Unarousable	No response to voice or physical stimulation.

The five point questionnaire as described by De Jonghe et al.[18] was also used to determine if the patient was responsive. According to De Jonghe et al.[18] and Tzanis et al.[73] a patient is regarded as awake and cooperative when answering three out of five *(hereafter indicated as 3/5)* of the questions (Table 3.3).

Table 3.3: Description of the Five point questionnaire[18,73]

	Instructions
1	Open / close your eyes.
2	Look at me.
3	Nod your head.
4	Stick out your tongue.
5	Raise your eyebrows.

The five point questionnaire is not a validated scale but has been used extensively in several research studies in critical care.[18,78,86,91]

Manual muscle testing can only be assessed if the patient is awake and cooperative. A pilot study conducted by De Beer et al.[20] showed that patients can be considered awake and cooperative if the RASS is "-1," "0" or "+1" and the total five point questionnaire score is 3/5. Patients with these scores were included in the study and muscle strength were tested.

The rapid shallow breathing index (RSBI), electrolytes and partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2 ratio) were documented as described in Appendix 3. The documentation was done before muscle strength testing was commenced.

Manual muscle testing was evaluated with the standard Medical Research Council score (MRC-score) and Oxford grading scale. The MRC-score (Table 3.4)[69,86] was used to evaluate the patient's general muscle strength. Patients were positioned supine or sitting to facilitate testing and to include or illuminate the influence of gravity. Muscle testing started with the position of a grade three muscle and then adapted according to the patient's ability. All six muscle groups were tested before the patient rested for a minimum of five minutes or until the heart rate and oxygen saturation was back to baseline.

Table 3.4: Description of the Medical Research Council score[69,86]

Muscle groups evaluated:	
Shoulder abduction Elbow flexion Wrist extension	Hip flexion Knee extension Ankle dorsiflexion
Grade	**Description**
0	No muscle contraction.
1	Flicker or trace of muscle contraction without movement of the limb.
2	Active movement with gravity eliminated.
3	Reduced power but movement against gravity.
4	Reduced power but active movement against gravity and resistance.
5	Normal power against full resistance.

The muscle strength of deltoid, sternocleidomastoid, trapezius and pectoralis major was evaluated with the Oxford grading scale (Table 3.5).

Table 3.5: Description of the Oxford grading scale[84]

Grade	Description
0	No contraction, no twitch.
1	Palpable contraction but no movement.
2	Full range of movement with gravity excluded, no resistance.
3	Full range of movement against gravity but no resistance.
4	Full range of movement against gravity and resistance but not necessarily full functional resistance.
5	Full range of movement against gravity with full functional resistance. Repeat movement for 10 repetitions.

Patients need to have a grade three muscle strength (full range of movement, against gravity) to be able to do functional activities including washing themselves, feeding or sitting over the side of the bed. The researcher first demonstrated the movement before testing was commenced. The muscle testing procedure for the deltoid, sternocleidomastoid, trapezius and pectoralis major muscles using the Oxford grading scale is described in Table 3.6 to Table 3.9.

Table 3.6: Oxford muscle testing – Grade 3[84]

Grade 3				
Muscle	**Starting position**	**End position**	**Command**	**Points to notice**
Trapezius (Upper fibres)	• Sitting upright in bed • Shoulder joint and scapula in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint (AC)	• Sitting, upright in bed • Full scapula elevation in the frontal plane	• "Lift up your shoulder to your ear."	• No scapula protraction or shoulder medial rotation • Acromion at the mid-cervical level • ROM to be equal L & R against gravity
Deltoid (Middle fibres)	• Sitting, upright in bed • Shoulder joint and scapula in neutral alignment confirmed with the plumb line. Plumb line: earlobe - C2 - shoulder joint • Arm by side • Elbow 90^0 flexion, thumb facing towards the roof and fingers facing straight forward	• Sitting, upright in bed • Shoulder joint in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint • Arm away from the body in the frontal plane up to 90° shoulder abduction, elbow in line with the shoulder • Elbow 90° flexion with forearm parallel to floor and thumb facing perpendicular to the roof	• "Lift your elbow up, away from the body to shoulder level." • "Keep your elbow bend."	• No scapula protraction / elevation • Elbow level with shoulder • Shoulder joint to move in the frontal plane with no rotation (earlobe, AC joint and elbow to be in line) • ROM to be equal L & R against gravity

Table 3.6: Oxford muscle testing – Grade 3[84] (Continue)

Muscle	Starting position	End position	Commands	Points to notice
Sternocleidomastoid (Unilateral testing)	• Supine in bed. • Neck in neutral alignment confirmed with the plumb line. Plumb line: chin tucked – earlobe – C2 – shoulder joint.	• Supine in bed. • Chin on mid clavicle, (away from side being tested) with neck flexion, no rotation of cervical spine. Lifting chin from the collar bone.	• "Turn your head to your side and lift up your neck, put your chin on your collar bone."	• No scapula protraction. • No poking chin. • ROM to be equal L & R against gravity.
Pectoralis Major (Sternal & clavicular fibres)	• Supine in bed. • Shoulder 110° flexion and slight medial rotation, elbow in extension. • Shoulder and scapula in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint.	• Supine in bed. • Shoulder adducted towards the opposite iliac crest. • Elbow extended.	• "Push your arm down towards your opposite hip, keep your elbow straight."	• No trunk rotation. • No trunk side flexion. • No hip rotation / adduction. • No hip hitch / pelvic elevation. • ROM to be equal L & R against gravity.

Table 3.7: Oxford muscle testing – Grade 2[84]

Grade 2				
Muscle	**Starting position**	**End position**	**Commands**	**Points to notice**
Trapezius (Upper fibres)	• Supine in bed. • Shoulder joint and scapula in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint.	• Supine in bed. • Full scapula elevation in the frontal plane.	• "Lift up your shoulder to your ear."	• No scapula protraction or shoulder medial rotation. • Acromion at the mid cervical level. • ROM to be equal L & R gravity eliminated.

Table 3.7: Oxford muscle testing – Grade 2[84] (Continue)

Muscle	Starting position	End position	Commands	Points to notice
Deltoid (Middle fibres)	• Supine in bed. • Shoulder joint and scapula in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint. • Arm by side. • Elbow 90º flexion, thumb facing towards the roof and fingers facing straight forward.	• Supine in bed. • Shoulder joint in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint. • Arm away from the body in the frontal plane up to 90°shoulder abduction, elbow in line with the shoulder. • Elbow 90° flexion with forearm perpendicular to floor and thumb facing parallel to the roof.	• "Try to move your elbow to the side, away from your body to shoulder level."	• No scapula protraction / elevation. • Elbow level with shoulder. • Shoulder joint in the frontal plane with no rotation (earlobe, AC joint and elbow to be in line). • ROM to be equal L & R gravity eliminated.
Sternocleidomastoid (Unilateral testing)	• Side lying in bed. • Neck in neutral alignment confirmed with the plumb line. Plumb line: chin tucked – earlobe – C2 – sh joint	• Side lying in bed. • Chin on mid clavicle, with neck flexion, no rotation of cervical spine.	• "Turn your head to your side and try to lift up your neck, put your chin on your collar bone."	• No scapula protraction. • No poking chin. • No trunk flexion. • ROM to be equal L & R gravity eliminated.
Pectoralis major (Sternal & clavicular fibres)	• Sitting in bed. • Shoulder and scapula in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint. • Shoulder 90° flexion and slight medial rotation, elbow 90°flex.	• Sitting in bed. • Arm adducted towards opposite iliac crest. • Elbow extended.	• "Push your arm down towards your opposite hip, make your elbow straight."	• Shoulder joint in the frontal plane, no rotation. • No trunk rotation. • No trunk side flexion. • No hip rotation / add. • No hip hitch / pelvic elevation. • ROM to be equal L & R gravity eliminated.

Table 3.8: Oxford muscle testing – Grade 1[84]

Grade 1				
Muscle	**Starting position**	**End position**	**Command**	**Points to notice**
Trapezius (Upper fibres)	• Supine in bed. • Shoulder joint and scapula in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint.	• Supine in bed. • Shoulder joint in the frontal plane with no scapula elevation.	• "Try to lift your shoulder to your ear."	• Visible muscle contraction. • No scapula protraction / shoulder medial rotation. • Palpable muscle contraction over upper trapezius.
Deltoid (Middle fibres)	• Supine in bed. • Shoulder joint and scapula in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint. • Arm by side. • Elbow 90º flexion, thumb facing towards the roof and fingers facing straight forward.	• Supine in bed. • Shoulder joint in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint. • Arm by side. • Elbow 90º flexion, thumb facing towards the roof and fingers facing straight forward.	• "Try to move your elbow to the side, away from your body."	• Visible contraction. • No scapula protraction / elevation. • Researcher support elbow and wrist. • Palpable muscle contraction over middle deltoid.

Table 3.8: Oxford muscle testing – Grade 1[84] (Continue)

Muscle	Starting position	End position	Commands	Points to notice
Sternocleidomastoid (Unilateral testing)	• Side lying in bed. • Neck in neutral alignment confirmed with the plumb line. Plumb line: chin tucked – earlobe – C2 – shoulder joint.	• Side lying in bed. • Neck in neutral alignment confirmed with the plumb line. Plumb line: chin tucked – earlobe – C2 – shoulder joint.	• "Try to turn your head to your side and try to lift up your neck, put your chin on your collar bone."	• Visible contraction. • No scapula protraction. • No poking chin. • No trunk flexion. • Palpable muscle contraction over sternocleidomastoid.
Pectoralis major (Sternal & clavicular fibres)	• Sitting in bed. • Shoulder and scapula in neutral alignment confirmed with the plumb line: earlobe – C2 – shoulder joint. • Shoulder 90° flexion and slight medial rotation, elbow in 90° flexion.	• Sitting in bed. • Shoulder and scapula in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint. • Shoulder 90° flexion and slight medial rotation, elbow in 90° flexion.	• "Try to push your arm towards your opposite hip, keep your elbow straight."	• Visible contraction. • Researcher support the arm. • Shoulder girdle in the frontal plane with no rotation. • No trunk rotation. • No trunk side flexion. • No hip rotation / adduction. • No hip hitch / pelvic elevation. • Palpable contraction over pectoralis major.

Table 3.9: Oxford muscle testing – Grade 0[84]

Grade 0				
Muscles	**Starting position**	**End position**	**Commands**	**Points to notice**
Trapezius (Upper fibres)	• Supine in bed. • Shoulder joint and scapula in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint.	• Supine in bed. • Shoulder joint in the frontal plane with no scapula elevation.	• "Try to lift your shoulder to your ear."	• No visible movement. • No scapula protraction / shoulder rotation. • No palpable muscle contraction over upper trapezius.
Deltoid (Middle fibres)	• Supine in bed. • Shoulder joint and scapula in neutral alignment confirmed with the plumb line. Plumb line: earlobe - C2 - shoulder joint. • Arm by side. • Elbow 90º flexion, thumb facing towards the roof and fingers facing straight forward.	• Supine in bed. • Shoulder joint in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint • Arm by side. • Elbow 90º flexion, thumb facing towards the roof and fingers facing straight forward.	• "Try to move your elbow to the side, away from your body."	• No visible movement. • No scapula protraction / elevation. • Researcher support elbow and wrist. • No palpable muscle contraction over middle deltoid.
Sternocleidomastoid (Unilateral testing)	• Side lying in bed. • Neck in neutral alignment confirmed with the plumb line. Plumb line: chin tucked – earlobe – C2 – shoulder joint.	• Side lying in bed. • Neck in neutral alignment confirmed with the plumb line. Plumb line: chin tucked – earlobe – C2 – shoulder joint.	• "Try to turn your head to your side and try to lift up your neck, put your chin on your collar bone."	• No visible movement. • No scapula protraction. • No poking chin. • No trunk flexion. • No palpable muscle contraction over sternocleidomastoid.

Table 3.9: Oxford muscle testing – Grade 0[84] (Continue)

Muscle	Starting position	End position	Commands	Points to notice
Pectoralis major (Sternal & clavicular fibres)	• Sitting in bed. • Shoulder and scapula in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint. • Shoulder 90° flexion and slight medial rotation, elbow in 90° flexion.	• Sitting in bed. • Shoulder and scapula in neutral alignment confirmed with the plumb line. Plumb line: earlobe – C2 – shoulder joint. • Shoulder 90° flexion and slight medial rotation, elbow in 90° flexion.	• "Try to push your arm towards your opposite hip, keep your elbow straight."	• No visible movement. • Researcher support the arm. • Shoulder girdle in the frontal plane with no rotation. • No trunk rotation. • No trunk side flexion. • No hip rotation / adduction. • No hip hitch / pelvic elevation. • No palpable contraction over pectoralis major.

Muscle testing was discontinued immediately when a patient developed any sign of haemodynamic instability (any changes of 20% of the baseline heart rate, blood pressure or oxygen saturation). Patients rested for a minimum of five minutes or until their heart rate and oxygen saturation were back to baseline between positional changes (sitting to supine) and the different tests.

After completing the muscle strength testing, the patients were positioned in an upright position in bed with arms by side and elbow 90° flexed to test the handgrip strength[88] with the handgrip dynamometer (Figure 3.2). The forearm was allowed to rest on the thigh. For all patients the maximum contraction was determined as the highest of three contractions.[88] The dynamometer handle was in the second position as described by published recommendations from the American Society of Hand Therapists.[76] There were one minute rest periods between contractions. The dominant and non-dominant hand were tested.

Figure 3.2: Handgrip dynamometer

Exercise endurance was tested with the MOTOmed® letto2 cycle ergometer (Figure 3.3) after the handgrip assessment was completed.

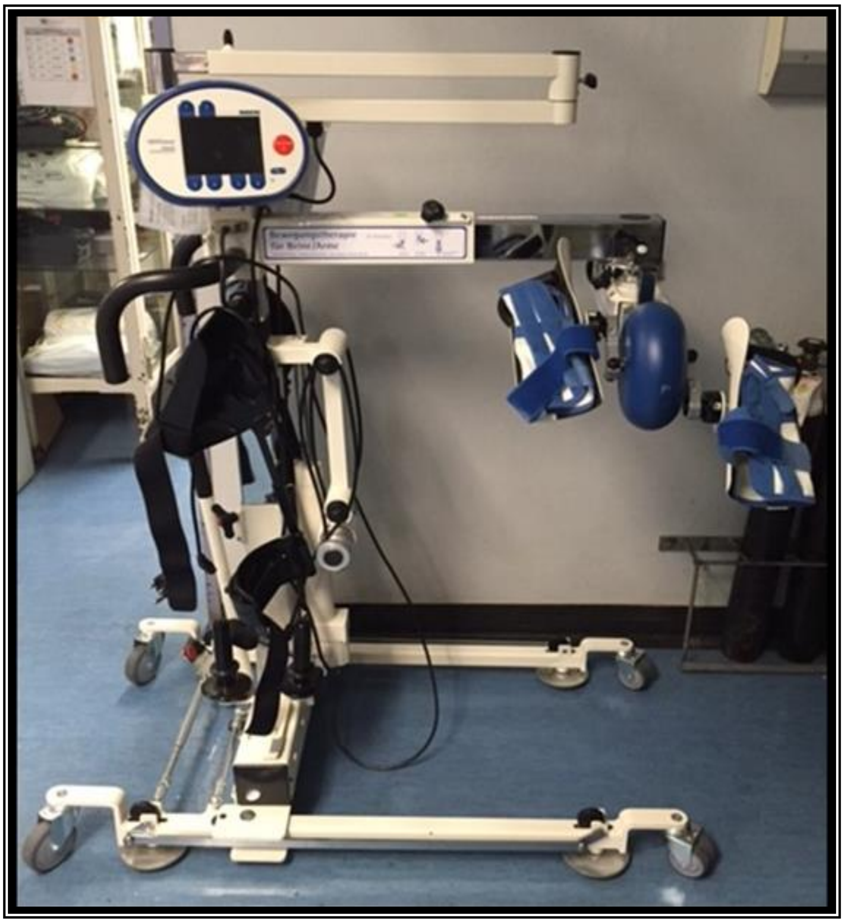

Figure 3.3: MOTOmed® letto2cycle ergometer

The linear results from an earlier pilot study[20] illustrated that similar patients as the current study riding a mean distance of 0.5 km in 4.12 minutes with the MOTOmed® letto2 cycle ergometer had a strong association (*P* = 0.014) to be extubated successfully. The handgrip dynamometer and cycle ergometer were automatically calibrated before every test.[110] Patients rested for five minutes or until the heart rate and oxygen saturation were back to baseline before exercise endurance testing was commenced. Patients were positioned in the semi-fowler's position (45° hip flexion), in bed. This is the standard position for care in the ICU. The patient's upper limbs were placed in the forearm shells with arm cuffs (Figure 3.4).[110] The cycle ergometer was fixated with the four brake stop next to the bed.[110] Patients rode the cycle ergometer for six minutes[95] with the upper limbs. The Servo Cycle program was used during the study. Patients rode against a resistance of one gear (1 gear = 0.85 kg).

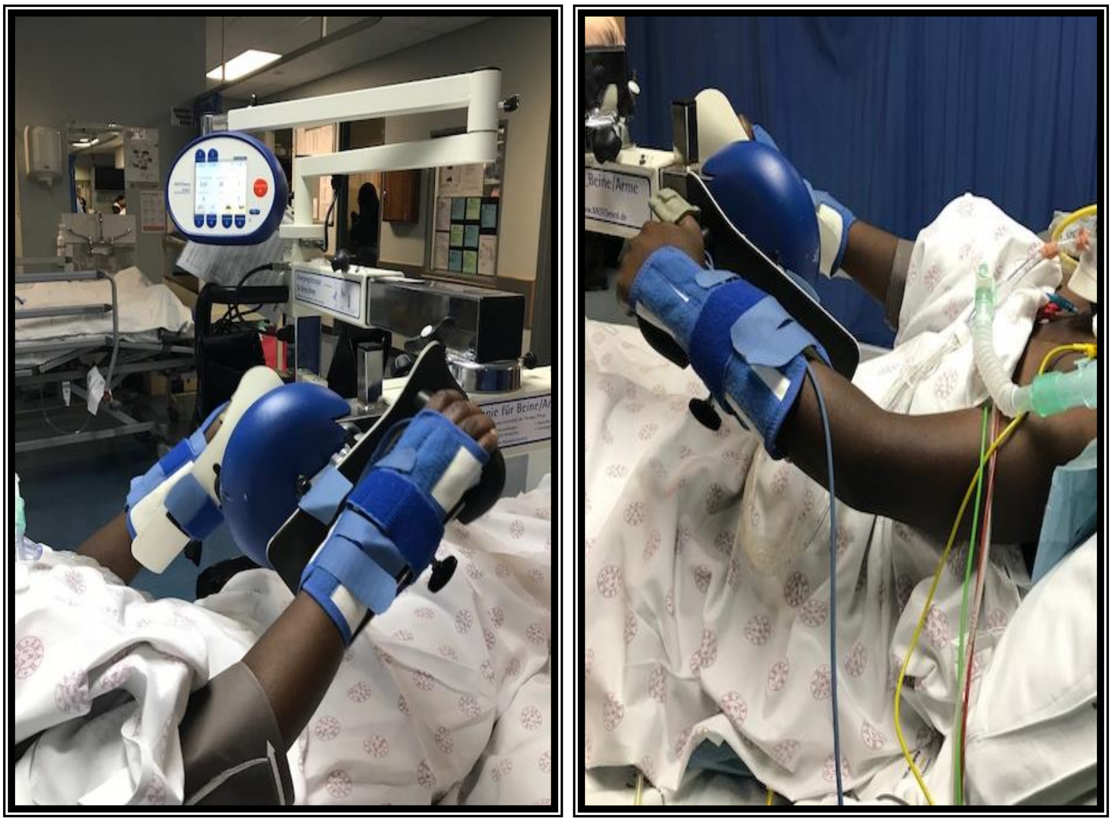

Figure 3.4: Upper limbs in forearm shells with cuffs

According to the pilot study conducted by De Beer et al.[20] a resistance of one gear is including the weaker and stronger patients. The time and distance the patient rode actively (pushing the pedals themselves) as well as passively (machine is moving the pedals) were documented. Riding the cycle ergometer was stopped immediately when the patient developed any sign of haemodynamic instability (any changes by 20% from the baseline heart rate, systolic blood pressure or oxygen saturation). The MOTOmed® letto2 cycle ergometer is a safe tool with a CE 0124 and ISO safety certificates and qualifications.

The MIP was measured after five minutes rest or until the patient's heart rate and oxygen saturation were back to baseline. Patients remained in the semi-fowler's position in bed for the MIP measurements. The manometer was connected to the endotracheal tube / tracheostomy (Figure 3.5). Each patient did three measurements and the best reading was used in the study.

Figure 3.5: MIP measurement with manometer

Patients started with the SBT and extubation process 30 minutes after completion of the muscle strength and endurance tests. The SBT and extubation process was done according to usual care in the unit. Patients were evaluated for 48 hours to 72 hours post SBT or extubation to determine whether the patient passed the SBT and whether the patient was successfully extubated. Patients who were unable to complete the study were excluded during data analysis. After each patient, the MOTOmed® letto2 cycle ergometer, handgrip dynamometer and MIP manometer were cleaned according to the infection control policy of the Steve Biko Academic Hospital.

3.6 Safety measurements and adverse events

Muscle testing or exercise endurance testing were discontinued immediately when a patient developed any sign of haemodynamic instability (any changes of 20% of the baseline heart rate, blood pressure or oxygen saturation). Patients rested for a minimum of five minutes or until their heart rate and oxygen saturation were back to baseline between positional changes (sitting to supine) and the different tests. Patients also had to respond to the qualitative question whether they were comfortable or not before any test commenced.

No further testing was commenced if the heart rate, blood pressure or oxygen saturation did not return to baseline after five minutes.

No adverse events were reported during the study. All patients completed the process of data collection.

3.7 Pilot study

The pilot study was conducted in the Trauma-Surgery and Medical ICU's of the Steve Biko Academic Hospital to clear all time and logistical associated problems. Five patients who gave informed consent were recruited during the pilot study. The patients' peripheral and respiratory muscle strength and exercise endurance were evaluated. The endurance was tested with the MOTOmed® letto2 cycle ergometer in the semi-fowler's position. The muscle strength was tested with the MRC-score, Oxford grading scale and handgrip dynamometer. Respiratory muscle strength was tested with the MIP. The electrolytes, PaO_2/FiO_2 ratio, RSBI, days ventilated and days in ICU were documented according to the data sheet. Patients were evaluated for 48 hours to 72 hours post SBT or extubation to determine whether the patient passed the SBT and whether the patient was successfully extubated. The results of the pilot study were not included in the results of the current study.

The process of data collection during the pilot study is presented in Figure 3.6.

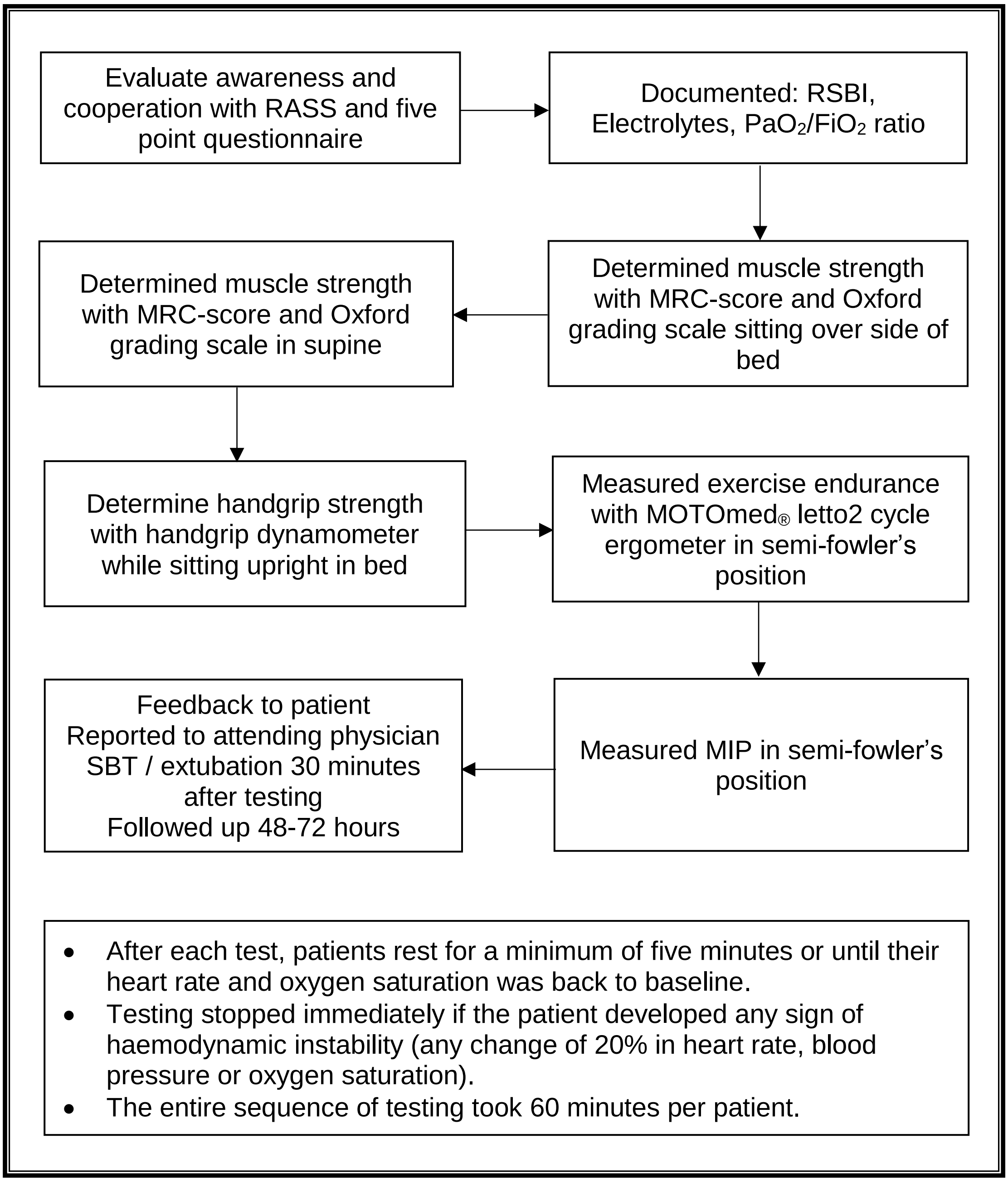

Figure 3.6: Flow diagram indicating the research process of the pilot study

The results of the pilot study demonstrated that four of the five patients were successfully extubated. One patient failed extubation. This patient had an oesophagostomy, jejenostomy, gastrostomy and pneumothorax after a stab neck injury. The patient was also diagnosed with pulmonary tuberculosis (TB). The patient was ventilated for 18 days. The patients who were successfully extubated were ventilated between three and eight days. In order to increase the comfort of the patient and avoid exhaustion due to position changes (sitting over the side of the bed → supine → sitting up in bed → semi-fowler's), the muscle testing positions were adapted to sitting up in bed. During the pilot study, it took 60 minutes to complete data collection, but after adapting to sitting up in bed, data collection only took 45 minutes. Previous research studies conducted by Vanpee et al.[65] and Hermans et al.[78] supported the position changes of the researcher. They adapted the MRC-score by extrapolation of the limb's result with the contralateral limb results when one limb was affected by orthopaedic reasons and could not be tested.[65,78]

3.8 Statistical considerations

The statistical analysis of the study was conducted in collaboration with the statistical consultant, Prof PJ Becker. The statistical objective of this study was to develop a prediction equation based on upper limb muscle strength (deltoid, sternocleidomastoid, trapezius and pectoralis major muscles) and exercise endurance for outcome of extubation.

3.8.1 Sample size

Multivariable logistic regression modelling was employed to develop the prediction equation for the 40% expected failure of extubation. No more than six predictor variables were expected to enter the prediction equation based on muscle strength (muscles tested with the Oxford grading scale, MRC-score and MIP). Based on the methodology of Peduzzi et al.[111] a sample of 60 patients was required to ensure that the events per variable ≥ 5, (that is when events ≥ 5 x 5 = 25) and the expected failure rate is 0.4 (40%). Furthermore, for the prediction equation based on exercise endurance also less than six (maximum of five) predictor variables were expected to enter in the prediction equation and hence this sample of 60 patients were adequate.

3.8.2 Data analysis

Data summary of continuous variables reported descriptive statistics, mean, standard deviation, median, inter quartile range and 95% confidence intervals. For discrete parameters frequency, percentage, cross tabulation and 95% confidence intervals were reported. Univariable analyses were done to assess the association of the observed variables/factors with extubation outcome. For continuous data use was made of Student's two-sample T-test while for discrete data Pearson's chi-square test and univariable logistic regression was employed. The purpose of the univariable analysis was to identify possible factors for inclusion in a multivariable logistic regression analysis to develop the prediction equation. In the modelling process variables/factors which were no longer significant in the multivariable model dropped out, multicollinearity among variables/factors was also responsible for dropout. Testing was done at the 0.05 level of significance.

The predictive ability of the prediction equation was assessed using cross validation for the latter best equation, i.e. for each patient outcome was predicted using the prediction equation fitted to the remaining 56 patients. Note that 57/60 patients had complete data for the variables that remained in the prediction equation.

3.9 Data storage

The raw data will be safely stored in the Physiotherapy Department of the University of Pretoria for 15 years.

The results of the current study will be presented in tables and figures in Chapter 4.

CHAPTER 4
RESULTS

The study was conducted from 1 February 2018 to 30 September 2019 in the Steve Biko Academic Hospital, Pretoria, South Africa. During this 19 month period, no data collection could be performed for six months due to logistical challenges. The data were collected from the Trauma / Surgery and Medical Intensive Care Units (ICU's). A total of 463 patients were recruited but only 57 patients were included in the study procedure and data analysis. In Chapter 3, it was indicated that 60 patients will be included, but due to the events per variate that were less than five, the 57 patients demonstrated statistically significant results. The 406 patients who were excluded from the study according to the exclusion criteria as described in Chapter 3. The reasons for exclusion from the study are presented in Figure 4.1.

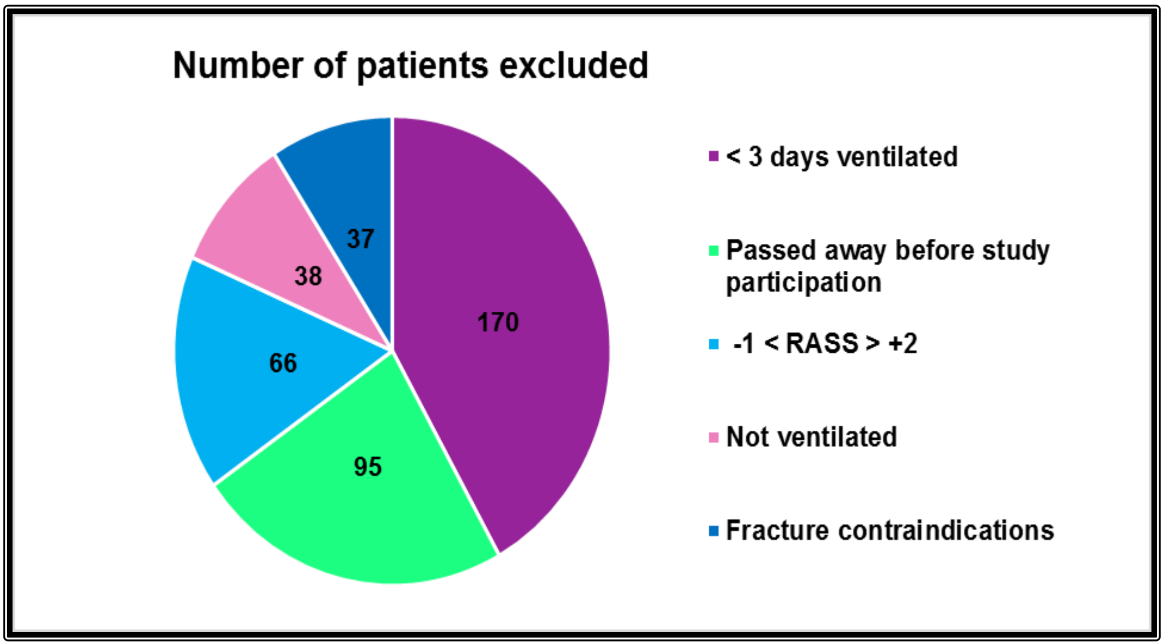

Figure 4.1: Number of patients excluded from the current study

The 57 patients included represent 34 males and 23 females. All the included patients completed the assessment. No adverse events were recorded. The results will be presented according to the objectives of the study. The flow diagram in Figure 4.2 explain the research procedure and data management.

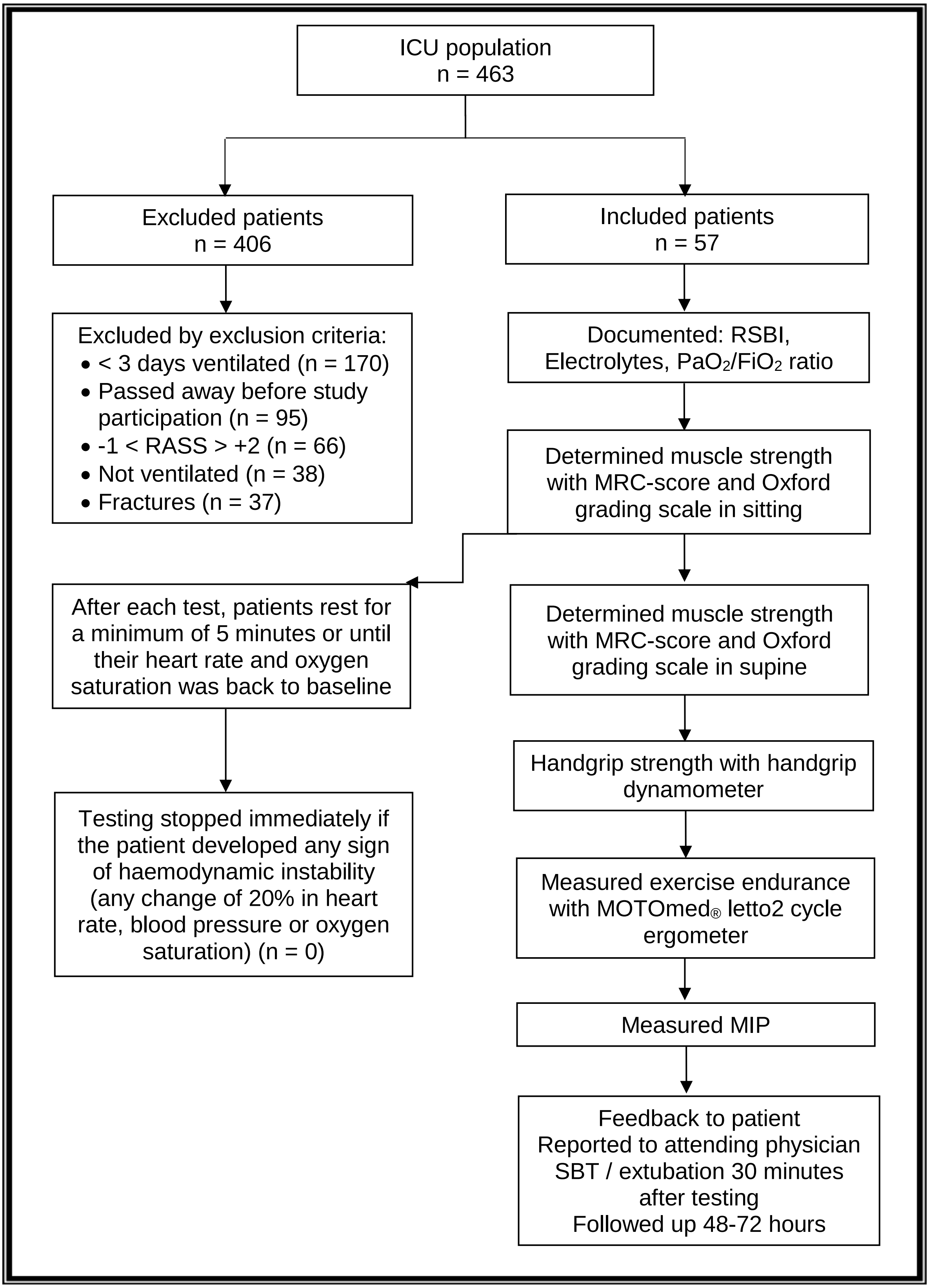

Figure 4.2: Flow diagram explaining the research procedure and data management

The diagnosis of the patients are summarised in Figure 4.3.

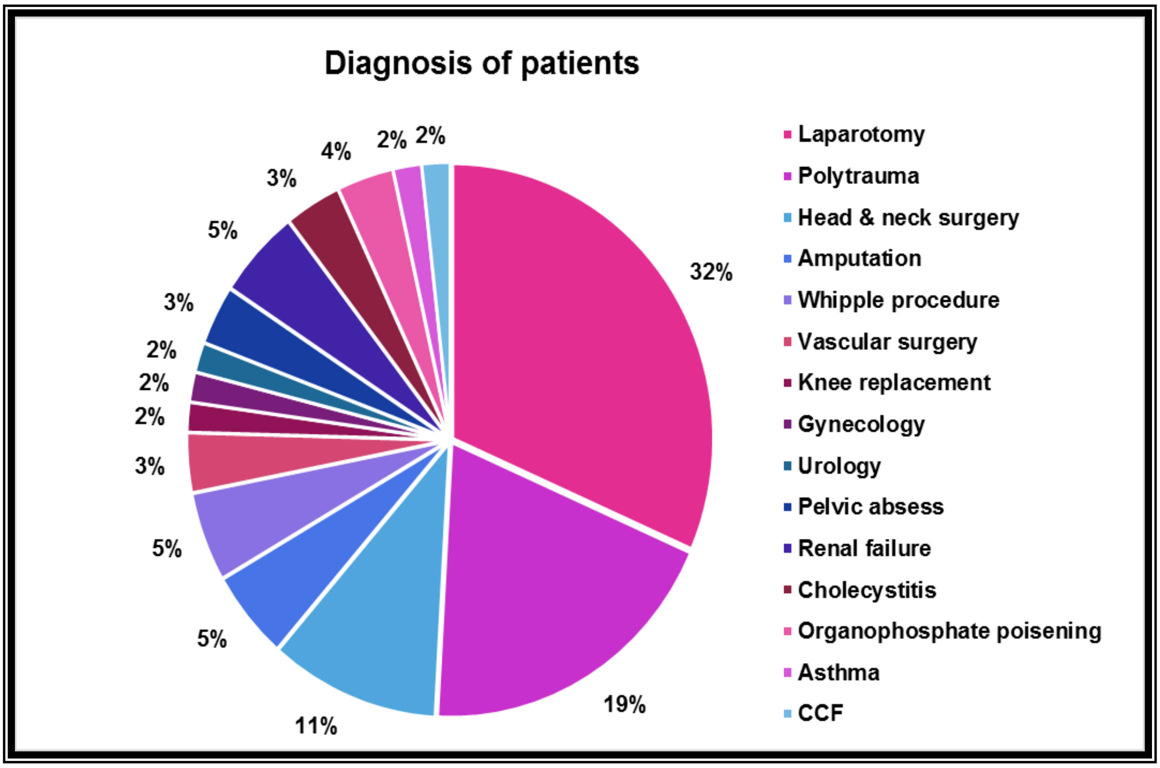

Figure 4.3: Diagnosis of patients

Continuous data were analysed with Student's two-sample T-test and summarised using mean, standard deviation, median, interquartile range and 95% confidence intervals. Univariable logistic analysis was performed to identify the marginal significant and significant factors to be included in the multivariable logistic regression analysis to develop the final prediction equation. Due to multicollinearity elimination of factors were done. The predictive ability of the prediction equation was assessed using cross validation. Testing was based on a 0.05 level of significance. $P \leq 0.05$ was regarded as statistically significant, $0.05 < P \leq 0.1$ was marginally significant and $P > 0.1$ was not significant. Data analysis employed STATA version 15.1 software.[112] The outcome of extubation in this chapter is referred to and divided into successful extubation and failed extubation.

The demographic data of the patients are represented in Table 4.1.

Table 4.1: Demographic data of the cohort

Variable	Successful extubation n = 35	Failed extubation n = 22	*P*- value
Male	19 (55.9%)	15 (44.1%)	0.407
Female	16 (69.6%)	7 (30.4%)	0.407
Age	43.171 (14.475)*	47.455 (17.522)*	0.321
Number of days ventilated	5.714 (3.304)*	7.754 (6.197)*	0.001

** mean (SD – standard deviation)*

Seven female (30.4%) and 15 male (44.1%) patients failed extubation. Sixteen female (69.6%) and 19 male (55.9%) patients were successfully extubated. The Fisher's exact test demonstrated that gender (*P* = 0.407) is not statistically significantly associated with successful extubation. Logistic regression analysis indicated a relative risk of 1.8 (*P* = 0.30). The difference in the ages of the successful and unsuccessful extubated patients was also not significant (*P* = 0.321).

Results to assess whether upper limb muscle strength could predict successful extubation in mechanically ventilated patients who are critically ill will be explained in Table 4.2. to Table 4.4.

The upper limb muscle strength of the sternocleidomastoid (*P* = 0.058) and trapezius muscles (*P* = 0.095), tested with the Oxford grading scale, demonstrated with the Fisher's exact test a marginally significant association with successful extubation. The muscle strength of the deltoid (*P* = 0.366) and pectoralis major (*P* = 0.417) muscles were not significantly associated with successful extubation. Successfully extubated patients had a marginally significant greater proportion of grade 3 muscle strength of sternocleidomastoid (*P* = 0.058: 71,4% vs 45,5%) and trapezius (*P* = 0.095: 94,3% vs 77,3%) muscles than failed extubated patients.

Logistic regression analysis for the upper limb muscle strength in Table 4.2 also reflected that the sternocleidomastoid and trapezius muscles were marginally significantly associated with successful extubation.

Table 4.2: Univariable logistic regression: Upper limb muscle strength tested with Oxford grading scale

Variable	Odds Ratio	Std. Err	*P*-value	95% Conf. Interval
Sternocleidomastoid muscle	3	1.706	0.053	0.984 – 9.144
Trapezius muscle	4.853	4.311	0.075	0.851 – 27.679
Deltoid muscle	1.929	1.155	0.273	0.596 – 6.235
Pectoralis major muscle	1.715	0.944	0.327	0.583 – 5.047

The Student two-sample T-test showed that the mean body muscle strength, tested with the Medical Research Council score (MRC-score), was significantly (*P* = 0.003) greater in the successfully extubated group (Table 4.3). A one point increase in the MRC-score was associated with a 7% reduction in the risk for failing extubation (Table 4.4). The extubation groups were marginally significantly different with regards to the mean handgrip strength measured with the handgrip dynamometer and respiratory muscle strength measured with the maximum inspiratory pressure (MIP) respectively.

Table 4.3: Student two-sample T-test: MRC-score, handgrip strength and MIP

Variable	Mean	Std. Dev	*P*-value	95% Conf. Interval
MRC-score: Successful extubation	42.514*	9.642	0.003	39.202 – 45.826
MRC-score: Unsuccessful extubation	32.909*	13.815		26.784 – 39.034
Handgrip strength: Successful extubation	13.314**	12.129	0.052	9.148 – 17.481
Handgrip strength: Unsuccessful extubation	7.682**	6.841		4.649 – 10.715
MIP: Successful extubation	-19.857[#]	6.459	0.089	-22.076 – -17.639
MIP: Unsuccessful extubation	-17[#]	3.678		-18.829 – -15.171

** Score out of 60; ** Measured in kg, [#] Measured in cmH*$_2$*O*

Logistic regression analysis of the MRC-score, handgrip strength and MIP, presented in Table 4.4, indicated that only the MRC-score was significantly associated with successful extubation. The handgrip strength and MIP were only marginally significantly associated with successful extubation.

Table 4.4: Univariable logistic regression: MRC-score, handgrip strength and MIP

Variable	Odds Ratio	Std. Err	*P*-value	95% Conf. Interval
MRC-score	0.931	0.025	0.007	0.884 – 0.980
Handgrip strength	0.943	0.030	0.061	0.887 – 1.003
MIP	1.148	0.095	0.095	0.976 – 1.351

Results to determine whether exercise endurance could predict successful extubation in mechanically ventilated patients who are critically ill will be explained in Table 4.5 to Table 4.6.

Exercise endurance (time rode actively) tested with the cycle ergometer was significantly associated with successful extubation (Table 4.5). The Student two sample T-test showed that successfully extubated patients rode the cycle ergometer significantly (P = 0.003) longer by themselves (actively), than the failed extubated patients.

Table 4.5: Student two-sample T-test: Exercise endurance

Variable	Mean	Std. Dev	*P*-value	95% Conf. Interval
Active time rode: Successful extubation	236.743*	135.380	0.003	190.238 – 283.248
Active time rode: Unsuccessful extubation	122.091*	132.274		63.444 – 180.738
Passive time rode: Successful extubation	121.829*	134.271	0.004	75.705 – 167.952
Passive time rode: Unsuccessful extubation	230.818*	133.969		171.420 – 290.217
Active distance covered: Successful extubation	0.628**	0.534	0.012	0.443 – 0.813
Active distance covered: Unsuccessful extubation	0.286**	0.367		0.124 – 0.449
Passive distance covered: Successful extubation	0.198**	0.221	0.006	0.122 – 0.274
Passive distance covered: Unsuccessful extubation	0.370**	0.222		0.272 – 0.468

** Time in seconds; ** Distance in km*

The logistic regression analysis indicated that for every 15 seconds that the patient rode actively on the cycle ergometer with the upper limbs, their relative risk (Odds ratio: 0.994) to fail extubation decreased with 5% (Table 4.6).

Table 4.6: Logistic regression: Exercise endurance

Variable	Odds ratio	Std. err	*P*-value	95% Conf. interval
Time rode actively	0.994	0.002	0.005	0.990 – 0.998
Time rode passively	1.006	0.002	0.007	1.002 – 1.010
Active distance covered	0.161	0.125	0.018	0.035 – 0.735
Passive distance covered	27.882	35.457	0.009	2.306 – 337.122

Post testing the successfully extubated patients did not differ significantly from the failed extubated patients with respect to mean heart rate (% of maximum heart rate) (*P* = 0.125: 54.8% vs 59.4%). In Table 4.7, the Student two sample T-test showed that the resting heart rate was marginally associated with successful extubation. Systolic and diastolic blood pressure measurements were not significantly associated with successful extubation.

Table 4.7: Student two-sample T-test: Heart rate and blood pressure

Variable	Mean	Std. Dev	*P*-value	95% Conf. Interval
Resting heart rate: Successful extubation	51.241*	11.520	0.055	47.284 – 55.198
Resting heart rate: Unsuccessful extubation	57.126*	10.227		52.592 – 61.660
Heart rate post testing: Successful extubation	54.756*	11.442	0.125	50.827 – 58.688
Heart rate post testing: Unsuccessful extubation	59.412*	10.208		54.886 – 63.938
Systolic blood pressure: Successful extubation	133.629**	20.084	0.957	126.730 – 140.528
Systolic blood pressure: Unsuccessful extubation	133.909**	16.653		126.526 – 141.293
Diastolic blood pressure: Successful extubation	71.914**	11.444	0.154	67.983 – 75.845
Diastolic blood pressure: Unsuccessful extubation	76.500**	12.011		71.175 – 81.825

** Measured in b/m; ** Measured in mmHg*

Logistic regression analysis (Table 4.8) indicated that the resting heart rate is only marginally significantly associated with successful extubation, but the heart rate post exercise was not significantly associated with successful extubation.

Table 4.8: Logistic regression: Heart rate and blood pressure

Variable	**Odds ratio**	**Std. err**	***P*-value**	**95% Conf. interval**
Resting heart rate	1.051	0.028	0.060	0.998 – 1.108
Heart rate post testing	1.041	0.272	0.127	0.989 – 1.096
Systolic blood pressure	1.001	0.015	0.956	0.972 – 1.030
Diastolic blood pressure	1.036	0.026	0.157	0.987 – 1.087

The Fisher's exact test showed that the Richmond Agitation-Sedation scale (RASS) was marginally significantly (P = 0.088) associated with successful extubation.

The logistic regression analysis indicated with an Odds ratio of 0.115, standard error of 0.129, P = 0.053 and 95% confidence interval (0.130 – 1.027) that the RASS was only marginally significantly associated with successful extubation.

In Table 4.9, the Student two-sample T-test of the continuous data showed that the rapid shallow breathing index (RSBI) is significantly (P = 0.018) associated with successful extubation. The partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2 ratio) was only marginally significantly (P = 0.098) associated with successful extubation.

The Student two-sample T-test also indicated that successfully extubated patients were significantly (P = 0.001) shorter ventilated.

Table 4.9: Student two-sample T-test: Continuous data (RSBI, PaO_2/FiO_2 ratio and number of days ventilated)

Variable	Mean	Std. dev	*P*-value	95% Conf. interval
RSBI: Successful extubation	35.486*	18.421	0.018	29.158 – 41.813
RSBI: Unsuccessful extubation	50.941*	29.713		37.767 – 64.115
PaO_2/FiO_2 ratio: Successful extubation	298.657	71.388	0.098	274.135 – 323.178
PaO_2/FiO_2 ratio: Unsuccessful extubation	262.095	89.429		221.388 – 302.803
Days ventilated: Successful extubation	5.714**	3.304	0.001	4.579 – 6.849
Days ventilated: Unsuccessful extubation	7.754**	6.197		7.377 – 14.623

** fR/VT = breaths/min.L; ** Number of days*

The logistic regression analysis in Table 4.10 indicated that for every day a patient was ventilated, the higher the relative risk (Odds ratio = 1.242) was to fail extubation.

Table 4.10: Logistic regression: Continuous data (RSBI, PaO_2/FiO_2 ratio and number of days ventilated)

Variable	Odds ratio	Std. err	*P*-value	95% Conf. interval
RSBI	1.030	0.014	0.031	1.006 – 1.057
PaO_2/FiO_2 ratio	0.994	0.004	0.102	0.987 – 1.001
Days ventilated	1.242	0.956	0.005	1.068 – 1.444

In an attempt to develop a prediction equation for extubation a multivariable logistic regression was employed considering the factors marginally significantly associated and significantly associated with successful extubation. These factors included the sternocleidomastoid muscle strength, trapezius muscle strength, MRC-score, handgrip strength, MIP, exercise endurance (time rode actively on the cycle ergometer), resting heart rate, RASS, PaO_2/FiO_2 ratio, number of days ventilated and RSBI as exposure factors, i.e. modelling started out considering those factors significant at the liberal 0.10 level of significant.

Furthermore, also of interest was the correlation of the MRC-score with exercise endurance and handgrip strength respectively. The MRC-score and exercise endurance were strongly correlated (r = 0.7247; P < 0.001) and the linear relationship was found as MRC-score = 26.97 + 0.062 x exercise endurance (active time rode) (Figure 4.4).

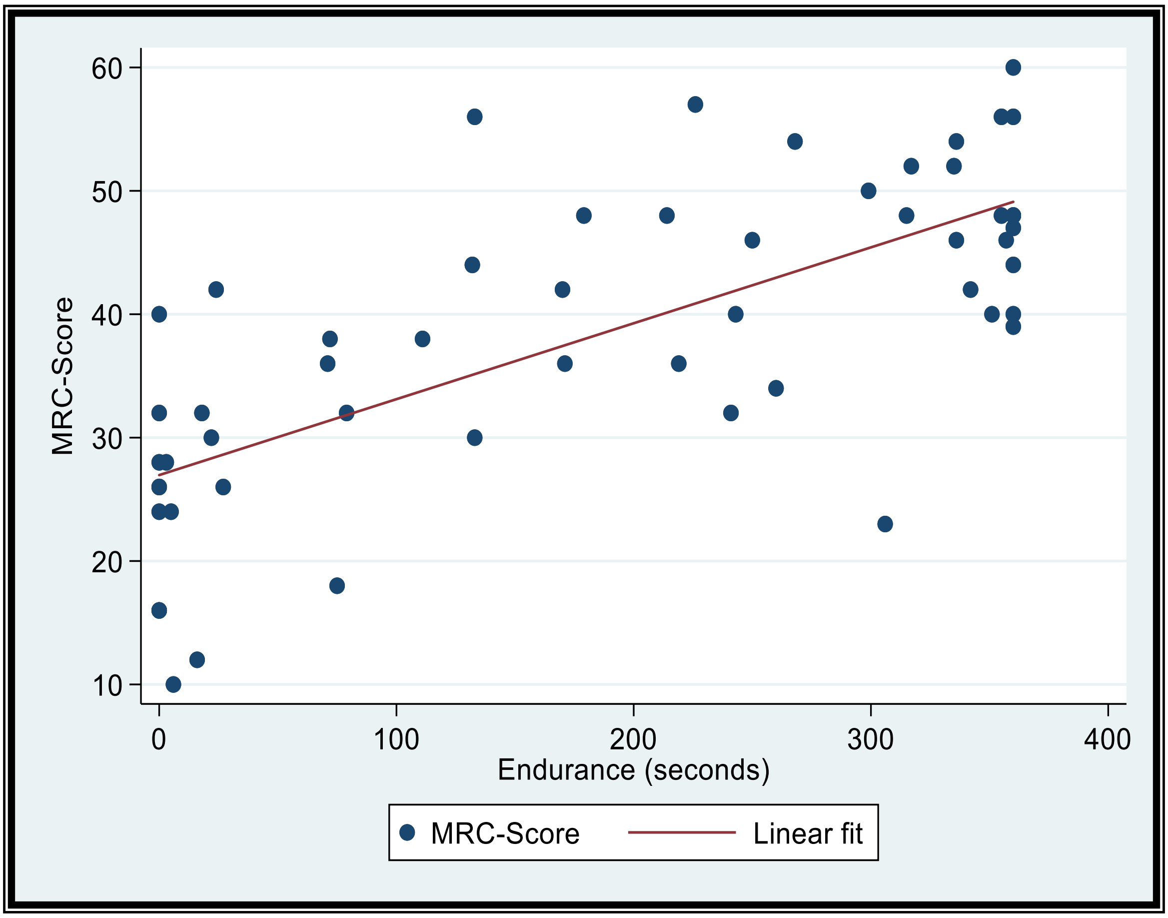

Figure 4.4: Regression line – MRC-score and exercise endurance

The MRC-score and handgrip strength also correlated (r = 0.5323; P < 0.001) and the linear relationship was found as MRC-score = 32.01 + 0.610 x handgrip strength (Figure 4.5). The handgrip strength and exercise endurance correlated (r = 0.5276; P < 0.001) with a lower correlation coefficient than the MRC-score and exercise endurance.

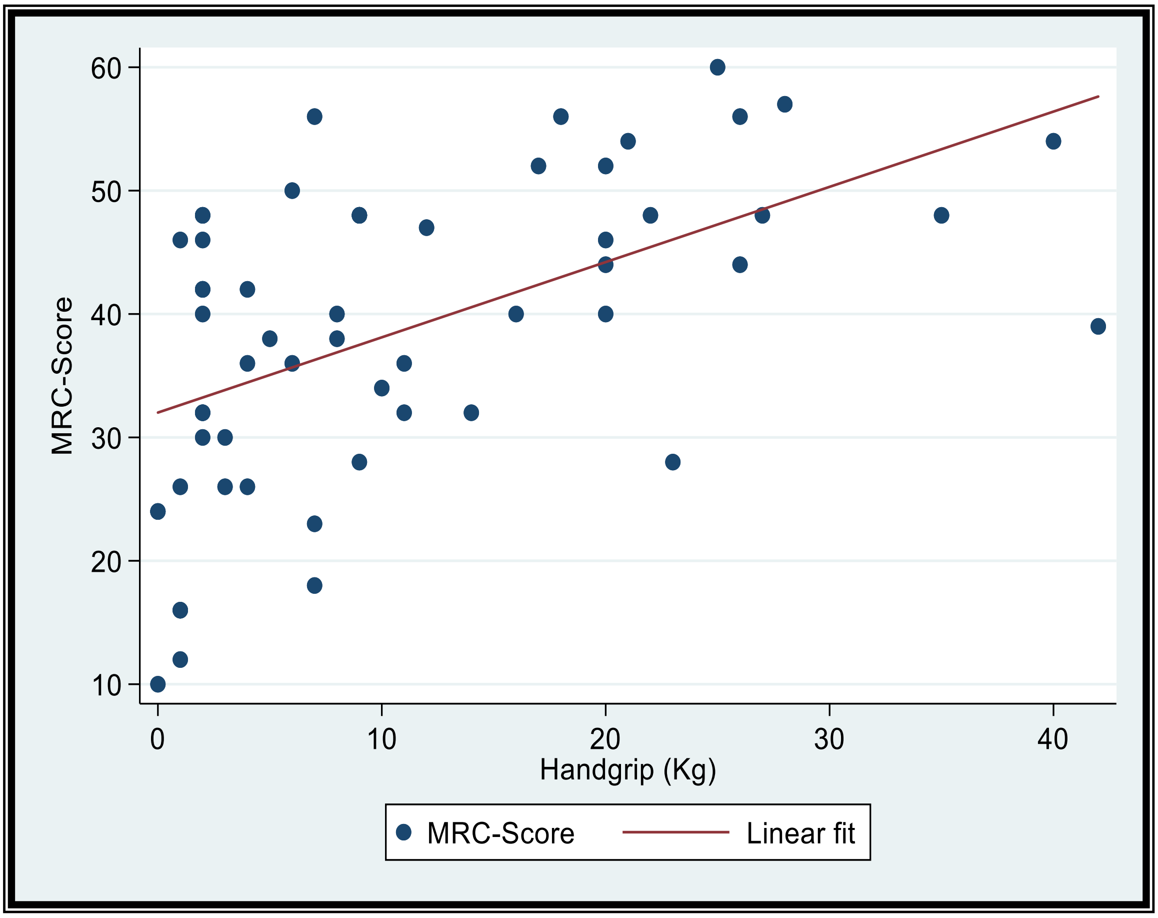

Figure 4.5: Regression line – MRC-score and handgrip strength

Comment: In view of the correlation between the MRC-score, exercise endurance and handgrip strength, there was multicollinearity when developing the prediction equation, hence the inclusion of exercise endurance only. After the elimination process due to multicollinearity, modulation of the remaining factors were performed. The final multivariable logistic regression prediction model included only the factors exercise endurance (active time the patient was riding in 15s units) and the number of days ventilated (Table 4.11) as the other factors did not contribute to the predictive value of the model.

Table 4.11: Multivariable logistic regression: Predictive equation model (Exercise endurance and number of days ventilated)

Variable	Odds ratio	Coef.	Std. err	*P*-value	95% Conf. interval
Active time (15s units)	0.899	-0.107	0.344	0.005	0.834 – 0.969
Days ventilated	1.258	0.230	0.109	0.008	1.062 – 1.491

This model had a sensitivity of 81.82% and a specificity of 77.14% for a 0.43 cut-off in the probability of a poor extubation outcome (Table 4.12).

Table 4.12: Sensitivity and specificity of predictive equation model (Exercise endurance and number of days ventilated)

Prevalence	Percentage
Sensitivity	81.82%
Specificity	77.14%
Positive predictive value	69.23%
Negative predictive value	87.10%
False positive rate for classified	30.77%
False negative rate for classified	12.90%
Area under ROC curve	84.4%

The predictive ability of the prediction equation was assessed using cross-validation for the latter best equation, based on number of days ventilated and exercise endurance respectively. The outcome for patient 1 was predicted from the above equation fitted to the data excluding patient 1. The data for patient 1 were then replaced and that of patient 2 removed before predicting the outcome for patient 2. This process was repeated up to the omission of patient 57.

The results in Table 4.13 indicate that the model has a sensitivity of 77.3% to predict failed extubation.

Table 4.13: Diagnostic statistics of the prediction model (Exercise endurance and number of days ventilated) after cross validation percentage (95% confidence interval)

Prevalence	**39% (26%; 52.4%)**
Sensitivity	77.3% (54.6%; 92.2%)
Specificity	74.3% (56.7%; 87.5%)
Positive predictive value	65.4% (44.3%; 82.8%)
Negative predictive value	83.9% (66.3%; 94.5%)
ROC area	0.758 (0.642; 0.874)
Odds ratio	9.82 (2.87; 33.4)

Remark: Including the RSBI in the multivariable logistic prediction model together with exercise endurance and number of days ventilated, the model had a sensitivity of 86.36% and specificity of 80% (Table 4.14)

Table 4.14: Sensitivity and specificity of predictive equation model (RSBI, exercise endurance and number of days ventilated)

Prevalence	**Percentage**
Sensitivity	86.36%
Specificity	80.00%
Positive predictive value	73.08%
Negative predictive value	90.32%
False positive rate for classified	26.92%
False negative rate for classified	9.68%
Area under ROC curve	86.1%

After cross validation the predictive model (RSBI, exercise endurance and number of days ventilated) demonstrated only a sensitivity of 68.2% and specificity of 74.3% (Table 4.15), therefore the final prediction model included only the factors exercise endurance (active time the patient was riding in 15s units) and the number of days ventilated.

Table 4.15: Diagnostic statistics of the prediction model (RSBI, exercise endurance and number of days ventilated) after cross validation percentage (95% confidence interval)

Prevalence	**39% (26%; 52.4%)**
Sensitivity	68.2% (45.1%; 86.1%)
Specificity	74.3% (56.7%; 87.5%)
Positive predictive value	62.5% (40.6%; 81.2%)
Negative predictive value	78.8% (61.1%; 91%)
ROC area	0.712 (0.589; 0.836)
Odds ratio	6.19 (1.95; 19.7)

The final model to predict extubation failure for a particular patient followed from equation:

$$\hat{y} = -1.0064 - (0.17 \text{ x active time}) + (0.230 \text{ x ventilator days})$$

A cut off value for $\hat{y}$, to predict poor outcome was determined as follows:

Prob (poor outcome) = $e^{\hat{y}}/(1+e^{\hat{y}})$ and when > 0.43 the patient is predicted to have a poor outcome, thus

$e^{\hat{y}}/(1+e^{\hat{y}}) > 0.43$

so that

$e^{\hat{y}} > 0.43(1+e^{\hat{y}}) = 0.43 + 0.43e^{\hat{y}}$

$e^{\hat{y}} - 0.43e^{\hat{y}} > 0.43$

$e^{\hat{y}}(1 - 0.43) > 0.43$

$e^{\hat{y}} > 0.43/0.57$

Hence $\hat{y} > \ell n(0.43/0.57) = -0.282$ predicts a poor outcome (failed extubation)

or

$\hat{y} \leq -0.282$ indicates successful extubation.

The calculations demonstrated that if the equation,

$$\hat{y} = -1.0064 - (0.17 \text{ x active time}) + (0.230 \text{ x ventilator days})$$

is used and the value for $\hat{y}$ is less than or equal to -0.282, the model has a sensitivity of 81.8% (Table 4.16) to predict successful extubation.

Table 4.16: Sensitivity and specificity of prediction model (Exercise endurance and number of days ventilated) with ŷ ≤ -0.282 percentage (95% Confidence interval)

Prevalence	**39% (26%; 52.4%)**
Sensitivity	81.8% (59.7%; 94.8%)
Specificity	77.1% (59.9%; 89.6%)
Positive predictive value	69.2% (44.3%; 85.7%)
Negative predictive value	87.1% (70.2%; 96.4%)
ROC area	0.795 (0.686; 0.903)
Odds ratio	15.2 (4.1; 55.7)

The electrolyte data were documented as part of the clinical data. All the values for the electrolytes were within normal limits and did not influence the extubation outcome. A summary of the results is presented in Table 4.17.

Table 4.17: Summary of results

Variables significantly associated with successful extubation (*P* ≤ 0.05)	**Variables marginally significantly associated with successful extubation (0.05 < *P* ≤ 0.1)**	**Variables not significantly associated with successful extubation (*P* > 0.1)**
• Exercise endurance (active time rode) • Number of days ventilated • MRC-score • RSBI	• Muscle strength of the sternocleidomastoid muscle • Muscle strength of the trapezius muscle • Handgrip strength • Resting heart rate • PaO_2/FiO_2 ratio • RASS • MIP	• Muscle strength of the deltoid muscle • Muscle strength of the pectoralis major muscle • Blood pressure • Gender • Age
Prediction equation: ŷ = -1.0064 – (0.17 x active time) + (0.230 x ventilator days) ŷ ≤ -0.282		

The results and limitations of the study will be discussed in the next chapter. Lastly recommendations and conclusions for this study will be presented.

CHAPTER 5
DISCUSSION

5.1 Discussion

Weaning from mechanical ventilation is a complex process. Many studies have been conducted to predict successful extubation and various predictors were reported. The reality is that none have been found to be individually highly accurate in terms of their predictive capacity. As a result, we still grapple with predicting extubation success with certainty and we also tend to utilise an individualised approach in terms of which tools to use to try and improve our predictive capacity.

The aim of this study was to determine if successful extubation in mechanically ventilated critically ill patients can be predicted by using upper limb muscle strength and exercise endurance.

The findings of the study will be discussed in accordance with the objectives set for this study, but the flow of the discussion will deviate from the order of the objectives outlined in chapter one. The primary objectives will be discussed firstly and thereafter the secondary objectives followed by integration of the various objectives / findings.

The main finding of this study is that successful extubation in mechanically ventilated critically ill patients may be predicted by exercise endurance. If using the newly developed prediction equation based on exercise endurance and number of days ventilated - $\hat{y}$ = -1.0064 – (0.17 x active time) + (0.230 x ventilator days) and the value for $\hat{y}$ is less than or equal to -0.282, the model has a sensitivity of 81.8% to predict successful extubation. The individual factors contributing to the development of the equation will be discussed next.

According to literature risk factors for extubation failure include neurological disorders, abundant secretions, a weak cough, respiratory or cardiac diseases, delirium, muscle weakness (< grade 3) and patients older than 65 years of age.[9-10,12-13,24] Failed extubation has a clinical impact on the patient and is associated with increase in the intensive care unit (ICU) length of stay, hospital length of stay and mortality rate.[12-13] Currently the challenge is that 10% to 20% of patients who successfully completed the spontaneous breathing trial (SBT), still fail extubation.[43]

Prediction of successful extubation is therefore of utmost importance to decrease the mortality rate and to avoid prolonged mechanical ventilation. Over the years several predictors including rapid shallow breathing index (RSBI), fluid balance, pneumonia, amount of secretions, cough strength, age, respiratory rate (RR), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), vital capacity (VC), partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2 ratio) and tidal volume (VT) have been investigated to determine successful extubation, but unfortunately, none of the predictors can be used in isolation and even combined their overall predictive accuracy remains unacceptably low and causes prolonged mechanical ventilation.[11,16-17]

Prolonged mechanical ventilation is associated with the development of respiratory muscle weakness,[24] nosocomial infections and critical illness myopathy or polyneuropathy. It is also associated with an increase in the ICU length of stay, hospital length of stay and mortality rate.[11] An increase in the ICU length of stay is associated with the development of ventilator associated pneumonia (VAP),[11] deep vein thrombosis and ICU acquired weakness (ICU-AW).[40] It has been demonstrated that ICU-AW is an independent predictor of prolonged mechanical ventilation.[41] Respiratory as well as peripheral muscle strength decrease after one week of mechanical ventilation.[41] Respiratory muscle endurance is also reduced with longer periods of mechanical ventilation.[24] Repeated weaning and extubation failure were associated with an imbalance between the increase load on the respiratory system and the reduced capacity of the respiratory muscles and cardiovascular system.[3,45]

A physiotherapist plays an important role in managing the patient's respiratory system as well as musculoskeletal system. Early mobilisation and rehabilitation according to a patient centred program are essential to decrease the development of peripheral muscle weakness and respiratory muscle weakness.[18,21]

Previously, extubation readiness was only determined by the physician.[35] The factors they evaluated to determine readiness for extubation included hemodynamic stability, mental and cognitive status, cough strength, nutritional status, reversal of the primary cause of intubation and specific lung function parameters like the MIP and RSBI.[35] None of these factors included muscle strength or exercise endurance. Keeping in mind the association between the extubation failure and reduced capacity of the cardiovascular system, respiratory muscle weakness, and peripheral muscle weakness the researcher hypothesised that muscle strength and exercise endurance might be used as predictors of successful extubation.

Exercise endurance represents the maximum amount of oxygen (VO_2max) a person can use to produce adenosine triphosphate (ATP) aerobically on a per minute basis.[92] VO_2max serves as a standard to compare performance estimates of aerobic capacity and endurance fitness.[92] According to Fletcher et al.[93] exercise endurance is a common physiological stress that can elicit cardiovascular or pulmonary abnormalities not present at rest. To maintain maximum oxygen uptake (exercise endurance) integration of the respiratory, cardiovascular and neuromuscular systems is necessary.[92] An increase in the cardiac output during exercise cause an increase in oxygen uptake by the working muscles as well as increase of blood flow to the lungs.[94]

Transferring the patient from pressure support ventilation during mechanical ventilation to spontaneous breathing after extubation lead to an increase in the work of breathing, myocardial oxygen consumption and haemodynamic changes.[113] According to Pinsky et al.[114] spontaneous breathing is regarded as exercise because patients should be able to maintain adequate oxygenation and ventilation with low levels of respiratory support that causes an increase in the work of breathing.

Evaluating the patient's exercise endurance should therefore assist the physiotherapist in determining whether the patient has the oxygen uptake and capacity to maintain the work of breathing that will be needed after extubation. A multidisciplinary approach is a very important aspect in the prevention of complications and the treatment of critically ill patients.[23] Cork et al.[14] showed that physiotherapists demonstrated a sensitivity of 100% and specificity of 68% to detect extubation failure in surgery and medical patients in ICU. Variables that were significantly associated with the physiotherapists' high risk classification were copious amount of secretions, RSBI, failure of the SBT and number of days ventilated. Plani et al.[23] state that the use of a weaning and extubation protocol that is led by nursing staff and physiotherapists results in a reduction in the number of days ventilated.

Our results which indicate that the number of days ventilated is associated with successful extubation are in agreement with Thille et al.[12] and Baptistella et al.[25] who indicated that the longer the patients are ventilated, the higher the risk for developing ICU-AW and extubation failure.

During our study exercise endurance was measured according to the time the patient rode the MOTOmed® letto2 cycle ergometer actively with their upper limbs while in a semi-fowler's position (45° hip flexion), in their ICU bed. In the study conducted by Sommers et al.115[115] to determine the feasibility and safety of exercise testing in ICU, the patients rode a cycle ergometer with the lower limbs in the semi-recumbent position as described in our study. Mitropoulos et al.[116] found that an arm crank ergometer can be used to evaluate exercise endurance when a person can't cycle with the lower limbs. The critically ill population were not included in the study conducted by Mitropoulos et al.,[116] they only included healthy subjects. Using the upper limb cycle ergometer for six minutes in our current study is in agreement with both Hol et al.[95] and Bulthuis et al.[100] who recommend the six-minute arm test (6-MAT) with a cycle ergometer to determine exercise endurance.

Hol et al.[95] evaluated the reliability and validity (*ICC* = 0.81) of the 6-MAT on spinal cord injured patients whereas Bulthuis et al.[100] evaluated the reliability and validity (*ICC* = 0.76) of the 6-MAT among 30 healthy volunteers. To our knowledge this is the first study that has included more than 30 patients when evaluating exercise endurance with an arm ergometer in ICU.

A prospective, observational study conducted by Sommers et al.[115] found that exercise endurance can be safely tested with a cycle ergometer in ICU. During the study, Sommers et al.[115] reported only one adverse event of bradycardia. Our study did not report any adverse events. One of the reasons for not reporting any adverse events might be due to us using the MOTOmed® letto2 cycle ergometer which is a safe tool with a CE 0124 and ISO safety certificates and qualifications. Another reason for not having any adverse event might be due to the stringent safety guidelines implemented in our inclusion criteria. Stiller et al.[117] reported that mobilisation caused a significant increase in the heart rate (HR) and blood pressure (BP) but the magnitude of the changes were not of clinical significance. Stiller et al.[117] concluded that critically ill patients can be safely mobilised if the safety criteria are monitored before and during mobilisation. Our inclusion criteria included the baseline safety guidelines as explained by Liu et al.,[17] Burton et al.,[21] Sommers et al.[91] and Stiller et al.[117] A patient was not included in our study if they did not comply with the safety guidelines of our inclusion criteria.

The training intensity of our patients was 54% of the patients' maximum heart rate. This is in agreement with Swain and Franklin[96] and the American College of Sports Medicine (cited Swain and Franklin[96]) who suggest that a 70% - 30% heart rate reserve is required to produce an exercise training effect and result in improved aerobic capacity in unfit people. Exercise endurance indicates that a patient has the sufficient maximal oxygen uptake to perform an activity. Riding the cycle ergometer with the upper limbs causes a higher oxygen uptake, HR and pulmonary ventilation than riding with the lower limbs.[96] This difference is due to the smaller muscle mass and vasculature of the arms that offer greater resistance to blood flow than the larger mass and vasculature of the legs.[96] Greater cardiovascular output is required due to the increased work requirement of the myocardium. According to Mitropoulos et al.[116] there are an increase in anaerobic metabolism, greater carbohydrate oxidation, lactate release and lower oxygen extraction capacity in the arms than the legs. The lower oxidative capacity in the arms are probably related to deconditioning due to non-postural nature of upper body muscles.[116] Our current study only evaluated exercise endurance using the upper limbs. The researcher recommend that future studies compare the measurement of exercise endurance using the MOTOmed® letto2 cycle ergometer with the upper limbs and lower limbs.

Evaluating exercise endurance can be challenging when not performed in a laboratory where the VO_2 max can confirm a change in the training intensity and aerobic capacity. Due to logistical and infrastructure challenges we could not calculate the oxygen uptake with the new cardiopulmonary exercise testing systems.

Another factor together with exercise endurance we investigated was upper limb muscle strength. Upon using the univariable logistic regression analysis we have demonstrated that the individual muscle strength tested with the Oxford grading scale of sternocleidomastoid and trapezius muscles is marginally associated with successful extubation ($P = 0.058$; $P = 0.095$).

The sternocleidomastoid and trapezius muscles are part of the accessory inspiratory muscles that contract when the ventilator demands are higher than normal.[51] The sternocleidomastoid muscles elevate the ribs during forced breathing while the trapezius assist with stabilising the neck for the sternocleidomastoid to function.[54] Our results demonstrated that successfully extubated patients had a greater proportion of grade three sternocleidomastoid and trapezius muscle strength than patients who failed extubation. When the muscle strength of the sternocleidomastoid and trapezius muscles are increasing, the diaphragm will be able to function better when the ventilator needs are increased. Critically ill patients usually fixate their neck/cervical spine and do not move the upper limbs due to being afraid of the central lines, arterial lines and ventilator tubes that might be pulling and preventing movement. This continuous fixation can lead to contraction of the trapezius and sternocleidomastoid muscles that will lead to a decrease in muscle atrophy. The sternocleidomastoid and trapezius muscles might therefore have a grade three muscle strength and could explain why there are some association with successful extubation.

The muscle strength of deltoid (*P* = 0.095) and pectoralis major (*P* = 0.417) muscles is not associated with successful extubation. The deltoid muscle is responsible for shoulder abduction whereas the pectoralis major muscles can contract during forced expiratory tasks.[51] Electromyography (EMG) activities of the pectoralis major showed a correlation with the peak expiratory flow.[51]

A recent prospective, observational study conducted by Vivier et al.[27] showed that pectoral muscle atrophy was associated with prolonged weaning from mechanical ventilation. During mechanical ventilation, the work of breathing is decreased due to pressure support given by the ventilator. The decrease in the negative pressure causes a decrease in the cough strength.[27] Due to the correlation between the EMG activity of the pectoralis major muscle and the peak expiratory flow, the decrease work of breathing and weak cough might indicate that the pectoralis major muscle function is also decreased. The researcher recommend that future studies determine the correlation between pectoralis major muscle strength and cough strength. Due to the deltoid and pectoralis major muscles consisting mainly of fast twitch muscle fibres, inactivity might cause these muscles to atrophy quicker and are therefore not associated with successful extubation.

Ventilated patients also tend to have shoulder stiffness and decrease shoulder range of movement due to a lack in shoulder movement. This shoulder immobility might also add to the development of muscle atrophy and lead to a decrease in muscle strength. A decrease in pectoralis major muscle strength was not influencing our patients while riding the cycle ergometer, because according to Mitropoulos et al.[116] the primary working muscles during arm cycle ergometry included the biceps and triceps brachii muscles.

Many studies have been performed to evaluate the general body muscle strength in ICU. The mean body muscle strength tested with the Medical Research Council score (MRC-score) was associated with successful extubation in our study. Patients with a higher MRC-score were more likely to be successfully extubated. Our results showed that a one point increase in the MRC-score is associated with a seven (7%) reduced risk for failing extubation. These findings are in agreement with Dres et al.[63] who mentioned that patients who failed extubation, had significant lower MRC-scores than the successfully extubated patients (weaning failure; 43 +/-14 vs weaning success 51 +/- 10). Dres et al.[63] used the MRC-score < 48 to diagnose ICU-AW. Patients diagnosed with ICU-AW were associated with prolonged mechanical ventilation and an increase in hospital length of stay.[63]

After logistic regression analysis Dres et al.[63] concluded that the MRC-score is not independently associated with weaning failure (OR = 0.96; P = 0.20).[63] Although our results demonstrated that the MRC-score was associated with extubation failure, our final multivariable logistic regression prediction model was in agreement with Dres et al.[63] and did not include the MRC-score.

In view of the correlation between the MRC-score, handgrip strength and exercise endurance (r = 0.7247; r = 0.5323; P < 0.001), there was multicollinearity when developing the prediction equation, hence the inclusion of exercise endurance only. Our correlation between the MRC-score and handgrip strength is in agreement with Yosef-Brauner et al.[28] who also indicated a positive correlation between the MRC-score and handgrip strength (r = 0.619).

In our study, the handgrip strength measured with the handgrip dynamometer was only marginally (P = 0.052) associated with successful extubation. This result is in disagreement with Cottereau et al.[89] who found that there is no association between handgrip strength and extubation outcome (P = 0.14). Cottereau et al.[89] is of the opinion that the reason for the handgrip strength not being associated with extubation outcome might be due to the handgrip strength evaluation that represent patients with predominant proximal muscle weakness and not distal, hand weakness. On the other hand, Efstathiou et al.[90] demonstrated a strong correlation between MIP and handgrip strength. A study conducted by Parry et al.[86] also indicated a high inter-rater reliability [*ICC* = 0.93 (R); 0.98 (L)] for handgrip strength testing and defining ICU-AW. The difference between results of our study, Cottereau et al.[89] and Efstathiou et al.,[90] maybe due to the difference in numbers evaluated. Cottereau et al.[89] evaluated 84 patients whereas our study and Efstathiou et al.[90] only evaluated 57 and 24 subjects respectively. The only other difference between the last two mentioned studies are the inclusion criteria. Our study included patients ventilated for three and more days and the studies conducted by Cottereau et al.[89] and Efstathiou et al.[90] included patients ventilated for 48 hours and longer. Due to limited research available to support or reject our findings we recommend that future research has to determine factors such as hand dominancy, oedema and number of days ventilated that might influence handgrip strength and the assessment thereof.

The Richmond Agitation-Sedation scale (RASS) demonstrated marginal association (P = 0.053) with successful extubation in our study. Limited research is available to agree or disagree with our findings. The prospective cross sectional study done by Dos Santos Bien et al.[15] revealed that successfully extubated patients had a significantly higher Glasgow Coma Scale (GCS: 10.64 +/- 0.5) than the failed extubated group (9.22 +/- 0.5). These findings are supported by Mokhlesi et al.[48] who indicated that the GCS can determine successful extubation (P = 0.004). Ely et al.[82] reported a high correlation between the RASS and GCS (r = 0.91; P < 0.0001). Although we had statistically significant results with 57 patients, our smaller sample size in comparison to the 122 and 195 respectively in the other studies might have influenced our results.

Our study indicated that the PaO_2/FiO_2 ratio is marginally associated (P = 0.098) with successful extubation. On the other hand, Piriyapatsom et al.[13] and Dos Santos Bien et al.[15] indicated no difference between successfully extubated and failed extubated groups with regard to their PaO_2/FiO_2 ratio's.

The RSBI is associated (P = 0.018) with successful extubation according to this study. This is partially in agreement with Dos Santos Bien et al.[15] who indicated that the MIP and RSBI had a sensitivity of (93%; 84%) and specificity of (95%; 91%) respectively to predict successful extubation. According to their results, the MIP had a greater precision in predicting weaning success than the RSBI.[15] In our results the MIP was only marginally associated (P = 0.095) with successful extubation. Baess et al.118[118] as well as Tu et al.[119] supported Dos Santos Bien et al.[15] by indicating that RSBI had a sensitivity of (87%; 90%) and specificity of (100%; 18%) respectively to predict successful extubation. Including the RSBI in the multivariable logistic prediction model together with exercise endurance and number of days ventilated in our study, the model had a sensitivity of 86.36% and specificity of 80%. After cross validation the predictive model (RSBI, exercise endurance and number of days ventilated) had only a sensitivity of 68.2% and specificity of 74.3%, therefore the final prediction model included only the factors exercise endurance (active time the patient was riding in 15s units) and the number of days ventilated.

A systematic review conducted by Baptistella et al.[25] in 2018 revealed 56 parameters or scores to predict weaning and extubation outcomes of patients. They found that the RSBI was the most studied parameter followed by age and MIP.[25] RSBI < 105 b/min was a good predictor for weaning, but did not have the power to be used in isolation.[25] The difference in results with regard to the MIP and RSBI as predictors of successful extubation might be due to the MIP being difficult for patients to perform, whereas the RSBI is only a calculation that needs to be done. Understanding the MIP test is difficult for ventilated patients to perform although they are awake and cooperative.

During the development of the prediction equation, the factors marginally significantly and significantly associated with successful extubation were included in the multivariable logistic regression. These factors included the sternocleidomastoid muscle strength, trapezius muscle strength, MRC-score, handgrip strength, MIP, resting HR, RASS, RSBI, PaO_2/FiO_2 ratio, number of days ventilated, and exercise endurance (time rode actively on the cycle ergometer). Factors were considered at the liberal 0.10 level of significant. Due to correlation between the MRC-score, handgrip strength and exercise endurance, there was multicollinearity when developing the prediction equation, hence the inclusion of exercise endurance only. The final multivariable logistic regression prediction model included only the factors exercise endurance (active time the patient was riding in 15s units) and the number of days ventilated as the other factors did not add to the predictive value of the model.

Predicting readiness for successful extubation is of the utmost importance to prevent failed extubation and the development of complications such as organ failure, ICU-AW and VAP.[13] The current available predictors of successful extubation focus mainly on the function of the respiratory system with regards to secretion management and respiratory muscle strength only. Our prediction equation consisting of number of days ventilated and exercise endurance represent the combined functionality of the respiratory, cardiovascular and musculoskeletal systems. To maintain oxygen uptake there is a need for integration of the respiratory, cardiovascular and neuromuscular systems.[91] Therefore our newly developed prediction equation can be useful as an additional tool to assist physiotherapists, nursing staff and physicians in the decision to extubate. Successful extubation ought to assist in reducing the patient's length of ICU stay and consequently the development of ICU-AW. Patients' functional ability and health-related quality of life (HRQOL) post ICU discharge should also benefit.

5.2 Limitations

After careful reflection on the methodology of the study the following limitations were identified:

The study was conducted in a single centre academic hospital, evaluating the medical and surgical patients only, which limits the generalisation of the findings to other settings and sub-specialty critical care. Our inclusion criteria were very strict and therefore we had a small number (12%) of screened patients enrolled for the study. Although the principal researcher worked with a team of intensivists, nursing staff and other technical staff in the mentioned setting it was impossible to include a blinded researcher or assistant due to the unpredictable times (day and night) patients were ready for extubation. Patients were not exposed to the handgrip dynamometer or the MOTOmed® letto2 cycle ergometer before the testing was commenced. It was the first time they used the equipment. The researcher only used clinical questions and baseline safety guidelines to determine the safety of the patient during assessment. Other instruments like the Borg scale or pain scale were not included. The respiratory, metabolic, cardiac and peripheral musculoskeletal response to exercise were not evaluated.

CHAPTER 6
CONCLUSION

6.1 Conclusion

This study demonstrates that exercise endurance can predict successful extubation of mechanically ventilated patients when using the prediction equation based on exercise endurance and number of days ventilated. Multicollinearity between exercise endurance and muscle strength tested with the MRC-score, resulted in exclusion of muscle strength in the equation because it does not contribute to the predictive value of the model. Using the prediction equation $\hat{y} = -1.0064 - (0.17 \times \text{active time}) + (0.230 \times \text{ventilator days})$ and the value for $\hat{y}$ is less than or equal to -0.282, the model has a sensitivity of 81.8% to predict successful extubation.

This newly developed prediction equation can contribute to the array of available methods to assist the multidisciplinary health care team including the physicians, nurses and physiotherapists in determining readiness for the spontaneous breathing trial (SBT) or extubation. This is the first study to evaluate exercise endurance with the upper limbs using a cycle ergometer in the intensive care unit (ICU). As the prediction equation consists of more than one factor, it represents the respiratory, cardiovascular and musculoskeletal systems at the same time.

Theoretically the prediction equation indicated that if the number of days the patient is ventilated decrease and the exercise endurance increase the risk to fail extubation will decrease. Patients ventilated for a shorter duration had a reduce risk for developing peripheral muscle weakness, respiratory muscle weakness and decrease exercise endurance. To maintain exercise endurance an integration of the respiratory, cardiovascular and neuromuscular system is necessary. Early patient centred rehabilitation programs incorporating the International Classification of Function (ICF) framework might assist physiotherapists to optimally strengthen the patient and increase the exercise endurance to prepare patients for successful extubation.

Taking into account that clinically, successful extubation may reduce the ICU length of stay, hospital length of stay, mortality rate and total financial expenditures as well as it may increase the patients' functional level and health-related quality of life (HRQOL) post ICU and hospital discharge, the findings of this study have the potential to impact positively on patient outcomes.

Figure 6.1 is a graphic presentation of the newly developed prediction equation.

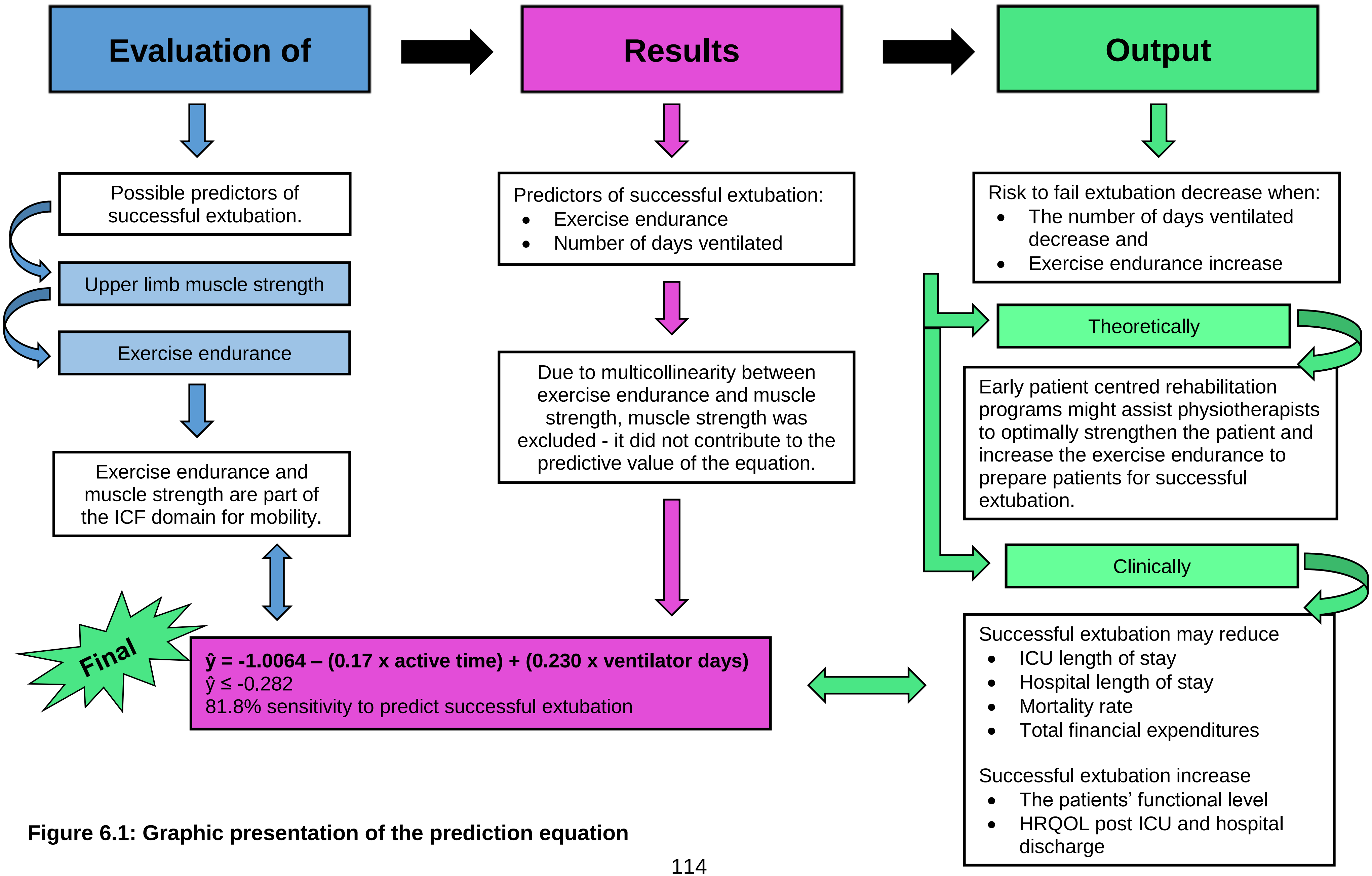

Figure 6.1: Graphic presentation of the prediction equation

6.2 Future research agenda

The researcher recommends further studies to cross validate the prediction equation in different ICU settings locally, nationally and internationally with a bigger sample size that include patients ventilated for 48 hours. Subspecialty ICU's (such as cardiothoracic) need to be included in future studies. Patients should also be familiarised with the MOTOmed® letto2 cycle ergometer and handgrip dynamometer before testing is commenced. Determining factors such as hand dominancy, oedema and number of days ventilated that can influence handgrip strength in the critical care setting are also recommended.

Future studies should determine the association between the cough strength and successful extubation as well as the association between the maximum inspiratory pressure (MIP) and upper limb muscle strength. Assessing the physiological response to exercise and the contribution of the cardiac, respiratory and musculoskeletal impairment to exercise endurance is also recommended. Determining the association between exercise endurance, B-type natriuretic peptide (BNP) and successful extubation is recommended.

Results from the exercise testing might be used as baseline values for exercise prescription during the rehabilitation process. The researcher recommends that the intra- and inter-rater reliability of the Motomed® letto2 cycle ergometer is being evaluated with the six-minute arm test (6-MAT). Since this was the first study evaluating exercise endurance using the Motomed® letto2 cycle ergometer in ICU, the researcher recommends the testing of exercise endurance for six minutes with the Motomed® letto2 cycle ergometer randomising patients into an upper limb group and lower limb group. During exercise testing the Borg scale should be included in the safety criteria and not only physiological parameters.

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APPENDIX 1

Table with critical appraisal of literature

Author & Date	Patients	Methodology	Results	Critique
Roberson AR et al. 2018.	• Four databases: ○ Pubmed ○ Medline ○ Cinahl ○ Cochrane • Studies from 2000-2015 were included. • 97848 publications found. • 9 articles analysed in the review, all other were part of the exclusion criteria.	• Systematic review with meta-analysis. Aim: • To determine what measurements have been used to assess muscle strength in adults receiving mechanical ventilation. • To determine which measurements demonstrate readiness for early mobilisation in adults receiving mechanical ventilation. Keywords: • Muscle strength • Intensive care • Mechanical ventilation • Muscle weakness	• The MRC-score and hand-held dynamometer provide objective measures of muscle strength in ICU population. • MIP measurements revealed severe respiratory muscle weakness that was associated with limb weakness. • Only one article examined the relationship between muscle strength and the development of criteria for early mobilisation. Conclusion: • Future research is needed to determine a standardised method for assessment of muscle strength in ICU and the influence on early mobilisation.	• Methodology repeatable: ○ Search method explained in detail. ○ Inclusion and exclusion criteria described. ○ Data were systematically summarized using Garrard's Matrix Method. ○ Quality assessment done by using the PRIMSA checklist. ○ Quality assessment procedure explained. • Statistical analysis: ○ Reasons mentioned for excluding publications from analysis. • Limitations: ○ Only limitations to the studies were mentioned, no limitations mentioned for the systematic review. • Future research suggested to identify factors that influence muscle strength in the adult receiving mechanical ventilation. • Studies measuring muscle strength and its impact on early mobilisation are needed. • Level of evidence: 1a

Author & Date	Patients	Methodology	Results	Critique
Baptistella AR et al. 2018.	• Four databases: ○ Pubmed, ○ Embase ○ Pedro ○ Cochrane • 132 publications found. • 43 articles analysed in the review, all other were part of the exclusion criteria.	• Systematic review with meta-analysis. Aim: • To identify, describe and discuss the parameters used to predict weaning from mechanical ventilation and extubation outcomes. Keywords: • Weaning • Extubation • Withdrawal • Discontinuation • Mechanical ventilation • Predictive factors • Predictive parameters • Predictors for success	• RSBI most common predictor followed by age and MIP. • 53 parameters found. Conclusion: • RSBI most frequently studied predictor and seems to be important measurement tool in deciding whether to wean/extubate a patient. • Weaning and extubation should be guided by several parameters, not only respiratory ones.	• Methodology repeatable: ○ Search method explained in detail. ○ Inclusion and exclusion criteria described. ○ Quality assessment done by using the PRIMSA checklist. ○ Quality assessment procedure explained. • Statistical analysis: ○ Reasons mentioned for excluding publications from analysis. • Limitations: ○ Different designs, statistical analysis and protocols used to define weaning and extubation success. • Future research suggested to test the predictive capacity of the different scores used. • Level of evidence: 1a

Author & Date	Patients	Methodology	Results	Critique
Magalhães PAF et al. 2018.	• Four databases: ○ Pubmed ○ LILAGS ○ Pedro ○ Web Science	• Clinical review. Aim: • To discuss evidence for assessment of readiness and the effectiveness of interventions for liberation from mechanical ventilation, with attention to the role of IMT. Keywords: • Ventilator weaning • Inspiratory muscle training • Respiratory muscle training • Mechanical ventilation • Artificial respiration	• Methods to identify respiratory muscle weakness in critically ill patients are feasible. • Individualised and supervised rehabilitation programs including IMT, SBT and early mobilisation should be encouraged for patients with inspiratory muscle weakness.	• Methodology not repeatable: ○ Resources mentioned. ○ Search strategies mentioned. • No critical analysis of data. • No statistical analysis. • Limitations: None mentioned. • Recommendation for future research: ○ Research should investigate new therapeutics and tools for assessment of respiratory muscle function. ○ Spontaneous breathing trials as a surrogate marker of endurance training should be investigated. • Study report findings of the literature, not a systematic review. • Level of evidence: 5
Supinski GS et al. 2018	• None	• Literature review. Aim: • Examines the presentation, causes, consequences, diagnosis and treatment of disorder that result in acquired diaphragm dysfunction during critical illness.	• Diaphragm dysfunction is a common medical problem and can occur in response to a range of underlying medical disorders. • Treatments are disease specific and can range from serial assessment over time to more innovative approaches such as diaphragm pacing.	• Methodology not repeatable: ○ Resources not mentioned. ○ Search strategies not mentioned. • No critical analysis of data. • No statistical analysis. • Limitations: None mentioned. • Recommendation for future research: Mentioned. • Study report findings of the literature, not a systematic review. • Level of evidence: 5

Author & Date	Patients	Methodology	Results	Critique
Eggmann S et al. 2018	• 130 patients recruited • 115 patients analysed • Mixed ICU • Tertiary hospital	• Two arm, assessor-blinded randomised controlled trial. • 6 months follow up. Aim: • To evaluate effects of an early progressive rehabilitation intervention in mechanically ventilated adults at risk.	• Experimental group received more physiotherapy sessions and had less days with sedation. • Adverse events were rare. • No significant difference between groups regarding 6-MWD or functional independence. • Improved mental health in experimental group after 6 month follow up. Conclusion: • Early endurance and resistance training in ICU does not improve functional capacity or independence at hospital discharge, but improves mental health 6 months after ICU discharge.	• Methodology repeatable: ○ Single-centre study. ○ Inclusion and exclusion criteria described. ○ Procedure explained. ○ Interventions explained. ○ Flow of the study explained with CONSORT diagram. • Statistical analysis complete: ○ Continuous variables expressed as mean and standard deviation or median and interquartile range. ○ Correlations determined with Spearman correlation coefficients. ○ Student T-test or Mann-Whitney test for intergroup comparison. • Limitations: ○ Blinding of physiotherapists were impossible. ○ Loss of follow-up at 6 months was unequally distributed. ○ Small sample size. • Recommendation for future research: Mentioned. • Level of evidence: 1a

Author & Date	Patients	Methodology	Results	Critique
Toosizadeh N et al. 2017	• 49 patients recruited. • Pulmonary function laboratory.	• Cross sectional study. • Single centre study. Aim: • To evaluate an upper-extremity function test for assessing functional capacity in older adults with COPD. Measurements: • Pulmonary function • 6MWD	• Speed, power and moment upper-extremity function were associated with 6MWD. Conclusion: • Speed and strength of upper extremity motion were closely associated with pulmonary function measures and 6MWD.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria explained. • Statistical analysis significant: ○ Linear Pearson correlations and Spearman's rank for normally distributed variables. ○ ANOVA performed. ○ Multivariable linear regression model used. • Limitations included: ○ Upper extremity disability or injury may limit the exercise. ○ Small sample size. ○ Lack intra and inter-rater reliability assessment. • Recommendation for future research: Mentioned. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Kawahara K et al. 2017.	• 41 patients recruited. • Medical ICU patients.	• Prospective, observational study. • Single centre study. Aim: • To assess the degree of skeletal muscle atrophy in the upper and lower limbs. Measurements: • Degree of skeletal muscle atrophy was evaluated by measuring the limb circumference in ADL-dependent and ADL independent patients at five different sites.	• Degree of muscle atrophy was more sever in the lower limbs than upper limbs. Conclusion: • Acute muscle atrophy progressed even during a six day stay in the ICU and advanced faster in ADL-independent patients than in ADL-dependent patients.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria explained. ○ Study procedure explained. • Statistical analysis significant: ○ Normality distributions evaluated by Levine's test. ○ ANOVA and post hoc analysis. ○ Multiple linear regression performed. ○ Variables compared with Student T-test or Mann-Whitney test. • Limitations include: ○ Quantity and frequency of mobilisation therapy and physical therapy as usual care not programmed. ○ Limb oedema not evaluated. ○ Small sample size. • Recommendation for future research: None mentioned. • Level of evidence: 3

Author & Date	Patients	Methodology	Results	Critique
Dinglas V et al. 2017.	• 754 patients recruited. • 156 patients analysed.	• Longitudinal prospective cohort study. • Multi-centre study. • 13 ICU's in 4 hospitals. Aim: • To evaluate the association of post ICU muscle weakness over time with a 5 year survival. • Evaluate muscle strength prior to hospital discharge and thereafter.	• Muscle strength evaluated with MRC-score. • Greater strength at discharge was associated with improved 5 year survival. Conclusion: • At discharge, greater than one third of ARDS patients had muscle weakness.	• Methodology repeatable: o Multi-centre study. o Inclusion and exclusion criteria described. o Procedure explained. o Equipment explained. o Flow of the study explained with flow diagram. • Statistical analysis complete: o Wilcoxon rank-sum and Fisher exact test for continuous variables and percentages for categorical variables. o LOESS for linearity of association between continuous variable and survival. o Kaplan-Meier curve describe survival from hospital discharge to 5 year. • Limitations: o Did not measure pre-ICU muscle strength. o Not generalizable to other ICU population, only ARDS patients were included. • Recommendation for future research: Mentioned. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique

Dres M et al. 2017.	• 330 patients recruited.
	• 76 patients included in the study.
	• Medical ICU patients.
		• Prospective, observational study.
		• Single centre study.
		
		Aim:
		• To assess whether diaphragm dysfunction and ICU-AW are or not two distinct entities with their own specific prevalence and risk factors.
		
		Measurements:
		• Diaphragm function assessed by phrenic nerve stimulation and ultrasound.
		• Limb muscle strength assessed with MRC-score.
			• Weak correlation between MRC-score and twitch pressure.
			• MRC-score not independently associated with weaning failure.
			• Diaphragm dysfunction associated with higher ICU and hospital mortality.
			• Limb weakness associated with longer duration of mechanical ventilation and hospital stay.
			
			Conclusion:
			• Diaphragm dysfunction twice as frequent as limb muscle weakness.
			• Diaphragm dysfunction has direct negative impact on weaning outcome.
				• Methodology repeatable:
				  o Single centre study.
				  o Inclusion and exclusion criteria explained.
				  o Single blinded study.
				• Statistical analysis significant:
				  o Consort diagram explain inclusion of patients in analysis.
				  o Continuous variables expressed as mean and standard deviation or median and interquartile range.
				  o Multi regression model used to identify effect of exposure on pre-SBT variables.
				  o Chi-square or Fisher's exact also for comparison.
				  o Variables compared with Student T-test or Mann-Whitney test.
				• Limitations include:
				  o Using phrenic nerve stimulation excluded some eligible patients in whom the technique was contraindicated.
				  o Only used MRC-score and not dynamometer as well.
				• Recommendation for future research: Mentioned.
				• Level of evidence: 3

Author & Date	Patients	Methodology	Results	Critique
Walterspacher S et al. 2017.	• 9 patients included for analysis.	• Prospective, observational study. • Single centre study. Aim: • Assessed the acute effects on the neural respiratory drive in 3 different body positions during mechanical ventilation and while breathing spontaneously without ventilator assistance through a tracheostomy tube.	• Unassisted breathing showed that breathing frequency was lowest in semi-recumbent position, but highest during sitting. • Diaphragm remains most active respiratory muscle while supine and in semi-recumbent position, whereas diaphragmatic activation decreases while sitting. Conclusion: • Body positioning influences respiratory drive to the diaphragm in tracheotomised patients with prolonged weaning from mechanical ventilation during unassisted breathing. • Sitting position reduces respiratory drive compared with semi-recumbent and supine positioning.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria explained. ○ Study procedure explained. • Statistical analysis significant: ○ Continuous variables expressed as mean and standard deviation or median and interquartile range. ○ Comparing more than 2 conditions was calculated using repeated measure ANOVA with post hoc analysis using Student-Newman Keuls test. ○ Variables compared with Student T-test or Mann-Whitney test. • Limitations include: ○ Use of surface EMG is prone to signal disturbances ○ Small number of participants. • Recommendation for future research: Mentioned. • Level of evidence: 3

Author & Date	Patients	Methodology	Results	Critique
Machado A et al. 2017.	• 49 patients recruited. • 38 patients included in the study. • Medical, neurological and surgery conditions.	• Randomised clinical trial. • Single centre study. Aim: • To evaluate the effect of passive cycling on peripheral muscle strength, duration of mechanical ventilation and length of hospital stay. Process: • Intervention group received conventional therapy and passive cycling for five days a week. • Control group received conventional therapy for five days a week. • Measured muscle strength with MRC-score. • Determined duration of mechanical ventilation. • Determined length of hospital stay.	• Range of muscle strength increase was more in interventional group than control group. • No significant difference between groups for length of stay / duration of mechanical ventilation. Conclusion: • Continuous passive mobilisation with a bed cycle help to recover peripheral muscle strength in ICU patients.	• Hypothesis supported by background information and explanation. • Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria explained. ○ Single blinded study. ○ Patients blinded to group assignment. ○ Randomisation performed with a computerised random number generator. ○ Clear description of evaluating and intervention techniques performed. ○ No clear indication of follow up. • Statistical analysis significant: ○ Consort diagram explain inclusion of patients in analysis. ○ Continuous variables expressed as mean and standard deviation or median and interquartile range. ○ Variables tested for normality with Shapiro-Wilk test. ○ Paired student t-test or Wilcoxon test used for intragroup comparison. ○ Unpaired Student T-test or Mann-Whitney test for intergroup comparison. • Limitations include: ○ Muscle strength testing was limited to ICU, no testing at hospital discharge. ○ Impossible to ensure no muscle contraction during cycling. • Recommendation for future research: Mentioned. • Level of evidence: 1a

Author & Date	Patients	Methodology	Results	Critique
Efstathiou ID et al. 2016	• 24 subjects included in data analysis. • Healthy volunteers.	• Observational study. • Single centre study. Aim: • To examine the relationship between handgrip force and MIP. • To determine ability of various parameters such as handgrip force, gender and BMI to predict MIP. Measurements: • MIP with U-type water manometer. • Handgrip force by hydraulic hand dynamometer.	• Strong correlation (r = 0.76) between MIP and handgrip force. • MIP can be predicted by 80% with equation of handgrip force, BMI and gender. • Significant correlation between hand flexors force and strength of inspiratory muscles. Conclusion: • Strong correlation between handgrip force and MIP.	• Methodology repeatable: o Single centre study. o Inclusion and exclusion criteria explained. o Study procedure explained. • Statistical analysis significant: o Continuous variables expressed as mean and standard deviation or median and interquartile range. o Variables tested for normality with Shapiro-Wilk test. o Spearman's rho determined. o Linear regression analysis was performed to evaluate variables independently associated with MIP. • Limitations include: o Study did not represent the critically ill patients. • Recommendation for future research: Mentioned. • Level of evidence: 1a

Author & Date	Patients	Methodology	Results	Critique
Schellekens WJM et al. 2016.	• None	• Review Aim: • To discuss strategies that prevent the development of respiratory muscle weakness or restore respiratory muscle function in weak ICU patients.	• Pathophysiology of respiratory muscle weakness in the critically ill • Evaluation of respiratory muscle function in ICU. • Respiratory muscle training. • Antioxidants and nutrition.	• Methodology not repeatable: ○ No resources mentioned. ○ No search strategies mentioned. • No critical analysis of data. • No statistical analysis. • Limitations: None mentioned. • Recommendation for future research: None mentioned. • Study is only a report of the literature, not a systematic review. • Level of evidence: 5
Lai CC et al. 2016.	• Medical and surgery ICU's. • 14933 intubated patients. • 6583 patient included in analysis.	• Observational study. • Single centre study. Aim: • To establish predictors for successfully planned extubation. Measurements: • MIP • MEP • Cuff leak test (CLT) • RSBI	• 3 independent risk factors for successful extubation after successful breathing trial, including CLT of 2+, MEP > 55 cmH2O and RSBI > 68 b/min/ml. • The measures represented the patency of the upper airway, cough strength and respiratory capacity.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria described. ○ Procedure explained. ○ Equipment explained. ○ Flow of the study explained with flow diagram. • Statistical analysis complete: ○ Continuous variables expressed as mean and standard deviation or median and interquartile range. ○ Student T-test and Pearson chi-square test for categorical variables. • Limitations: ○ Single centre study. ○ Delayed extubation can occur. • Recommendation for future research: None mentioned. • Level of evidence: 3

Author & Date	Patients	Methodology	Results	Critique
Samosawala N et al. 2016.	• 184 patients screened. • 78 patients recruited. • 64 patients complete. • Tertiary care hospital.	• Observational cohort study. • Single centre study. Aim: • To observe the changes in dynamometry values for upper and lower extremity muscles during ICU stay. Measurements: • Handheld dynamometer was used to measure the force generated by each muscle (Mm. biceps, triceps, deltoid, quadriceps, plantar flexors and dorsiflexors) on day 3 of admission. • Measurements repeated on day 5 and day 7 of ICU stay.	• Reduction in force generated by each muscle from day 3 to day 5 as well as from day 5 to day 7 of ICU stay. • Overall reduction in peripheral muscle strength was 10% – 13% during ICU stay. • Weakness more in proximal muscles than peripheral muscles. Conclusion: • Progressive reduction in peripheral muscle strength as measured by handheld dynamometer during early ICU stay. • Dynamometer can be proposed as alternative to MMT in routine physiotherapy assessment.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria described. ○ Procedure explained. ○ Equipment explained. ○ Flow of the study explained with flow diagram. • Statistical analysis complete: ○ ANOVA analysed changed in force • Limitations: ○ Did not assess fatigue level during dynamometry measurement. ○ Previously undiagnosed neuropathies were not segregated in the study. • Recommendation for future research: Mentioned. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Turton P et al. 2016.	• 22 patients recruited.	• Observational study. • Single centre study. Aim: • To establish changes in pennation angle and fascicle length as markers of altered fascicle arrangement in critical illness. • Compare muscle wasting in areas of the upper limb and lower limbs. Measurements: • Ultrasound scanning of right elbow flexor compartment, right medial head of gastrocnemius and right vastus lateralis muscles on day 1, day 5 and day 10 after admission.	• Handgrip strength had 0.76 sensitivity and 0.69 specificity to identify difficult or prolonged weaning at 11 kg. Conclusion: • Handgrip strength is an independent prognostic factor of mechanical ventilation weaning outcome and ICU stay. • No association between handgrip strength and extubation outcome.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria described. ○ Procedure explained. ○ Equipment explained. ○ Flow of the study explained with flow diagram. • Statistical analysis complete: ○ Quantitative data tested with Student T-test or Mann-Whitney test. ○ Qualitative data compared with chi-square test. ○ Logistic regression analysis • Limitations: ○ Single centre. ○ Small number of patients with extubation failure. • Recommendation for future research: None mentioned. • Level of evidence: 2b
Zein H et al. 2016	• None	• Educational review. • Keywords: ○ Weaning predictors ○ Weaning criteria ○ Weaning procedure ○ Assessment for extubation	• Weaning predictors: ○ Heart rate variability ○ Sleep quality ○ Handgrip strength ○ Diaphragmatic dysfunction ○ Oxidative stress markers • Three strategies to perform Spontaneous breathing trial (SBT). • SBT can be 30-120 min.	• Methodology not repeatable: ○ No resources mentioned. ○ No search strategies mentioned. • No critical analysis of data. • No statistical analysis. • Limitations: None mentioned. • Recommendation for future research: None mentioned. • Study is only a report of the literature. • Level of evidence: 5

Author & Date	Patients	Methodology	Results	Critique
Doorduin J et al. 2016	• None	• Clinical Review. Aim: • Discuss causes for failed weaning trial and diagnostic tests that could be conducted to identify the causes for weaning failure.	• Impaired respiratory mechanics, respiratory muscle dysfunction and cardiac dysfunction is causes for weaning failure. • Metabolic disorders and cognitive dysfunction can also cause weaning failure. • Ultrasound and electromyography can evaluate respiratory muscle function. • BNP can determine cardiac dysfunction and weaning failure.	• Methodology not repeatable: ○ No resources mentioned. ○ No search strategies mentioned. • No critical analysis of data. • No statistical analysis. • Limitations: None mentioned. • Recommendation for future research: None mentioned. • Study is only a report of the literature, not a systematic review. • Level of evidence: 5
Berger D et al. 2016	• None	• Review • Keywords: ○ Mechanical ventilation ○ Ventilator induced diaphragmatic dysfunction ○ Diaphragm ○ Weakness ○ Weaning failure ○ ICU-Acquired weakness (ICU-AW) ○ Sepsis ○ Cachexia	• Pathophysiology of respiratory muscle dysfunction and VIDD ○ Conduction abnormalities ○ Diaphragm loses force- and pressure-generating capacity ○ Proteolysis increases ○ Protein synthesis decreases ○ Assess with ultrasound ○ Respiratory muscle training	• Methodology not repeatable: ○ No resources mentioned. ○ No search strategies mentioned. • No critical analysis of data. • No statistical analysis. • Limitations: None mentioned. • Recommendation for future research: None mentioned. • Study is only a report of the literature, not a systematic review. • Level of evidence: 5

Author & Date	Patients	Methodology	Results	Critique
Piriyapatsom A et al. 2016	• 917 patients recruited. • 764 patients included. • Surgery ICU's.	• Prospective, observational study. • Single centre – two ICU's in one hospital. Aim: • To determine the risk factors for re-intubation in surgical ICU population. • Hypothesised that preoperative comorbidities, acquired muscle weakness and renal dysfunction will be predictors of re-intubation in surgical ICU population. Measures: • Tested muscle strength before the SBT.	• Limited information regarding risk factors that predispose patients to re-intubation. • 8.5% of patients need re-intubation. • Independent risk factors of re-intubation were blood urea nitrogen level > 8.2mmol/L, haemoglobin level < 75g/L and muscle strength <3. Conclusion: • Surgery patients with elevated blood urea nitrogen level, low haemoglobin level and muscle weakness were at risk for re-intubation.	• Methodology repeatable: ○ Single centre - two ICU's, one hospital. ○ Inclusion and exclusion criteria described. ○ Procedure explained. ○ Equipment described. ○ Flow of the study explained in flow diagram. • Statistical analysis: ○ Mann-Whitney U test compare the groups. ○ Categorical variables were compared using chi-square test or Fisher exact test. ○ Univariate analysis and logistic regression analysis were done. • Limitations: ○ Single centre study. ○ High flow nasal oxygen was not implemented in the beginning of the study. • Recommendation for future research: ○ None mentioned. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Bissett B et al. 2015.	• 43 patients participated in the study. • Medical / surgery ICU.	• Prospective, observational study. • Single centre. Aim: • To establish whether ICU patients have impaired inspiratory muscle (IM) endurance immediately following weaning from prolonged mechanical ventilation. • To establish whether IM weakness is related to function or perceived exertion. Measures: • IM endurance measured with fatigue resistance index.	• IM endurance is often impaired in ICU patients who have been recently weaned from mechanical ventilation of at least 7 days. • No close relationship between IM weakness and either function or perceived exertion in cohort. Conclusion: • IM endurance is reduced in one third of patients, while IM weakness does not appear closely associated with function or perceived exertion immediately following successful weaning.	• Methodology repeatable: ○ Single centre. ○ Inclusion and exclusion criteria described. ○ Procedure explained in flow diagram. ○ Equipment described. • Statistical analysis: ○ Parametric correlations were performed. ○ Non-parametric correlations were tested using Spearman's rho. • Limitations: ○ Results may be valid only for ICU where minimal sedation and early mobilisation protocol are followed. ○ Small sample size. • Recommendation for future research: None mentioned. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique

Yosef-Brauner O et al. 2015.	• 18 patients participated in the study.
	• 9 in control group and 9 in intervention group.
	• General ICU.
		• Prospective, single blinded study.
		• Single centre.
		
		Aim:
		• To evaluate the effect of an intensive physical therapy protocol in patients who contract ICU-AW.
		
		Measures:
		• Tested muscle strength with MRC-score.
		• Tested handgrip strength with hand dynamometer.
		• Sitting balance test.
		• Maximum inspiratory pressure.
			• Improvement in MIP and MRC scores between initial and second measurement for intervention group.
			• Intervention group had shorter ICU length of stay.
			
			Conclusion:
			• It is possible that an intensive therapy protocol may facilitate initial recovery in patients suffering from ICU-AW.
				• Methodology repeatable:
				  ○ Single centre.
				  ○ Inclusion and exclusion criteria described.
				  ○ Procedure explained.
				  ○ Equipment described.
				  ○ Intervention program described.
				• Statistical analysis:
				  ○ Chi-squared test for nominal variables.
				  ○ Mann-Whitney for ordinal variables.
				  ○ T-test for ratio variables.
				  ○ Correlations between tests were examined using Spearman's rho and Pearson's rho.
				• Limitations:
				  ○ Single centre study.
				  ○ Small sample size.
				  ○ There was no "untreated" group due to ethical concerns.
				• Recommendation for future research:
				  ○ Diet and caloric intake should be included to evaluate effect of treatment protocols.
				• Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Parry SM et al. 2015.	• None	• Review • Keywords: ○ Critical illness ○ Muscle wasting ○ Intensive care unit-acquired weakness ○ Sepsis ○ Muscle protein turnover	• Describe the current literature on bed rest models for examining immobilisation-induced changes in the musculoskeletal system and pathophysiology of immobilisation in critical illness. • Examines current barriers to early activity and mobilisation and potential rehabilitation strategies.	• Methodology not repeatable: ○ No resources mentioned. ○ No search strategies mentioned. • No critical analysis of data. • No statistical analysis. • Limitations: None mentioned. • Recommendation for future research: None mentioned. • Study is only a report of the literature, not a systematic review. • Level of evidence: 5
Sommers J et al. 2015	• None	Aim: • To formulate an evidence-based, expert driven, practical statement within the ICF domains. Adhere to EBRO method	• Three clinical domains were identified: ○ Initiate treatment; ○ Assess patient ○ Effective treatments Conclusion: • Evidence and expert knowledge lead to set of criteria determining when to safely mobilise a patients in ICU.	• Methodology repeatable: ○ Search method explained in detail. ○ Feedback from experts explained. • Statistical analysis: ○ No statistical analysis ○ Results summarised in tables and figures. • Limitations: Mentioned. • Future research suggested to identify the ideal dose and timing of exercise and the effect of exercise. • Level of evidence: 4

Author & Date	Patients	Methodology	Results	Critique
Kho ME et al. 2015.	• 688 patients recruited. • Medical ICU.	• Prospective study. Aim: • To evaluate the feasibility and safety of in-bed cycling as part of routine physiotherapy.	• Only a single event occurred during the 12 physiological abnormality assessment. Conclusion: • In-bed cycling as part of standard physiotherapy is safe and feasible.	• Methodology repeatable: ○ Single-centre study. ○ Inclusion criteria described. ○ Procedure explained. ○ Equipment explained. • Statistical analysis complete: ○ Mean and SD calculated for continuous data. Median and interquartile range determined for not normally distributed data. ○ Fisher exact test for continuous variables and percentages for categorical variables. • Limitations: ○ More prospective research using the in bed cycling is needed. • Recommendation for future research: Mentioned. • Level of evidence: 3

Author & Date	Patients	Methodology	Results	Critique
Thille AW et al. 2015.	• 533 patients recruited. • 225 patients analysed. • Medical ICU.	• Prospective, observational study. • Single centre study. Aim: • To determine the influence of delirium, ICU-AW and cardiac performance on extubation outcome. • To assess the accuracy of prediction of extubation failure by caregivers. Measurements: • Muscle strength, cough strength, amount of secretions. • SOFA • Left ventricular (LV) ejection fraction.	• Caregivers predicted failure with a low sensitivity. Conclusion: • Strongest predictors of planned extubation failure: o Duration of mechanical ventilation. o Ineffective cough. o Severe systolic LV dysfunction.	• Methodology repeatable: o Single centre study. o Inclusion and exclusion criteria not described. o Procedure explained. o Equipment explained. o Flow of the study explained with flow diagram. • Statistical analysis complete: o Quantitative data tested with Student T-test or Mann-Whitney test. o Qualitative data compared with chi-square test. o Logistic regression analysis. • Limitations: o Single centre. o Small number of patients with extubation failure. • Recommendation for future research: None mentioned. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Cottereau G et al. 2015.	• 722 patients recruited. • 465 patients excluded. • 84 patients included.	• Prospective study. • Single centre – two ICU's in one hospitals. Aim: • Evaluate handgrip strength as a predictor of weaning duration. • Test the value of handgrip strength in predicting extubation outcome. Measures: • Tested handgrip strength before the SBT.	• Handgrip strength had 0.76 sensitivity and 0.69 specificity to identify difficult or prolonged weaning at 11 kg. Conclusion: • Handgrip strength is an independent prognostic factor of mechanical ventilation weaning outcome and ICU stay. • No association between handgrip strength and extubation outcome.	• Methodology repeatable: ○ Single centre - two ICU's. ○ Inclusion and exclusion criteria described. ○ Procedure explained. ○ Equipment described. ○ Flow of the study explained in flow diagram. • Statistical analysis: ○ Mann-Whitney U test and Kruskal Wallis test compare the groups. ○ Categorical variables were compared using Chi-square test or Fisher exact test. ○ Univariate analysis and logistic regression analysis were done. ○ Exclusion of patients described. • Limitations: ○ Small sample size. ○ Muscle strength with MRC-score not done. • Recommendation for future research: ○ Studies with a larger sample size. • Level of evidence: 2b.

Author & Date	Patients	Methodology	Results	Critique
Dos Santos Bien U et al. 2015.	• 195 patients included. • Surgery / medical ICU.	• Prospective, cross-sectional study. • Single centre study. Aim: • Investigate the ability of maximum inspiratory pressure (MIP) and rapid shallow breathing index (RSBI) to predict weaning success in ventilated patients. Measurements: • Minute volume • Respiratory frequency. • Expiratory tidal volume • RSBI • SBT for 30 min with T-tube • MIP measured digitally after 5 min of support pressure ventilation and immediately after 30 min of SBT.	• Successful extubated patient group had higher GSC and MIP measurements than the failed extubated patient group. • Successful extubated patient group had lower RSBI, shorter duration of MV, decrease number of weaning attempts and lower APACHE scores than the failed extubated patient group. • MIP has greater sensitivity and specificity than RSBI. Conclusion: • Both MIP and RSBI contributed to predicting ventilator weaning success.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria explained. ○ Study procedure explained. ○ Equipment explained. ○ Recruiting of patients explained with flow diagram. • Statistical analysis complete: ○ Kolmogorov-Smirnov test used to determine the data distribution. ○ Logistic regression analysis performed. ○ Positive likelihood ratio, Negative likelihood ratio determined. • Limitations: None mentioned. • Recommendation for future research: None mentioned. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique

Peñuelas O et al. 2015.	• None	• Clinical Review.
		• Keywords:
		  ○ Mechanical ventilation
		  ○ Weaning
		  ○ Extubation
		  ○ SBT
		Aim:
		• To critically update the recent literature regarding the period of weaning from mechanical ventilation and extubation failure.
			• RSBI and HRV can predict extubation failure.
			• SBT should be 30 – 120 minutes.
			• Diaphragmatic function plays important role to determine the patient's ability to be successfully weaned.
			• Sedation protocols lead to shorter duration of weaning.
				• Methodology not repeatable:
				  ○ Searching strategy not explained.
				  ○ Resources recruited not explained.
				• No statistical analysis of data.
				• No critical analysis of data.
				• Study is only mentioning all literature and studies available.
				• Future clinical research is needed to identify patients at high risk for extubation failure.
				• Level of evidence: 5

Liu Y et al. 2015.	• 4539 patients admitted to 10 ICU's.
	• 530 patients analysed.
		• Prospective, validation cohort study.
		• Multi-centre study.
		
		Aim:
		• To validate and update a predictive model previously developed using a classification and regression tree (CART) algorithm for predicting successful extubation.
			• Original CART model showed high discrimination but moderate calibration with predicted probabilities.
			• Updated model preserved excellent discrimination and near perfect calibration.
			
			Conclusion:
			• Updated CART model may be used to estimate the predicted probability of successful extubation after a successful SBT.
				• Methodology repeatable:
				  ○ Multi-centre study.
				  ○ Inclusion and exclusion criteria explained.
				  ○ Study procedure explained.
				  ○ Study protocol explained.
				  ○ Recruiting of patients explained with flow diagram.
				• Statistical analysis complete:
				  ○ Logistic regression analysis performed.
				  ○ Decision curve analysis was used to quantify the clinical usefulness of the updated CART model.
				• Limitations:
				  ○ Selection bias may have occurred.
				  ○ Single country.
				• Recommendation for future research: None mentioned.
				• Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique

Hermans G & Van den Berghe G 2015.	• None	• Clinical review.
		
		Aim:
		• Update the knowledge regarding ICU-AW, its characteristics and diagnostic properties.
		• Predisposing factors.
		• Medical and socioeconomic consequences.
			• ICU-AW affects the peripheral and respiratory muscles.
			• Risk factors include sepsis, multiple organ failure, prolonged immobilisation and hyperglycaemia.
			• Diagnosed with MRC-score when patient is awake and cooperative.
			• Respiratory muscle strength can be measured with MIP.
			• ICU-AW is associated with increase duration of mechanical ventilation, ICU LOS, hospital LOS and mortality.
			• Associated with decrease in QOL post ICU stay.
				• Methodology not repeatable:
				  ○ No resources mentioned.
				  ○ No search strategies mentioned.
				• No critical analysis of data.
				• No statistical analysis.
				• Study is only a report of the literature, not a systematic review.
				• Level of evidence: 5

Author & Date	Patients	Methodology	Results	Critique
Chlan L et al. 2015.	• 120 patients recruited. • 12 ICU's in 5 hospitals.	• Descriptive, correlational study. • Multi-centre study – 12 ICU's in 5 hospitals. Aim: • To describe daily peripheral muscle strength measurement in ICU and to identify factors that area associated with peripheral muscle strength. Measurements: • Handgrip dynamometer was used for daily measurement of peripheral muscle strength.	• Baseline grip strength was lower than the norm. • Grip strength decrease over time. • Older female patients have greatest decrease in grip strength. Conclusion: • Hand grip strength decrease over time in ventilated patients. • Hand grip dynamometer is reliable method for evaluation of muscle strength in cooperative patients. • Authors suggest handgrip dynamometer can be used in future research to develop interventions to prevent ICU-AW.	• Methodology repeatable: ○ Multi-centre study. ○ Inclusion and exclusion criteria explained. ○ Study procedure explained. ○ Equipment explained. ○ Recruiting of patients not explained with flow diagram. • Statistical analysis complete: ○ Descriptive statistics and mixed modelling were used. ○ Positive likelihood ratio, Negative likelihood ratio determined. • Limitations: ○ No pre-ICU disability data obtained. ○ No data regarding QOL post ICU stay. ○ No respiratory muscle strength measured. • Recommendation for future research: ○ Determine feasibility of handgrip assessments throughout the entire ventilation time. ○ Evaluate the predictive value of handheld dynamometry on functional outcomes • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique

Parry S et al. 2015.	• 29 patients analysed.
	• Medical and surgery ICU.
		• Prospective, observational study.
		• Single centre study.
		
		Aim:
		• To determine the inter-rater reliability and agreement of manual muscle strength testing using both isometric and through-range techniques.
		
		Measurements:
		• Manual muscle testing with MRC-score (isometric and through range) using 6-point and 4-point scale were performed.
		• Handgrip strength was evaluated with handgrip dynamometer.
			• Difference between isometric and through-range techniques for assessing manual muscle strength and the isometric technique is preferred technique.
			• HGD is valid and reliable surrogate tool for diagnosing ICU-AW.
			
			Conclusion:
			• Two-tier approach to muscle strength testing is recommended, handgrip strength testing and thorough manual muscle strength testing if below the handgrip cut off levels.
				• Methodology repeatable:
				  ○ Single-centre study.
				  ○ Inclusion and exclusion criteria explained.
				  ○ Study procedure explained.
				  ○ Equipment explained.
				  ○ Recruiting of patients not explained with flow diagram.
				• Statistical analysis complete:
				  ○ Intra class correlation coefficients and weighted linear kappa statistics calculated.
				  ○ Paired T-test and Bland-Altman analysis utilised to determine mean differences between isometric and through range techniques.
				  ○ Chi-square analysis and ROC curve were used to determine test performance of HGD.
				• Limitations:
				  ○ Possibility of recall bias as therapist not blinded from results.
				  ○ Small sample size.
				  ○ Single-centre study.
				• Recommendation for future research:
				  ○ Non-volitional clinical measures at the bedside on admission to identify at risk for ICU-AW is warranted.
				• Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Parry S & Puthucheary Z. 2015.	• None	• Clinical review. • Update the knowledge regarding the impact of bedrest on the musculoskeletal system in the ICU. • Examines the barriers to early activity and mobilisation.	• Prolonged immobility causes reduction in muscle mass, bone density and impairment in other body systems. • Changes are seen within the first week of bed rest. • Early rehabilitation and mobilisation strategies need to be developed.	• Methodology not repeatable: ○ No resources mentioned. ○ No search strategies mentioned. • No critical analysis of data. • No statistical analysis. • Limitations: None mentioned. • Recommendation for future research: None mentioned. • Study is only a report of the literature, not a systematic review. • Level of evidence: 5
Diaz MC et al. 2014.	• None	• Literature review • Keywords: ○ Respiratory muscle dysfunction ○ Mechanical ventilation ○ Weaning from mechanical ventilation ○ Sepsis ○ Critical patient ○ Proteolysis ○ Protein synthesis ○ Malnutrition in the critically ill patient	Factors associated with respiratory muscle dysfunction: • Age • Duration and mode of ventilation • Nutritional and Metabolic Status • Comorbidities • Pharmacological treatment • Proteolysis and/or reduction of protein synthesis • Peripheral muscles also affected by the multi-causal nature of the disorder.	• Methodology not repeatable: ○ No resources mentioned. ○ No search strategies mentioned. • No critical analysis of data. • No statistical analysis. • Limitations: None mentioned. • Recommendation for future research: None mentioned. • Study is only a report of the literature, not a systematic review. • Level of evidence: 5

Author & Date	Patients	Methodology	Results	Critique
Wang S et al. 2014.	• Four databases: ○ Medline ○ Embase ○ Web Science ○ Cochrane • 43 publications found. • 9 articles analysed in the review, all other were part of the exclusion criteria.	• Systematic review with meta-analysis. Aim: • To identify, risk factors for extubation failure in neurocritical patients. Keywords: • Extubation • Neuro • Brian-injured • Cerebral	• Following parameters were predictive for extubation failure: ○ Pneumonia ○ Atelectasis ○ Mechanical ventilation > 24 h ○ Low GCS ○ Inability to follow commands ○ Thick secretions ○ No intact gag reflex Conclusion: • Besides pneumonia, atelectasis and duration of mechanical ventilation, other factors like GCS, secretion texture and presence of gag reflex should be taken in consideration.	• Methodology repeatable: ○ Search method explained in detail. ○ Inclusion and exclusion criteria described. ○ Quality assessment done by using the NOS. ○ Quality assessment procedure explained. • Statistical analysis: ○ Q-test examine between-study heterogeneity. ○ Reasons mentioned for excluding publications from analysis. • Limitations: ○ Due to deficiencies in data, only main predictors drawn from the articles were analysed. ○ Small sample size of articles that analysed the predictors. • Future research: Mentioned. • Level of evidence: 1a

Author & Date	Patients	Methodology	Results	Critique

Seely A et al. 2014.	• 721 patients recruited.
	• 434 patients included in the study.
	• 287 patients excluded due to poor data quality.
		• Prospective, blinded observational cohort study.
		• Multicentre (12 centres).
		• Hypothesized that cardiorespiratory variability might be used as a marker of the cardiopulmonary system to tolerate increased workload.
		
		Measurements:
		• Carbon dioxide (CO_2) monitors were attached to the ventilator circuit.
		• ECG and CO_2 readings were documented 30 min prior, during and 30 min after SBT.
			• Altered Heart Rate Variability (HRV) and Respiratory Rate Variability (RRV) are significantly associated with extubation failure. ($P < 0.0041$, 5% false discovery rate).
			• WAVE score to be used in conjunction with existing extubation readiness tests for optimal prediction.
				• Methodology repeatable:
				  ○ Multicentre study (12 centres).
				  ○ Inclusion and exclusion criteria described in detail.
				  ○ Procedures explain in detail.
				  ○ Recruiting of patients explained with flow diagram.
				• Statistical analysis complete:
				  ○ Univariate logistic regression models used.
				  ○ Repeated randomized sub-sampling with machine, learning analysis were used to derive and compare predictive models.
				• Limitations:
				  ○ No strict protocol regarding how the SBT was performed.
				  ○ External validation of the WAVE score is required.
				• Recommendation for future research:
				  ○ Need validation and randomized trial to assess clinical utility.
				• Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique

Vanpee G et al. 2014.	• Two databases:
	  ○ Pubmed
	  ○ Embase
	• 196 publications recruited. 159 publications were excluded due to various reasons.
	• 22 publications analysed but only 6 were used in the review.
		• Systematic Review.
		
		Aim:
		• To determine the reliability of different methods available for assessment of muscle strength in critical ill patients.
		• To define recommendations for assessment of muscle strength in ICU.
		
		Keywords:
		• Adult
		• Critical illness
		• Muscle strength
		• Muscle strength dynamometer
		• Muscle weakness
		• Reliability of results
		
		• Two electronic databases were searched for relevant studies.
		• Two reviewers independently checked the titles, abstracts and reference lists.
			• Interrater reliability of the MRC-score varied from fair to very good.
			• Reliability of the MRC-sum score was very good.
			• Interrater reliability of handheld dynamometry was good to very good.
			• Interrater reliability of Handgrip dynamometry was very good.
			• Intra-rater reliability of HHD and HGD was very good.
			
			Conclusion:
			• Voluntary muscle strength testing is reliable in ICU, provided that strict guidelines are followed on standardized test positions.
				• Methodology repeatable:
				  ○ Search method explained in detail.
				  ○ Inclusion and exclusion criteria described.
				  ○ Quality assessment done by using the COSMIN checklist.
				  ○ Quality assessment tool described in detail.
				  ○ Quality assessment procedure explained.
				• Statistical analysis:
				  ○ Intra-class correlation coefficients and Pearson product moment correlation coefficients were used.
				  ○ Reasons mentioned for excluding publications from analysis.
				• Limitations:
				  ○ Only limitations to the studies were mentioned, no limitations mentioned for the systematic review.
				• Future research suggested to investigate the ability of manual muscle testing and dynamometry to assist in guiding the rehabilitation process.
				• Level of evidence: 1a

Author & Date	Patients	Methodology	Results	Critique
Wieske L et al. 2014.	• 604 patients screened. • 312 excluded by exclusion criteria. • 212 patients analysed.	• Prospective, observational, cohort study. • Single centre study. • 30 bed mixed medical and surgery ICU. Aim: • To determine of a 3 variable model can predict ICU-AW. • Authors hypothesised that early prediction of ICU-AW is possible and reliable.	• High lactate levels, treatment with aminoglycoside in the first two day of admission and age were predictors of ICU-AW. Conclusion: • Fair discriminative performance of the new 3 variable prediction model.	• Methodology repeatable: o Single centre study. o Inclusion and exclusion criteria described. o Study procedure explained. o Assessment method explained. o Recruitment of patients explained with flow diagram. • Statistical analysis: o Discriminative performance was analysed with AUC-ROC. o Chi-square test determined differences between proportions. o Welch's T-test determined differences between normally distributed variables. o Non-normally distributed continuous variables assessed with Wilcoxon rank-sum test. • Limitations: o Composite candidate predictors not included. • Recommendations for future research: o Prediction model needs external validation. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Pires-Neto RC et al. 2013.	• 268 patients admitted. • 19 patients included in analysis.	• Case series. • Single centre study. • Hypothesized that an earlier intervention of mobilisation might improve clinical outcomes. Aim: • To evaluate the hemodynamic, respiratory and metabolic effects of a cycling exercise performed during the first 72 hours of mechanical ventilation. Measurements: • Cardiac output • Heart rate • Mean arterial pressure • Central venous pressure • Systemic vascular resistance • SpO_2 • Respiratory rate • Tidal volume	• Early cycling exercise is feasible. • Exercise did not change hemodynamic, respiratory and metabolic rest parameters. Conclusion: • Early passive cycling in sedated, critically ill, mechanically ventilated patients was considered safe. • There were no significant alterations in haemodynamic, respiratory or metabolic variables.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria described. ○ Study procedure explained. • Statistical analysis: ○ Distribution was analysed with Kolmogorov-Smirnov test. ○ Data presented as mean and standard deviation or median and 25-75% IQR. • Limitations: ○ Used FloTrac-Vigileo system to measure CO. ○ Do not have metabolic data available for all patients ○ Study was not designed to examine benefits of the early intervention. • Recommendations for future research: Mentioned. • Level of evidence: 4

Author & Date	Patients	Methodology	Results	Critique

Pires-Neto RC et al. 2013.	• 38 patients included in analysis.
	• Respiratory ICU.
		• Case series.
		• Single centre study.
		
		Aim:
		• To evaluate the associated cardiorespiratory changes and to verify the patient's satisfaction with the device.
		
		Measurements:
		• Single intervention of riding cycle ergometer for 5 minutes with lower limbs.
		• HR, BP, RR, peripheral oxygen saturation and Borg dyspnoea scale evaluated before, during and after exercise.
		• Patients answered questionnaire to evaluate their satisfaction with the exercise.
			• HR increased with 3% above initial value.
			• RR increased with 20%.
			• 95% of patients reported they would rather pedal than perform free movements with the legs.
			
			Conclusion:
			• During the cycle ergometer exercises, minor cardiorespiratory changes were observed in patients.
			• Patients reported a high satisfaction with this type of activity.
				• Methodology repeatable:
				  o Single centre study.
				  o Inclusion and exclusion criteria described.
				  o Study protocol explained.
				  o Measurements explained.
				• Statistical analysis:
				  o Distribution was analysed with Kolmogorov-Smirnov test.
				  o Correlation analysis of HR, RR and Borg variables were performed using Spearman's correlation test.
				• Limitations:
				  o Single centre study.
				  o Short evaluation period.
				• Recommendations for future research: None mentioned.
				• Level of evidence: 4

Doorduin, J et al. 2013	• None	Critical care perspective:
		
		• Keywords:
		  o Critical Illness
		  o Diaphragm
		  o Intensive care
		  o Mechanical ventilation
		  o Muscle weakness
			• MIP and MEP indicated respiratory muscle strength, but patient need to cooperate.
			• Trans diaphragmatic pressure indicate respiratory muscle strength, but invasive.
			• Phrenic nerve stimulation is too invasive.
			• Chest X-ray not clear for paralysis.
			• B-mode ultrasonography measure diaphragm thickness.
				• Methodology not repeatable:
				  o No search strategy explained.
				  o Data not critically analysed.
				  o Sample size of data not explained.
				  o No inclusion or exclusion criteria.
				  o Resources not mentioned.
				• No statistical analysis of data.
				• Study is only mentioning all relevant data, not a systematic review.
				• Level of evidence: 5

Author & Date	Patients	Methodology	Results	Critique
Cappati KRK et al. 2013.	• 130 patients recruited. • 6 ICU's of 3 hospitals.	• Observational, prospective study. • Multicentre study. Aim: • To measure the SBT inter-observer agreement of physicians and respiratory therapists. • Two therapists and two physicians rated the SBT while patients were performing the SBT.	• Moderate inter-observer agreement for SBT. • *k* coefficient for physicians = 0.46 • *k* coefficient for therapists = 0.57 • Percentage agreement between 2 different observers for the SBT is 79.2% and 92.3% Conclusion: • The SBT inter-observer agreement rate is only moderate for physicians and respiratory therapists.	• Methodology repeatable: ○ Multicentre study. ○ Inclusion and exclusion criteria described. ○ Study procedure explained. ○ Flow of the study explained in a flow diagram. • Statistical analysis complete: ○ Cohen coefficient was calculated. ○ Credible interval calculated with Bayesian inference. • Limitations: ○ Observers could be influenced by primary physician verdict. ○ The observers were not asked about the reason why they considered that the SBT failed. • Recommendation for future research: ○ Likelihood function be offered as an alternative method to measure the inter-observer agreement. • Level of evidence: 2a

Author & Date	Patients	Methodology	Results	Critique
Thille AW et al. 2013.	• None	• Clinical Review. • Keywords: ○ Laryngeal injury ○ Weaning ○ Non-invasive ventilation ○ Organ dysfunction ○ Endotracheal tube	• Extubation failure is need of re-intubation within 48-72 hours post extubation. • Mortality increases with extubation failure. • Reasons for extubation failure: ○ Respiratory failure ○ Congestive cardiac failure ○ Surgical complications ○ In-effective cough with airway secretions ○ Aspiration ○ Upper airway obstruction ○ New onset of sepsis ○ Neurological impairment • ICU-acquired weakness is associated with prolonged mechanical ventilation. • Extubation readiness test: SBT with T-piece or SBT with ventilator with low levels of PS. • Future research recommended to identify new factors associated with extubation failure: ○ Delirium, Poor sleep quality. ○ Limb muscle and diaphragmatic weakness.	• Methodology not repeatable: ○ Searching strategy not explained. ○ Resources recruited not explained. • No statistical analysis of data. • No critical analysis of data. • Study is only mentioning all relevant data, not a systematic review. • Future research recommended to identify new factors associated with extubation failure. • Randomised control trials suggested. • Level of evidence: 5

Author & Date	Patients	Methodology	Results	Critique
Thille AW et al. 2013.	• None	• Clinical Review. • Keywords: ○ Extubation ○ ICU ○ Spontaneous breathing trial ○ Weaning from mechanical ventilation	• Mortality increases with extubation failure. • Non-invasive ventilation post extubation can increase mortality due to delay in re-intubation time. • First weaning trial must be performed when: ○ Reason for intubation reversed. ○ Cardiovascular stability with minimal vasopressors. ○ No continuous sedation. ○ PaO_2/FiO_2 ratio at least 150 mmHg. ○ PEEP = 8 cmH_2O. • Factors associated with extubation failure: ○ Age ○ Neurological dysfunction ○ In-effective cough ○ Amount of secretions ○ Delirium ○ Prolonged sedation ○ ICU-AW • ICU-AW is affecting peripheral and respiratory muscles. • Extubation readiness test: SBT with T-piece or SBT with ventilator with low levels of pressure support. • Upper airway obstruction causes extubation failure in 7%-20% of patients.	• Methodology not repeatable: ○ Searching strategy not explained. ○ Resources recruited not explained. • No statistical analysis of data. • No critical analysis of data. • Study is only mentioning all relevant data, not a systematic review. • Limitations: None mentioned. • Future research recommended: None mentioned. • Level of evidence: 5

Author & Date	Patients	Methodology	Results	Critique

Supinski GS et al. 2013.	• 60 patients recruited.
	• 57 patients included in data analysis.
	• Medical ICU.
		• Descriptive, observational study.
		
		• Aim:
		  ○ Measure diaphragm strength in mechanically ventilated patients.
		  ○ Test hypothesises that the severity of diaphragm weakness would correlate with one or more of the clinical factors.
		
		Measurements:
		• Trans-diaphragmatic twitch pressure (PdiTw) in response to bilateral magnetic stimulation of the phrenic nerve. Best measurement of 3 was documented.
		• Respiratory static system compliance and airway resistance with the ventilator.
			• 49% mortality for patients with PdiTw< 10 cmH_2O and only 7% mortality for patients with PdiTw> 10 cmH_2O.
			• PdiTw< 10 cmH_2O need longer ventilation than PdiTw> 10 cmH_2O.
			• Diaphragm weakness is associated with poor patient outcomes including increased mortality, increased transfer to long term care facility and longer duration required for weaning from mechanical ventilation.
			
			Conclusion:
			• Infection is major risk for diaphragm weakness.
			• Diaphragm weakness is important determinant of poor outcomes in the patient population.
				• Methodology repeatable:
				  ○ Study design not documented. Descriptive, observational study.
				  ○ Single centre study.
				  ○ Explain exclusion criteria.
				  ○ Measuring technique and equipment explained in detail.
				  ○ Recruitment of patients not explained.
				• Statistical analysis:
				  ○ Data analysed using mean, standard errors of the mean, Fisher exact testing, confidence intervals.
				  ○ ANOVA employed to compare across cohorts of patients with different levels of ventilator triggering.
				  ○ Explain exclusions of 3 patients for analysis of data.
				• Limitations: None mentioned.
				• Future research recommended: None mentioned.
				• Level of evidence: 4

Author & Date	Patients	Methodology	Results	Critique
Huang CT et al. 2013.	• 357 patients recruited. • 331 patients analysed. • Intermediate respiratory care unit.	• Retrospective study. • Single centre study. Aim: • To test the predictive value of usual variables for extubation outcome in prolonged mechanically ventilated patients. • One year survival of patients with regard to extubation outcome was analysed.	• Cough effectiveness is only variable independently predicting extubation outcome. • Sensitivity and specificity of 85% and 71% respectively for cough effectiveness. • One year survival of successfully extubated patients is higher than failed extubated patients. Conclusion: • Ineffective cough best predictor of extubation failure. • Extubation failure associated with mortality.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria described. ○ Study procedure explained. ○ Flow of the study explained in a flow diagram. • Statistical analysis complete: ○ Inter-group differences compared using independent sample T-test for continuous data and Chi-square or Fisher exact for categorical data. ○ Multivariate logistic regression analysis performed. • Limitations: ○ Study only conducted in specialised unit, might not be universally applied. ○ Small sample size. ○ Could not evaluate the reliability and reproducibility of assessment of cough. • Recommendation for future research: ○ None mentioned. • Level of evidence: 3

Author & Date	Patients	Methodology	Results	Critique
Hilbert M et al. 2012.	• 9 patients analysed.	• Observational study. • Single centre study. Aim: • To examine the effect of acid-base disturbances, which were within physiological range, resulting from respiratory acidosis and alkalosis on muscle performance and excitability during dynamic, high-intensity handgrip exercise performed with maximal power. Measurements: • pH, potassium and sodium concentration were measured in venous and arterialized blood. • Compound action potentials were elicited to examine excitability of the sarcolemma. • Surface EMG was recorded to estimate the central drive to the muscle.	• Acidification reduced the decline in contraction speed but decrease the M-wave area of the initial value. • Acidification diminished the reduction in performance, although the M-wave area during exercise was decreased. Conclusion: • Did not find a direct link between performance and alteration of excitability of sarcolemma due to changes in pH.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria described. ○ Study procedure explained. ○ Study protocol explained. • Statistical analysis complete: ○ Two-way ANOVA was used for comparison of three groups. ○ Schéffé test as post hoc test for multiple comparisons of the means. • Limitations: None mentioned. • Recommendation for future research: None mentioned. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Grosu HB et al. 2012.	• 7 newly intubated patients. • Emergency department, Medical wards, ICU.	• Longitudinal observational, pilot study. • Single centre study. Aim: • To quantify the rate and degree of daily diaphragm thinning with ultrasonography. Measurements: • Daily ultrasonographic measurements of diaphragm thickness from day 1 of intubation till extubation, tracheostomy or death were documented. • Two-dimensional B-mode ultrasound.	• Diaphragm thickness decreases over time at a rate of 6% per day on mechanical ventilation. • Trend was notice that high positive end expiratory pressure (PEEP) and high respiratory rate is protective for diaphragm thinning, but high tidal volume progressively decreases diaphragm thickness. Conclusion: • Diaphragm thinning starts within 48 hours of mechanical ventilation.	• Methodology repeatable: o Single centre study. o Only 7 patients recruited. o No inclusion and exclusion criteria explained – all patients except tracheostomy patients were used. o Measuring tool and technique explained in detail. • Statistical analysis: o Need bigger sample size to accept data as clinically meaningful. • Limitations: o Small sample size. o Lacked control group. • Future research recommended: o To assess if the decrease in diaphragm thickness is due to diaphragm atrophy. • Level of evidence: 3

Author & Date	Patients	Methodology	Results	Critique
Hermans G et al. 2012.	• 735 patients recruited. • 415 patients included. • Surgical / medical ICU.	• Reliability, cross sectional study. • Single centre study. Aim: • Assess interrater reliability of MRC-score and hand grip strength. • Evaluate the reproducibility of cut-off values for weak patients with MRC-score. Measurements: • Muscle strength was evaluated with MRC-score and handgrip dynamometer when patient score 5/5 for cognitive questionnaire.	• Very good reproducibility of the MRC-sum score with ICC = 0.95. • Very good reproducibility of the handgrip strength R ICC = 0.93, L ICC = 0.97. • Identifying “significant weakness” as MRC-score <48 very good. • Identifying “severe weakness” as MRC-score < 36 excellent. Conclusion: • Interobserver agreement on MRC sum-score and handgrip strength in the ICU was very good.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria only mentioned in flow diagram. Not explained in detail. ○ Procedure explained. ○ Equipment explained. ○ Recruitment of patients described in flow diagram. • Statistical analysis: ○ Nonparametric tests performed (Mann Whitney U-test, Wilcoxon’s signed rank test). ○ Intra-class correlation coefficients determined. • Limitations: ○ Dominance was not register. • Recommendation for future research: ○ Determine predictive value of handgrip strength toward functional outcome. • Level of evidence: 2a

Author & Date	Patients	Methodology	Results	Critique

Lee JJ et al. 2012.	• 110 patients recruited in the Surgical ICU.
	• 107 patients were evaluated.
	• 3 patients excluded due to the exclusion criteria.
	• Tertiary hospital.
		• Prospective, observational study.
		• Single centre study.
		
		Aim:
		• To determine if manual muscle testing (MMT) and handgrip dynamometry would predict in-hospital mortality in SICU.
		• To determine if MMT and handgrip dynamometry would be associated with length of stay and ventilator days.
		
		Measurements:
		• Patients were evaluated for readiness after 48 hours of ventilation.
		• Patients assessed for being awake and oriented. Patients regarded awake if scoring at least -1 with the Richmond Agitation-Sedation scale (RASS) and 3/5 for cooperative questions.
		• Muscle strength was tested with the MRC-score.
		• Three measurements with the handheld dynamometer were taken in the dominant hand.
			• MMT was associated with mortality, SICU length of stay, hospital length of stay and the ventilator days.
			• If strength increases, mortality decreases.
			• The grip strength was not associated with mortality, length of stay or ventilator days.
			• Strength predicts the outcome of people in the ICU rather than reflecting the consequences of muscle wasting in the ICU.
			
			Conclusion:
			• Global muscle testing predicts mortality, ventilator days, ICU length of stay and hospital length of stay. Grip strength alone can't predict these outcomes.
				• Methodology repeatable:
				  ○ Single centre study.
				  ○ Inclusion and exclusion criteria explained.
				  ○ Measuring tools described in detail.
				  ○ Research procedure explained.
				  ○ Enrolment of patients explained with flow diagram.
				  ○ No follow up of patients.
				• Statistical analysis:
				  ○ Spearman correlation, logistic regression and multivariate analysis were completed.
				  ○ Mention the reasons for excluding patient's data from analysis.
				• Limitations:
				  ○ No muscle testing before admission.
				  ○ The patients included were only surgery patients with relatively low level of disease severity. The results can't be generalised to the medical ICU population.
				• Future research recommended to identify interventions that target muscle strength in ICU.
				• Level of evidence: 1c

Author & Date	Patients	Methodology	Results	Critique
Vanpee G et al. 2011.	• 60 patients recruited. • 39 patients were tested. • Surgical and medical ICU's.	• Cross-sectional, observational study. • Single centre study. Aim: • To determine the interobserver reliability of handheld dynamometry. • To quantify muscle weakness, to evaluate distribution of muscle weakness and to evaluate gender-related differences in muscle strength.	• Handheld dynamometer demonstrated good interobserver agreement with ICC > 0.90 in four muscle groups. • Elbow flexors, knee extensors and ankle dorsiflexors were mostly affected with decrease muscle strength. • Loss of muscle strength was comparable between men and women. Conclusion: • Handheld dynamometry is a tool with very good interobserver reliability to assess limb muscle strength in awake and cooperative critically ill patients.	• Methodology repeatable: o Single centre study. o Inclusion and exclusion criteria explained. o Testing procedure explained in detail. o Equipment used explained. • Statistical analysis complete: o Intra-class correlation coefficient was determined. o Analysis of variance (ANOVA) was used to compare test results. • Limitations: o Only patients with MRC-score > 3 were recruited. o Muscle strength was measured unilaterally. • Recommendation for future research: Mentioned. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Peñuelas O et al. 2011.	• 4968 patients recruited. • 2714 patients were analysed. • 349 ICU's in 23 countries.	• Prospective, observational, cohort study. • Multi-centre study. Aim: • To analyse outcomes based on the new weaning classification in a cohort of mechanically ventilated patients.	• Duration of weaning longer than 7 days had higher mortality than patients with simple weaning. • Duration of mechanical ventilation before the start of weaning is associated with weaning outcome. • Level of PEEP associated with prolonged weaning. Conclusion: • Only patients who need more than 7 days for weaning have an increased mortality.	• Methodology repeatable: ○ Multi-centre study. ○ Inclusion and exclusion criteria explained. ○ Research procedure explained. ○ Enrolment of patients explained with flow diagram. • Statistical analysis: ○ ANOVA and Kruskal-Wallis H test were used to compare continuous variable. ○ Chi-square or Fisher exact were sued to compare proportions. ○ Multinomial logistic regression with backward stepwise selection was performed to estimate the variables associated with difficult or prolonged weaning. • Limitations: ○ Did not analyse the influence of polyneuropathy associated with weaning time. ○ Have no information about the complications including delirium experienced over the weaning time. • Recommendation for future research: None mentioned. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Hough CL et al. 2011.	• 135 patients recruited in the Surgical ICU. • 34 patients were analysed. • Medical and surgery ICU.	• Prospective, observational study. • Single centre study. Aim: • To determine the feasibility of assessment and interobserver agreement regarding the diagnosis of ICU-AW and the MRC-score in critically ill patients. Measurements: • Patients were evaluated for readiness after 48 hours of ventilation. • Patients assessed for being awake and oriented. • Muscle strength was tested with the MRC-score.	• Observers agree on diagnosis of ICU-AW for 93% of patients. • Observer agreement was fair in the ICU. Conclusion: • Manual muscle testing during critical illness was not possible for most patients because of level of consciousness. • Interobserver agreement regarding ICU-AW was good. • Manual muscle testing is insufficient for early detection of ICU-AW in most patients and may be unreliable during critical illness.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria explained. ○ Research procedure explained. ○ Enrolment of patients explained with flow diagram. • Statistical analysis: ○ Interobserver agreement on ICU-AW was calculated on basis of Cohen's kappa statistics. • Limitations: ○ Small sample size. ○ Low incidence of ICU-AW. • Future research recommended to identify and develop tests to diagnose ICU-AW. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Reuter SE et al. 2011.	• 21 subjects recruited. • 16 subjects underwent both testing protocols.	• Reliability and validity study. • Single centre. Aim: • To determine test-retest reliability of indices of sub-maximal, static hand-grip testing in healthy adults. • To determine the concurrent validity of sub-maximal, static hand-grip testing in heathy subjects in relation to 6MWT. • Hand-grip testing and 6MWT conducted on three separate days by the same assessor. Measurements: • Initial maximum contraction • Final maximum contraction • Distance walked • Duration of 50% maximal contraction • Work performed • Strength Decrement Index	• Initial Max = 8.2 kg and 10 kg for dominant and non-dominant hand respectively. • Final Max = 7.2 kg. • Distance = 77.5 m. • Initial Max and Final Max (ICC > 0.9) were excellent and comparable with distance walked with 6MWT (ICC = 0.819). Conclusion: • Pre- and post-fatigue maximal contraction maybe used for assessment of ability and progression. • Indices of grip strength are predictive of exercise capacity.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria not explained. ○ Testing procedure explained in detail. ○ Equipment used explained. • Statistical analysis complete: ○ Intra-class correlation coefficient was determined. ○ Analysis of variance (ANOVA) was used to compare test results. ○ Linear regression was used to determine concurrent validity. • Limitations: None mentioned. • Recommendation for future research: Mentioned. • Level of evidence: 2a

Author & Date	Patients	Methodology	Results	Critique
Tzanis G et al. 2011.	• 74 patients. • Ventilated for >7 days. • Multi-disciplinary ICU.	• Prospective, observational study. • Single centre study. Aim: • To investigate development of ICU-AW by using MIP as surrogate for peripheral muscle strength. • MRC-score for clinical evaluation of muscle strength. • MRC-score was obtained on the day the patient was awake and orientated. Patient regard as awake when able to perform 3/5 of cooperative questions. • MIP measured with unidirectional valve method: 3 measurements. • MIP was measured 48 hours post sedation was discontinued.	• Significant correlation between MIP and MRC-score. • Patients with ICU-AW had longer weaning period than patients without ICU-AW. • 36 cmH_2O for MIP was defined for ICU-AW diagnosis. Conclusion: • MIP may be potential surrogate parameter for assessment of muscle strength compromise. • MIP useful for early detection of ICU-AW.	• Methodology not repeatable: ○ Single centre study. ○ Only exclusion criteria described. ○ Recruitment of patients not clearly described. ○ Measuring tools explained. • Statistical analysis: ○ Reasons for exclusion from analysis explained. ○ Unpaired student's T-test, Pearson's correlation coefficient and Kaplan-Meier method used for analysis of data. • Limitations mentioned: ○ Limited number of patients. ○ Lack of electrophysiological investigations. • Recommendation for future research: ○ Further investigation required to address the broad application of the method. • Level of evidence: 2a

Author & Date	Patients	Methodology	Results	Critique

Martin AD et al. 2011.	• 129 patients recruited.
	• 69 patients included.
	• Medical, surgical and burns ICU.
		• Single blind, randomised control trial.
		• Single centre study.
		
		Aim:
		• To test whether inspiratory muscle strength training would improve weaning outcome in failure to wean patients.
		
		Measurements:
		• MIP was evaluated using3 measurements with 2 min rest between attempts.
		• Inspiratory muscle strength training (IMST) performed 5 days/week:
		  ○ 4 sets of 6-10 breaths per day with 2 min rest between each set.
		• SHAM treatment:
		  ○ 4 sets of 6-10 breaths per day with 2 min rest between each set.
		• Daily breathing trials till patient can tolerate six-hour breathing trial.
			• IMST rehabilitation rapidly improved MIP and weaning outcome compared with SHAM.
			• Respiratory muscle weakness is a greater contributor to failed weaning than fatigue.
			
			Conclusion:
			• IMST program can lead to increased MIP and improved weaning outcome in failure to wean patients compared to SHAM treatment.
				• Hypothesis supported by background information and explanation.
				• Methodology repeatable:
				  ○ Single centre study.
				  ○ Inclusion and exclusion criteria explained, but clear definition of failure to wean with usual care not explained. Not clear when patients are classified as failure to wean in methodology.
				  ○ Single blinded study.
				  ○ Patients blinded to group assignment.
				  ○ Randomisation performed with a computerised random number generator.
				  ○ Clear description of evaluating and intervention techniques performed.
				  ○ No clear indication of follow up.
				• Statistical analysis significant:
				  ○ Consort diagram explain inclusion of patients in analysis.
				  ○ Chi-square tests, Student T-tests and analysis of variance tests were used for analysis.
				• Limitations:
				  ○ IMST not suitable for all failure to wean patients.
				  ○ Patients need to be awake and cooperative to perform IMST.
				  ○ Single centred study.
				• Level of evidence: 1a

Author & Date	Patients	Methodology	Results	Critique
Moodie LH et al. 2011.	Five electronic databases • Pedro • CENTRAL • PubMed • Embase • CINAHL	Protocol for systematic review: • To date no systematic reviews to evaluate the effectiveness of inspiratory muscle training (IMT) in facilitation of weaning from mechanical ventilation. Aim: • Evaluate effectiveness of IMT in increasing inspiratory muscle strength and endurance in mechanically ventilated patients. • Determine if IMT affects the duration of weaning from mechanical ventilation, duration of spontaneous breathing and rate of re-intubation. MIP • Duration of weaning period. • Hospital length of stay. • Meta-analysis comparable results.	• Isocapnic hyperpnoea ○ To improve respiratory muscle endurance. ○ Patient voluntarily breathes at high levels of ventilation for period of time. ○ Generate a low-pressure high-flow load. • Inspiratory resistive flow training: ○ Patient inhale through an orifice to the ET tube with a reduced diameter. ○ Amount of inspiratory resistance is dependent on the flow generated by the patient. • Inspiratory threshold pressure training: ○ IMT device is connected to the ventilator circuit. ○ A spring-loaded valve will open for inspiratory flow if a specific negative threshold pressure has been reached. • Ventilator sensitivity. • Adjust the pressure trigger sensitivity. • Inspiratory load gradually increased.	• Aim of the systematic review described. • Methodology repeatable: ○ Inclusion and exclusion criteria explained. ○ Only 5 databases to be electronically searched. No multiple resources will be evaluated. ○ Explain searching procedure. ○ Pedro scale will be used for quality assessment of studies. • Statistical analysis described: ○ To determine 95% confidence interval and mean difference. ○ Meta-analysis to follow. ○ Sensitivity analysis to follow. • Level of evidence: 5

Author & Date	Patients	Methodology	Results	Critique
Roberts HC et al. 2011.	• Three databases: ○ Medline ○ Web of Science ○ Cochrane • 11604 publications found. • 42 articles analysed in the review, all other were part of the exclusion criteria.	• Clinical Review. • Keywords: ○ Grip strength ○ Measurement ○ Protocol ○ Elderly	• Wide variability in choice of equipment and protocol for measuring grip strength. • Jamar hand dynamometer is most widely used instrument. Conclusion: • A standardised method would enable more consistent measurement of grip strength.	• Methodology not repeatable: ○ Inclusion and exclusion criteria described. ○ Resources recruited explained. • No statistical analysis of data. • Limitations: None mentioned. • Recommendation for future research: None mentioned. • Level of evidence: 5
Jaber S et al. 2011.	• None	• Clinical review. Aim: • To outline the key data that have demonstrated the adverse effects of controlled mechanical ventilation on the diaphragm in animal models.	• Studies performed on diaphragms of mechanically ventilated ICU patients confirmed with animal model data: ○ Increased oxidative stress. ○ Increased muscle fibre atrophy and injury. • Activation of several major proteolytic pathways.	• Methodology not repeatable: ○ No keywords available. ○ No search strategy applied. ○ Data not critically analysed. ○ Inclusion and exclusion not mentioned. ○ Resources not mentioned. • No statistical analysis. • Study only gives overview of all data available, not systematic review. • Level of evidence: 5

Author & Date	Patients	Methodology	Results	Critique
Terson de Paleville DGL et al. 2011.	• None	• Clinical review. Aim: • To describe the mechanisms of respiratory motor control and its change in individuals with spinal cord injury.	• None of the rehabilitative techniques for the restoration of respiratory motor control in patients with SCI have been proven to be effective. • Expectation that ongoing studies will support application of physiologically based rehabilitation strategies to manage these conditions as standard of care.	• Methodology not repeatable: ○ No keywords available. ○ No search strategy applied. ○ Data not critically analysed. ○ Inclusion and exclusion not mentioned. ○ Resources not mentioned. • No statistical analysis. • Study only gives overview of all data available, not systematic review. • Level of evidence: 5
Bulthuis Y et al. 2010.	• 30 healthy volunteers	• Cross over design. Aim: • To determine whether a submaximal arm crank test can be used for assessment of physical fitness in individuals. • Establish the reliability and validity of this method in predicting the VO_2 max.	• Healthy people physical fitness assessed on the lower limbs – patients lower limbs impaired. • Compared the results of the average heart rate during 5th and 6th minute on the arm ergometers and the bicycle. • Test-retest reliability of the arm test is good. • Excellent interobserver reliability for the arm test. • Submaximal test on the arm crank ergometer is a valid instrument to measure physical fitness.	• Hypothesis supported by background information and explanation. • Methodology not repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria not explained. ○ Clear description of evaluating and intervention techniques performed. ○ No clear indication of follow up. • Statistical analysis significant: ○ Bland-Altman plot was constructed. ○ ICC and 95% CI were determined. ○ Statistical analyses done with SPSS. • Limitations include: ○ Small selected population. ○ Validity not formally proven for disabled persons. • Level of evidence: 3

Author & Date	Patients	Methodology	Results	Critique
Hermans G et al. 2010.	• 25 patients recruited. • 17 analysed. • 8 patients excluded due to technical problems. • Medical ICU.	• Prospective, observational study. • Single centre study. Aim: • Evaluate the repeatability of BAMPS TwPdi on different occasions in critically ill patients. • Examine whether TwPdi would decrease with increasing duration of mechanical ventilation. Measurements: • TwPdi was measured by using bilateral anterior magnetic phrenic nerve stimulation. • Patients measured on two occasions with minimal time interval of 24h.	• Logarithmic decline in TwPdi with increasing duration of mechanical ventilation. • Diaphragmatic force diminish very soon after mechanical ventilation was started. • First report: Increased duration of mechanical ventilation is associated with decreased diaphragmatic force, measured with a non-volitional method, independent of patient cooperation. Conclusion: • Duration of mechanical ventilation is associated with a logarithmic decline in diaphragmatic force, which is compatible with the concept of VIDD.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria explained. ○ Testing procedure explained in detail. • Statistical analysis: ○ Calculated by using the mean values, within-occasion coefficient of variation, regression analysis and the logarithmic model. ○ Reasons for 8 exclusions from data analysis mentioned. • No follow up mentioned. • Limitations explained: ○ Limited number of patients – no stepwise regression analysis possible. ○ Confounders could be missed due to limited numbers. ○ Technique is highly sophisticated, fairly invasive and requires stable patients, therefore the technique is limited to a small subgroup. • Level of evidence: 2

Author & Date	Patients	Methodology	Results	Critique
Burtin C et al. 2009.	• 90 patients. • Surgical and medical ICU.	• Randomized control trial. • Single centre study. Aim: • To determine whether a daily exercise program with a cycle ergometer is safe and effective. Control group: • Routine physiotherapy with standardised mobilisation session of the upper and lower extremities for 5 days per week. Treatment group: • Routine physiotherapy like the control group, but added a 20 min cycling session for 5 days per week with the MOTOmed® letto2 cycle ergometer. • Primary outcome: ○ 6 MWD at hospital discharge. • Secondary outcomes: ○ Isometric quadriceps force. ○ Functional status. • Exploratory outcomes: ○ Weaning time. ○ ICU and hospital stay. ○ 1 year mortality. • Assessments on the day of discharge from ICU and on the day of discharge from hospital: ○ Short Form 36 Health Survey questionnaire (SF-36) and 6-min walking distance (6 MWD).	• Daily exercise with a MOTOmed® letto2 cycle ergometer is feasible and safe. • Improved functional exercise capacity. • Increase muscle force. • Perceived functional status at hospital discharge. Conclusion: • Early exercise training in ICU enhances recovery of functional exercise capacity, self-perceived functional status and muscle force at hospital discharge.	• Methodology repeatable: ○ Single centre study. ○ Randomisation according to sealed opaque envelopes in random block sizes. ○ Neither patients nor researcher were blinded. ○ Inclusion and exclusion criteria explained. ○ Techniques and equipment used explained in detail. • Statistical analysis: ○ Mean, standard deviation, Student's T-test, Mann-Whitney U tests, Fisher's exact test. ○ Flow diagram of data analysed. ○ Mentioned that no adverse events happened during the study. ○ Reasons for exclusion of patients from data analysis explained. • No follow up in this study. • Limitations: ○ The 20 min extra exercise can have a positive impact on the patients. ○ No prospective screening to determine if critical illness neuromuscular abnormalities are present. • Level of evidence: 1a

Author & Date	Patients	Methodology	Results	Critique
Bittner EA et al. 2009.	• 6 studies in table format.	• Clinical review.	• Quantitative assessment of skeletal muscle force is important for diagnosis of ICU-AW. • Selection of appropriate muscle is crucial for making prediction of patient's outcome. • ICU-AW is affecting peripheral and respiratory muscles. • Survivors of critical illness have prolonged neuromuscular complications that impair their physical function and quality of life.	• Methodology not repeatable: ○ No keywords available. ○ No search strategy applied. ○ Data not critically analysed. ○ Inclusion and exclusion not mentioned. ○ Resources not mentioned. • No statistical analysis. • Study only gives overview of all data available, not systematic review. • Level of evidence: 5
Carlucci A et al. 2009	• 74 patients recruited. • 30 patients analysed. • Respiratory ICU.	• Prospective, cohort study. • Single centre study. Aim: • To assess the determinants of weaning success in patients acting as their own control. Measurements: • Patients underwent T-piece trial 48 hours after admission. • Breathing pattern. • Respiratory mechanics. • Inspiratory muscle function. • Tension time index of diaphragm.	• Respiratory rate was higher in failure group. • Statistical significant association between mortality and weaning outcome. Conclusion: • Recovery of an inadequate inspiratory muscle force could be the major determinant of "late" weaning success, since this allows the patients to breathe far below the diaphragm fatigue threshold.	• Methodology not repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria described. ○ Process described. ○ Physiological measurements described. • Statistical analysis: ○ Kolmogorov-Smirnov statistics and Shapiro-Wilk test were used to test the normality of distribution of variables. ○ ANOVA and Chi-square test assessed the difference between groups. • Limitations: None mentioned. • Recommendation for future research: None mentioned. • Level of evidence: 3

Author & Date	Patients	Methodology	Results	Critique
Esteban A et al. 2008.	• 4968 patients recruited. • 1675 patients analysed. • 349 ICU's in 23 countries.	• Prospective, observational cohort study. • Multicentre – international. Aim: • To describe current mechanical ventilation practices and to assess the influence of interval randomised trials when compared with findings from a 1998 cohort.	• Non-invasive ventilation increased from 1998 to 2004. • Tidal volumes decrease and PEEP increased. • More patients were successfully extubated after first attempt. • Use of SIMV fell dramatically. Conclusion: • The translation of clinical research to clinical practice is happening.	• Methodology repeatable: ○ Multicentre study – international. ○ Inclusion and exclusion criteria described. ○ Process described. ○ Hypotheses explained. • Statistical analysis: ○ Student T-test and Mann-Whitney U test to compare continuous variables. ○ Chi-square test was used for categorical variables. • Limitations: ○ Did not collect information to describe the process by which practice changed. • Recommendation for future research: None mentioned. • Level of evidence: 3

Author & Date	Patients	Methodology	Results	Critique
Levine S et al. 2008.	• 14 brain dead organ donors.	• Prospective, observational study. • Single centre study. Hypothesis: • Combination of complete diaphragm inactivity and mechanical ventilation elicits disuse atrophy of myofibres in animals. The same will occur in human diaphragm. Measurements: • Obtained biopsy specimens from costal diaphragms of 14 brain-dead organ donors before organ harvest, compare with intraoperative biopsy specimens from diaphragms of patients undergoing surgery for either benign lesions or localised lung cancer.	• Decreased cross-sectional areas of slow-twitch and fast-twitch fibers of ventilated humans. Conclusion: • Combination of 18 – 69 hours of complete diaphragmatic inactivity and mechanical ventilation results in marked atrophy of human diaphragm myofibres.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria explained. ○ Data collection procedure explained in detail. • Statistical analysis: ○ Mean and median calculated for continuous data. ○ T-test were used for normally distributed continuous data and Mann-Whitney for non-normally distributed data. ○ Fisher's exact test for categorical data. • Limitations: None mentioned. • Recommendation for future research: None mentioned. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Ali NA et al. 2008.	• 3475 patients recruited. • 136 patients enrolled. • 3339 patients excluded due to exclusion criteria and refusing consent. • Medical ICU's.	• Prospective, cohort study. • Multicentre – 5 hospitals. • Hypothesised that ICU-AW is associated with increased mortality. • Hypothesised that handgrip strength with dynamometry would provide a measure of global strength. • Measure muscle strength with MRC-score when patient awake and responsive. • Measure handgrip strength with hand dynamometry.	• Patients with ICU-AW had lower maximum handgrip strength. Handgrip strength: • Males < 11 kg force • Females < kg force • Sensitivity = 80.6% • Specificity = 83.2% • Negative predictive value = 92.3% • Positive predictive value = 63.0% Conclusion: • ICU-AW is independently associated with increase mortality rate. • Handgrip strength can be a surrogate for MRC-Score and is independently associated with hospital mortality.	• Methodology repeatable: ○ Multicentre study – 5 hospitals. ○ Inclusion and exclusion criteria described. ○ Process described. ○ Equipment described. ○ Enrolment of patients explained with flow diagram. • Statistical analysis: ○ Logistic regression and negative binomial regression analysis were done. ○ Pearson's and Spearman's correlation coefficients determined. • Limitations: ○ Neurologist not consulted for strength exams. ○ No information regarding causes of respiratory failure / death. • Recommendation for future research: Mentioned. • Level of evidence: 3

Author & Date	Patients	Methodology	Results	Critique

De Jonghe B et al. 2007.	• 324 patients with mechanical ventilation for more than 7 days.
	• Only 116 included in the study.
	• Medical and surgical ICU's.
		• Prospective observational study.
		• Multicentre study.
		
		Aim:
		• Assess the severity of respiratory neuromuscular function in patients mechanically ventilated for more than 7days.
		• Investigate the correlation between respiratory and limb muscle strength.
		• Determine the contribution of respiratory neuromuscular involvement to delayed weaning.
		
		• MIP, MEP, VC and muscle strength were measured on the first day of awakening.
		• Awakening defined as a patient scoring 3/5 for co-operative questions on two consecutive evaluations at a 6 hour interval.
		• Patients daily evaluated for extubation readiness.
		• Patient extubated after completing T-piece trial successfully.
		• Patients followed up for 15 days to be classified successful extubated if not re-intubated within 15 days.
			• Median MRC-score = 41 for 115 patients.
			• 105 patients:
			  ○ MIP = 30 cmH_2O
			  ○ MEP = 30 cmH_2O
			  ○ VC = 11.1 ml/kg
			• Correlation between MRC-score, MIP, MEP and VC.
			• Low MIP, MEP and MRC-score is independent predictors of delayed extubation.
			• Septic shock is associated with a low MIP and MEP.
			
			Conclusion:
			• Respiratory muscle weakness is associated with limb weakness.
			• Septic shock is a predictor of respiratory muscle weakness.
			• Respiratory muscle weakness is associated with delayed extubation and prolonged ventilation.
				• Methodology repeatable:
				  ○ Multicentre study (3 hospitals).
				  ○ Medical and surgery ICU's.
				  ○ Inclusion and exclusion criteria described.
				  ○ Procedure and techniques were explained in detail.
				  ○ No intervention, only observation and measurement.
				• Statistical significant:
				  ○ Categorical variables compared with chi-square or Fisher's exact test.
				  ○ Quantitative date are presented as median and compared with Mann-Whitney test.
				  ○ Spearman's correlations and analysis of variance determine associations.
				  ○ Search for interaction and confounding was systematically performed.
				  ○ Multivariable model implemented.
				  ○ $P < 0.05$ was considered significant.
				  ○ Reasons for exclusion of 208 patients explained.
				• Limitations and confounders: Described in detail.
				• Recommendation for future research: Mentioned.
				• Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Mokhlesi B et al. 2007.	• 637 patients recruited. • Only 122 included in the study. • Medical and surgical ICU's.	• Prospective observational cohort study. • Single centre study. Aim: • To derive a clinical prediction rule that uses bedside clinical variables to predict extubation failure. Measurements: • GCS • Amount of secretions • $PaCO_2$	• Three clinical variables predicted reintubation: o Copious endotracheal secretions o GCS < 10 o Hypercapnia Conclusion: • The clinical prediction rule that incorporates an assessment of mental status, endotracheal secretions and pre-extubation $PaCO_2$ can predict extubation failure despite a successful SBT.	• Methodology repeatable: o Single centre study. o Inclusion and exclusion criteria described. o Procedure and techniques were explained in detail. o No intervention, only observation and measurement. • Statistical significant: o Logistic regression analysis to identify variables. o Bootstrap resampling to internally validate the predictors. • Limitations: o Did not have external validation set. o Small sample size with low event-per candidate variable ratio. • Recommendation for future research: None mentioned. • Level of evidence: 3

Author & Date	Patients	Methodology	Results	Critique
Hol AT et al. 2007.	• 30 patients recruited. • SCI rehab centre.	• Prospective, exploratory, methodological study. • Single tertiary rehabilitation centre. Aim: • To design a submaximal arm ergometer test (6-MAT) for spinal cord injured patients. • Determine the test-retest reliability and concurrent validity of the test. Measurements: • VO_2 • VCO_2 • Borg's 24 • Blood pressure • Respiratory exchange ratio • Blood lactate. • Complete 6-minutes of submaximal exercise on arm cycle ergometer. • Determine VO_2-peak with braked arm ergometer and 12 lead ECG.	• Excellent correlation between VO_2 peak and 6-MAT VO_2. • Good correlation between 6-MAT HR and VO_2 peak. Conclusion: • 6-MAT has acceptable values for test-retest reliability and validity.	• Methodology repeatable: ○ Single centre study. ○ Inclusion and exclusion criteria described. ○ Study procedure explained. ○ Equipment explained. • Statistical analysis: ○ Skewness coefficients calculated. ○ Intra-class correlation coefficients with standard error of measurement determine test-retest reliability. • Limitations: None mentioned. • Recommendation for future research: ○ Test responsiveness of 6-MAT as clinical tool for measurement of cardiovascular fitness in SCI patients. • Level of evidence: 2a

Author & Date	Patients	Methodology	Results	Critique
Cuthbert SC et al. 2007	• Two databases: ○ Pubmed ○ Cinahl • 100 publications found. • 12 RCT's reviewed.	• Literature review. Aim: • To provide an historical overview, literature review, description, synthesis and critique of the reliability and validity of manual muscle testing in the evaluation of musculoskeletal and nervous systems. • Keywords: ○ Manual muscle testing ○ Manual muscle test	• Manual muscle testing showed to be a clinically useful tool, but its ultimate scientific validation and application requires testing.	• Aim of the review described. • Methodology not repeatable: ○ Inclusion and exclusion criteria explained. ○ Only 2 databases to be electronically searched. No multiple resources will be evaluated. • Statistical analysis not described. • Limitations: Mentioned. • Level of evidence: 5

Author & Date	Patients	Methodology	Results	Critique
Frutos-Vivar F et al. 2006.	• 37 hospitals in 8 countries. • 980 patients recruited. • 78 patients excluded due to incomplete data. • 2 patients excluded due to immediate re-intubation.	• Observational, cohort study. • Multi-centre study. Aim: • Assess the variables associated with reintubation in a heterogeneous group of mechanically ventilated patients who are extubated after successful completion of the SBT. Measurements: • Patients were daily screened for extubation readiness. • Data were recorded according to the explained data sheet. • Patients successfully completed SBT were extubated and followed up for 24-48 hours post extubation for re-intubation.	• Re-intubation in 121 of the 900 patients. • Re-intubation within 72 hours was associated with: ○ RSBI > 57 breaths/min/L. ○ Positive fluid balance within 24 hours prior extubation. ○ Pneumonia as the cause for initial intubation.	• Methodology repeatable: ○ Multi centre international study. ○ Inclusion and exclusion criteria explained. ○ Research procedure explained. ○ Follow up patients 24 and 48 hours after extubation. • Statistical analysis: ○ Median, interquartile range, proportions and standard deviations were analysed with Student T-test, Mann-Whitney U test and Fisher exact test. ○ Logistic regression analysis and Odd's ratio were completed. ○ Mention the reasons for excluding data from analysis. • Limitations: ○ Didn't collect any hemodynamic or ECG measurements to correlate positive fluid balance with ventricular dysfunction. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Dourado VZ et al. 2006.	• 38 patients evaluated. • Pulmonary rehabilitation centre.	• Prospective, cross sectional study. • Single centre study. Aim: • To investigate the influence of thoracic and upper limb muscle function on 6-min walk distance in patients with COPD. • Pulmonary function and baseline dyspnoea index were assessed. • Handgrip strength • MIP • 6MWD	• Correlation between 6MWD and weight. • Correlation between 6MWD and lung function and MIP. • Negative correlation between 6MWD and dyspnoea at end of 6MWT. Conclusion: • Importance of skeletal musculature of the thorax and upper limbs in submaximal exercise tolerance could open new perspective fore training programs in COPD patients.	• Methodology repeatable: o Single centre study. o Inclusion and exclusion criteria explained. o Measuring instruments explained in detail. o Research procedure explained. • Statistical analysis: o Spearman's and Pearson's coefficients of correlation were analysed. o Multi regression analysis to evaluate independent variables. • Limitations: None mentioned. • Recommendation for future research: Mentioned. • Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Chang AT et al. 2005.	• 20 patients included. • Tertiary hospital.	• Prospective study. • Single centre study. Aim: • Assess inspiratory muscle endurance following successful weaning and discharge from ICU. • Study the relationship between respiratory muscle endurance and duration of mechanical ventilation. Measurements: Session 1: • Patient's FVC and FEV1 were measured with a spirometer. Session 2: • MIP was measured with a two-way valve at the beginning of the session and after a 2 minute inspiratory loading protocol.	• The decrease inspiratory muscle endurance worsens with the duration of mechanical ventilation. • Prolonged mechanically ventilated patients may benefit from respiratory muscle training. Conclusion: • Patients who received mechanical ventilation for >48 hours have reduced inspiratory muscle endurance (lower FRI).	• Methodology repeatable: ○ Single centre study. ○ Exclusion criteria explained. ○ Measuring instruments explained in detail. ○ Research procedure explained. ○ Fatigue resistance index (FRI) was calculated as the MIP measured after a 2 min inspiratory loading protocol divided by the initial MIP. ○ Follow up period was not constant in the study. • Statistical analysis: ○ Spearman's correlations, Kruskal-Wallis analysis were used. • Limitations: ○ Not all the patients received the same resistance. ○ Only long term ventilated patients were recruited, future studies should also include short term ventilated patients. • Recommendation for future research: Mentioned. • Level of evidence: 2

Author & Date	Patients	Methodology	Results	Critique
Porta MD et al. 2005.	• 228 patients recruited. • 66 patients included. • Respiratory ICU's.	• Prospective, randomised control trial. • Multicentre study – 3 ICU's. Aim: • To determine the feasibility of adding arm exercise training to general physiotherapy in ICU. Measurements: • Lung function (FEV1, FVC) • Arterial blood gases • MIP • Arm exercise test. • Endurance test • Control group received general physiotherapy. • Study group received general physiotherapy and 20 min arm exercises with cycle ergometer.	• Maximum workload and endurance increase with arm exercises. • Muscular fatigue decrease with arm exercises. • Sensation of dyspnoea decrease with arm exercises. Conclusion: • Early addition of arm exercise to general physiotherapy is feasible and safe in ICU. • Early arm exercise program can enhance the effects on strength and endurance of the upper-girdle muscles.	• Methodology repeatable: o Multicentre study – 3 ICU's. o Inclusion and exclusion criteria described. o Study procedure described. o Equipment described. o Randomization done by computer. o Recruiting of patients explained with flow diagram. • Statistical analysis: o Two-sample T-test explore differences in baseline characteristics. o Non-parametric data analysed with Wilcoxon matched-paired tests and Mann-Whitney U- test. o Logistic regression models were also analysed. • Limitations: o No control group with no rehabilitation due to ethical considerations. • Recommendation for future research: Mentioned. • Level of evidence: 1a

Author & Date	Patients	Methodology	Results	Critique

Ely EW et al. 2003.	• 38 patients for reliability testing.
	• 275 patients for validity testing.
	• Medical and coronary ICU.
		• Prospective cohort study.
		• Single centre study.
		
		Aim:
		• To further test the reliability and validity of the RASS.
		
		Measurements:
		Phase 1:
		• Two nurses take RASS at the same time. An Intensivist and neuropsychiatric expert performed their RASS evaluation 4hours after the nurses. The investigators didn't have access to each other's readings.
		• Nurses perform GCS and Ramsay scale.
		
		Phase 2:
		• Validity determined according to 3 criteria:
		• Criterion validity.
		• Construct validity.
		• Face validity.
			• Validated for its ability to detect changes in sedation status over consecutive days of ICU stay.
			• Correlate with the administered dose of sedative and analgesic medications.
			
			Conclusion:
			• RASS demonstrated excellent interrater reliability and criterion, construct and face validity.
				• Methodology repeatable:
				  ○ Single centre study.
				  ○ Exclusion criteria explained.
				  ○ Evaluation procedure explained in detail.
				  ○ Investigators were blinded to each other's readings.
				• Patients were followed up because the RASS score was evaluated daily during the ICU stay.
				• Statistical analysis:
				  ○ Means, standard deviations, weighted K indices, 95% confidence interval, Wilcoxon rank sum test, Spearman correlation coefficient were used to analyse data.
				  ○ Reason for excluding patient's data for analysis mentioned.
				• Limitations:
				  ○ Only one RASS score per patient assessment was done, do not know the number of times patients were assigned negative RASS
				• Recommendation for future research:
				  ○ To determine the relative importance of other covariates contributing to level of consciousness.
				  ○ Investigate the usefulness of this tool in multicentre clinical trials.
				• Level of evidence: 2b

Author & Date	Patients	Methodology	Results	Critique
Sessler CN et al. 2002.	• 246 patients recruited, 54 excluded. • Tertiary Care hospital. • Medical, Coronary, Trauma / Surgery, Neuro-surgery, Cardio-thoracic ICU.	• Validity and reliability testing. • Single centre study. Aim: • Test validity and inter-rater reliability of the Richmond Agitation-Sedation Scale (RASS) in two phases. Measurements: Phase 1: • 5 investigators observed the patient's level of alertness and agitation for 30 seconds. All investigators recorded independently a RASS score. Phase 2: • Evaluate inter-rater reliability after implementation of the RASS in the ICU. • The bedside nurse as well as the nurse educator documented separately a RASS score. • 15 minutes after the RASS score was taken, the GCS and Ramsay sedation scale score were measured by the bedside nurse and Principal investigator respectively.	• Lower RASS for ventilated than non-ventilated patients. • Lower RASS for patients receiving continuous infusion sedative or analgesic medication. • Excellent inter-rater reliability for RASS among ICU population. • High validity for RASS score. • Single-item numerical structure. Conclusion: • RASS has high reliability and validity in medical and surgical, ventilated and non-ventilated and sedated and non-sedated adult ICU patients.	• Methodology repeatable: ○ Single centre study. ○ Exclusion criteria explained. ○ Variety of investigators to determine validity and inter-rater reliability. ○ Assessment techniques explained in detail. • Statistical analysis: ○ Mean and standard deviation, median and interquartile range were displayed. ICC and weighted K test used. ○ Reason for exclusion of patient's data for analysis described. • Phase 1 was followed up with phase 2 after implementation of the RASS score in ICU. • Limitations: ○ The extent to which the instrument can detect important changes in sedation (responsiveness), was not tested. • Level of evidence: 1c

Author & Date	Patients	Methodology	Results	Critique
Swain D et al. 2001.	• 18 studies recruited.	• Systematic review. Aim: • Analysis was designed to determine the threshold intensity for improving cardiorespiratory fitness express as %VO_2R units.	• The analysis of training studies supports the use of 45% VO_2R as minimal effective training intensity for higher fit subjects. • 30% VO_2R for lower fit subjects.	• Methodology not repeatable: ○ Study design not explained. ○ Inclusion and exclusion criteria of studies explained. ○ Research procedure explained. • Statistical analysis: None mentioned. • Limitations: None mentioned. • Level of evidence: 5
Esteban A et al. 1995.	• 546 patients participated in the study. • Medical-surgery ICU of 14 hospitals.	• Prospective randomised study. • Multicentre study. Aim: • To further test the reliability and validity of the RASS. Four techniques: • Intermittent mandatory ventilation. • Pressure support ventilation. • Intermittent trials of spontaneous breathing conducted several times a day. • Once-daily trial of spontaneous breathing.	• Median duration of weaning for intermittent mandatory ventilation was 5 days. • Median duration of weaning for pressure support ventilation was 3 days. • Successful weaning was higher with a once-daily trial of spontaneous breathing than with intermittent mandatory ventilation or pressure support ventilation. Conclusion: • Once-daily trial of spontaneous breathing led to extubation about three times more quickly than intermittent mandatory ventilation and twice as quickly as pressure support ventilation.	• Methodology repeatable: ○ Multicentre study. ○ Inclusion and exclusion criteria explained. ○ Study procedure explained. • Statistical analysis: ○ Chi-square test used to compare categorical data. ○ Kruskal-Wallis test used to compare continuous variables among the groups. ○ Kaplan-Meier method was used to determine probability of success of particular method of weaning. • Limitations: None mentioned. • Recommendation for future research: None mentioned. • Level of evidence: 3

APPENDIX 2

Informed consent form

UNIVERSITY OF PRETORIA

Patient's / participant's information leaflet and informed consent document

Title of the study

Upper limb muscle strength and endurance as predictors of successful extubation in mechanically ventilated patients: A predictive correlational study.

Principle investigator

Rubine de Beer (phone: 082 655 4625) (email: crdebeer@gmail.com)

Date and time of first informed consent discussion

dd_____________mm_______________yr_______________ Time:_____________

Dear Prof / Dr / Mr / Ms

1. Introduction

Good day. My name is …………………….……….. I work at Steve Biko Academic Hospital as a ………………..……… in the department of …………..……………….. I would like to invite you to consider participating in a research study. This information leaflet is to help you to decide if you would like to participate. Before you agree to take part in this study you should understand what is involved. If you have any questions, which are not fully explained in this leaflet, please do not hesitate to ask me. You should not agree to take part unless you are completely happy about all the procedures involved.

2. Purpose of the study

You are invited to participate in a research study about the influence your muscle strength and endurance will have on your body when we remove the tube that assisted you with breathing. The purpose of this study is to determine if your muscle strength and endurance can give us an indication if your body is strong enough to remove the breathing tube successfully. By doing so I wish to learn more about your muscle strength and endurance. The research will only be conducted in patients in the Surgery-Trauma and Medical Intensive Care Units in Steve Biko Academic Hospital. The research will be conducted in your ICU bed.

3. Procedure to be followed

This study involves some tests that will be conducted. The investigator will test how strong your arm and shoulder muscles are. During this testing, the investigator will ask you to lift up your shoulders to the ears, bend your neck forward – put your chin on your collar bone, lift up your arms to the side and push your arm towards your opposite hip. The investigator will also test the strength of your legs. You will have to bend and straiten the knees and hips. The strength of your hands will be determined by squeezing the handgrip dynamometer. You will ride a bicycle (MOTOmed® letto2 cycle ergometer) with your arms for 6 minutes while lying in bed. While riding the bicycle you will have to bend and straiten your elbows.

The investigator will test how strong your lungs are while you are taking deep breaths in and out. Measurements will be taken during your breathing. While the physician is doing your routine blood tests in the morning, they will test the amount of proteins and electrolytes in your blood.

Your participation will last approximately 60 minutes per session. Only one session is required. The study will not interfere with your daily treatment.

4. Risks and discomfort involved

The possible discomfort involved is that your arms can feel tired after the exercises. You may also feel short of breath after measuring your breath strength. There are no other foreseeable risks involved in the study.

5. Possible benefits of this study

The study will provide no financial benefit to you. Many of the tests are done on a regular basis on patients. The results of this study may benefit patients in the future.

6. I understand that if I do not want to participate in this study, I will still receive standard treatment for my illness.

7. I may at any time withdraw from this study.

8. Ethical approval

The clinical protocol was submitted to the Faculty of Health Sciences Research Ethics Committee, University of Pretoria, telephone numbers 012 356 3084 / 012 356 3085 and written approval has been granted by that committee.

The study has been structured in accordance with the Declaration of Helsinki (last update: October 2013), which deals with the recommendations guiding researchers in biomedical research involving humans/subjects. A copy of the Declaration may be obtained from the investigator should you wish to review it.

9. Information

You may ask any questions about the research study. If you have questions concerning this study after the investigator leaves today, you should contact the investigator, Me R de Beer at 082 655 4625.

10. Confidentiality

All records obtained in this study will be regarded as confidential. Results will be published or presented in such a manner that you will remain anonymous.

11. Consent to participate in this study

I have read or had the form read to me in a language that I understand the above information before signing this consent form. The content and meaning of this information have been explained to me. I have been given opportunity to ask questions and I am satisfied that they have been answered satisfactorily. I understand that if I do not participate it will not alter my management in any way. I hereby volunteer to take part in this study.

I have received a signed copy of this informed consent agreement.

______________________	______________________
Patient's name	Date
______________________	______________________
Patient's signature	Date
______________________	______________________
Investigator's name	Date
______________________	______________________
Investigator's signature	Date
______________________	______________________
Witness's name and signature	Date

Verbal patient informed consent (applicable when patients cannot read or write)

I, the undersigned, Me R de Beer, have read and have explained fully to the patient, named________________________________ and/or his/her relative, the patient information leaflet, which has indicated the nature and purpose of the study in which I have asked the patient to participate. The explanation I have given has mentioned both the possible risks and benefits of the study and the alternative treatments available for his/her illness. The patient indicated that he/she understands that he/she will be free to withdraw from the study at any time for any reason and without jeopardizing his/her treatment.

I hereby certify that the patient has agreed to participate in this study.

______________________________	______________________________
Patient's name (Print)	Patient's signature
______________________________	
Date	
______________________________	______________________________
Investigator's name (Print)	Investigator's signature
______________________________	
Date	
______________________________	______________________________
Witness's name (Print)	Witness's signature
______________________________	
Date	

APPENDIX 3

Research data sheet

1. Personal information

Subject number: ________________ **Date:** _______________ **Time:** ______

Gender: Male _________ Female _________ **Age:** _______

Nationality: White ☐ Coloured ☐ African ☐ Indian ☐ Other ☐

Medical diagnosis: ____

Medication: ____

Total days in ICU: _______________ Ventilated days in ICU: _________________

ICU: 4.9 ☐ 6.7 ☐ APACHE with admission: ____________________

Electrolytes: Sodium (Na^{+}) ______________ Magnesium (Mg^{2+}) _____________
Potassium (K^{+}) _____________ Calcium (Ca^{2+}) ________________
Phosphate (PO_{4}^{3-}) __________ Bicarbonate (HCO_{3}^{-})_____________

2. Assessment

2.1 Richmond Agitation-Sedation Scale

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff.
+3	Very agitated	Pulls on or removes tubes or catheters or has aggressive behaviour towards staff.
+2	Agitated	Frequent non-purposeful movement or patient ventilator dyssynchrony.
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous.
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening with eye contact to voice.
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice.
-3	Moderate sedation	Any movement (but no eye contact) to voice.
-4	Deep sedation	No response to voice, but any movement to physical stimulation.

Total RASS: ____________________

2.2 Cognitive questions

Question	Score	Question	Score
“Close / open your eyes”		“Nod your head”	
“Look at me”		“Raise your eyebrows”	
“Stick out your tongue”		**Total**	

2.3 Medical Research Council Score

Muscle group	Left	Right
Shoulder abduction		
Elbow flexion		
Wrist extension		
Hip flexion		
Knee extension		
Ankle dorsiflexion		
Total	**/60**	

2.4 Oxford Muscle Testing

Muscle	Grading	
	Left	Right
Trapezius		
Deltoid		
Sternocleidomastoid		
Pectoralis major		

2.5 Handgrip strength

Measurement	Left	Right
1		
2		
3		
Best		

2.6 MOTOmed® letto2 cycle ergometer

Program	Servo cycle		
Active distance (km)		Active time (min)	
Passive distance (km)		Passive time (min)	
Total distance (km)		Total time (min)	
Energy (kcal / KJ)		Speed (rpm)	
		Resistance (gear)	1 Gear

2.7 Respiratory measurements and Pro-BNP

Pro-BNP	N/A			
PaO_2/FiO_2 ratio				
RSBI				
MVV (L/min)	N/A			
MIP measurements	**1**	**2**	**3**	**Best**
MIP ($cmH_2 0$)				

3. Spontaneous breathing trial / extubation

Passed ☐ Failed ☐

48 hours: Re-intubated Y N **72 hours:** Re-intubated Y N

APPENDIX 4

Summary of data collection

General Information						MRC	Trapezius		Deltoid		Sternocl		Pecs Maj		Handgrip			MOTOmed letto$_2$ cycle ergometer							Respiratory			Electrolytes					Cardiovascular				Extubation outcome			
Nr.	Gender	Age	ICU days	Vent days	RASS	MRC	L	R	L	R	L	R	L	R	L	R	Com	Act Dis	Pass Dis	Act Time	Pas Time	Speed	Kcal	KJ	MIP	PaO_2/FiO_2	RSBI	Na^+	K^+	PO^-	Mg^{2+}	Ca^{2+}	HRb	Hra	MaxHR	BP	SBT	48 Hours	72 Hours	Outcome
1	1	42	19	18	0	36	3	3	3	3	3	3	3	3	10	12	11	0,55	0,28	02:51	03:10	42	2,6	11	-21	173	143	131,0	4,9	1,3	0,7	1,8	129	132	178	146/90	2	*2*	2	2
2	2	47	7	6	1	44	3	3	3	3	3	3	3	3	20	20	20	0,38	0,25	02:12	02:37	40	2,1	8,8	-20	155	25	142,0	3,9	1,0	0,9	1,9	66	69	173	129/74	1	1	1	1
3	1	57	9	3	0	39	3	3	1	3	3	3	1	3	22	62	42	1,09	0	06:00	00:00	37	5,5	22,9	-14	338	33	137,0	4,7	0,9	0,7	1,9	88	95	163	164/73	1	1	1	1
4	1	32	4	4	0	28	3	3	2	2	2	2	2	2	22	24	23	0	0,58	00:00	06:00	0	0	0	-14	423	14	147,0	4,4	1,7	0,7	2,1	89	89	188	150/90	1	1	1	1
5	1	53	8	8	-1	48	3	3	3	3	1	1	3	3	4	14	9	0,64	0	06:00	00:00	22	5,3	22,3	-22	255	28	141,0	3,9	1,0	0,6	2,1	83	80	167	113/57	1	1	1	1
6	2	32	3	3	0	56	3	3	3	3	3	3	3	3	18	34	26	1,04	0	05:55	00:05	37	5,4	22,5	-23	420	18	134,0	4,1	0,8	0,8	2,0	119	127	188	122/66	1	1	1	1
7	2	68	11	11	0	26	2	2	2	2	1	1	2	2	3	5	4	0	0,59	00:00	06:00	0	0	0	-21	321	21	140,0	4,3	0,4	1,0	2,3	79	81	152	120/47	1	1	1	1
8	2	65	4	4	-1	40	3	3	3	3	3	3	2	2	18	22	20	0,31	0,21	04:03	0,10903	18	3,4	14,8	-18	302	28	152,0	3,4	0,9	0,8	1,9	100	112	155	131/57	1	1	1	1
9	2	81	6	6	-1	12	1	1	1	1	1	1	1	1	2	0	1	0,01	0,61	00:16	05:44	9	0,2	1	-21	318	18	147,0	3,5	0,6	0,8	1,9	96	97	139	113/88	1	2	2	2
10	1	36	6	6	0	48	3	3	3	3	3	3	3	3	38	32	35	1,26	0	06:00	00:00	41	5,6	23,6	-42	301	28	135,0	4,1	1,0	0,8	1,8	83	82	182	132/74	1	1	1	1
11	2	63	7	6	-1	26	2	2	1	1	1	1	1	1	2	4	3	0,03	0,54	00:27	05:33	20	0,4	1,6	-20	280	28	143,0	4,3	0,7	0,6	2,0	99	96	157	110/54	1	1	1	1
12	1	70	7	7	-1	16	3	3	1	1	1	1	1	1	1	1	1	0	0,57	00:00	06:00	0	0	0	-13	150	20	151,0	4,0	0,5	0,9	2,1	64	67	150	124/51	2	2	2	2
13	1	35	9	9	0	47	3	3	3	3	1	1	2	3	10	14	12	0,43	0	06:00	00:00	15	5,3	22	-43	316	48	133,0	4,7	1,3	0,8	2,0	79	83	185	130/71	1	1	1	1
14	1	70	15	15	0	30	3	3	2	2	3	3	2	2	4	1	3	0,3	0,37	02:13	03:47	33	2	8,4	-17	388	23	140,0	4,3	1,0	1,1	2,1	64	71	150	107/55	1	1	1	1
15	2	48	5	4	0	48	3	3	3	3	1	1	3	3	16	28	22	2,11	0	06:00	00:00	71	6,7	27,9	-16	378	36	135,0	4,0	0,8	0,8	2,0	109	100	172	170/90	1	1	1	1
16	1	53	4	4	-1	32	3	3	2	3	1	1	2	2	12	16	14	0,02	0,56	00:18	05:43	15	0,3	1,1	-20	179	34	141,0	4,1	0,6	0,9	2,0	82	84	167	109/72	1	1	2	2
17	1	29	10	9	-1	38	3	3	3	3	2	2	3	3	6	4	5	0,26	0,38	01:51	04:09	31	1,7	7	-20	390	35	139,0	4,4	0,4	0,7	1,8	132	135	191	119/76	2	2	2	2
18	1	20	7	5	0	54	3	3	3	3	3	3	3	3	41	38	40	0,73	0,04	05:36	00:25	28	5	21	-21	116	90	128,0	5,1	1,2	0,7	2,0	99	106	200	133/74	1	1	1	1
19	1	29	15	14	0	57	3	3	3	3	3	3	3	3	18	38	28	0,52	0,21	03:46	02:14	29	3,4	14,1	-21	251	47	135,0	5,1	1,0	0,7	2,1	120	127	191	143/77	2	2	2	2
20	1	35	3	3	-1	44	3	3	3	3	3	3	3	3	28	24	26	0,77	0	06:00	00:00	30	5,4	22,5	-20	344	51	131,0	0,7	0,8	0,8	1,9	102	110	185	148/79	1	1	1	1
21	1	54	10	9	-1	18	2	2	2	2	1	1	1	1	8	6	7	0,09	0,47	01:15	04:46	17	1,1	4,6	-20	268	38,7	140,0	3,9	0,8	0,8	2,0	122	128	166	137/78	1	1	2	2
22	2	28	13	13	0	48	3	3	3	3	3	3	3	3	14	4	9	0,39	0,3	02:59	03:02	30	2,6	11,1	-20	226	80	138,0	4,0	1,5	0,8	2,0	73	79	192	125/93	1	1	1	1
23	1	35	4	4	0	46	3	3	3	3	3	3	3	3	18	22	20	1,24	0	05:57	00:03	45	5,6	23,5	-20	279	30	132,0	4,7	0,9	0,7	1,9	116	122	185	147/70	1	1	1	1
24	2	43	9	9	0	32	3	3	3	3	3	3	2	2	1	2	2	0,33	0,2	04:01	02:11	18	3,5	14,8	-18	262	31	131,0	3,8	0,5	1,0	1,9	81	87	177	143/56	1	1	1	1
25	2	63	3	3	-1	42	3	3	3	3	3	3	3	3	1	2	2	0,35	0,3	02:50	03:11	29	2,6	11	-22	227	30	140,0	4,3	0,5	1,0	2,1	99	106	157	167/83	1	1	1	1
26	1	36	8	8	0	52	3	3	3	3	3	3	3	3	16	18	17	0,88	0,04	05:35	00:25	32	5	21,1	-21	489	21	137,0	4,1	1,0	0,9	2,0	86	95	184	140/80	2	2	2	2
27	1	45	8	8	-1	36	3	3	3	3	3	3	2	2	4	4	4	0,21	0,48	01:11	04:49	38	1,1	4,6	-16	267	36	137,0	4,2	1,0	0,8	2,1	118	123	175	146/72	1	1	1	1
28	2	34	5	3	0	56	3	3	3	3	3	3	3	3	16	20	18	2,06	0	06:00	00:00	68	6,9	28,7	-22	298	16	136,0	5,7	1,9	1,1	2,0	95	99	186	121/79	1	1	1	1
29	1	23	14	13	-1	42	3	3	3	3	2	2	2	2	2	2	2	0,56	0,02	05:42	00:19	25	5,1	21,2	-18	347	46	136,0	4,6	1,1	0,1	2,0	70	89	197	115/77	1	1	1	1
30	1	61	39	39	0	48	3	3	3	3	3	3	3	3	8	10	9	0,88	0	06:00	0	29	5,4	22,6	-21	206	32	136,0	4,6	1,0	0,8	1,9	78	82	159	132/76	2	2	2	2
31	2	29	14	12	0	30	3	3	3	3	2	2	2	2	2	2	2	0,04	0,56	00:22	05:38	25	0,3	1,3	-17	247	67	139,0	4,4	1,6	1,1	2,0	104	114	191	137/87	1	1	2	2
32	2	25	16	16	0	23	3	3	2	3	1	1	2	2	5	9	7	0,43	0,07	05:06	00:55	18	4,5	18,9	-14	219	41	137,0	4,9	1,0	0,8	2,1	83	87	195	114/63	1	2	2	2
33	1	45	22	22	0	32	3	3	3	3	1	1	2	2	10	11	11	0,13	0,19	01:19	01:56	24	1,2	5	-16	201	68	139,0	4,4	1,3	0,9	2,2	92	94	175	164/69	2	2	2	2
34	1	35	19	19	-1	16	2	2	1	1	1	1	1	1	1	1	1	0	0,57	00:00	06:00	0	0	0	-14	285	54	135,0	4,6	2,0	1,1	1,9	93	101	185	122/64	2	2	2	2
35	1	68	19	9	1	34	3	3	3	3	3	3	3	3	10	10	10	0,6	0,14	04:20	01:40	33	3,9	16,4	-20	407	34	134,0	3,9	1,3	1,0	2,2	81	77	152	148/73	1	2	2	2
36	2	44	4	4	-1	38	3	3	3	3	3	3	2	2	6	10	8	0,07	0,46	01:12	04:48	13	1	4,4	-16	371	42	144,0	3,8	0,6	0,7	2,1	101	110	176	136/76	1	1	1	1
37	1	26	5	5	0	40	3	3	3	3	3	3	3	3	2	2	2	0,51	0	06:00	0	19	5,3	22,1	-12	303	20	142,0	4,4	0,9	0,6	2,1	105	125	194	148/59	1	1	1	1
38	2	55	9	9	0	36	3	3	3	3	1	1	2	2	5	7	6	0,31	0,23	03:39	02:21	18	3,2	13,4	-18	187	43	139,0	4,5	1,1	0,8	2,2	74	78	164	90/76	1	1	1	1
39	2	66	4	4	-1	40	3	3	3	3	3	3	3	3	7	8	8	0	0,6	00:00	06:00	0	0	0	-12	355	28	138,0	4,4	1,5	0,6	2,0	97	93	155	148/80	2	2	2	2
40	2	27	7	7	0	40	3	3	3	3	3	3	3	3	16	16	16	1,3	0,02	05:51	00:14	43	5,7	23,7	-24	279	76	136,0	3,9	0,5	0,7	1,9	127	131	202	124/69	2	2	2	2
41	1	40	3	3	-1	52	3	3	3	3	3	3	3	3	20	20	20	0,99	0,06	05:17	00:43	38	4,8	20	-23	232	69	135,0	4,0	0,9	0,8	2,0	87	90	180	144/75	1	1	1	1
42	2	71	4	4	-1	24	3	3	3	2	3	3	1	1	0	0	0	0	0,58	00:05	05:55	17	0,1	0,3	-16	255	18	139,0	4,3	1,9	0,7	2,1	94	93	149	95/69	1	1	1	1
43	1	40	5	5	-1	28	3	3	3	3	3	3	1	1	8	10	9	0	0,59	00:03	05:57	23	0	0,2	-18	245	46	134,0	5,0	1,0	0,9	1,9	77	81	180	136/91	2	2	2	2
44	1	37	3	3	1	60	3	3	3	3	3	3	3	3	18	32	25	0,96	0	06:00	00:00	35	5,4	22,5	-18	328	15	142,0	4,7	1,2	1,4	2,1	64	84	183	174/89	1	1	1	1
45	2	43	4	4	1	48	3	3	3	3	3	3	3	3	2	2	2	1,01	0,07	05:15	00:45	38	4,8	19,9	-18	293	36	126,0	3,6	0,9	0,8	2,0	57	61	177	154/77	1	1	1	1
46	1	32	3	3	1	48	3	3	3	3	3	3	3	3	26	28	27	1,38	0	05:55	00:05	47	5,6	23,3	-25	323	66	140,0	4,0	0,7	0,9	1,8	112	120	188	114/77	1	1	1	1
47	1	28	5	5	1	54	3	3	3	3	3	3	3	3	20	22	21	0,63	0,15	04:28	01:33	34	4,2	17,7	-20	229	24	138,0	3,6	0,8	0,9	1,9	47	52	192	144/69	1	1	1	1
48	1	22	4	4	1	24	3	3	1	1	1	1	1	1	0	0	0	0	0,56	00:00	06:00	0	0	0	-12	320	37	133,0	4,2	6,5	0,7	1,8	93	99	198	124/62	1	1	1	1
49	2	51	3	3	1	46	3	3	3	3	3	3	3	3	2	2	2	0,54	0,18	04:10	01:50	28	3,8	15,7	-16	409	49	140,0	4,0	0,8	0,9	1,8	111	120	169	131/90	1	1	1	1
50	1	55	3	3	1	50	3	3	3	3	3	3	2	2	4	8	6	0,8	0,11	04:59	01:02	39	4,7	19,6	-20	394	13	143,0	3,6	0,8	0,6	1,6	121	127	165	116/63	1	1	1	1
51	2	52	11	11	2	48	3	3	3	3	3	3	2	2	2	1	2	0,35	0,23	03:34	02:26	22	3,2	13,3	-14	143	80	134,0	4,7	1,0	0,9	2,0	94	112	168	122/78	2	2	2	2
52	1	62	5	5	2	26	3	3	3	3	2	2	2	2	1	1	1	0	0,58	00:00	06:00	0	0	0	-11	321	25	146,0	4,7	0,7	0,9	1,9	103	104	158	164/73	2	2	2	2
53	2	30	3	3	1	42	3	3	3	1	3	3	3	1	8	1	4	0,04	0,61	00:24	05:37	22	4	1,5	-20	279	45	142,0	4,3	0,9	0,7	1,8	104	118	190	139/77	1	1	1	1
54	1	45	7	7	1	46	3	3	3	3	1	1	3	3	1	1	1	0,51	0,03	05:36	00:26	25	0,4	1,6	-14	287	25	140,0	4,6	1,4	0,9	1,9	68	88	175	145/67	1	1	1	1
55	2	18	3	3	2	56	3	3	3	3	3	3	3	3	6	8	7	0,24	0,35	02:13	03:47	29	2	8,2	-14	188	74	143,0	4,6	1,1	0,8	1,8	129	136	202	141/106	2	2	2	2
56	1	62	5	5	2	10	1	1	1	1	1	1	0	0	0	0	0	0	0,54	00:06	05:54	25	0,1	0,4	-14	226	94	150,0	4,1	1,5	0,8	2,0	109	109	158	108/59	1	2	2	2
57	1	60	10	10	2	32	2	2	2	2	1	1	1	1	2	2	2	0	0,58	00:00	06:00	0	0	0	-20	282	45	144,0	4,8	1,1	0,9	2,0	75	78	160	155/83	1	2	2	2

APPENDIX 5

Summary of Turnitin report

Turnitin Originality Report
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APPENDIX 6

Progress reports

STUDY PROGRESS REPORT

A. Research Ethics Committee Reference Number & Title of Study:

Ref nr: 394/2017
Title: Upper limb muscle strength and endurance as predictors of successful extubation in mechanically ventilated patients: A predictive correlational study

B. MCC Reference Number (if applicable):

N/A

C. Number of patients (if applicable):

1. **Yet to be recruited locally:** 46
2. **Already enrolled at this site:** 14
3. **Premature withdrawn from Study:**

   Provide reason:

D. Summary of findings to date (if available):

Data collection in progress.

E. Summary of Adverse Effects Encountered (if applicable):

Relation to the research: None

- **Related** ☐
- **Not Related** ☐
- **Possible** ☐
- **Unknown** ☐

Principal Investigator

April 2018
Date

STUDY PROGRESS REPORT

A. Research Ethics Committee Reference Number & Title of Study:

Ref nr: 394/2017
Title: Upper limb muscle strength and endurance as predictors of successful extubation in mechanically ventilated patients: A predictive correlational study

B. MCC Reference Number (if applicable):

N/A

F. Number of patients (if applicable):

4. **Yet to be recruited locally:** 26

5. **Already enrolled at this site:** 34

6. **Premature withdrawn from Study:**

   Provide reason:

G. Summary of findings to date (if available):

Data collection in progress.

H. Summary of Adverse Effects Encountered (if applicable):

Relation to the research: None

Related ☐
Not Related ☐
Possible ☐
Unknown ☐

Principal Investigator

October 2018
Date

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

STUDY PROGRESS REPORT

A. Research Ethics Committee Reference Number & Title of Study:

Ref nr: 394/2017
Title: Upper limb muscle strength and endurance as predictors of successful extubation in mechanically ventilated patients: A predictive correlational study

B. MCC Reference Number (if applicable):

N/A

I. Number of patients (if applicable):

7. **Yet to be recruited locally:** 20

8. **Already enrolled at this site:** 40

9. **Premature withdrawn from Study:**

   Provide reason:

J. Summary of findings to date (if available):

Data collection in progress.

K. Summary of Adverse Effects Encountered (if applicable):

Relation to the research: None

- **Related** ☐
- **Not Related** ☐
- **Possible** ☐
- **Unknown** ☐

Principal Investigator

April 2019
Date

STUDY PROGRESS REPORT

A. Research Ethics Committee Reference Number & Title of Study:

Ref nr: 394/2017
Title: Upper limb muscle strength and endurance as predictors of successful extubation in mechanically ventilated patients: A predictive correlational study

B. MCC Reference Number (if applicable):

N/A

L. Number of patients (if applicable):

10. **Yet to be recruited locally:** 0

11. **Already enrolled at this site:** 57

12. **Premature withdrawn from Study:**

Provide reason:

M. Summary of findings to date (if available):

Data collection done.

N. Summary of Adverse Effects Encountered (if applicable):

Relation to the research: None

Related ☐
Not Related ☐
Possible ☐
Unknown ☐

Principal Investigator

October 2019
Date